CYCLOISOMERIZATION REACTIONS CATALYZED BY TRANSITION METAL COMPLEXES. SYNTHESIS OF OXYGEN- AND NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS

by

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A scientist in his laboratory is not a mere technician:
he is also a child confronting natural phenomena
that impress him as though they were fairy tales.

Marie Curie

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ABSTRACT

The increasing need for environmentally responsible means of preparing a wide diversity of chemical products demanded by society drives the quest for synthetic efficiency. Transition metal-catalyzed cyclizations of polyunsaturated system, which are both selective and atom-economical, represent an important starting point for this long-term goal.

We describe herein four different class of transition metal-catalyzed reactions that provided an atom- and step-economical entry into a range of oxygen- and nitrogen-containing heterocycles: (1) ring-closing metathesis, (2) Pauson-Khand reactions, (3) platinum-, gold- and iridium-catalyzed electrophilic activation of alkynes and (4) gold-catalyzed cyclizations of allenes. All these transformations allow for a rapid increase in molecular complexity from relatively simple starting materials. Moreover, since these processes exhibit an excellent chemoselectivity towards C-C π systems, the cyclized products usually retain different functional groups that can be used for further synthetic transformations.

Manuscripts adding to the scope of transition metal-catalyzed reactions are being published at a rapid rate attesting to their interest in the chemical community. With the development of new asymmetric methodologies, the transformations described in this thesis will continue to occupy, in the next future, a remarkable role in organic synthesis.

KEYWORDS

- Metathesis;
- Pauson-Khand;
- Cycloisomerizations;
- Unsaturated substrates;
- Oxygen compounds;
- Nitrogen heterocycles.

LIST OF ABBREVIATIONS

Ac	Acetyl (CH_3CO)
AcOEt	Ethyl acetate (solvent)
ADMET	Addition metathesis polymerization
AIBN	Azobis(isobutyronitrile) (radical initiator)
Ar	Aromatic group
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Biphemp	2,2'-Dimethyl-6,6'-bis(diphenylphosphino)biphenyl
BITIAMP	2,2'-Bis(diphenylphosphino)-3,3'-dibenzo[*b*]thiophene
Bn	Benzyl group ($CH_2C_6H_5$)
Boc	*tert*-Butyloxycarbonyl ($CO\mathit{t}C_4H_9$)
Boc_2O	*tert*-Butyl dicarbonate
br	Broad (NMR)
BuLi	Butyl lithium
BuSMe	Butyl methyl sulfide
CAN	Ceric ammonium nitrate
Cat.	Catalyst
CH_2Cl_2	Dichloromethane (solvent)
$CHCl_3$	Chloroform (solvent)
CI	Chemical ionization (MS)
CM	Cross metathesis
CO	Carbon monoxide
COD	1,5-Cyclooctadiene
COSY	Correlation spectroscopy (NMR)
Cp*	Pentamethylcyclopentadieny
Cy	Cyclohexyl
δ	Chemical shift (NMR)
d	Doublet (NMR)
DCD	Dewar-Chatt-Duncanson model
DCE	Dichloroethane (solvent)
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarization transfer (NMR)

Difluorphos	Bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine (base, catalyst)
DME	1,2-Dimethoxyethane (glyme, solvent)
DMF	Dimethylformamide (solvent)
DMSO	Dimethyl sulfoxide (solvent)
dppm	1,1-Bis(diphenylphosphino)methane
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
E	Ethoxycarbonyl ($CO_2CH_2CH_3$)
E	Entgegen (opposite, *trans*)
EDG	Electron-donating group
ee	Enantiomeric excess
EI	Electron impact (MS)
eq.	Equivalent
ESI	Electrospray ionisation
Et	Ethyl (C_2H_5)
Et_2O	Diethyl ether (solvent)
EtOH	Ethanol (solvent)
EWG	Electron-withdrawing group
GC	Gas chromatography
h	Hours
HMBC	Heteronuclear multiple bond correlation (NMR)
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spettroscopy
Hz	Hertz
IBX	2-Iodoxybenzoic acid
***i*Pr**	*iso*-Propyl group (C_3H_7)
IR	Infrared spettroscopy
J	Coupling constant (NMR)
KAPA	7-Keto-8-aminopelargomic acid

L	Ligand
M	Metal
m	Multiplet (NMR)
Me	Methyl (CH_3)
MeOH	Methanol (solvent)
Mes	Mesityl (2,4,6-trimethylphenyl)
min	Minutes
MOM	Methoxymethyl ether (alcohol protecting group)
Mp	Melting point
MS	Mass spettroscopy
MS	Molecular sieves
Ms	Methanesulfonyl (Mesyl, CH_3SO_2)
MW	Microwave irradiation
ν	Wave number (IR)
NHC	*N*-heterocyclic carbenes
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
n.r.	No reaction
P-Phos	2,2′,6,6′-Tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine
PE	Petroleum ether (solvent)
PG	Protecting group
Ph	Phenyl (C_6H_5)
phox	Phosphinooxazolines
PKR	Pauson-Khand reaction
PPFA	2-(1-(Dimethylamino)ethyl)-1-(diphenylphosphino)ferrocene
ppm	Parts per million
ppy	Phenylpyridine
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine (solvent, base, catalyst)
q	Quartet (NMR)
quant.	Quantitative
R	Alkyl or aryl group

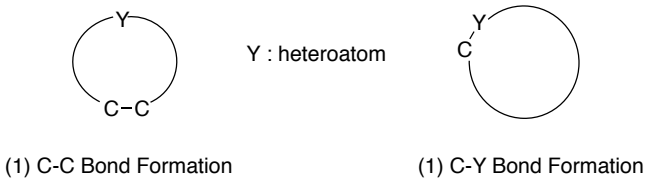
r.t.	Room temperature
rac.	Racemic
RCEYM	Ring-closing enyne metathesis
RCM	Ring-closing metathesis
ROMP	Ring-opening metathesis polimerization
s	Singlet (NMR)
SIPHOS	*N*-dimethyl-(1,1′-spirobiindane-7,7′-diyl)phosphoramidite
SM	Starting material
SYNPHOS	[(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenyl-phosphine)
t	Triplet (NMR)
TADDOL	α,α,α',α'-Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
***t*Bu**	*tert*-Butyl group (C_4H_9)
TES	Triethylsilyl
tetraMe-BITIOP	2,2'-Tetramethyl-4,4'-bis(diphenilphosphino)-3,3'-bithiophene
Tf	Triflate (CF_3SO_2)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran (solvent)
THP	Tetrahydropyran (alcohol protecting group)
TLC	Thin layer hromatography
TMANO	Trimethylamine *N*-oxide
TMS	Tetramethylsilane
TMSA	Trimethylsilyl acetylene
TOF	Turnover frequency
tol-BINAP	2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TON	Turnover number
TPP	Tetraphenylporphyrin
T_R	Retention time
Ts	Tosyl (p-$CH_3C_6H_4SO_2$)
UV	Ultraviolet
X	Heteroatom
Z	Zusammen (together, *cis*)

General introduction

The increasing need for environmentally responsible means of preparing a wide diversity of chemical products demanded by society drives the quest for synthetic efficiency. Thus, in order to minimize the use of raw materials and waste production, a chemical reaction should proceed with high levels of step and atom economy.[1] Indeed, an ideal chemical synthesis takes place in quantitative yield, with complete control of chemo-, regio- and stereoselectivity, without the formation of byproducts. Syntheses involving the use of external reagents, *i.e.* A + B ⟶ C + D, fail to address the latter issue as they inevitably generate byproducts as a result of the stoichiometry of the reaction. For transition metal catalyzed cyclization of polyunsaturated system, in which A ⟶ B, the possibility of addressing all issues of selectivity and atom economy exists. In this perspective, the high synthetic potential of polyunsaturated systems has made possible the preparation of a wide variety of cyclic building blocks.[2]

In this dissertation we focus our attention on four different classes of transition-metal-catalyzed reactions: (1) ring-closing diene and enyne metathesis, (2) Pauson-Khand reactions, (3) platinum-, gold-, and iridium-catalyzed activation of alkynes towards nucleophiles and (4) gold-catalyzed cyclizations of allenic systems. In particular, these extremely versatile methodologies are employed for the synthesis of oxygen- and nitrogen-containing heterocyles, ubiquitous constituent in pharmacophoric fragments, natural molecules and prodrugs.

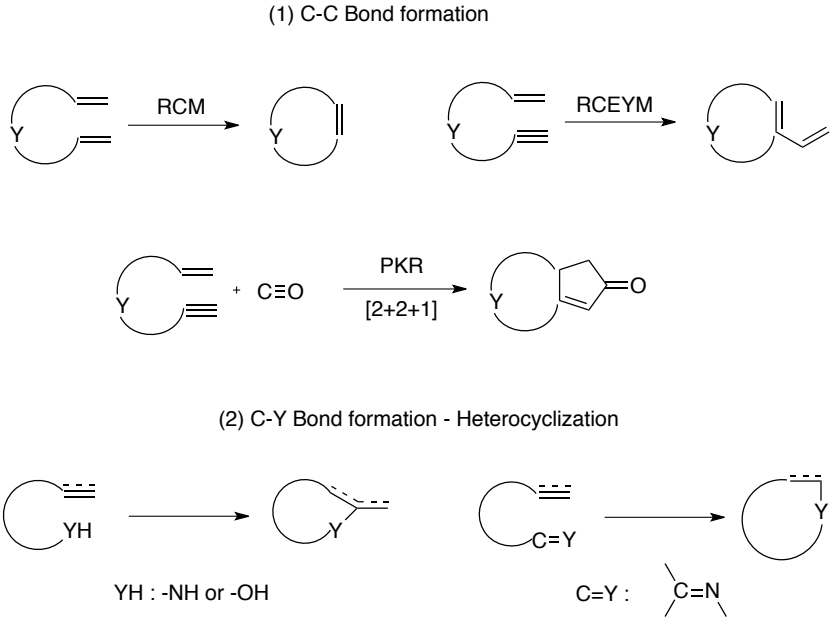
The transition-metal-catalyzed construction of heterocyclic skeletons can be classified into two major processes, as shown in Scheme 0.1: (1) C-C bond formation from the corresponding acyclic precursors and (2) C-Y bond formation from the corresponding acyclic precursors.



Scheme 0.1. *Two major processes of heterocycle synthesis*

The synthesis of heterocycles *via* metathesis, Pauson-Khand reactions and cycloisomerizations of 1,*n*-dienes and 1,*n*-enynes (Scheme 0.2) belongs to process 1 (Scheme 0.1). On the other hand, the heterocyclization of allenes and alkynes bearing a heteroatom Y at an appropriate position of the carbon chain (Scheme 0.2) can be classified under process 2 (Scheme 0.1).

Ring-closing metathesis of 1,*n*-dienes and 1,*n*-enynes has frequently played crucial role to complete the total synthesis of natural products. The first chapter of this manuscript presents the use of such reactions for the synthesis of five- and six-membered ethers, lactones and lactams, as well as the regioselective formation of differently substituted 1- and 2-benzazepine frameworks or benzofused eight- and nine-membered derivatives.



Scheme 0.2. *Classification of heterocycle synthesis, based on starting substrates and reaction patterns*

The catalytic Pauson-Khand cycloaddition of two carbon-carbon multiple bonds with carbon monoxide has nowadays become a general synthetic method for the formation of cyclopentenone derivatives. These reactions and their application to the construction of oxygen-containing bicyclic products are the topic of chapter two.

Platinum, gold and iridium salts can promote interesting substrate-dependant chemical transformations at room temperature and in short reaction times. Chapter three focuses on platinum-, gold- and iridium-catalyzed activation of alkynes toward nucleophiles, with a particular emphasis on the cycloisomerization of bis-homopropargylic alcohols and nitrogen-tethered 1,6-enynes.

Finally, the fourth chapter of this dissertation covers the less frequently studied gold-catalyzed cyclizations of allenes and their use for the formation of multisubstituted *N*-amino pyrroles.

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Chapter 1

Ring-closing metathesis reactions

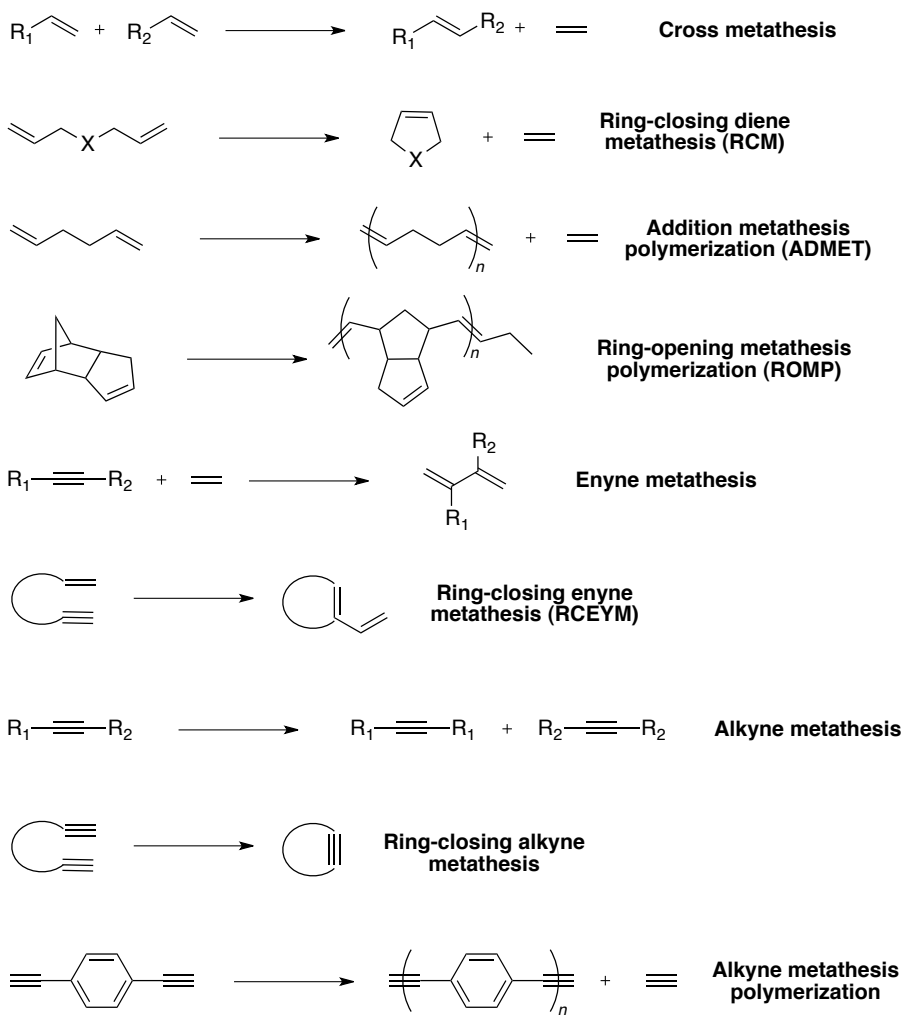
Synthesis of oxygen and nitrogen-containing heterocycles

1.1. INTRODUCTION

Olefin metathesis represents one of the most powerful and attractive tools in organic synthesis. The term metathesis, first introduced in 1967 by Calderon[1] to describe the catalytic reorganization of two double bonds, derives from the Greek words *meta* (change) and *thesis* (position). In fact, metathesis reactions cleave carbon-carbon multiple bond and reassemble them to generate products containing new carbon-carbon multiple bonds.

Olefin metathesis was first discovered in the 1950s and was initially conducted with heterogeneous catalysts.[2] Well-defined homogeneous catalysts have now been developed, including some that tolerate a wide range of functional groups.

Nowadays, metathesis, with its multiple facets, has become one of the most important chemical transformations.



Scheme 1.1. *Different classes of metathesis reactions*

Depending on the type of unsaturated bond involved in the process, three major categories of metathesis reactions can be distinguished: diene, enyne and diyne metathesis. The structural change, which occurs during the process, can be further subdivided into ring closing, ring opening, and cross metathesis (Scheme 1.1).

In this chapter, we focus our attention on ring-closing diene (RCM) and ring-closing enyne metathesis (RCEYM) (Scheme 1.1), which has recently resulted to be among the most employed and powerful methods for the generation of ring structures from functionalized molecules with tethered alkenes and alkynes.

1.1.1. History of metathesis reactions

A timeline for the development of metathesis reactions, adapted from a review by Grubbs,[3] is shown in Figure 1.1.

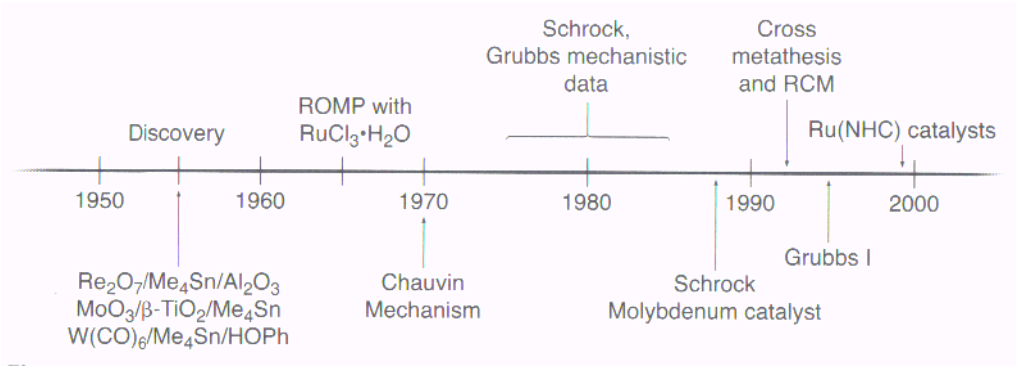


Figure 1.1. *Timeline of olefin metathesis*

Olefin metathesis was first observed in the 1950s during researches on Ziegler-Natta polymerization processes.[2] Initially the reaction was conducted with poorly defined, multicomponent homogeneous and heterogeneous catalytic systems. These systems consisted of transition metal salts combined with main group alkylating agents or deposited on solid supports. Some of the classic combinations include WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and Re_2O_7/Al_2O_3 among many others. The utility of these catalysts, however, was limited by the harsh conditions and the strong Lewis acids that they required and that made them incompatible with most functional groups. In addition, the reactions were difficult to be initiated and controlled because very little of the active species were formed in the catalyst mixtures. These problems motivated extensive works to better understand olefin metathesis, including detailed mechanistic studies. Many mechanisms were proposed over the years, but

ultimately, the one developed by Chauvin in the 1970s, was found to be most consistent with experimental evidences, and it remains the generally accepted scheme today.

The mechanistic studies led to the development of improved well-defined catalysts, which exhibited higher activity under milder conditions and better functional group tolerance. Schrock molybdenum catalyst was prepared in the late 1980s, while the first-generation Grubbs' catalyst was isolated in the mid-1990s. Nowadays, the commercially available catalytic systems are so effective that metathesis reactions have gained widespread use.

In 2005, the Nobel Prize in Chemistry was equally shared by Yves Chauvin (Institut Français du Pétrole, Rueil-Malmaison, France), Robert H. Grubbs (California Institute of Technology, Pasadena, USA) and Richard R. Schrock (Massachusetts Institute of Technology, Cambridge, USA) for their outstanding contributions in the area of olefin metathesis reactions.[4] As apparent from today's textbooks, their discoveries had a tremendous impact on modern organic chemistry and both academia and industry largely benefited from their findings.

1.1.2. Catalysts for olefin metathesis

Several of the important catalysts nowadays employed in olefin metathesis reactions are well-defined metal carbene complexes. Throughout the 1980s, Schrock,[5] Osborn[6] and Basset[7] isolated the first stable, catalytically active W-alkylidene complexes (**1-3** respectively, Figure 1.2). Schrock also developed a range of single-component imido alkylidene species, in which two bulky alkoxide ligands contributed to the relative stability of the complexes (Figure 1.2). These compounds are still among the most active catalysts known to date and one version (**4**) is commercially available.

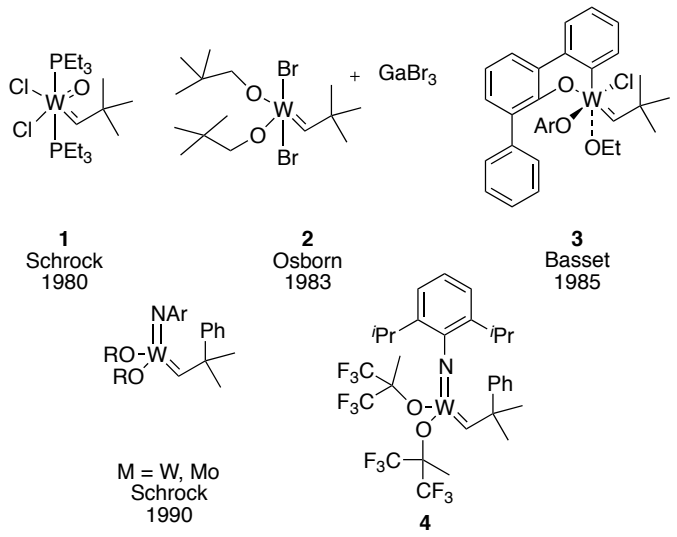
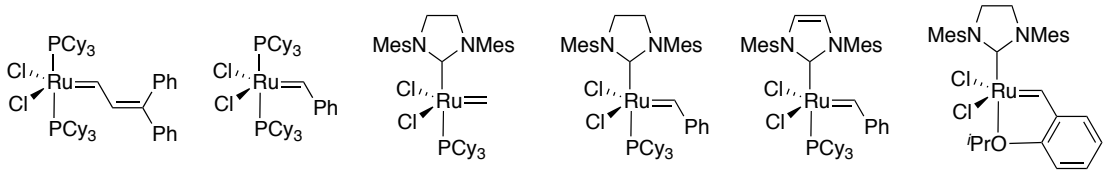


Figure 1.2. *W- and Mo-based metathesis catalysts*

The main disadvantages of Schrock catalysts are their incompatibility with a number of polar functional groups and their high sensitivity to air, requiring handling under an inert atmosphere.

In 1992, the group of Grubbs achieved an important breakthrough in terms of catalyst versatility. Indeed, focusing on ruthenium instead of tungsten and molybdenum, complex **5** was discovered to be a suitable metathesis catalyst[8] (Figure 1.3).

Although **5** is not as active as the molybdenum-based catalysts, it is significantly more versatile due to its remarkable functional group tolerance. In addition, it is air-stable as a solid and fairly resistant to water, alcohols and acids.[8b] Shortly after, Grubbs and co-workers also synthetized benzylidene complex **6**, whose initiation rate was considerably higher than that of the diphenylvinylcarbene analogue **5**.[9]



5 Grubbs 1992 | **6** Grubbs 1995 | **7** Grubbs 1999 | **8** Grubbs 1999 | **8'** Nolan/Hermann 1999 | **9** Hoveyda 2000

Figure 1.3. *Ru-based metathesis catalysts*

Despite the remarkable stability and functional group-tolerance, the "first generation" Grubbs catalysts **5** and **6** were still an order of magnitude less active than the molybdenum-based Schrock complexes. An important step in narrowing this gap was made by substituting one phosphine by a more strongly electron-donating *N*-heterocyclic carbene (NHC) ligand, resulting in the "second generation" catalysts **7**, **8** and **8'** (Figure 1.3). As a result of the increased activity achieved by using NHC ligands,[10] catalyst **8** broadened the scope of ruthenium-catalyzed olefin metathesis to a degree that had thus far only been observed for the most active early transition-metal catalysts.[11]

The development of catalyst **8** with its impressive activity, stability and scope has led to a dramatic increase in research activities involving the design of novel olefin metathesis catalysts.[12] One of the first and most important modification of **8** was reported by Hoveyda and co-workers in 2000. The introduction of a chelating styrenyl ether moiety resulted in the formation of phosphine-free catalyst **9** (Figure 1.3), which was found to be particularly stable and reactive. An additional advantage of the styrenyl moiety of this catalyst is its suitability for extensive modification. Over the recent years, variations on this catalyst have been reported, most of which are based on steric and electronic alterations as well as attachment of

the complex to various solid supports (catalysts **10**, **11** and **12**, Figure 1.4).[13]

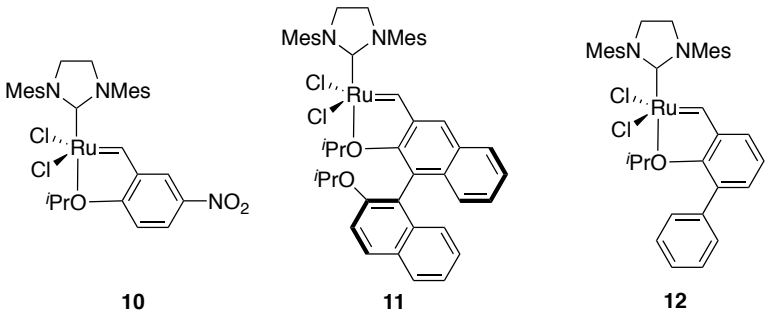
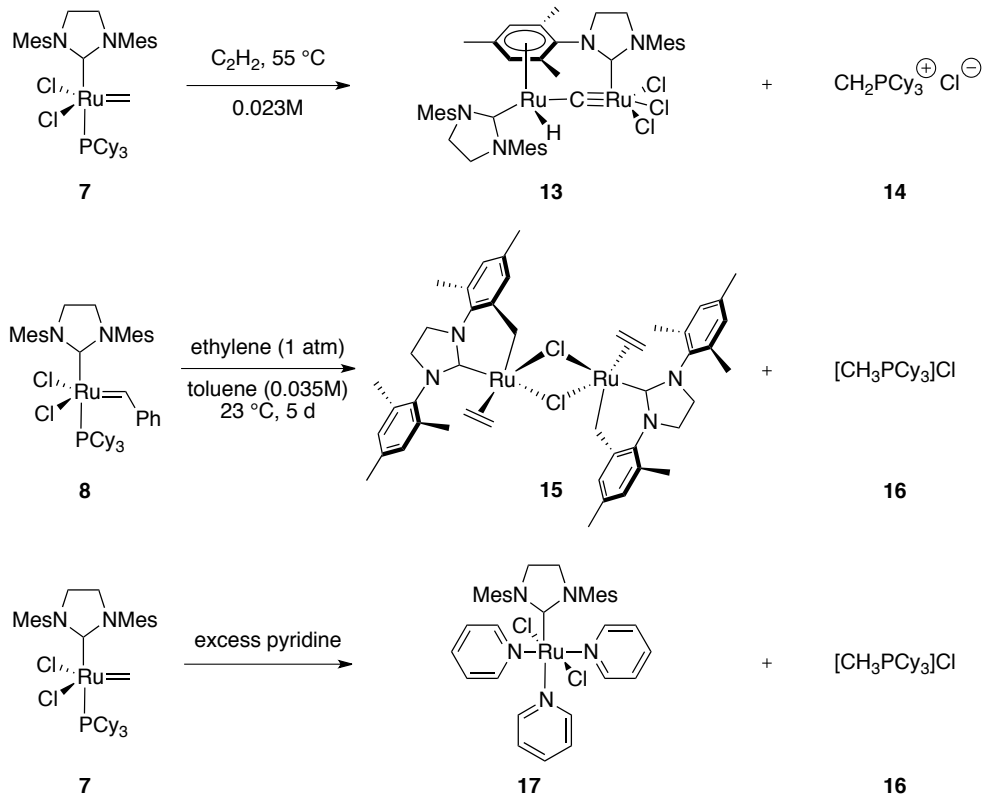


Figure 1.4. *Variations of the Hoveyda –Grubbs catalyst*

1.1.3. Catalysts decomposition

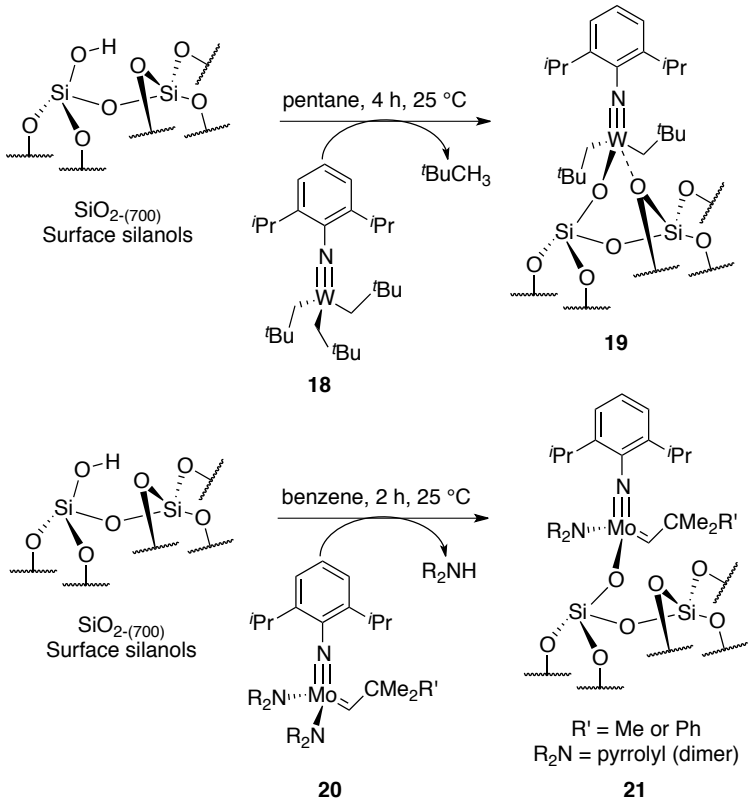
Despite their outstanding activities, ruthenium-based catalysts easily undergo thermolytic decomposition, which limits their usefulness in many challenging reactions. Understanding and controlling the decomposition pathways is essential to increase the efficiency of these catalysts. Indeed, several studies have been conducted to identify the reactions that lead to catalyst degradation.



Scheme 1.2. *Ruthenium-based catalysts decompositions*

Grubbs and co-workers found that heating the second-generation catalyst **7** alone in benzene led to the formation of the bridging carbene complex **13** (Scheme 1.2).[14] On the other hand, heating the benzylidene catalyst **8** with ethylene generated complex **15**, which resulted from cyclometallation at the *o*-methyl group of the aryl substituent (Scheme 1.2).[15] Moreover, the methylphosphonium salt **16** was formed as a co-product in quantitative yield. Finally, treatment of the methylidene complex **7** with pyridine also turned into the formation of the methylphosphonium salt **16**, which could be isolated together with the 18-electron trispyridine complex **17** (Scheme 1.2).[16] The proposed mechanisms for the formation of these species are speculative, but they are thought to originate from the attack of a dissociated phosphine on the methylidene ligand.

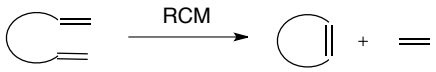
On the contrary, pathways to deactivation of the Schrock-type catalyst are supposed to proceed by association of two catalysts forming bridged structures. Thus, it might be possible to improve the catalyst activities and lifetime by isolating the complexes on a solid support, so that the two catalysts do not interact with each other. Schrock, Coperet and Basset have worked to support Schrock tungsten and molybdenum catalysts **18** and **20** on a partially dehydrated silica support (Scheme 1.3).[17] This work has led to more active catalysts (**19** and **21**), partly from site isolation and partly from the unsymmetrical structure of the supported catalyst, which best balance the electronic requirements of the carbene and the metallacycle structures.



Scheme 1.3. *Schrock tungsten and molybdenum catalysts on a partially dehydrated silica support*

1.1.4. Ring-closing diene metathesis reactions (RCM)

Ring-closing diene metathesis is one of the most extensively studied metathesis process and it involves 1,*n*-dienes and it is now commonly used in complex molecule synthesis.[18] In this reaction, fission of two double bonds occurs and a new double bond is formed at the same time to produce a cyclic compound (Scheme 1.4).

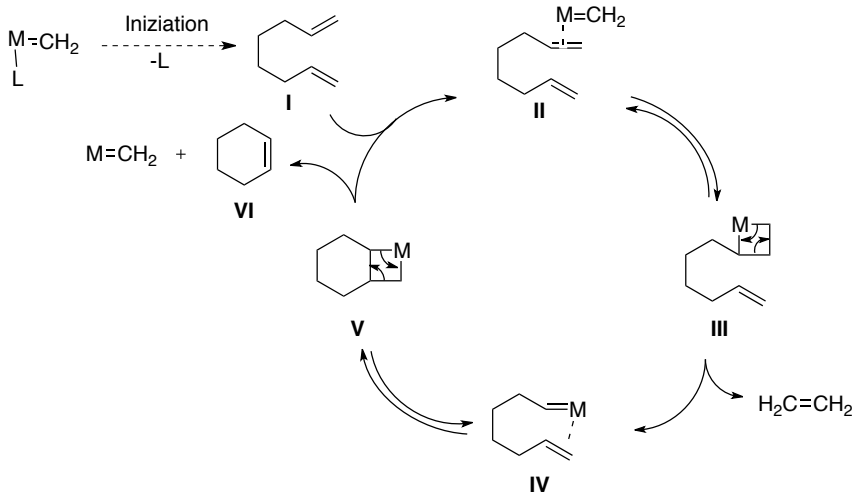


Scheme 1.4. *Ring-closing diene metathesis*

The thermodynamics for the ring-closing process are favored by entropic benefits arising from the generation of two molecules from one. Moreover, these reactions are often conducted in an open system under non-equilibrium conditions that release ethylene.
Although some of the most favorable RCM reactions form five- and six-membered rings, ring-closing metathesis has also been successfully used to form macrocyclic units in natural products and pharmaceutical candidates.

1.1.4.1. Mechanism of ring-closing diene metathesis reactions

Ring-closing diene metathesis occurs by a sequence of [2+2] cycloaddition and cycloreversion reactions, which can be depicted as a catalytic cycle (Scheme 1.5).



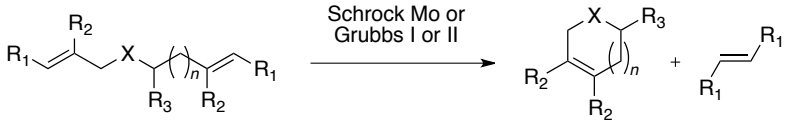
Scheme 1.5. *Mechanism of ring-closing metathesis reactions*

In this mechanism, the initial carbene catalyst reacts with the olefin reagent **I** in an initiation step. Depending on the presence of an open coordination site in the catalyst precursor, this step can involve ligand dissociation. This initiation is followed by a [2+2] cycloaddition and cycloreversion, in which the driving force is the loss of ethylene. The resulting metallacarbene **IV** then undergoes a new [2+2] cycloaddition with the second olefin of the chain to form the metallacyclobutane **V**. This metallacycle finally cleaves to give the cyclized olefin **VI** and the regenerated methylidene catalyst.

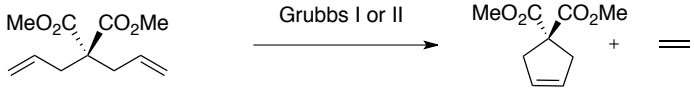
Nowadays, this mechanism is generally accepted and new theoretical[19] as well as experimental[20] evidence for the involvement of different intermediates in the catalytic cycle is continuously being reported.

1.1.4.2. Representative examples of ring-closing diene metathesis applications

Simple prototypal examples of ring-closing metathesis applications are shown in Scheme 1.6. In general, dienes can easily undergo RCM to form five-, six- or seven membered carbocycles and heterocycles.[8b,21]



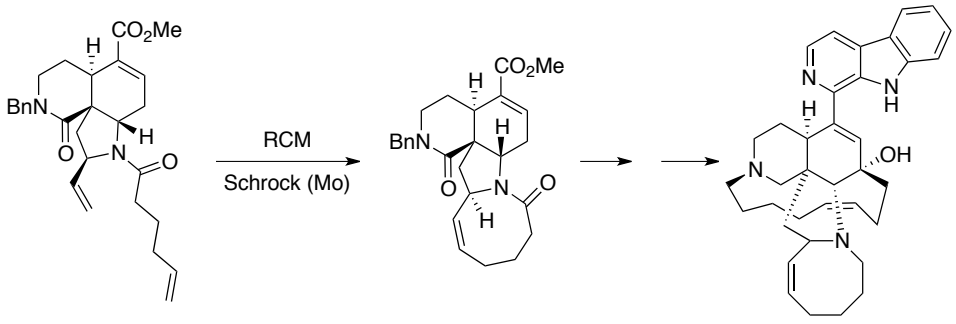
X = O or NBn; R_1 = Me or H; R_2 = Me or H; R_3 = Ph or H; *n* = 0,1 or 2



22 **23**

Scheme 1.6. *Examples of ring-closing metathesis applications*

On the contrary, the formation of medium-sized rings remains a challenge and success largely depends on the conformation of the reactant diene.[22]

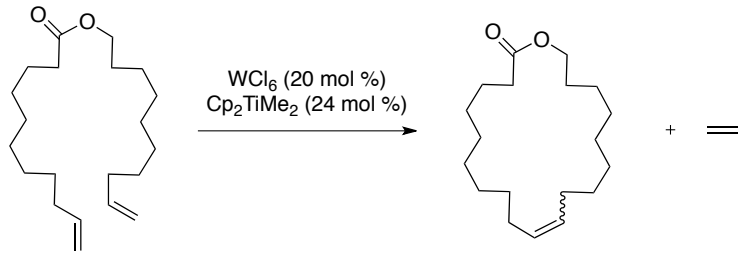


24 **25** **26**

Scheme 1.7. *Synthesis of manzamine A*

In this context, manzamine A (**26**), a polycyclic alkaloid that exhibits antimicrobial and antileukemic activity, was first obtained by Martin and co-workers in one of the earliest demonstrations of how RCM could be applied as a key step in natural product synthesis. The ring-closing metathesis in this case was conducted starting from compound **24**, with Schrock molybdenum catalyst, as shown in Scheme 1.7.[23]

The formation of large rings is another particularly successful application of ring-closing metathesis. Macrocyclizations were first reported by Tsuji and later extensively developed by Fürstner. The double bond in macrocycles synthetized by RCM, however, often forms as a mixture of *E*- and *Z*- isomers. This is the case of the synthesis of macrolactone **28** (Scheme 1.8), in which the selective formation of *E*- or *Z*- olefins is difficult to be accomplished.[24]

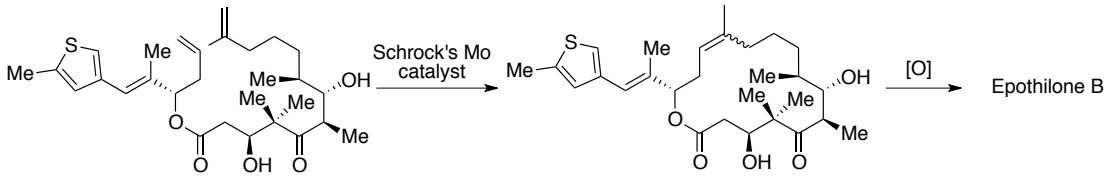


27 **28**

Scheme 1.8. *An example of macrocyclization*

The epothilones, a new class of cancer drugs, are other important natural products easily accessible by RCM. A 16-membered ring containing an alkene in the macrocycle or an epoxide, which can be generated from the alkene, characterizes these molecules. One of the first reported syntheses of epothilone B was conducted using the ring-closing metathesis of diene **29**, in which the two alkenes were linked by the formation of an acyclic ester. This strategy, however, generated a mixture of *E*- and *Z*- olefins, as shown in Scheme 1.9.[25]

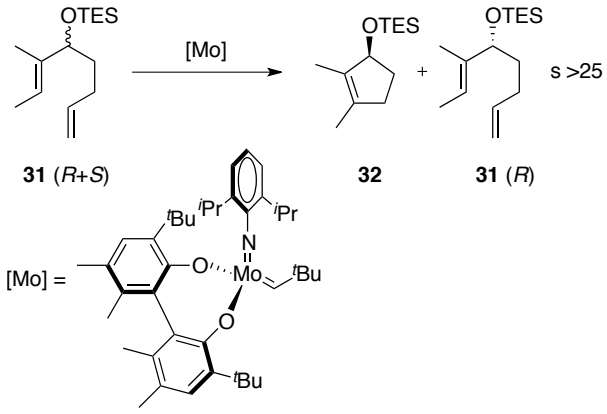
Ring-closing metathesis has also been developed into enantioselective processes, even if this methodology does not form a new bond at a tetrahedral carbon. Indeed, metathesis reactions can be conducted as kinetic resolutions or desymmetrizations to generate optically active products containing a new stereocenter.



29 **30**

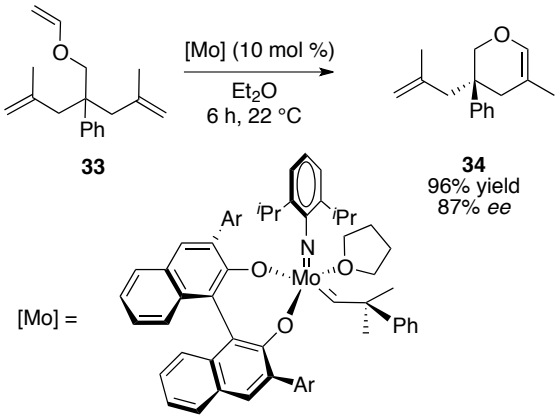
Scheme 1.9. *Synthesis of epothilone B*

One particularly selective kinetic resolution is shown in scheme 1.10.[26] The diene **31**, containing a protected allylic alcohol, undergoes ring-closing metathesis to generate optically active, cyclic products in the presence of a chiral, non-racemic molybdenum catalyst. The selectivity factor is greater than 25 in this case, allowing the product **32** and the remaining reactant to be isolated with high *ee*.



Scheme 1.10. *A particularly selective kinetic resolution*

On the other hand, one valuable application of the desymmetrization processes is the formation of quaternary stereocenters. For example, the achiral, symmetric triene **33** reported in scheme 1.11 can be converted to the chiral, non-racemic diene **34** with 87% *ee*.[27]



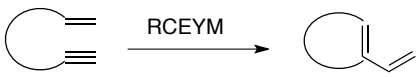
Scheme 1.11. *An exemplificative desymmetrization process*

These representative examples clearly show that, during the past decade, the scope of olefin metathesis and specifically RCM has continuously widened, particularly in terms of functional group tolerance.

Nevertheless, in several cases, direct functionalization of the double bond has proven to complicate RCM. Although many of such olefins have recently been cyclized, the grounds for (un)reactivity of specific substrates are still somewhat unclear and the use of functionalized olefins often remains a matter of trial-and-error.

1.1.5. Ring-closing enyne metathesis reactions (RCEYM)

The ring-closing metathesis of enynes, molecules that contain tethered alkene and an alkyne moieties, was first reported by Katz and Sivavec in 1985.[28] In this cyclization, the double bond is cleaved, a carbon-carbon bond is formed between the double and triple bonds together with an exocyclic vinylic residue, producing a cyclic compound having a 1,3-diene moiety (Scheme 1.12).



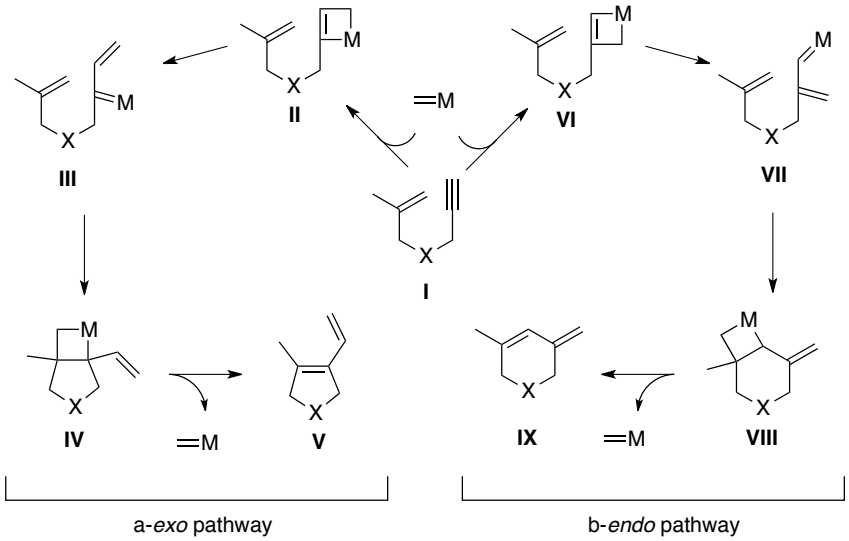
Scheme 1.12. *Ring-closing enyne metathesis*

To date, this reaction has been studied most extensively with ruthenium carbene complexes, therefore the tolerance for heteroatom functionalities is extremely high. For this reason, in the past years, enyne metatheses have been successfully used to access a great number of natural products with high degree of complexity.[29]

1.1.5.1. Mechanism of ring-closing enyne metathesis reactions

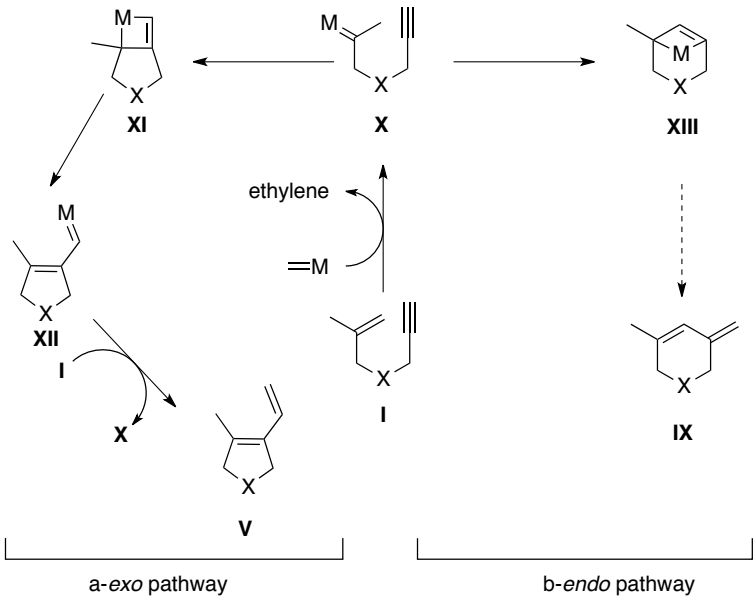
Enyne metathesis, as well as diene metathesis, is proposed to occur by the sequence of [2+2] cycloaddition and cycloreversion steps shown in scheme 1.13 and 1.14. The driving force for this conversion is the formation of a thermodynamically stable conjugated butadiene.
Despite the great knowledge achieved in olefin metathesis (mechanism, catalyst, development, product selectivity), less is known about the enyne reaction, for which several points still remain unclear. For instance, two different mechanisms have been postulated.[30] If the RCEYM proceeds by initial reaction of the alkynylic part of enyne **I**, the sequence of events is called 'yne-then-ene pathway' (Scheme 1.13). The catalytic process is quite complex, since two different routes can be distinguished depending on the substrate orientation, the *exo* (Scheme 1.13 a) and the *endo* (Scheme 1.13 b) approaches, which in general lead to different products. On one hand, the metal side of the carbene complex can combine with the internal carbon of the alkyne of **I** forming the metallacyclobutene **II**. Ring-opening of **II** leads to

vinylic metal carbene complex **III**, and subsequent intramolecular [2+2] cycloaddition affords metallacyclobutane **IV**. Consequently, upon ring-opening of **IV** the *exo* product **V** is formed.
On the other hand, when the metal center of the carbene catalyst combines with the terminal carbon of the alkyne part of **I**, metallacyclobutene **VI** results, which upon ring opening is converted into metal carbene complex **VII**. When **VII** then reacts intramolecularly with its terminal olefinic part by [2+2] cycloaddition, formation of metallacyclobutane **VIII** occurs, which finally leads to the *endo* product **IX**. On both routes the metal carbene catalyst is regenerated in the last step.



Scheme 1.13. *Mechanism involving an "yne-then-ene" sequence*

On a so-called 'ene-then-yne pathway' (Scheme 1.14) the metal carbene catalyst first reacts with the olefinic moiety of **I** to produce alkylidene **X**. Then again, two possible event sequences can be distinguished.
The *exo* pathway (Scheme 1.14 a) involves the ring closure of **X** to give metallacyclobutene **XI** followed by fragmentation of the 4-membered ring to afford vinyl carbene **XII**. Subsequent reaction with a second equivalent of enyne **I** leads to **V** (*exo* product) and regenerates alkylidene **X** for the next catalytic cycle.
Alternatively, the *endo* pathway (Scheme 1.14 b) involves the formation of bicyclic metallacyclobutene **XIII** resulting from the combination of the metal side of **X** with the internal carbon of the triple bond. Ring-opening then leads to **IX** (*endo* product). Assuming that the intermediacy of the highly strained metallacyclobutene **XIII** is improbable, one would expect the 'ene-then-yne process' to result in the formation of *exo* product **V** with high preference.

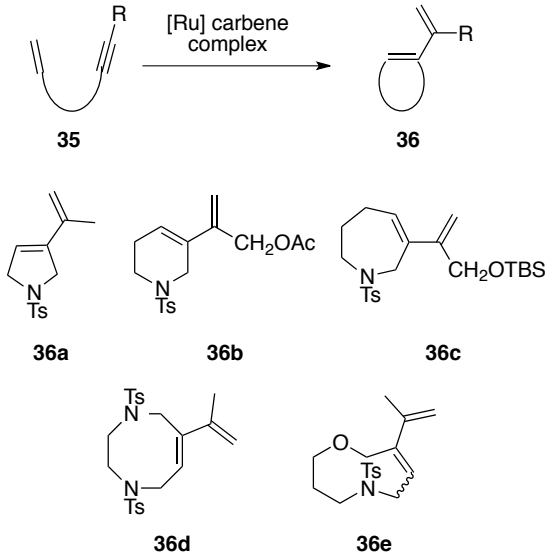


Scheme 1.14. *Mechanism involving an "ene-then-yne" sequence*

Noteworthily, several recent works have suggested that the 'ene-then-yne process' and the 'yne-then-ene pathway' may occur simultaneously and that the preferred route may depend on factors such as the catalyst, the reactants and the reaction conditions.[31]

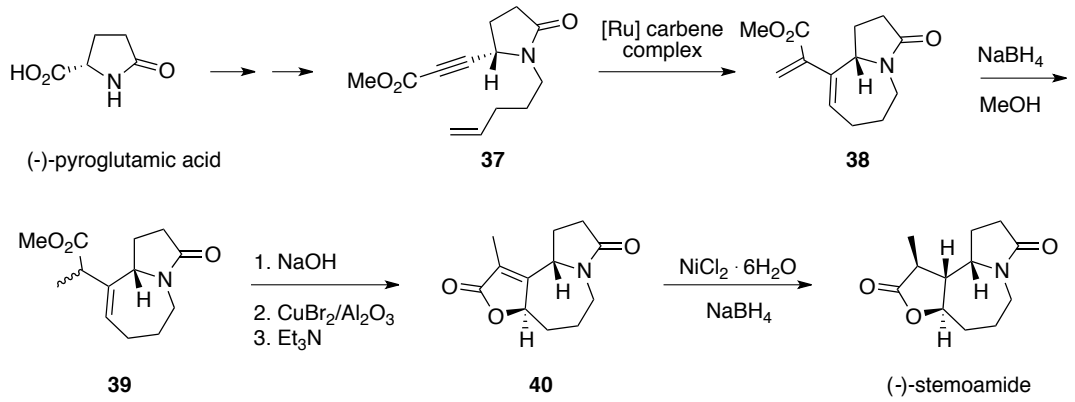
1.1.5.2. Representative examples of ring-closing enyne metathesis applications

Using commercially available ruthenium carbene catalyst, five- to nine-membered heterocycles could be synthesized by RCEYM from the corresponding enynes (Scheme 1.15).[31]



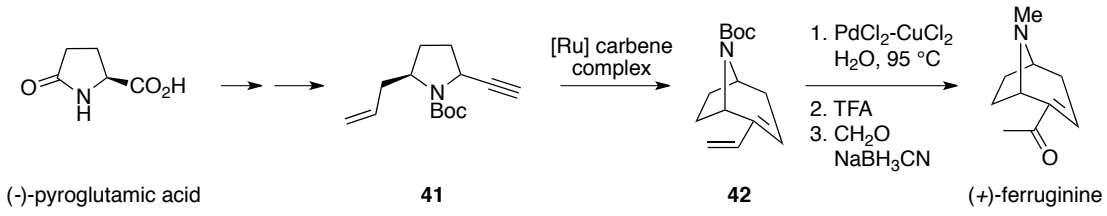
Scheme 1.15. *Synthesis of nitrogen-containing heterocyles by RCEYM*

Moreover, in the last few years, a great number of natural products have been obtained by enyne metathesis. The first example was the synthesis of (-)-stemoamide.[32] RCEYM of enyne **37**, readily prepared from (-)-pyroglutamic acid, afforded the bicyclic compound **38**, which, in turn, was easily further functionalized to yield the desired (-)-stemoamide (Scheme 1.16).



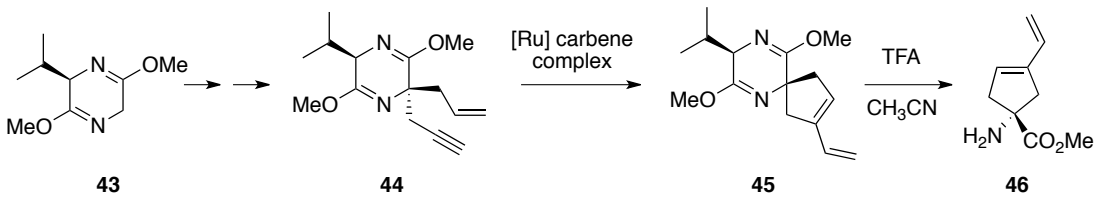
Scheme 1.16. *Synthesis of (-)-stemoamide*

Starting from (-)-pyroglutamic acid,[33] the construction of an azabicyclo[3.2.1]octane ring system was also carried out using enyne metathesis. Cyclization of compound **41** and subsequent Wacker oxidation of the resultant diene **42**, followed by deprotection of the nitrogen atom and methylation, allowed the formation of (+)-ferruginine (Scheme 1.17).



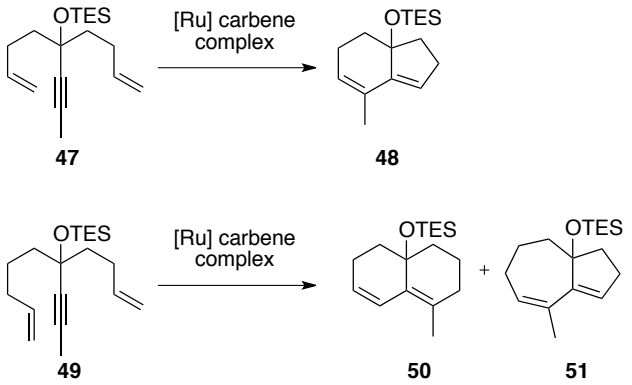
Scheme 1.17. *Synthesis of (+)-ferruginine*

A stereoselective synthesis of the unusual chiral amino acid **46** could also be performed by RCEYM as well.[34] In this case, the starting enyne was synthesized in stereochemically pure form by stepwise alkylations of compound **43**. Cyclization of enyne **44** with Grubbs catalyst gave the spiro-compound **45**, which was finally treated with TFA to form the desired amino acid **46** (Scheme 1.18).



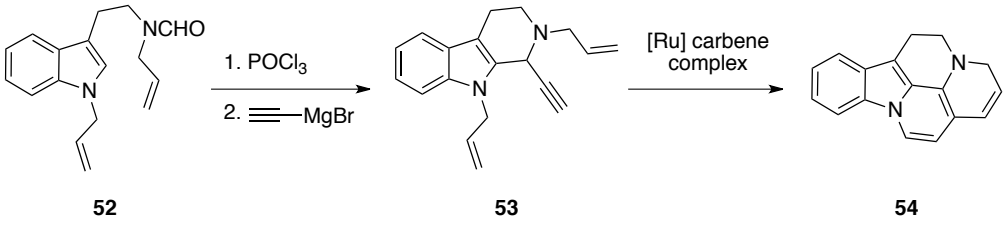
Scheme 1.18. *Synthesis of an unusual chiral amino acid*

In 1994, Grubbs discovered an ingenious dienyne metathesis and synthesized various bicyclic compounds from dienynes in one single reaction step (Scheme 1.19).[35]



Scheme 1.19. *Dienyne metathesis for the synthesis of bicyclic compounds*

In particular, dienyne metathesis of *β*-carboline derivative **53** afforded the oxidized pentacyclic compound **54** that is related to alkaloids containing a *β*-carboline unit. In this case, the starting material **52** was readily synthesized from tryptamine (Scheme 1.20).[36]



Scheme 1.20. *Synthesis of alkaloids containing a β-carboline unit*

As is evident from the examples cited so far, RCEYM found widespread application to the synthesis of complex and highly functionalized organic molecules. Improved catalysts for specific purposes, including enantioselective synthesis, continue to be developed, and it seems likely this area of research will remain fruitful for some time to come.

1.2. RESULTS AND DISCUSSION

In 1992, Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis (RCM) to the synthesis of simple five-, six- and seven-membered monocyclic systems, containing heteroatoms.[21a] The high selectivity and reactivity of molybdenum- and ruthenium-based catalysts for carbon-carbon π-bonds minimized protecting group manipulations while enabling the use of metatheses as an excellent alternative to other ring-forming reactions for the efficient construction of cyclic targets molecules.

After this exciting report, we and many others became interested in using RCM and RCEYM to form the functionalized rings present in natural products or in biologically active compounds, and a number of elegant applications of metathesis in total synthesis have been recorded.[37]

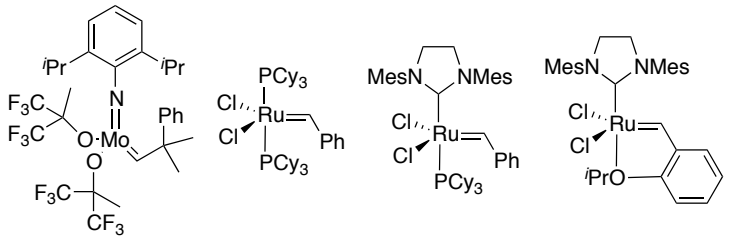
Focusing on nitrogen- and oxygen-containing heterocycles, we began our investigations by developing a suitable strategy to access 5- and 6-membered cyclic ethers, lactones and lactams, which are ubiquitous constituents in pharmacophoric fragments or natural molecules. We next turned our attention to benzoanellated nitrogen-containing seven-membered heterocycles. In this context, selective RCEYM allowed the formation of 1- and 2-benzazepine scaffolds, crucial pharmacophores in drug discovery. Finally, using RCM we were able to isolate a benzazocine derivative and a nine-membered ring heterocycle, containing both oxygen and nitrogen atoms.

In this section, results are roughly organized by the different classes of compounds isolated, as well as by the size of the ring formed during the cyclization process.

1.2.1. RCM and RCEYM reaction conditions

Due to the wide variety of commercially available catalysts, the selection of one over the others to promote RCM and RCEYM can be a real challenge. Previous literature reports[38] clearly showed that no single catalyst is the best for all multiple-bond reorganizations. Since there are many substrate-dependent variables as well as catalyst stability, activity, and initiation rate considerations that determine catalyst efficiency for a given reaction, different metal complexes were employed in our metathetic process depending upon the starting material submitted to the cyclization (Figure 1.5).

Initial reaction parameters were chosen on the basis of the results from a recent study on catalyst efficiency.[39] In this work, methylene chloride, a solvent frequently used in diene and enyne cyclizations, was shown to greatly decrease the catalyst efficiency, therefore toluene was used in all our experiments.



4 **6** **8** **9**

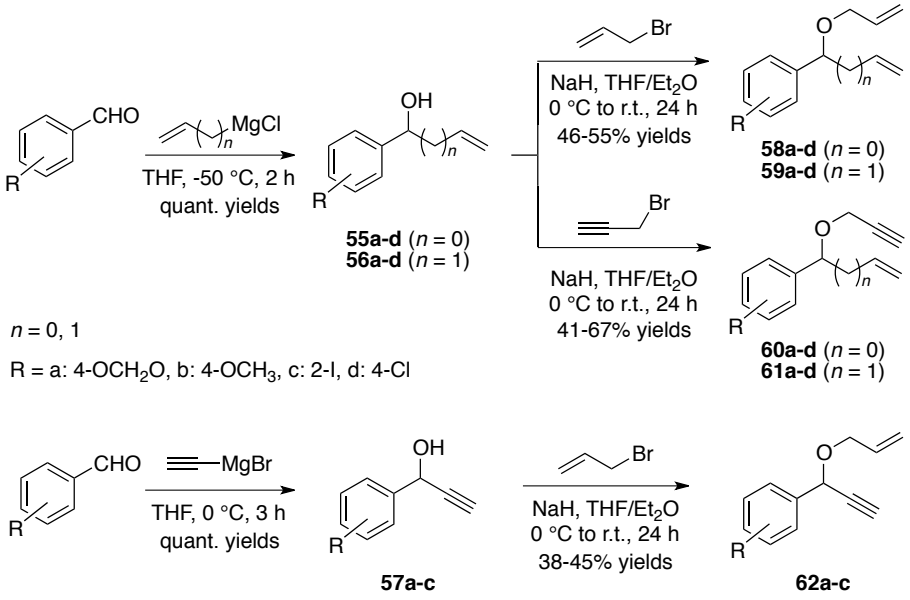
Figure 1.5. *Commercially available metathesis catalysts employed*

Temperatures among 50 °C and 70 °C resulted to be the best compromise between fast reaction rates, solvent loss and precursor or catalyst degradation.

The substrate concentration also has remarkable effects on RCM and RCEYM. As the ring size increases from five to seven, more diluted solutions are needed to achieve the complete conversion of the starting materials. In particular, five- and six-membered rings can be efficiently formed in 0.1M solutions, while concentration between 0.05M and 0.02M are recommended for the formation of seven-membered heterocycles and macrocycles.[40]

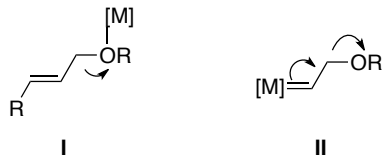
1.2.2. Five- and six-membered cyclic ethers

Ring-closing metathesis reactions of acyclic diene- and enyne-ethers resulted to be a particular efficient method to access dihydrofurans and dihydropyrans from readily available starting materials. Indeed, as shown in Scheme 1.21, ring-closing metathesis precursors were easily synthetized in good yields from the corresponding commercially available aromatic aldehydes. This two-step process involves an addition of Grignard reagents to the carbonyl group and a subsequent Williamson etherification reaction of the resulting secondary alcohol.



Scheme 1.21. *Synthesis of ring-closing metathesis precursors*

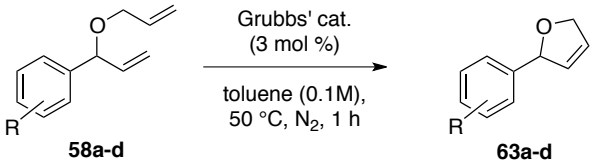
The potential incompatibility of allylic ethers with the metathesis reaction conditions initially represented a cause for concern. Decomposition of this functionality, as well as the catalyst, had been previously observed in some olefin metathesis systems[21a] possibly due to Lewis acid activation by the metal (Figure 1.6, **I**) or to elimination from an alkylidene intermediate (Figure 1.6, **II**).



I **II**

Figure 1.6. *Potential incompatibility of allylic ethers with metathesis catalysts*

However, treatment of diallyl ethers **58a-d** with 3 mol% of Grubbs' catalysts **6** and **8** (Figure 1.3), in toluene, at 50 °C afforded the desired 2,5-dihydrofurans **63a-d** without any complication (Table 1.1, entries 1-8). The absence of decomposition may be attributable to the relatively low Lewis basicity of compounds **58a-d**, as well as to the short lifetime of the species **II** (Figure 1.5), due to rapid intramolecular trapping by the tethered olefin.

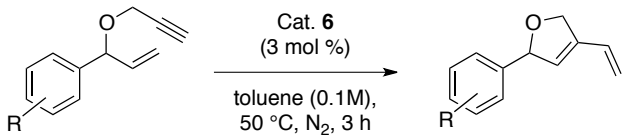


58a-d **63a-d**

Entry	R	Reactant	Product	Catalyst	Yield (%)
1	4-OCH_2O	**58a**	**63a**	**6**	86
2	4-OCH_2O	**58a**	**63a**	**8**	91
3	4-OCH_3	**58b**	**63b**	**6**	93
4	4-OCH_3	**58b**	**63b**	**8**	quant.
5	2-I	**58c**	**63c**	**6**	73
6	2-I	**58c**	**63c**	**8**	84
7	4-Cl	**58d**	**63d**	**6**	78
8	4-Cl	**58d**	**63d**	**8**	85

Table 1.1. *Synthesis of the 2,5-dihydrofurans* ***63a-d***

Under the same reaction conditions, Grubbs' catalyst **6** also promoted the RCEYM of allyl propargyl ethers **60a-d**, extending the general scope of the reaction. Thus, dienes **64a-d** were isolated as yellow pale oils, albeit in moderate but encouraging yields (Table 1.2, entries 1-4). To our delight, RCEYM, as well as RCM, tolerated both electron-withdrawing groups (EWG) and electron-donating groups (EDG) on the aromatic ring of the starting materials.

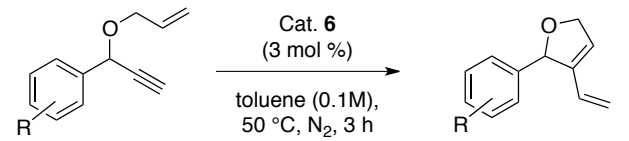


60a-d **64a-d**

Entry	R	Reactant	Product	Yield (%)
1	4-OCH_2O	**60a**	**64a**	28
2	4-OCH_3	**60b**	**64b**	36
3	2-I	**60c**	**64c**	32
4	4-Cl	**60d**	**64d**	26

Table 1.2. *Synthesis of dihydrofurans* ***64a-d***

Prompted by these promising results, precursors **62a-c** were produced as intermediates in the synthesis of RCEYM derivatives using an acetylenic Grignard instead of allyl or vinyl magnesium chloride (Scheme 1.21). While running the cyclization using catalyst **6**, the dienic products **65a-c**, which differ from compounds **64a-c** for the position of the exocyclic vinylic residue, were isolated in good yields after a rapid purification over silica gel (Table 1.3, entries 1-3).

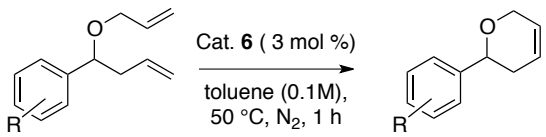


62a-c **65a-c**

Entry	R	Reactant	Product	Yield (%)
1	4-OCH_2O	**62a**	**65a**	76
2	4-OCH_3	**62b**	**65b**	71
3	2-I	**62c**	**65c**	64

Table 1.3. *Synthesis of dihydrofurans* ***65a-d***

Six-membered cyclic ethers such as dihydropyrans **66a-d** are other common structural motifs in natural products, resulted to be easily accessible by RCM.



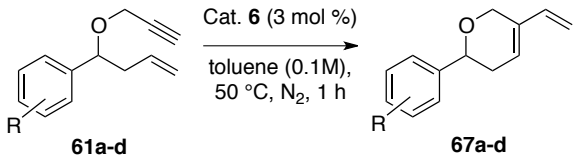
59a-d **66a-d**

Entry	R	Reactant	Product	Yield (%)
1	4-OCH_2O	**59a**	**66a**	92
2	4-OCH_3	**59b**	**66b**	90
3	2-I	**59c**	**66c**	quant.
4	4-Cl	**59d**	**66d**	93

Table 1.4. *Synthesis of dihydropyrans* ***66a-d***

Indeed, while precursors **59a-d** were submitted to the optimized reaction conditions, all ring-closed products were obtained in short reaction times and excellent yields (Table 1.4, entries 1-4).

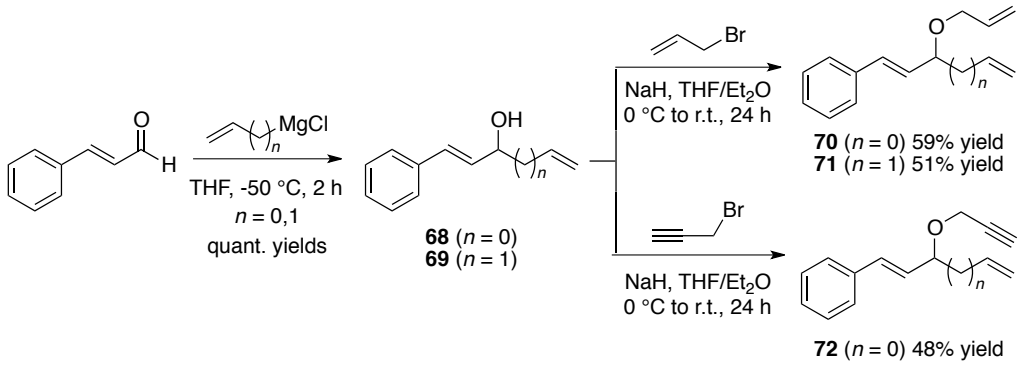
1,7-Enynes **61a-d**, as well as 1,7-dienes, smoothly reacted in the presence of catalyst **6**, allowing the dihydropyrans **67a-d** to be isolated in good yields (Table 1.5, entries 1-4).



Entry	R	Reactant	Product	Yield (%)
1	4-OCH_2O	**61a**	**67a**	62
2	4-OCH_3	**61b**	**67b**	81
3	2-I	**61c**	**67c**	87
4	4-Cl	**61d**	**67d**	70

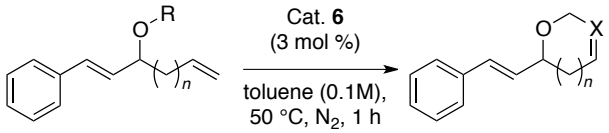
Table 1.5. *Synthesis of dihydropyrans* ***67a-d***

Finally, the same synthetic strategies were run starting from cynnamaldehyde instead of aryl aldehydes (Scheme 1.22).



Scheme 1.22. *Synthesis of ring-closing metathesis precursors starting from cynnamaldehyde*

In this case, five-membered RCM and RCEYM products **73** and **75** were obtained in good yields, while six-membered ring ether **74** could be isolated only in moderate yields (Table 1.6, entries 1-3).

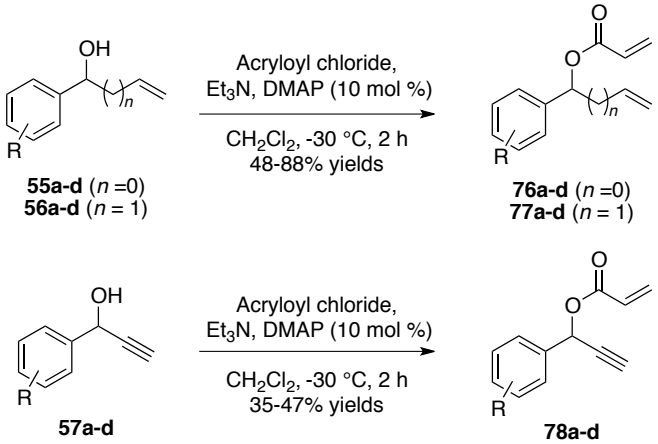


Entry	R	X	*n*	Reactant	Product	Yield (%)
1	$-CH_2CH=CH_2$	-CH	**0**	**70**	**73**	87
2	$-CH_2CH=CH_2$	-CH	**1**	**71**	**74**	27
3	$-CH_2C\equiv CH$	$-CCH=CH_2$	**0**	**72**	**75**	79

Table 1.6. *Synthesis of products* ***73-75***

1.2.3. Five- and six-membered lactones

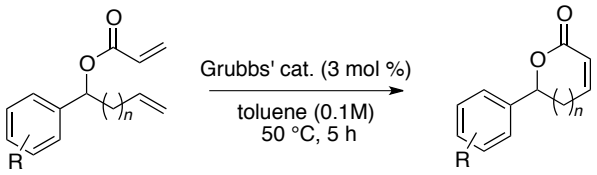
Five and six-membered lactone rings constitute a structural feature common to numerous biologically active natural products,[41] many of which exhibit antitumoral properties. To obtain such cyclic esters, a different synthetic strategy was developed to access RCM and RCEYM precursors. Starting from the previously synthetized allylic, homoallylic and propargylic alcohols **55a-d**, **56a-d** and **57a-d** (Scheme 1.21), a classical esterification reaction with acryloyl chloride allowed the desired acrylates **76a-d**, **77a-d** and **78a-d** to be formed in short reaction times and acceptable yields (Scheme 1.23).



R = a: 4-OCH_2O, b: 4-OCH_3, c: 2-I, d: 4-Cl

Scheme 1.23. *Synthesis of acrylates* ***76a-d****,* ***77a-d*** *and* ***78a-d***

Preliminary results, obtained while submitting compound **76a** to the metathesis reaction, clearly showed that the first generation Grubbs' catalyst **6** could not catalyze the RCM of acrylates, since only starting material was recovered after the reaction (Table 1.7, entry 1). Moreover, the second-generation catalyst **8** (Table 1.7, entry 2) gave somewhat poorer results than the Hoveyda–Grubbs second-generation catalyst **9**, which allowed the formation of all RCM adducts **79a-d** and **80a-d** in good to excellent yields (Table 1.7, entries 3-8).



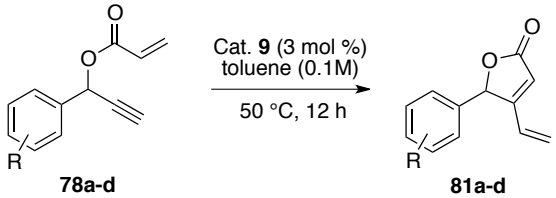
76a-d (*n* =0)
77a-d (*n* = 1)

79a-d (*n* =0)
80a-d (*n* = 1)

Entry	R	*n*	Reactant	Product	Catalyst	Yield (%)
1	4-OCH_2O	**0**	**76a**	**79a**	**6**	n.r.
2	4-OCH_2O	**0**	**76a**	**79a**	**8**	55
3	4-OCH_2O	**0**	**76a**	**79a**	**9**	86
4	4-OCH_3	**0**	**76b**	**79b**	**9**	93
5	2-I	**0**	**76c**	**79c**	**9**	91
6	4-Cl	**0**	**76d**	**79d**	**9**	84
7	4-OCH_2O	**1**	**77a**	**80a**	**9**	90
8	4-OCH_3	**1**	**77b**	**80b**	**9**	95
9	2-I	**1**	**77c**	**80c**	**9**	quant.
10	4-Cl	**1**	**77d**	**80d**	**9**	quant.

Table 1.7. *Synthesis of lactones* ***79a-d*** *and* ***80a-d***

On the contrary, RCEYM products **81a-d** were isolated in moderate yields after longer reaction times. In this case, the structural rigidity of the acryloyl moiety, as well as the conjugation of the double bond to the carbonyl group, probably turn into a decreased affinity of this side chain towards the electrophilic ruthenium catalyst (Table 1.8, entries 1-4) .[42]



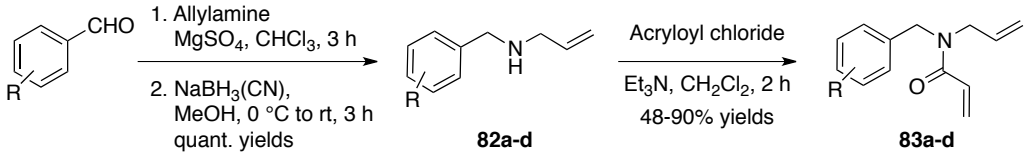
78a-d **81a-d**

Entry	R	Reactant	Product	Yield (%)
1	4-OCH_2O	**78a**	**81a**	27
2	4-OCH_3	**78b**	**81b**	35
3	2-I	**78c**	**81c**	52
4	4-Cl	**78d**	**81d**	42

Table 1.8. *Synthesis of lactones* ***81a-d***

1.2.4. Five- and six-membered lactams

The lactam skeleton is another important element in biologically active compounds. In particular, five- and six- membered lactams derivatives are found in many natural products, marketed drugs, and drug candidates,[43] therefore it is quite important to develop efficient methods to access this class of compounds. In this perspective, RCM precursors **83a-d**, specifically designed to yield benzylic lactams, were synthesized. A condensation reaction of different substituted benzaldehydes with allylamine and successive reduction of the imine intermediates with $NaBH_3CN$ provided substrates **82a-d** in quantitative yields. These compounds promptly reacted with acryloyl chloride under typical acylation conditions to give dienes **83a-d**, which were isolated as yellow pale oils (Scheme 1.24).

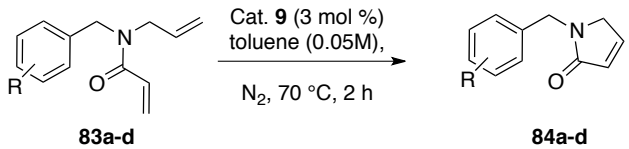


R = a: 2-I, b: 2-H, c: 4-NO_2, d: 4-Br

Scheme 1.24. *Synthesis of dienes* ***83a-d***

Satisfyingly, treatment of compounds **83a-d** with 3 mol% of catalyst **9,** in toluene at 70 °C, resulted in the rapid formation of products **84a-d**, which were isolated in excellent yields after purification over silica gel (Table 1.9, entries 1-4).

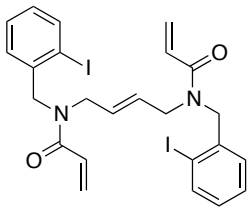
Noteworthily, 0.05M solutions are required to minimize the formation of cross-metathesis byproducts (Figure 1.7) and to achieve the efficient synthesis of the lactam ring.



83a-d **84a-d**

Entry	R	Reactant	Product	Yield (%)
1	2-1	**83a**	**84a**	95
2	4-H	**83b**	**84b**	quant.
3	4-NO_2	**83c**	**84c**	quant.
4	4-Br	**83d**	**84d**	quant.

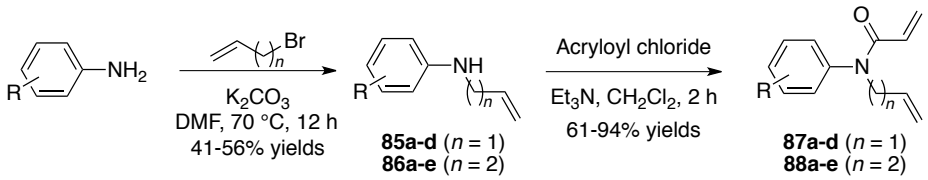
Table 1.9. *Synthesis of lactams* ***84a-d***



84'a

Figure 1.7. *Cross-metathesis byproduct* ***84'a***

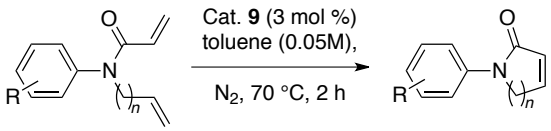
RCM also allowed the synthesis of five- and six-membered lactams from dienes **87a-d** and **88a-e**, in which the nitrogen atom is directly connected to the aromatic ring. These precursors were obtained starting from commercially available anilines, by a two-step process, which involves a classical alkylation reaction followed by acylation with acryloyl chloride and Et_3N (Scheme 1.25).



R = a: 4-H, b: 4-I, c: 4-OMe, d: 3-Br, e = 4-Me

Scheme 1.25. *Synthesis of dienes* ***87a-d*** *and* ***88a-e***

Metatheses proceeded efficiently starting from dienes **87a-d** and **88a-e** to afford the desired products **89a-d** and **90a-e** in 56% to quantitative yields (Table 1.10, entries 1-8).



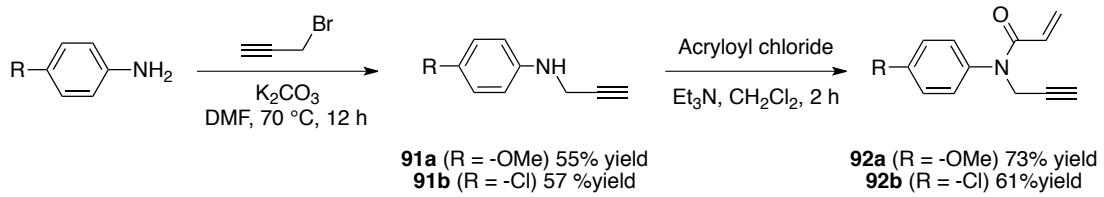
87a-d (*n* = 1)
88a-e (*n* = 2)

89a-d (*n* = 1)
90a-e (*n* = 2)

Entry	R	*n*	Reactant	Product	Yield (%)
1	4-H	**1**	**87a**	**89a**	73
2	4-I	**1**	**87b**	**89b**	91
3	4-OCH_3	**1**	**87c**	**89c**	56
4	3-Br	**1**	**87d**	**89d**	80
5	4-H	**2**	**88a**	**90a**	94
6	4-I	**2**	**88b**	**90b**	quant.
7	4-OCH_3	**2**	**88c**	**90c**	90
8	4-Me	**2**	**88e**	**90e**	93

Table 1.10. *Synthesis of lactams **89a-d** and **90a-e***

Finally, using propargyl bromide instead of allyl bromide in the synthetic sequence, precursors **92a** and **92b** were produced as possible intermediates in the synthesis of RCEYM derivatives (Scheme 1.26).



Scheme 1.26. *Synthesis of dienes **92a** and **92b***

Unfortunately, any attempt to obtain five-membered lactams from precursors **92a** and **92b** *via* RCEYM resulted in the recovery of the starting material after the reaction.

1.2.5. 1-Benzazepine and 2-benzazepine scaffolds

Many natural and synthetic seven-membered nitrogen heterocycles are currently an object of sustained interest due to the vast range of their biological activities[44] and, in particular, benzofused dia-, thia- and oxazepines have been the focus of much synthetic efforts in the past decades.[45] Surprisingly, the 1*H*-benzo[*b*]azepine (1-benzazepine) scaffold as well as its congener 1*H*-benzo[*c*]azepine (2-benzazepine) have been only scarcely explored, despite both ring systems represent crucial pharmacophores in drug discovery (Figure 1.8).[46,47]

The biological relevance of benzazepines recently prompted organic chemists to discover novel methodologies for the synthesis of such ring systems.[48]

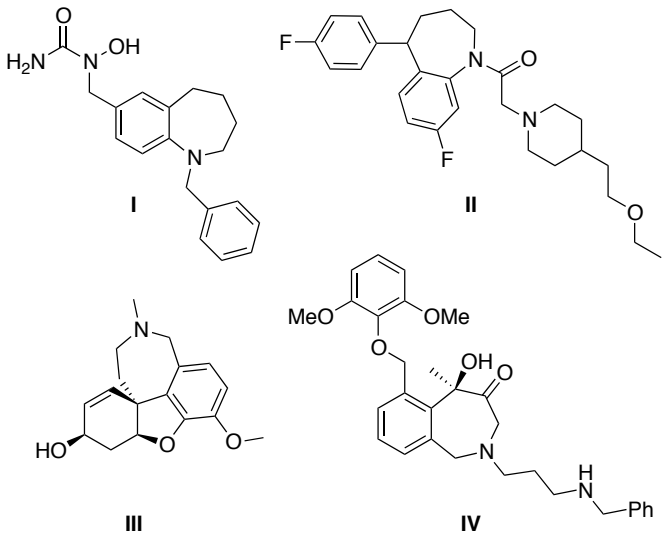


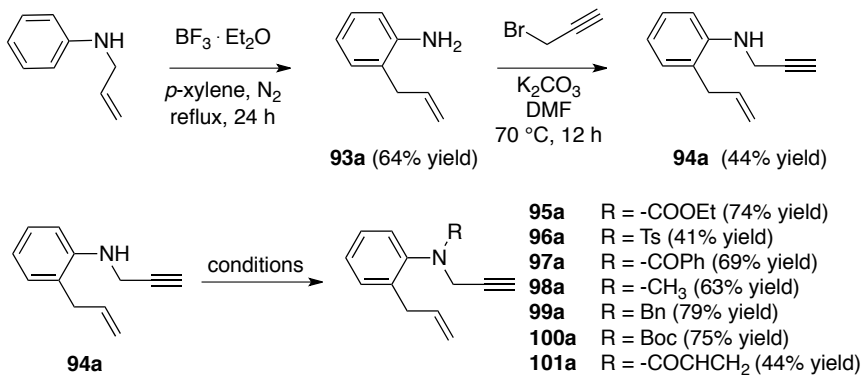
Figure 1.8. *Representative benzazepine-based biologically active compounds: a 5-lipoxy-genase inhibitor (**I**), an inhibitor of N-type calcium channels (**II**), a molecule used for the treatment of Alzheimer's disease (**III**), a muscarin M3 antagonist (**IV**).*

Medium-sized carbo- and hetero-cycles are difficult to be obtained and most of the classical strategies which allow their formation are hampered by enthalpic and entropic factors.[49] In the last few years, however, alkene metathesis has overbearingly emerged as a versatile synthetic technique, which can be used to access molecules which are difficult to achieve by conventional ways or previously unattainable.

Since RCM already proved to be an efficient method to access the benzazepine motif,[50] we turned our attention to syntheses relying on RCEYM, which have rarely been reported.[51]

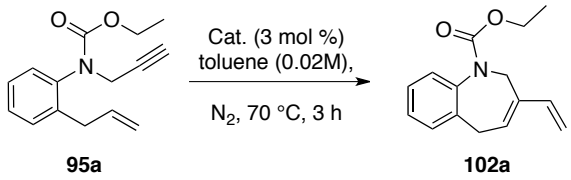
Due to the extraordinary versatility of ene-yne systems, we began our investigations by developing a suitable strategy to access RCEYM precursors (Scheme 1.27).

Starting from *N*-allyl aniline, a sigmatropic aza-Claisen rearrangement through the agency of a Lewis acid ($BF_3{\cdot}Et_2O$ in refluxing *p*-xylene) proved to be the better way to obtain 2-allyl aniline **93a.** This was subsequently alkylated with propargyl bromide in the presence of K_2CO_3 to give the intermediate ene-yne **94a** in 28% (unoptimized) overall yield and arrival at *N*-protected 1,8 enynes **95a-101a** was readily accomplished under standard conditions in good yields.[52]



Scheme 1.27. *Synthesis of RCEYM precursors*

With the required precursors in hand, we next turned our attention to the optimization of the cyclization conditions. Indeed, the reactivity of different metal complexes was screened in toluene, at 70 °C, using compound **95a** as model substrate (Table 1.11, entries 1-4) and Hoveyda-Grubbs' second-generation catalyst **9** quickly emerged as the best choice.



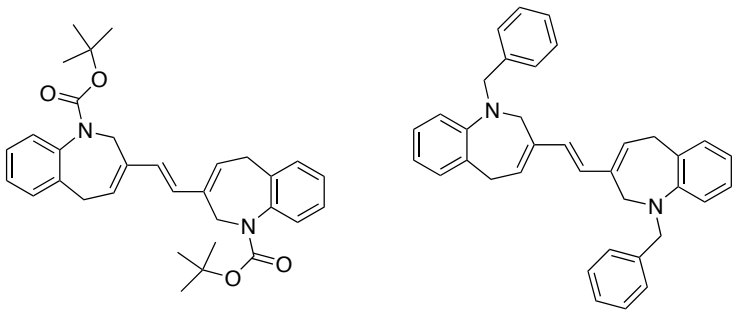
95a **102a**

Entry	Catalyst	Yield (%)
1	**6**	n.r.
2	**8**	21
3	**9**	45
4	**4**	n.r.

Table 1.11. *Catalyst screening*

Once experimental conditions were established, the scope of the cyclization was assessed using the *N*-propargyl-2-allyl-anilines **94a-101a** , *i.e.,* differing in the electronic and steric properties of the substituent located on the nitrogen atom. At the outset, substituent effect was investigated by the reaction of compounds **96a**, and **97a**. In both cases, RCEYM went without event to afford **103a** and **104a** in 39% and 57% yields, respectively (Table 1.12, entries 1 and 2). Unlike precursors embodying an EWG on the nitrogen atom, anilines **94a** and **98a** appeared reluctant to metathesis reaction and only starting materials were recovered (Table 1.12, entries 3 and 4). Surprisingly, when **99a** and **100a** were submitted to the latter conditions, no signs of any product arising from RCEYM could be detected in the crude reaction mixture and only dimeric compounds **105a** and **106a** (*i.e.,* tandem RCEYM/homo-

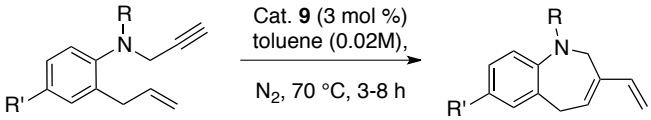
CM products) were isolated in 43% and 51% yields, respectively (Figure 1.9).[53] The configuration of the new formed exocyclic double bond was predominantly *E* for both dimers as assessed by ^{1}H NMR (narrow signals of the olefinic protons at 5.86-5.69 ppm).



105a **106a**

Figure 1.9. *RCEYM/homo-CM byproducts*

To our delight, reluctance of **99a** and **100a** to undergo RCEYM was overcome by running the reaction under an ethylene atmosphere as suggested by Mori and co-workers[54] and the expected 3-vinyl benzazepines **107a** and **108a** were successfully isolated in 49% and 51% yields, respectively (Table 1.12, entries 5 and 6).



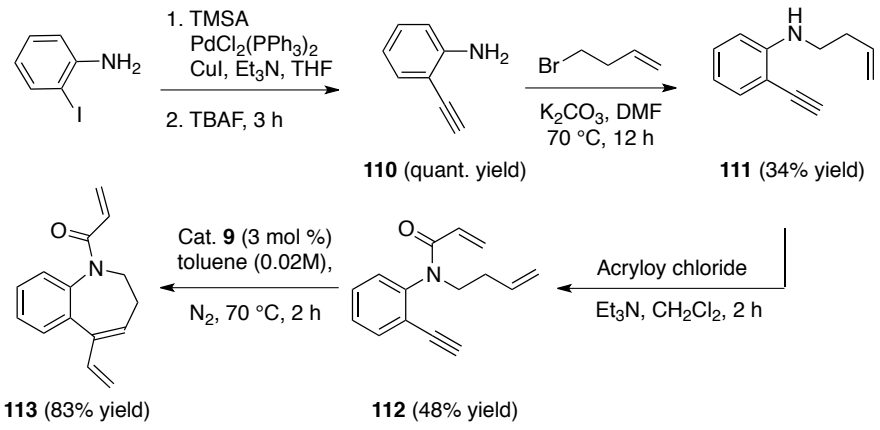
Entry	R	R'	Reactant	Product	Yield (%)
1	Ts	**H**	**96a**	**103a**	39
2	-COPh	**H**	**97a**	**104a**	57
3	H	**H**	**93a**	/	n.r.
4	Me	**H**	**98a**	/	n.r.
5	Bn	**H**	**99a**	**107a**	49
6	Boc	**H**	**100a**	**108a**	51
7	-$COCHCH_2$	**H**	**101a**	**109a**	46
8	-$COCHCH_2$	**4-Me**	**101b**	**109b**	39
9	-$COCHCH_2$	**4-Cl**	**101c**	**109c**	53
10	-$COCHCH_2$	**4-OMe**	**101d**	**109d**	27

Table 1.12. *Substrate scope of RCEYM reactions*

For comparison purposes, we have also investigated the behavior of **101a** featuring an internal acryloyl moiety. In principle, apart from homo-CM products, three different reaction pathways have been envisaged: RCM (ene-enone) was expected to give rise to a dihydrobenzazepinone skeleton while competing RCEYM (ene-yne) and RCEYM (enone-yne) might also produce isomeric 1,3-diene incorporated in seven- and five-ring systems, respectively. In the event, exposure of **101a** under our conditions furnished the corresponding *N*-acryloyl benzazepine **109a** in 46% yield (Table 1.12, entry 7). No detectable quantities of either dihydrobenzazepinones or RCEYM (enone-yne) products were found in the crude reaction mixtures. The observed selectivity favouring RCEYM (ene-yne) over other two reaction pathways is believed to be controlled by high reactivity of the C-C double and triple bonds *vs* low reactivity of enone subunit toward electrophilic Ru-carbene catalyst.[55] Finally, we cannot exclude that the nature of catalyst, the concentration, the electronic/steric effects and the *s*-cis/*s*-trans conformational ratio of the acrylamide precursor play a relevant role.[56]

This cycloisomerization tolerates different substituents on the aromatic ring of 1,8-enynes. Accordingly, exposure of **101b** and **101c** to the optimized reaction conditions provided the expected acrylamides **109b** and **109c,** which were isolated in moderate yields (Table 1.12, entries 8 and 9). Instead, the OMe group in compound **101d** interfered with Ru=C fragment of the catalyst, thereby explaining the low 27% yield of **109d** (Table 1.12, entry 10).

These findings prompted us to investigate the fate of substrate **112**, featuring a 5-aza-1,8-enyne framework (instead of the earlier 6-aza-1,8-enyne) under our RCM conditions. The synthesis of compound **112** is outlined in Scheme 1.28 and started with the commercially available 2-iodo aniline.

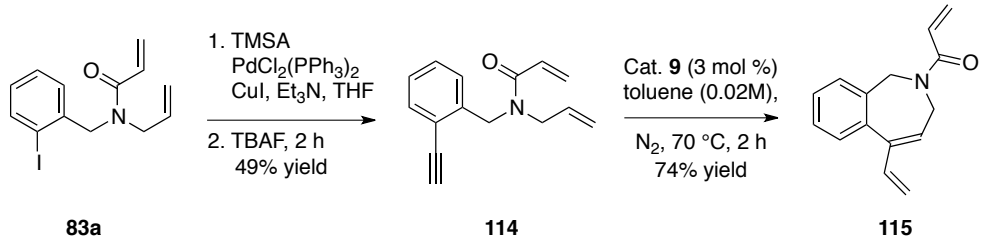


Scheme 1.28. *Synthesis of 1-benzazepine scaffold **113***

Thus, Sonogashira coupling and subsequent protodesilylation were readily effected and the ensuing alkyne **110** was subjected to *N*-alkylation with 4-bromo-butene followed by acylation

with acryloyl chloride leading to **112** in 16% (unoptimized) yield over all five steps. Exposure of **112** to catalyst **9** (3 mol %) in toluene (0.02 M) at 70 °C for 2 h led to the smooth formation of the expected 1,3-diene **113** in 83% isolated yield.

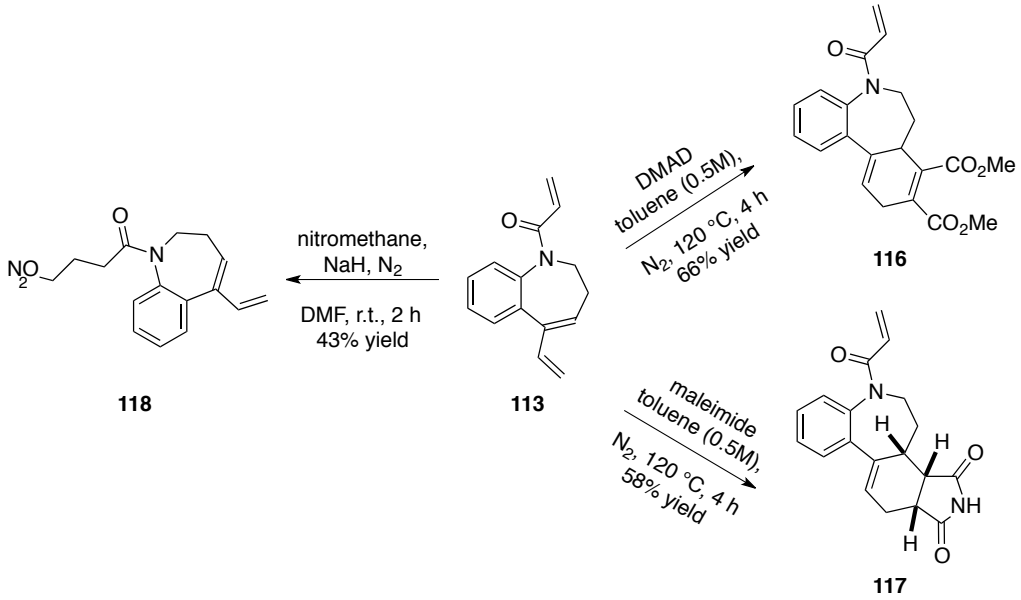
To further document the scope and limitations of our RCEYM, we opted to study the behaviour of **114** (i.e., a 4-aza-1,8-enyne connected to an aromatic ring) with the intention of obtaining a 2-benzazepine framework. The alkyne **114** needed for this study was prepared from previously synthetized acrylamide **83a** (Scheme 1.29).



Scheme 1.29. *Synthesis of 2-benzazepine scaffold **115***

Sonogashira coupling of **83a** to trimethylsilyl acetylene followed by desilylation provided **114** in 49% yield over all five steps. To our delight, when **114** was subjected to our RCM conditions it cyclized in an analogous manner to that encountered earlier (i.e. **112→113**) thereby generating the 2-benzazepine **115** in 74% yield.

The availability of the corresponding benzazepines (**109a-d, 113** and **115**), which incorporate, at least, two points of molecular diversity (i.e., 1,3-diene and acrylamide) gave us the opportunity for subsequent chemical transformations and construction of polycyclic compounds (complexity generation by post-metathesis transformations).

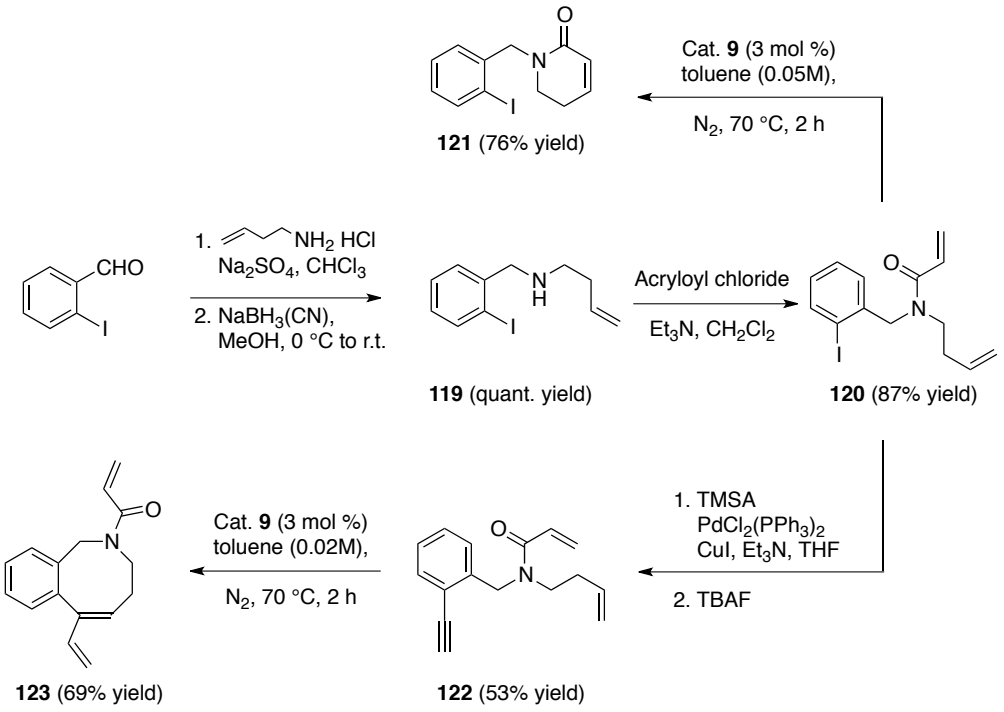


Scheme 1.30. *Post-metathesis functionalizations*

Thus, for instance, the 1,3-diene subunit in **113** smoothly reacted with either dimethyl acetylenedicarboxylate (DMAD) or maleimide leading to the expected Diels-Alder adducts **116** and **117** (*endo*-adduct) in 66% and 58% yields, respectively. Likewise, base-induced conjugate Michael addition with $MeNO_2$ proceeded satisfactorily to the acryloyl moiety in **113** delivering nitroalkane **118** in 43% yield without interference from the diene residue (Scheme 1.30). These orthogonal functionalizations emphasize the versatility of our heterocyclic scaffolds, attesting their potential as building blocks for the synthesis of more complex molecules.[57]

1.2.6. Regioselective synthesis of a benzazocine derivative

A further study to investigate the ability of catalyst **9** to form a benzofused eight-membered derivative *via* regioselective RCEYM reaction was also conducted (Scheme 1.31). In this case, the desired cyclization precursor (compound **122**), was obtained starting from *o*-iodobenzaldehyde by a reductive amination reaction with 3-butenylamine hydrochloride and $NaBH_3(CN)$. The resulting secondary amine **119** then reacted with acryloyl chloride to give the corresponding amide **120** in 87% yield. Noteworthily, compound **120** is good reactant for the RCM procedure, as demonstrated by the rapid formation of derivative **121**, which was isolated in 76% yield. Finally, the 1,9-enyne **122** was prepared by a Sonogashira reaction on substrate **120**.

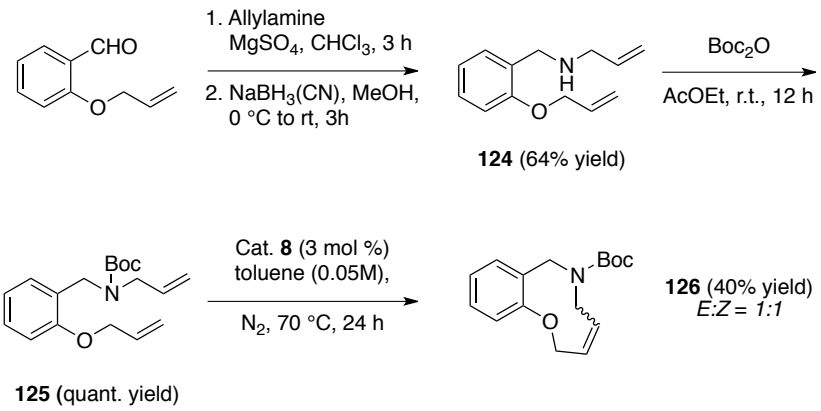


Scheme 1.31. *Regioselective synthesis of benzazocine derivative **123***

Analogously to the formation of benzazepine skeletons, compound **122** underwent the cyclization smoothly, to generate the expected benzazocine derivative **123** in 69% yield. No traces of six-membered lactam **121** were detected in the crude reaction mixture.
This result seems to suggest that the procedure we developed could be used as a general protocol for the regioselective preparation of medium/large nitrogen-containing heterocyclic rings.

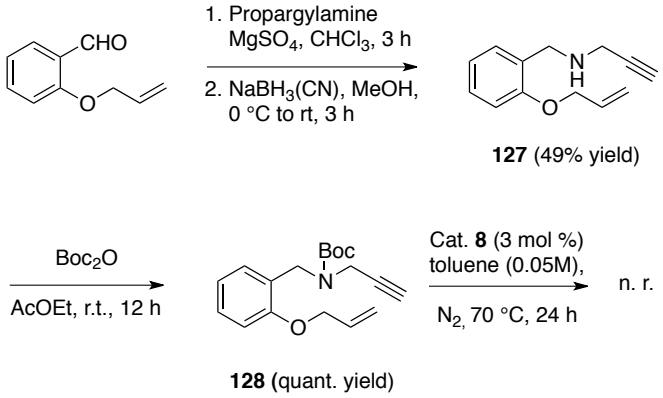
1.2.7. Large-sized ring heterocycles

The synthesis of large-sized ring systems from acyclic precursors may be difficult owing to entropic factors and transannular repulsions that develop as the ring is formed.[50] Like other cyclizations that produce such cyclic compounds, metathesis reactions tend to work best in the presence of conformational constraints that favor the ring formation. Such structural features include the presence of another ring, a *gem*-dimethyl group, or a *N*-tosyl group in the chain linking the reacting double bonds.[58] In this context, a benzene ring constituted an excellent conformational constraint, which could be used to form an oxygen- and nitrogen-containing nine-membered heterocycle *via* RCM. Indeed, 1,10-diene **125** was synthetized by a three steps procedure starting from 2-allyloxybenzaldehyde (Scheme 1.32).



Scheme 1.32. *Synthesis of an O- and N-containing nine-membered ring via RCM*

A condensation reaction with allylamine and successive reduction of the imine intermediate with $NaBH_3CN$, allowed the formation of compound **124**, which, in turn, was converted into **125** upon Boc-protection of the nitrogen atom. RCM of precursor **125** with Grubbs' catalyst **8** finally afforded the desired nine-membered ring, which was isolated as yellow pale oil in 40% yield. Unfortunately, since the control of the new double bond geometry is difficult to be accomplished, compound **126** was formed as a 1:1 mixture of *E*- and *Z*- isomers.



Scheme 1.33. *Synthesis of an O- and N-containing nine-membered ring via RCEYM*

Any attempt to obtain an oxygen- and nitrogen-containing nine-membered heterocycle *via* RCEYM resulted in no conversion of the starting material (compound **128**, Scheme 1.33) after the reaction.

1.3. CONCLUSIONS AND FUTURE DEVELOPMENT

Little more than a decade has elapsed since Grubbs and Fu reported that Schrock's molybdenum catalyst **4** (Figure 1.2) could be used to induce efficient cyclizations of functionalized 1,*n*-dienes to give carbocycles and heterocycles *via* metathesis reactions. Since then, there has been a real explosion of research in this area, as is evident from the examples cited in this chapter.

We have efficiently applied RCM and RCEYM to the synthesis of different functionalized rings, common skeletons in natural products or in biologically active compounds. Focusing on oxygen- and nitrogen-containing heterocycles, we began our investigations by developing a suitable strategy to access five- and six-membered ethers, lactones, and lactams.

Electron poor, electron rich and electron neutral 1,*n*-dienes and 1,*n*-enynes were employed in the metathetic processes, the first one giving best results in terms of yield, degree of purity and ease of isolation. In some cases (i.e., products **67a**, **81a**, **81b**, and **89c**), -OCH_2O- and -OMe groups interfered with Ru=C fragment of the catalysts coordinating the metal center, thereby explaining the low yields.

Natural and synthetic seven-membered nitrogen-containing heterocycles are currently attracting great interest because of their biological activities. In this context, the biological relevance of benzazepines encouraged us to develop new metathesis reactions for the synthesis of such ring systems. A variety of benzazepine frameworks were isolated through the cyclization of different substituted enyne precursors.

Interestingly, a selective formation of benzofused seven-membered rings *via* RCEYM was achieved starting from precursors showing an acryloyl group at the nitrogen atom. The observed selectivity is believed to be controlled by high reactivity of the C-C double and triple bonds *vs* low affinity of enone subunit toward electrophilic Ru-carbene catalyst.

A further study to investigate the possibility to form a benzofused eight-membered derivative *via* regioselective RCEYM reaction was also successfully carried out.

Finally, the synthetic utility of selected RCEYM products could be demonstrated by further funcionalizations (i.e., either *via* Diels–Alder reactions or Michael addition), attesting their potential as building blocks for the synthesis of more complex molecules.

An increasing number of applications of RCM and RCEYM to the synthesis of complex and highly functionalized organic molecules of importance in natural product chemistry, chemical biology, and material science have recently been described. Work is underway in our laboratory to afford other heterocyclic scaffolds by metathesis and to apply them in the total synthesis of natural products and analogues of biological interest.

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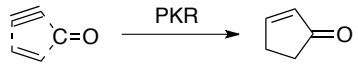
Chapter 2

Pauson-Khand reactions

Synthesis of oxygen-containing bicyclic compounds

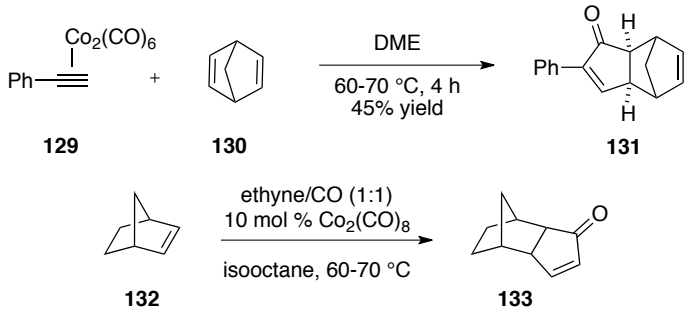
2.1. INTRODUCTION

The Pauson–Khand reaction (PKR) is formally a [2+2+1] cycloaddition in which a triple bond, a double bond and carbon monoxide react to yield a cyclopentenone skeleton. This implies the formation of three new C-C bonds and one or two cycles in the intermolecular or intramolecular versions respectively (Scheme 2.1). Indeed, few reactions can compete with the Pauson–Khand in the construction of great molecular complexity in one synthetic step.



Scheme 2.1. *Connectivity of the Pauson–Khand reaction*

The PKR was discovered by Pauson and Khand in the early 1970s[1] and was first reported as a stoichiometric reaction between norbornadiene and a complex of acetylene bound to hexacarbonyl dicobalt (Scheme 2.2). Pauson and co-workers also reported the first catalytic intermolecular formation of a cyclopentenone from an alkyne, an olefin and CO (Scheme 2.2).

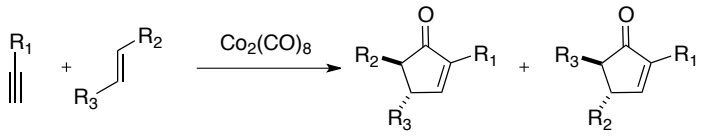


Scheme 2.2. *First reported Pauson–Khand reactions*

At the beginning, the PKR was carried out thermally, under relatively severe conditions and led to transformations of generally low efficiency. Although until the mid-nineties dicobalt octacarbonyl was the only cluster used to mediate the reaction, both dinuclear and mononuclear catalysts have now been developed for this process.

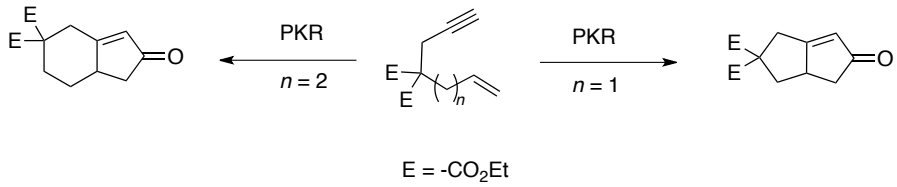
In the initial study of the intermolecular-type reactions, all alkynes underwent the cycloaddition, with the exception of propynoic acid derivatives. On the other hand, only strained olefins reacted efficiently under the original conditions. With respect to regioselectivity, the bulkier substituent of the alkyne is generally placed adjacent to the

carbonyl in the cyclopentenone product, while unsymmetrical olefins usually give mixtures of regioisomers (Scheme 2.3).[2]



Scheme 2.3. *Regiochemistry of the Pauson–Khand reaction*

In the early eighties, Schore introduced the intramolecular version of this reaction. Until recently this process allowed the formation of 5.5- and 5.6-fused bicycles (the former with generally greater levels of efficiency) and good conversions were achieved only with *gem*-disubstituted enynes (Scheme 2.4).[3]



Scheme 2.4. *Intramolecular PKR*

In addition to mechanistic studies, the main efforts in the developments of PKRs at present are directed towards: (1) increase the scope to new substrates; (2) establishment of efficient catalytic processes; (3) improvement of the asymmetric version of the reaction; (4) application of the PKR to the synthesis of natural products.

In this chapter, we focus our attention on the catalytic versions of the PKR: the synthetic applications that can be envisioned for the non-stoichiometric Pauson-Khand reactions make the development of new asymmetric catalytic processes an essential research target in this field.

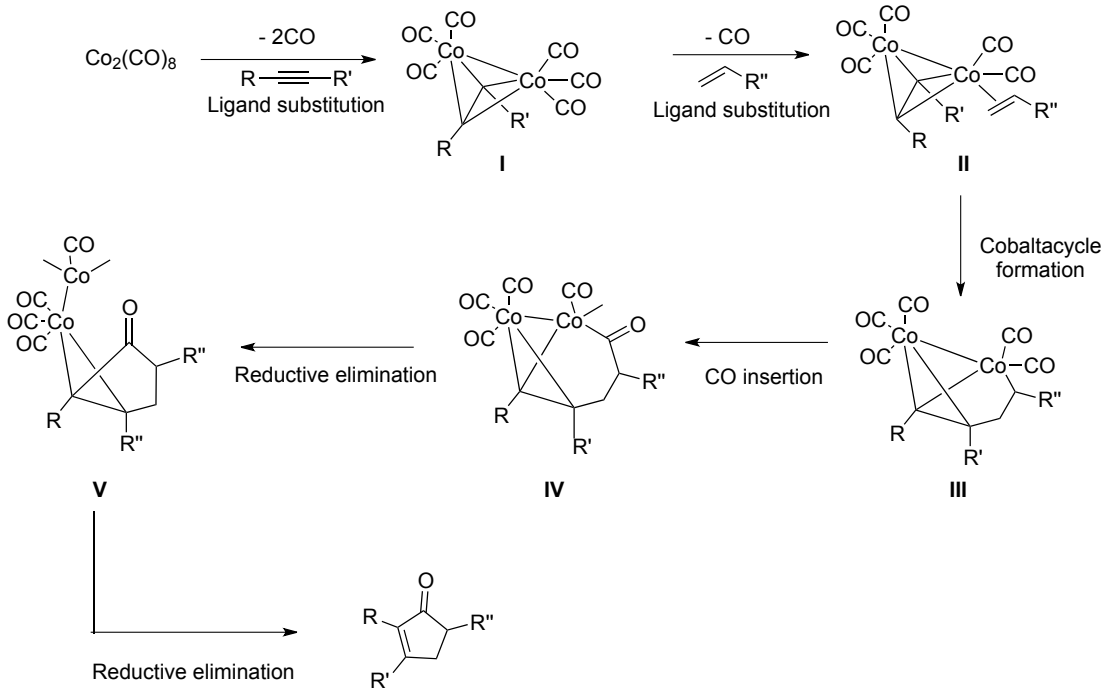
2.1.1. Mechanism of the Pauson-Khand reaction

The currently accepted mechanism of the Pauson-Khand reaction mediated by cobalt carbonyl systems was proposed by Magnus in 1985 (Scheme 2.5).[4] Several theoretical studies support this mechanism since it explains the regio- and stereochemical results of numerous examples.

According to these studies, the initial hexacarbonylalkyne complex **I** is formed in a first step followed by the loss of one CO ligand.

Because of its strongly endothermic character, this is the rate-determining step and, consequently, acceleration of the overall process usually involves the use of promoters that act at this point, labilizing one of the CO ligands.

The olefin then coordinates the cobalt and alkyne/alkene reductive coupling occurs. The resulting cobaltacycle **III** undergoes insertion of CO to give intermediate **IV**. Two reductive eliminations finally afford the desired ketone product and regenerate the starting dicobalt complex.



Scheme 2.5. *Mechanism of the PKR mediated by cobalt carbonyl*

Another confirmation of the proposed mechanism was introduced by Pericas and co-workers, who studied the reaction pathway using DFT calculations (Figure 2.1).[5]

This theoretical study implies that the dissociation of CO is endothermic by 33.5 Kcal/mol, while the coordination of the olefin is exothermic by 21.5 Kcal/mol. Thus, the ligand substitution is endothermic by 12 Kcal/mol. The reductive coupling step is approximately thermo-neutral, but the binding of CO to the unsatured product is strongly exothermic. Therefore, the overall formation of the cobaltacycle (steps from intermediate **I** to **III**, Scheme 2.5) is strongly exothermic and irreversible when the reaction is performed in the presence of CO.

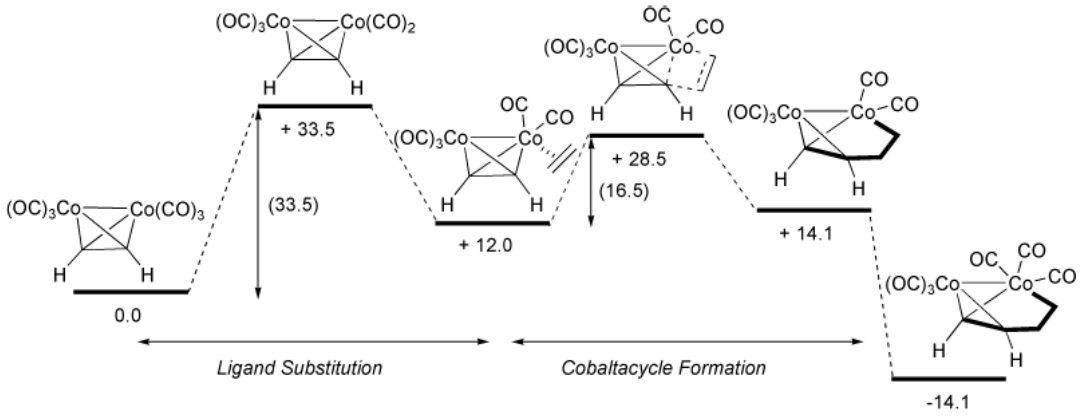
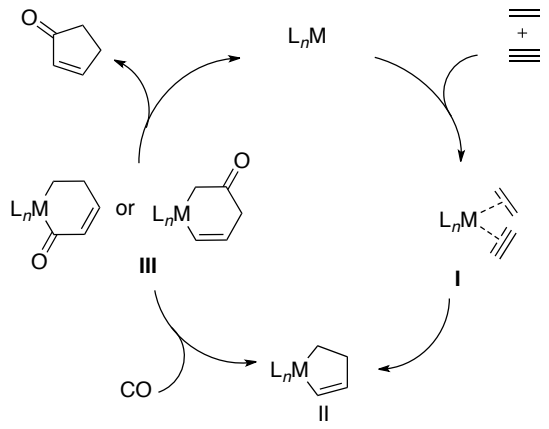


Figure 2.1. *Energies for the intermediates in the Pauson-Khand reaction mediated by cobalt carbonyl*

In a different theoretical study, Greene and Gimbert demonstrated that, besides steric effects, electronic factors undoubtedly plays an important role in determining the regiochemical outcome of the Pauson–Khand reactions. Accordingly to their results, the acetylenic carbon that carries the larger electron density will be the one involved in the formation of the crucial C–C bond by olefin insertion (from intermediate **II** to **III**, Scheme 2.5), even when geometrical factors are less favorable.[6]

PKRs catalyzed by complexes other than $Co_2(CO)_8$ have not been the subject of detailed mechanistic studies. However, the catalytic cycle is assumed to follow the path reported in Scheme 2.6. This mechanism begins with the coordination of the olefin and the alkyne to a single metal center (**I**). Reductive coupling of the two groups then generates the metallacyclepentene **II**. Insertion of CO followed by reductive elimination finally forms the ketone product and the starting catalyst.

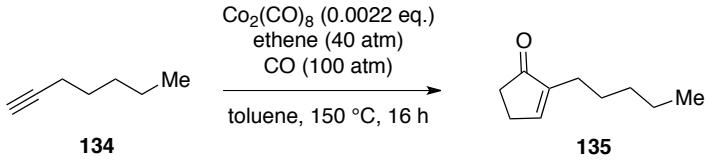


Scheme 2.6. *Mechanism of the PKR catalyzed by complexes other than $Co_2(CO)_8$*

2.1.2. Cobalt-catalyzed PKR

The classical Pauson–Khand reaction involves the stoichiometric use of highly toxic $Co_2(CO)_8$, which is environmentally unfriendly and not economical for industrial applications. For these reasons, during the past years there has been great interest in developing efficient protocols for catalytic versions of the PKR.

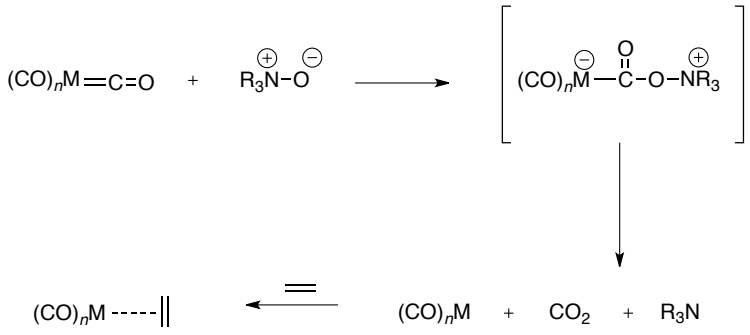
Following the pioneering work of Pauson and co-workers (Scheme 2.2),[1b] Rautenstrauch reported the first example of a real catalytic cycloaddition in 1990 (Scheme 2.7).[7] In this case, however, the reaction had to be conducted under very high partial pressures of carbon monoxide and ethene.



Scheme 2.7. *Rautenstrauch's catalytic PKR*

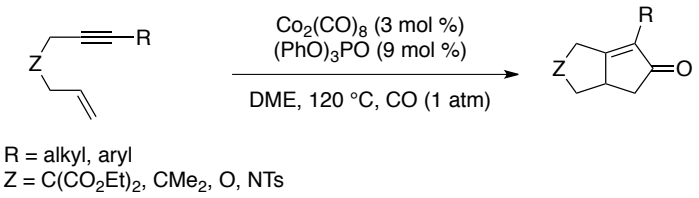
In attempts to improve the reaction efficiency, the introduction of various types of promoters – such as tertiary amine *N*-oxides, dimethyl sulfoxide, hard Lewis bases, sulfides, phosphanes, phosphates and phosphites – into the catalytic systems has been investigated.[8] Finally, the use of amine *N*-oxides has become the most popular and efficient way to promote the PKRs.[9]

Nowadays, the most used additives are trimethylamine *N*-oxide (TMANO) and *N*-methylmorpholine *N*-oxide (NMO). These compounds act by oxidizing one CO ligand, which is transformed into CO_2, thus favoring the formation of a vacant site in the cobalt cluster (Scheme 2.8).



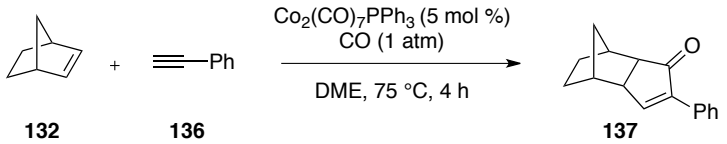
Scheme 2.8. *Catalyst activation by the action of amine N-oxides*

Alternatively, Jeong and co-workers reported successful carbonylative couplings of enynes, in which $Co_2(CO)_8$ and triphenyl phosphate were used as catalytic system (Scheme 2.9).[10] In this case, the reaction could be carried out at ambient CO pressure (1 atm). These achievements served as a platform for further development of new Co-based catalysts, in order to achieve practical [2+2+1] cycloaddition reactions, as well as their enantioselective variants.



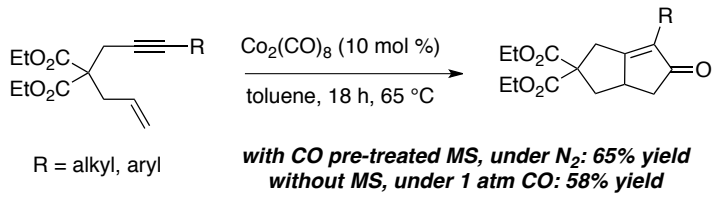
Scheme 2.9. *Jeong's catalytic PKR*

As reported by several research groups, the cobalt species $Co_2(CO)_8$ is not easy to handle since it is highly toxic and it ignites spontaneously upon contact with air. The development of more practical catalyst precursors, which can either retain or improve the performance of $Co_2(CO)_8$ without requiring reducing steps in situ, would bring substantial advantages to the catalytic versions of the PKR. In this context, Gibson and co-workers demonstrated that $Co_2(CO)_7PPh_3$ was able to catalyze Pauson–Khand reactions (Scheme 2.10) and that its efficiency was comparable with those of other mild systems.[11] In addition, $Co_2(CO)_7PPh_3$ does not ignite spontaneously upon contact with air and retains its catalytic activity for many months if stored at 4 °C, even after being exposed to air.



Scheme 2.10. *Gibson's catalytic PKR*

Another issue connected to Pauson-Khand reaction conditions is the use of carbon monoxide, which is a deadly, colorless, odorless, poisonous gas. Although gaseous CO is routinely used for PKR, Pérez-Castells and co-workers recently reported an interesting approach eliminating the requirement to purge CO gas during the course of the reaction.[12] They demonstrated that molecular sieves could entrap CO gas and then slowly released it under the reaction conditions. It is worthily of note that the desired product yield exceeded that obtained with traditional methods (Scheme 2.11).

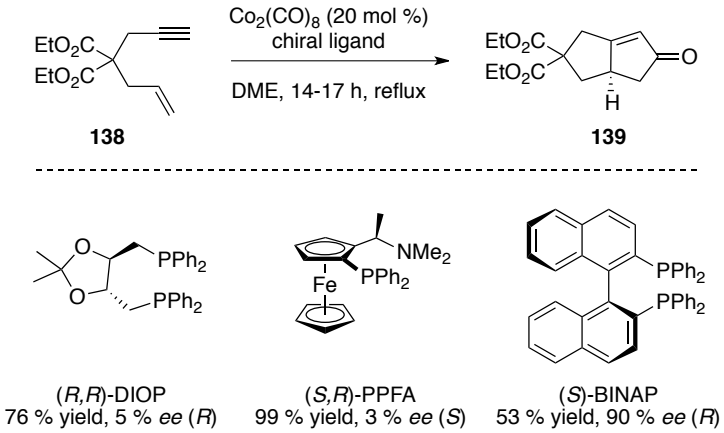


Scheme 2.11. *Use of CO-pretreated molecular sieves in Co-catalyzed PKR*

The asymmetric version of the Co-catalyzed Pauson– Khand reaction was first achieved by Hiroi in 2000.[13] A range of commercially available ligands for this enantioselective transformation were examined (Scheme 2.12).

The synthesis of optically active cyclopent-2-en-1-one derivatives was successfully accomplished with the aid of a catalytic amount of $Co_2(CO)_8$ and (*S*)-BINAP. Recently, Gibson and co-workers reported a detailed mechanistic study of the Co/BINAP system in the asymmetric Pauson–Khand reaction.[14]

The proposed stereoinduction steps were also described. These findings served as a foundation for future design of chiral Co complexes.



Scheme 2.12. *First example of asymmetric Co-catalyzed PKR*

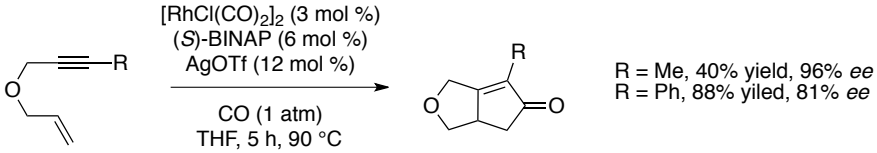
Unlike the catalytic intramolecular carbonylation, the enantioselective intermolecular Pauson-Khand reaction still remains mainly stoichiometric (non-catalytic amounts of Co complexes and chiral ligands are used).

2.1.3. Rhodium-catalyzed PKR

Several metals have been employed to catalyze the Pauson-Khand reaction besides cobalt. The first successful Rh-catalyzed asymmetric intramolecular PKR was reported by Jeong and

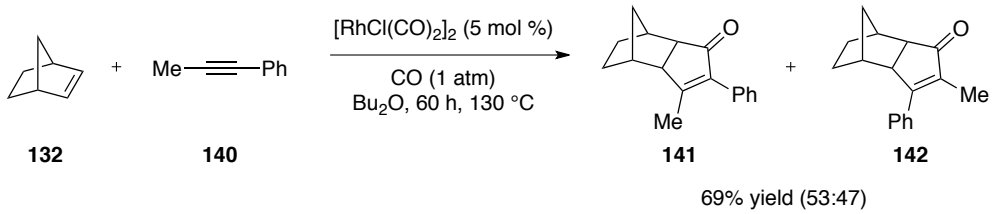
co-workers in 2000.[15] They disclosed that a system comprising $[RhCl(CO)_2]_2$ and (*S*)-BINAP was an effective catalyst for these enantioselective transformations (Scheme 2.13).

On the basis of literature reports describing the successful use of the $[RhCl(CO)_2]_2$ complex for catalyzing intramolecular cycloadditions, Narasaka and co-workers further applied this rhodium catalyst to intermolecular Pauson–Khand cyclizations.[16]



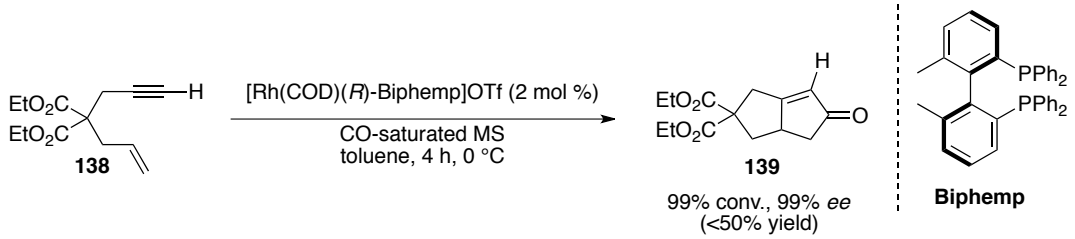
Scheme 2.13. *First example of asymmetric intramolecular Rh-catalyzed PKR*

They demonstrated that in the reaction between norbornene and 1-phenylpropyne, the cyclic enones were obtained as a mixture of regioisomers in 69% overall yield (Scheme 2.14). Additionally, they disclosed that reducing the CO partial pressure to less than 1 atm could accelerate the reaction.



Scheme 2.14. *Intermolecular Rh-catalyzed PKR*

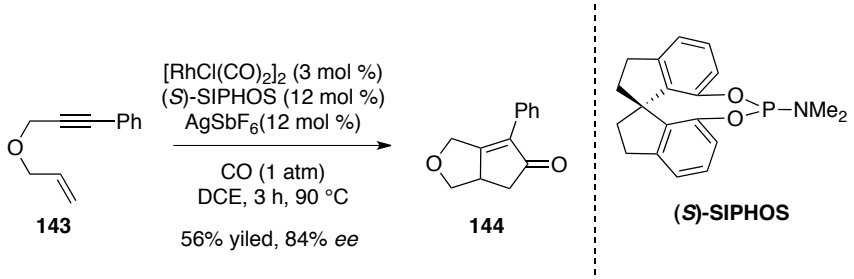
Recently, Consiglio *et al.* described another interesting system for the Rh-catalyzed PKR.[17] In this case, CO-saturated molecular sieves could be used as a CO reservoir for the carbonylative cyclization. Notably, their protocol represented the lowest temperature so far achieved for a Pauson–Khand-type reaction (Scheme 2.15). At 0 °C, the desired product was obtained in 99% conversion with 99 % *ee*.



Scheme 2.15. *Use of CO-saturated molecular sieves in Rh-catalyzed PKR*

As an alternative to chiral bidentate phosphane ligands, Zhou and co-workers demonstrated that new monodentate phosphoramidite **SIPHOS** ligands (Scheme 2.16) could catalyze the asymmetric carbonylative cycliation.[18]

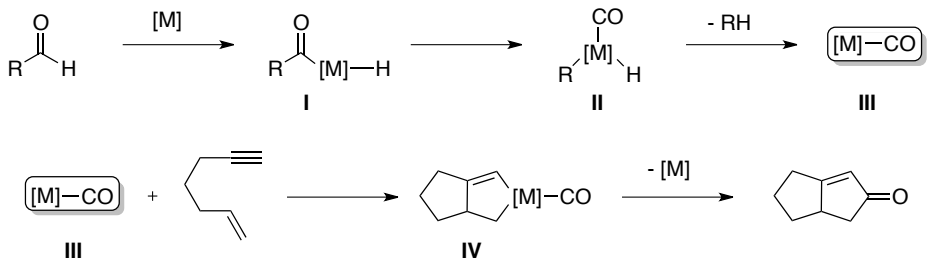
This finding represented the first example of a successful chiral monodentate ligand in an asymmetric Rh-catalyzed PKR, indicating that monodentate ligands have high potential for further utilization in related enantioselective reactions.



Scheme 2.16. *Use of monodentate phosphoramidite ligands in Rh-catalyzed PKR*

The Rh-catalyzed carbonylation has been successful in the area of organic synthesis, and is recognized as a powerful protocol for the direct synthesis of a wide variety of carbonyl-containing compounds.[19] However, the use of the highly poisonous carbon monoxide constitutes a drawback to these methodologies.

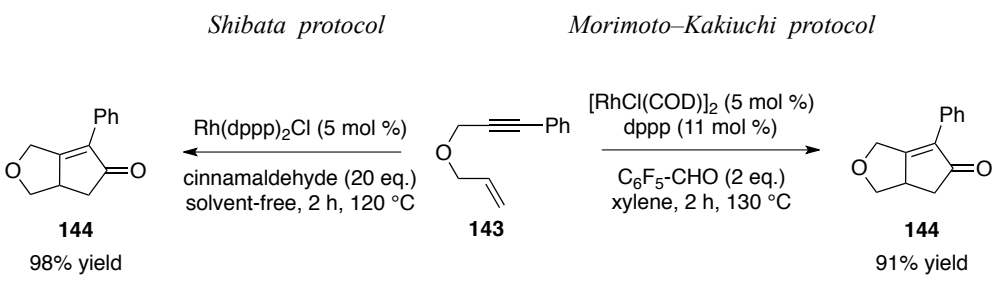
Recently, Morimoto and Kakiuchi[20] and Shibata[21] independently reported a conceptual evolution on the use of metal carbonyl systems to allow PKRs in the absence of gaseous carbon monoxide.[22] This approach involved an aldehyde decarbonylation process and a subsequent CO transfer reaction (Scheme 2.17).



Scheme 2.17. *Aldehyde decarbonylation and CO transfer in Rh-catalyzed PKR*

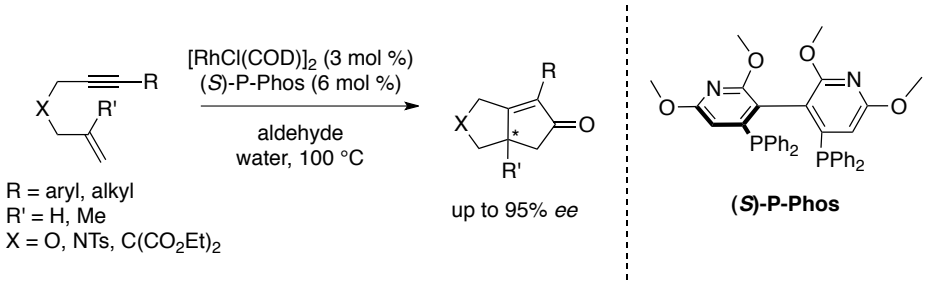
The Morimoto–Kakiuchi group reported that pentafluorobenzaldehyde was an efficient CO surrogate for PKR, whereas the Shibata group found that cinnamaldehyde was the best CO donor (Scheme 2.18).

Moreover, Shibata *et al.* later developed a protocol that used chiral BINAP ligands for the asymmetric Pauson-Khand reaction to give *ee*s of up to 92%.[23]



Scheme 2.18. *Morimoto–Kakiuchi and Shibata CO transfer in Rh-catalyzed PKR*

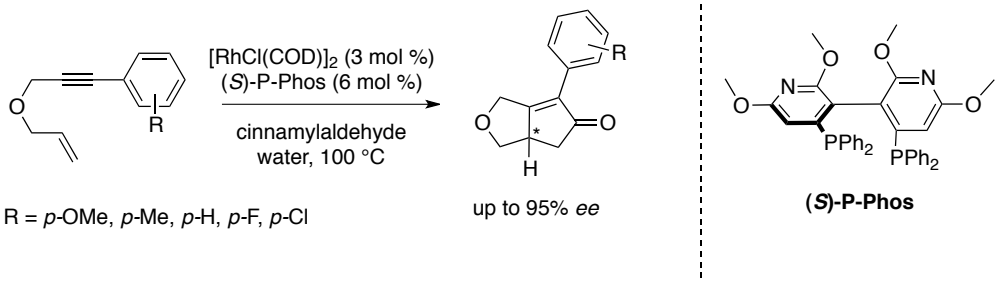
During the last few years, tremendous attention has been given to aqueous transition-metal-catalyzed reactions.[24] However, no catalytic asymmetric systems permitting the use of water as the only solvent (without a surfactant) in the PKR had been developed prior to 2005, when Kwong and co-workers presented a Rh-catalyzed asymmetric PKR in water, based on the use of the chiral dipyridyl diphosphane ligand **P-Phos** (Scheme 2.19).[25] A variety of 1,6-enynes were transformed into the corresponding cyclopentenones with *ees* of up to 95%.



Scheme 2.19. *Rh-catalyzed PKR in aqueous media*

Electronic effects in asymmetric catalysis are an important parameter to control the stereochemical outcome in the desired products.[26] In fact, electronic factors relating both to substrate and to catalyst (ligand) can significantly alter the enantioselectivity. Kwong and co-workers recently reported substrate-dependent electronic effects capable of affecting the levels of enantioselectivity of the desired products (i.e., bicyclic cyclopentenones) in 1,6-aromatic enynes (Scheme 2.20).[25]

Higher enantioselectivities were obtained when an electron-rich substituent was attached to the aromatic ring and it was speculated that the electron-rich enynes bound the Rh metal center more closely and thus gave better stereoinduction, whereas electron-poor enynes were loosely coordinated (Figure 2.2).



Scheme 2.20. *Substrate electronic effects on Rh-catalyzed PKR*

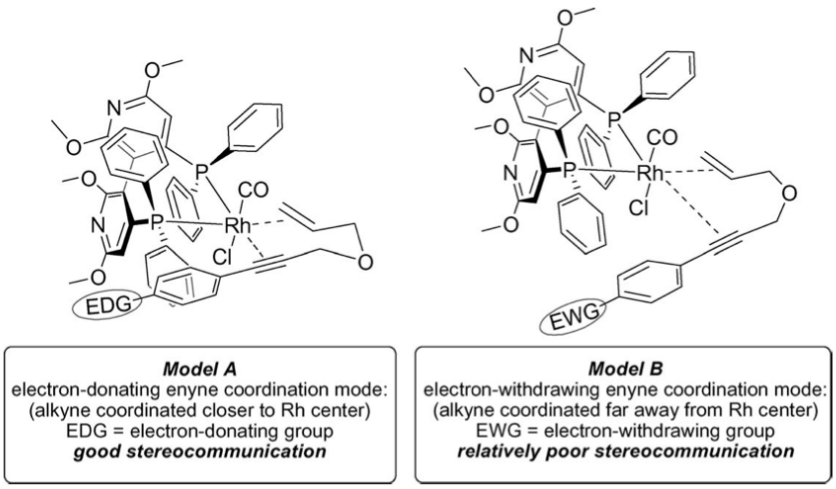
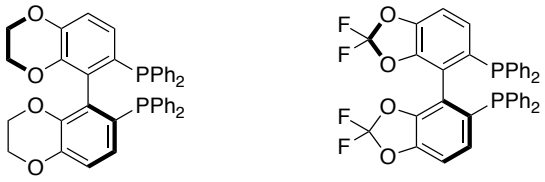


Figure 2.2. *Different coordination of electron-rich and electron poor enynes to the Rh metal center*

As well as substrate electronic effects, Ratovelomana-Vidal, Genêt and Jeong also reported a ligand electronic effect in the Rh-catalyzed PKR.[27] They demonstrated that both the rate and the enantioselectivity were significantly dependent on the electronic densities in the axially chiral BINAP class ligands. With ligands bearing relatively electron-deficient phosphorus donors [i.e., with EWG substituent(s) on the phosphorus-attached aromatic rings], the reaction rates were slower, but the PKR products were obtained with higher enantioselectivity.

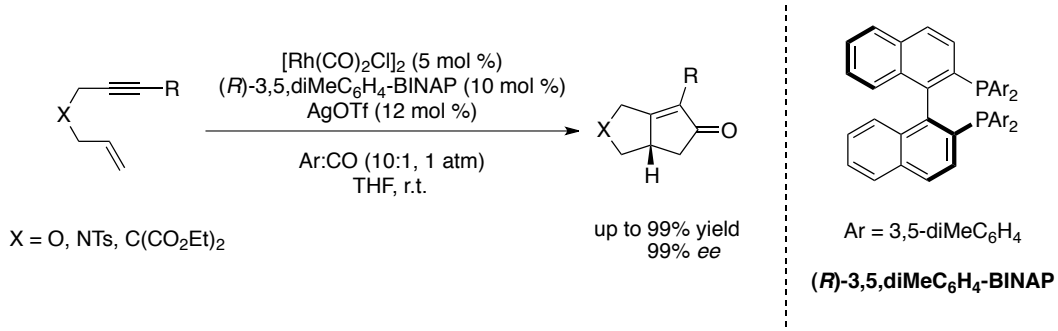
The same research groups carried out a detailed study on the effect of the catalyst (ligand) dihedral angle on the enantioselectivity in the PKR cycloadducts.[28] They found that the steric properties of the biaryl backbone of the ligand, especially the value of its dihedral angle, played a crucial role in the stereochemical outcome of the Rh-mediated PKR. Chiral ligands such as **SYNPHOS** and **Difluorphos**, with narrower dihedral angles than BINAP-type ligands, gave improved reactivity and enantioselectivity for most enyne substrates (Figure 2.3).



(*S*)-SYNPHOS (*S*)-Difluorphos

Figure 2.3. *Structures of* ***SYNPHOS*** *and* ***Difluorphos*** *ligands*

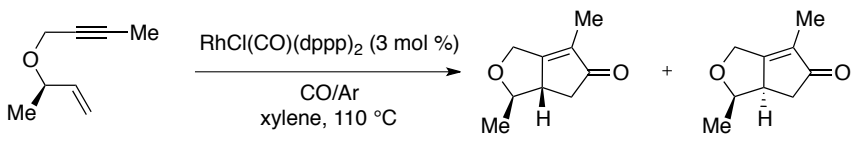
In 2008, Genêt and co-workers described another efficient asymmetric version of the Pauson-Khand reaction catalyzed by Rh-complexes (Scheme 2.21).[30] In this case several products were obtained at room temperature, in high chemical yields as well as high enantioselectivities, by using a reduced partial pressure of CO (0.1 atm).



Scheme 2.21. *Asymmetric Rh(I)-catalyzed PKR at ambient temperature*

Recently, Evans and Baik reported a mechanistic study on a diastereoselective Rh-catalyzed PKR and the role of the coordination number for governing the stereocontrol.[29]

They figured out a theoretical analysis that could provide two distinct mechanistic scenarios for the origin of diastereoselectivity, in which the optimum selectivity could be attributed to a five- rather than a four-coordinated organorhodium complex. The relative population of these complexes is strictly related to the carbon monoxide pressure (Table 2.1). These findings could help to determine relevant controlling factors to improve the stereochemical outcome of the PK reaction.



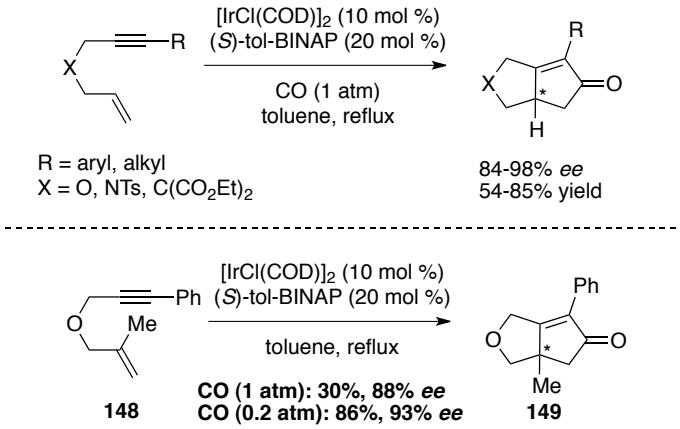
145 **146** **147**

Entry	CO pressure	Ar pressure	Yield (%)	dr (130:131)
1	1.00	0.00	88	>99:1
2	0.10	0.90	51	58:1
3	0.05	0.95	44	57:1

Table 2.1. *Diastereoselective Rh-catalyzed PKR*

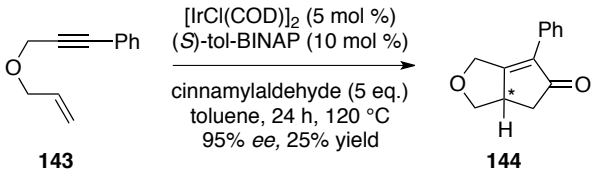
2.1.4. Iridium-catalyzed PKR

In 2000, the group of Shibata reported the first Ir-catalyzed asymmetric PKR,[31] employing $[Ir(COD)Cl]_2$ and (*S*)-tol-BINAP as the catalytic system (Scheme 2.22). Excellent *ee* values were obtained in the cycloadducts. Notably, higher yields and enantioselectivities were achieved when the CO pressure was less than 1 atm.



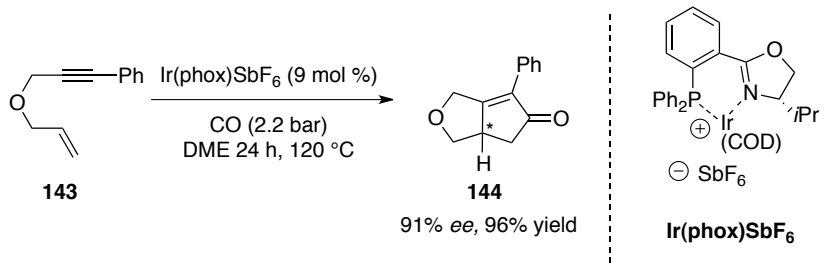
Scheme 2.22. *First example of Ir-catalyzed PKR*

Shibata further demonstrated that $[Ir(COD)Cl]_2$ was also efficient for decarbonylation of aldehydes and that the corresponding metal carbonyl complex could be used to catalyze the PKR (Scheme 2.23).[32] The enantioselectivity in this case was higher than that afforded by the analogous rhodium complex. Kwong and co-workers also independently reported a similar protocol to access a series of optically active bicyclic cyclopentenones in the presence of (*S*)-BINAP-iridium complex.[33]



Scheme 2.23. *Aldehyde decarbonylation and CO transfer in Ir-catalyzed PKR*

In 2007, Pfaltz and co-workers reported a chiral cationic Ir(phox)-complex that was effective in asymmetric Pauson–Khand reactions (Scheme 2.24).[34] Under optimized carbonylation conditions, high yields and enantioselectivities of 90% *ee* were obtained.



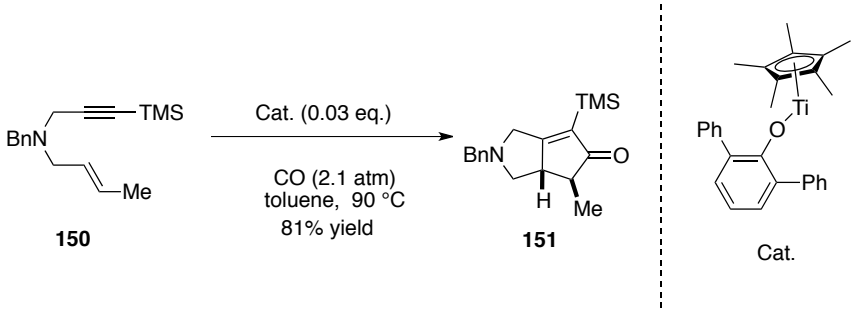
Scheme 2.24. *Use of a chiral cationic Ir-complex in PKR*

The influence of the anion was also studied: it was found that the hexafluoroantimonate was the most suitable counter ion for the complex to operate this catalysis.

2.1.5. Catalysis by other metals

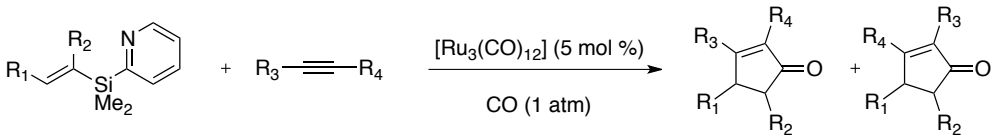
In addition to Rh and Ir, Ti, Ru or Mo complexes have also been successfully used to catalyze the Pauson-Khand reaction.

With respect to Ti, Buchwald has developed several titanocenes that act as efficient catalysts in the PKR and in PK-like reactions with cyanides. In particular, titanocene dicarbonyl is able to catalyze the reaction of different 1,6 and 1,7-enynes with excellent functional group tolerance, but it fails to react with sterically hindered olefins and alkynes. In a very recent contribution, this group has prepared a series of aryloxide complexes. These new catalysts are able to promote cyclisation with some sterically demanding enynes. The efficiency of the cyclisation reactions is dependent upon the substitution of the aryloxide ligand (Scheme 2.25).[35]



Scheme 2.25. *Example of Ti-catalyzed PKR*

Late transition metals were also introduced more recently. After the first reports by Murai and Mitsudo, in 1997, ruthenium complexes have been used by Itami and Yoshida. In their work, they remarkably contributed to the expansion of the scope of the intermolecular PKR. The strategy consists of using olefins bearing a pyridyl silyl group, which is readily removed after the reaction. These α or β substituted vinylsilanes are easily obtained from alkynes. The pyridyl group directs the PKR by a possible coordination of the nitrogen with the metal, which accelerates the process and gives complete regioselectivity. The directing group is eliminated in the reaction, giving rise directly to four- and/or five- substituted cyclopentenones. This avoids the use of ethylene or strained olefins in the intermolecular PKR and is a way to solve the problem of the regioselectivity with unsymmetrical olefins (Scheme 2.26).[36]



Scheme 2.26. *Example of Ru-catalyzed PKR*

On the other hand, Adrio and Carretero showed that the solvated molybdenum complex $Mo(DMF)_3(CO)_3$ catalyzed intramolecular PKRs with monosubstituted olefins, as well as electron-poor olefins.[37]

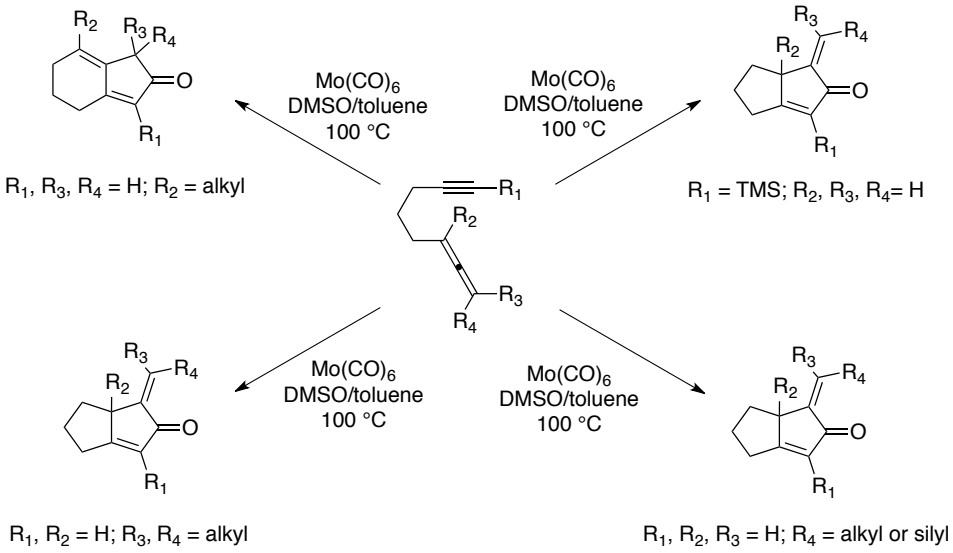
Finally, tungsten, iron and palladium complexes have also been reported to catalyze the PKR.[38]

2.1.6. Pauson–Khand reaction with allenes

Most Pauson-Khand reactions have been conducted with an alkene, an alkyne and gaseous CO. However, PKRs have been also developed with allenynes as shown in Scheme 2.27.

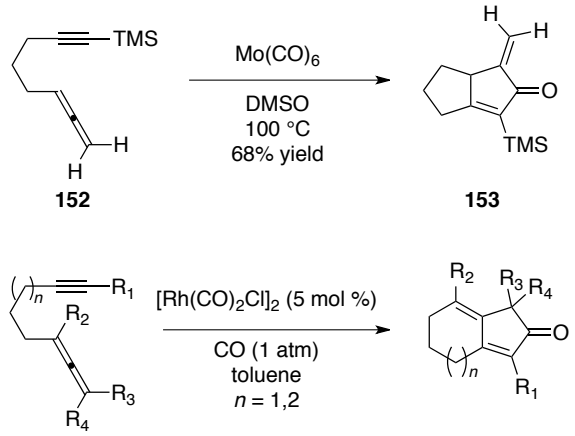
Narasaka reported the first example of an intramolecular allenyne PKR, catalyzed by an iron complex,[39] while Brummond and co-workers have extensively studied the allenic Pauson-Khand reaction catalyzed either by the combination of $Mo(CO)_6$ and DMSO or by $[Rh(CO)_2Cl]_2$ (Scheme 2.27).[40]

Interestingly, Mo- and Rh-catalyzed Pauson–Khand-type reactions showed different regioselectivities in allenyne cyclization (Scheme 2.28).



Scheme 2.27 *Pauson–Khand reaction with allenes*

Computational studies indicate that different geometries of octahedral Mo(0) and square-planar Rh(I) species account for the different regioselectivities.[41]

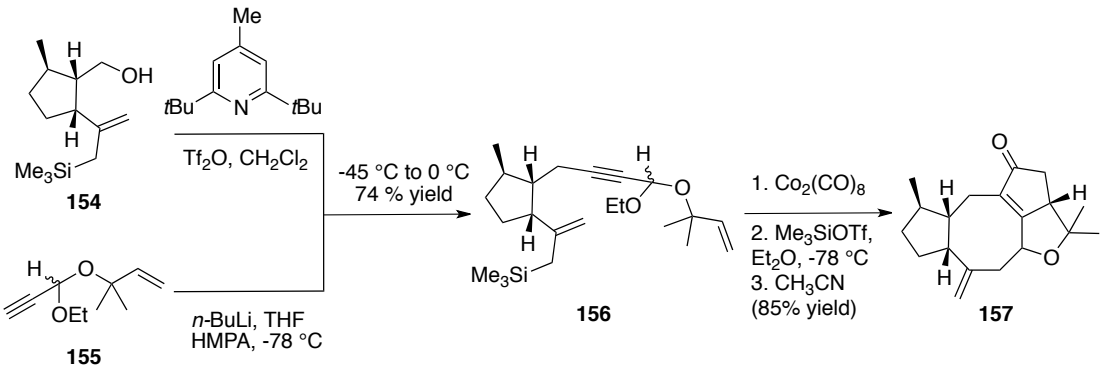


Scheme 2.28. *Different regioselectivities in allenyne cyclization*

2.1.7. Application of the PKR to natural product synthesis

The cyclopentane ring is quite common in nature and the PK adducts are easily functionalized. For these reasons, in the last few years there has been a permanent increase in the use of the PKR for the synthesis of natural products, even if a great number of applications still involve the stoichiometric version of this carbonylation process.

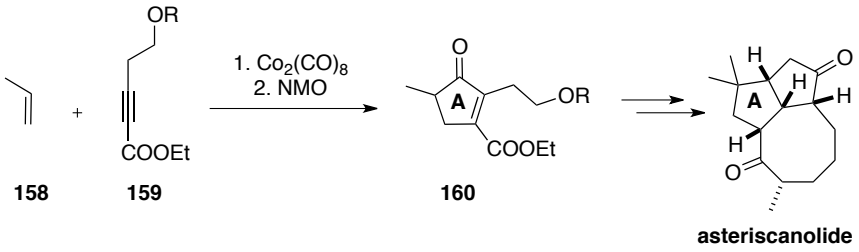
One of the most cited examples of the use of the PKR in a natural product synthesis is the construction of (+)-epoxydictimene reported by Schreiber and shown in Scheme 2.29.[42]



Scheme 2.29. *Synthesis of (+)-epoxydictimene via PKR*

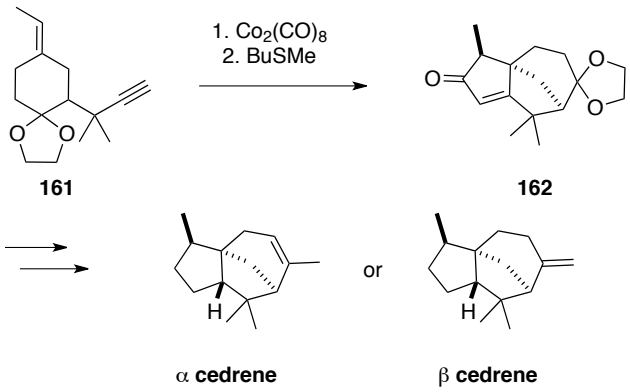
After synthetizing the enyne precursor **156**, this compound was allowed to react with $Co_2(CO)_8$ to form the dicobalt-akyne complex. The Nicolas reaction was then used to form a fused 5,8-ring system, which, in turn, was converted into the desired policyclic product **157** by a stoichiometric intramolecular PKR.

In a different example, Krafft reported the total synthesis of asteriscanolide, a sesquiterpene structurally related to epoxidictimene. This synthesis is based on a regioselective intermolecular PKR with propene. The formation of the cyclooctane ring is accomplished in the final stages by means of a ring closing metathesis reaction (Scheme 2.30).[43]



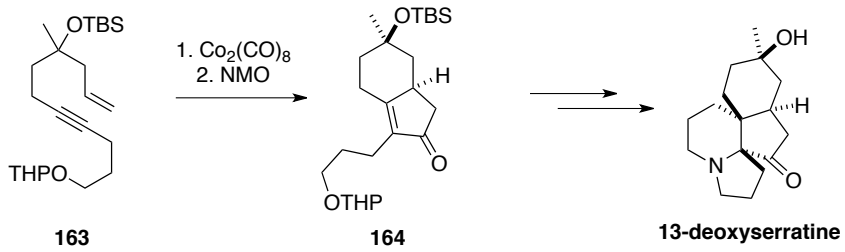
Scheme 2.30. *Synthesis of asteriscanolide via PKR*

An intermolecular PKR was also used as a key step for the synthesis of the cedrene skeleton. The starting material was a monocyclic enyne with an exocyclic olefin fragment. A bridged adduct was obtained in high yield and was further manipulated to provide a total synthesis of α- and β-cedrene (Scheme 2.31).[44]



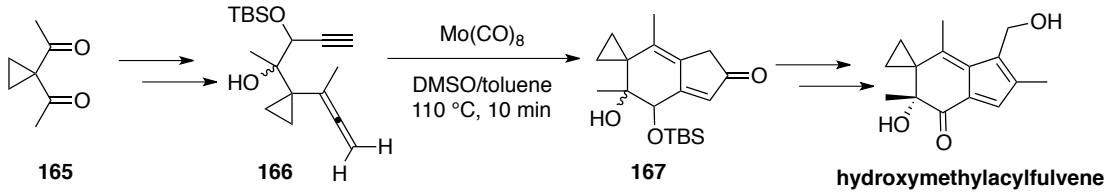
Scheme 2.31. *Synthesis of the cedrene skeleton via PKR*

Zard reported a total synthesis of 13-deoxyserratine, a lycopodium alkaloid with high structural complexity, in only 10 steps and 12% overall yield. The key steps in this synthesis were a highly diastereoselective PKR to obtain compound **164** and a radical cyclisation cascade (Scheme 2.32).[45]



Scheme 2.32. *Synthesis of 13-deoxyserratine via PKR*

An example of the allenic PKR in complex molecule synthesis, reported by Brummond, is shown in Scheme 2.33. The allenyne precursor **166** was synthetized in five steps starting from 1,1-diacetylcyclopropane. Treatment of this compound with $Mo(CO)_6$ and DMSO in toluene at 100 °C originated the desired product **167** containing a 6,5-fused ring system. This material was then carried forward to prepare the hydroxymethylacylfulvene natural product.



Scheme 2.33. *Synthesis of hydroxymethylacylfulvene via PKR*

New manuscripts adding to the application of the Pauson-Khand reaction to natural products synthesis are being published at a rapid rate attesting of its interest in the chemical community. With the development of new catalytic and asymmetric methodologies, in the next future the PKR will continue to occupy a prominent place within the pantheon of synthetic reactions.

2.2. RESULTS AND DISCUSSION

Diversity-oriented synthesis (DOS) is an emerging field involving the preparation of combinatorial libraries of diverse small molecules for biological screening. Rather than being directed toward a single biological target, DOS libraries can be exploited to identify new molecules for a variety of targets.

DOS can be achieved by using several different strategies. In particular, divergent reaction pathways are a very efficient technique to obtain diverse molecular frameworks. Indeed, skeletal diversity is generated by using different reagents to change a common substrate into a collection of products having varied molecular skeletons. In this field, the versatility of polyunsaturated systems such as dienes, diynes and, most of all, enynes is an interesting feature to get different functional group interconversions and to synthetize a variety of highly complex molecules.

Recently, we become interested in the application of the acyclic enyne precursors, previously engaged in RCEYM to form cyclic dienes (Chapter 1), to the construction of bicyclic skeletons *via* catalytic Pauson-Khand reactions. The development of a new asymmetric version of the Co-catalyzed and Rh-catalyzed PKR is the final goal of our research in this field.

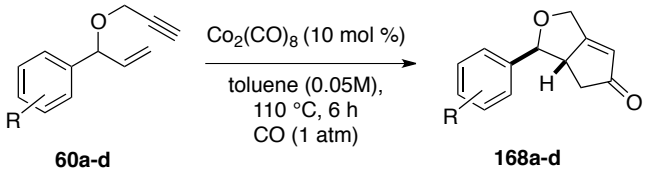
In this section, preliminary results are reported, concerning the synthesis of racemic oxygen-containing bicyclic compounds and first attempts to achieve asymmetric Co-catalyzed PKRs.

2.2.1. Racemic PKR with acyclic enyne ethers

While RCEYM of enyne-ethers resulted to be a particularly efficient method to access dihydrofurans and dihydropyrans (Chapter 1), Co-catalyzed Pauson-Khand reaction allowed the access to oxygen-containing bicyclic compounds of different size.

Indeed, previously synthetized enynes **60a, 60b** and **60d** (Chapter 1) underwent the carbonylation reaction in toluene, at 110 °C for 6h, using 10 mol % of $Co_2(CO)_8$ as catalyst under CO atmosphere (1 atm). Under these conditions the desired 5,5-fused bicyclic compounds **168a, 168b** and **168d** were isolated in moderate yields after purification over silica gel chromatography (Table 2.2, entries 1-4). Unfortunately, no improvement in yield could be observed while employing NMO as promoter of the reaction (Table 2.2, entry 2).

The low conversion of PK products mostly depends upon the formation of stable complexes between the cobalt catalyst and the enyne precursors, which could be detected in the reaction mixture.



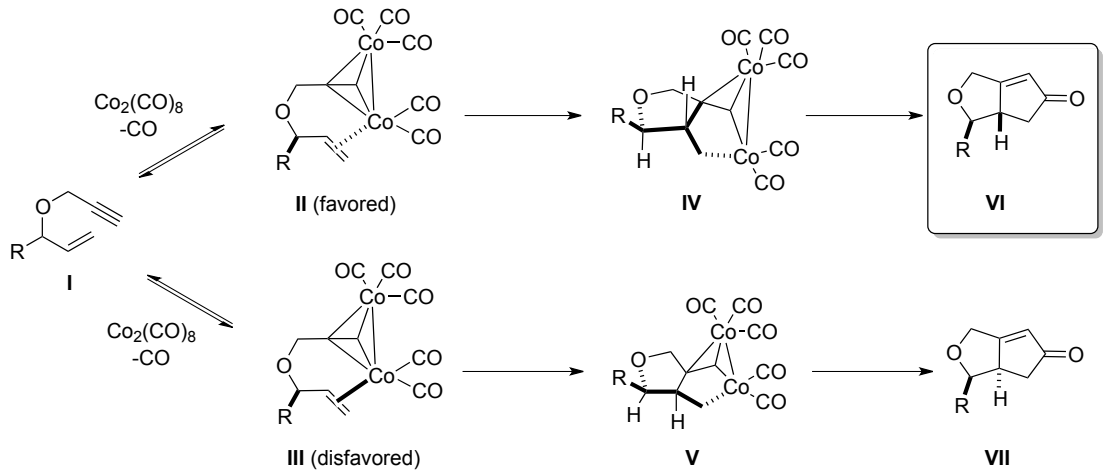
60a-d **168a-d**

Entry	R	Reactant	Promoter	Product	Yield (%)
1	4-OCH_2O	**60a**	/	**168a**	51
2	4-OCH_2O	**60a**	**NMO**	**168a**	53
3	4-OCH_3	**60b**	/	**168b**	55
4	4-Cl	**60d**	/	**168d**	49

Table 2.2. *Synthesis of bicyclic compounds* ***168a-d***

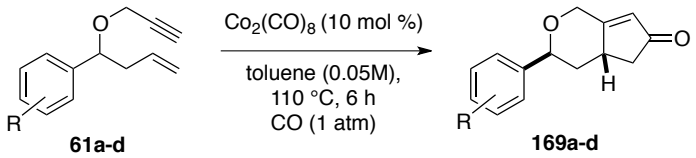
All bicyclic compounds were isolated as single diastereomer. The relative configuration of the major isomer was established by NMR (NOE), which confirmed the *cis*-relationship of the bridgehead proton with the phenyl group.

The origin of stereocontrol could be rationalized by invoking a facial selective metal binding, which was envisioned to originate from steric demands imposed by the substituent at the stereogenic center of the starting material.[46] Indeed, the diastereoselectivity in the Co-catalyzed Pauson- Khand annulation is consistent with the mechanistic hypothesis outlined in Scheme 2.34. Initial complexation of the enyne **I** presumably results in a mixture of diastereomeric complexes (**II**/**III**), where the relative population is influenced by the size of the substituent. Insertion of the metal then leads to the irreversible formation of the diastereomeric metallacycles **IV**/**V**, which are poised to undergo migratory insertion of metal bound carbon monoxide, followed by reductive elimination to afford bicyclic adducts **VI**/**VII**.



Scheme 2.34. *Mechanistic hypothesis for the diastereoselective Co-catalyzed PKR*

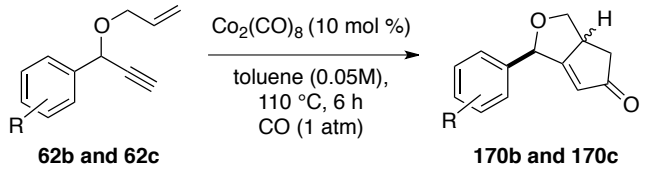
In an analogous manner, 1,7-enynes **61a-d** underwent the cyclization under the standard condition as well, giving rise to the diastereomerically pure products **169a-d** (Table 2.3, entries 1-3). In this case, however, the desired 6,5-fused bicyclic products could be isolated only in low yields. Satisfactory, PKRs of both 1,6- and 1,7-enynes tolerated either electron-withdrawing groups (EWG) or electron-donating groups (EDG) on the aromatic ring of the starting materials.



Entry	R	Reactant	Product	Yield (%)
1	4-OCH_2O	**61a**	**169a**	31
2	4-OCH_3	**61b**	**169b**	36
3	2-I	**61c**	**169c**	39
4	4-Cl	**61d**	**169d**	36

Table 2.3. *Synthesis of bicyclic compounds* ***169a-d***

Prompted by these results, precursors **62b** and **62c** were also employed as intermediates in the synthesis of Pauson-Khand derivatives. In this case, however, products **170b** and **170c** were obtained in low yield, as 1:1 mixtures of inseparable diastereomers (Table 2.4, entries 1 and 2).

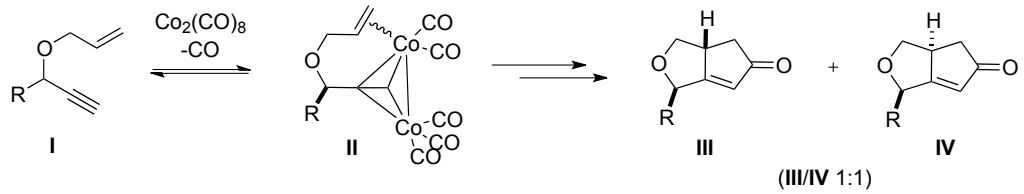


Entry	R	Reactant	Product	Yield (%)
1	4-OCH_3	**62b**	**170b**	31
2	2-I	**62c**	**170c**	44

Table 2.4. *Synthesis of bicyclic compounds* ***170b*** *and* ***170c***

This behavior could be explained considering the relative position of the aromatic substituent and the double bond in the PKR precursor. Indeed, the aromatic substituent is not close

enough to the olefin moiety to achieve facially selective metal binding, which results in the complete loss of the stereocontrol of the carbonylation process (Scheme 2.35).



Scheme 2.35. *Mechanistic hypothesis for the stereouncontrolled Co-catalyzed PKR*

2.2.2. Development of new protocols for enantioselective PKRs

2.2.2.1. Electronic and steric effects of chiral biheteroaromatic diphosphine ligands

After the determination of suitable conditions for the racemic Co-catalyzed PKR of enyne-ethers, we turned our attention to the development of new protocols for enantioselective carbonylation reactions.

In collaboration with Prof. Sannicolò and co-workers (Università degli Studi di Milano), we first envisaged to examine the electronic and steric effects of chiral biheteroaromatic diphosphine ligands on the Co-catalyzed PKR. In particular, we intended to delve into any potential relation between enantioselectivity and electronic density on the phosphorus ligand employed.

Previous literature reports[28] showed a clear tendency: for electron-rich ligands, the electron-richer the alkyne, the better enantioselectivities (but the lower yields); for electron-poor ligands, the more electron-deficient the enyne system, the higher enantioselectivities (almost no influence on the yield).

In 1996, Sannicolò and co-workers presented diverse five-membered biheteroaromatic diphosphines, a new class of chiral atropoisomeric diphosphine schematically represented by the general structure **I** (Figure 2.4).[47]

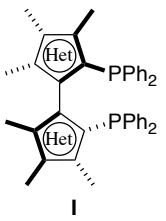


Figure 2.4. *General structure of five-membered biheteroaromatic diphosphines*

Compared with classical carbocyclic biaryls, the design of biheteroaromatic systems leads to the following structural and synthetic advantages.

(1) The electron-donor properties of the phosphorus atoms, a crucial parameter for catalytic activity, can be tuned by changing the supporting heterocyclic system. In fact, it is well known that aromatic five-membered heterocycles range from very electron-rich systems, like pyrrole, furan, and thiophene, to very electron-poor rings, like thiazole and triazole.[48] Alternatively, the electronic properties of the phosphinyl groups can be modulated by changing their positions on a given heterocycle.

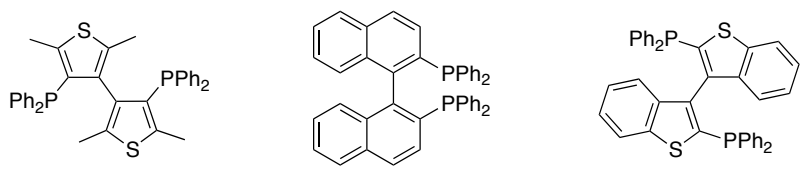
(2) A properly substituted biheteroaryl system can easily satisfy both symmetry and configurational stability requirements, since atropisomeric biaryls with C_2 symmetry are recognized among the most efficient ligands for many transition metal-catalyzed stereoselective reactions.

(3) The geometry associated with two interconnected five-membered rings is new, and it was interesting to compare it with the data reported in literature for known biaryl systems, all derived from the connection of two six-membered rings. Furthermore, the geometry of the chelated ring in the complexes should depend on the nature of the heterocycle, since it is well documented that each heteroaromatic system shows typical internal angles and external bond directions.

(4) The synthetic approaches to substituted pentatomic heteroaromatic rings are more flexible than those available for carbocyclic aromatic systems. The easy and regioselective metalation of heteroaromatic pentatomic rings[49] can be a very helpful tool in introducing the phosphine functions, as well as in forming the interanular bond.

In Figure 2.5, two selected biheteroaromatic diphosphine ligands, available in an enantiopure form, are reported each one associated with its own acronym and oxidative potential value, $E°_p$ (V) (BINAP was chosen as ligand reference).

As a matter of fact, Sannicolò and co-workers found this parameter, determined by voltammetry, to be a very significant probe of the electronic availability at the phosphorus atom in these compounds: the higher its value, the electron-poorer the phosphine.[50]



tetraMe-BITIOP — $E°_p$ = 0.57 V *vs* Ag/Ag$^+$

BINAP — $E°_p$ = 0,63 V *vs* Ag/Ag$^+$

BITIANP — $E°_p$ = 0,83 V *vs* Ag/Ag$^+$

Figure 2.5. *Structures of* ***tetraMe-BITIOP*** *and* ***BITIANP*** *ligands*

Experimental determinations of the oxidative potential value $E°_p$ were performed in an approximately 0.5×10^{-3}M acetonitrile solution, on a platinum anode, in the presence of 0.1M tetraethylammonium perchlorate as supporting electrolyte, under nitrogen at 25 °C.

The exemplificative cyclic voltammogram (0.1 V s^{-1}) reported in Figure 2.6 shows a single irreversible process, corresponding to the oxidation of the phosphinyl groups.

Oxidative potential increases along the series in the following order: tetraMe-BITIOP ($E°_p$ 0.57 V), BINAP ($E°_p$ 0.63 V), BITIANP ($E°_p$ 0.83 V). This order is in accordance with the expected decrease in the electronic availability of the supporting heterocycle and with a decrease in the electronic density of the position in which the diphenylphosphinyl group is carried.

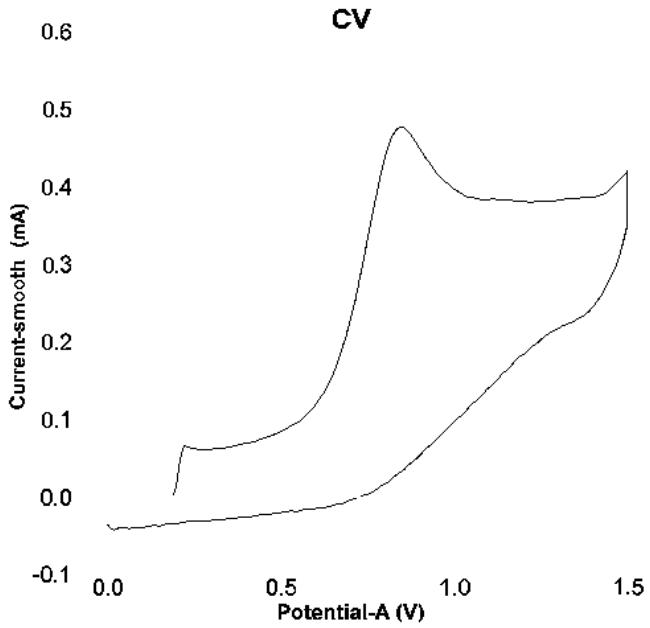


Figure 2.6. *Cyclic voltammogram of* ***BITIANP*** *ligand*

The quantification of steric properties of atropisomeric diphosphines is conveniently achieved by measuring the dihedral angle θ of the biaryl backbone. Although the biaryl moiety is a flexible backbone, allowing atropisomeric ligands to adapt their geometrical structure to the coordination sphere of the metal, the relative order of θ for tetraMe-BITIOP, BINAP and BITIANP is independent from the type of molecular structure containing the diphosphine (free ligand, Co or other metal complexes). For this reason, indicative values of the dihedral angles θ were conveniently determined by X-ray diffraction performed on diphosphine-$PdCl_2$ derivatives (Table 2.5).

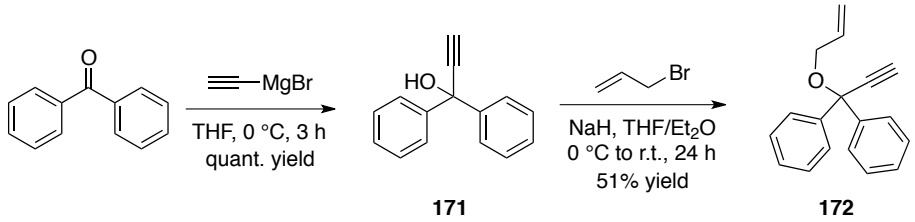
Entry	L*	P-Pd-P angle (bite, °)	Dihedral angle (q, °)
1	BINAP	92.7	60.8
2	tetraMe-BITIOP	92.0	68.4
3	BITIANP	93.1	62.6

Table 2.5. *P-Pd-P and dihedral angles θ in Pd-complexes*

Previous literature reports indicated that ligands characterized by narrow dihedral angle give improved reactivity and enantioselectivity for most PKR precursors.[28]

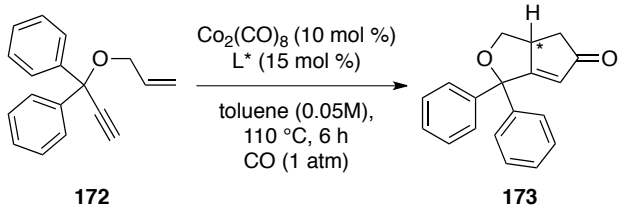
2.2.2.2. Asymmetric Co-catalyzed PKR with acyclic enyne ethers

To avoid any diastereoselection problem while testing tetraMe-BITIOP and BITIANP activity in Co-catalyzed PKR reactions, compound **172**, showing two phenyl groups at the C-2, was synthetized and chosen as model substrate. Thus, a two-step process, which involves an addition of ethynyl Grignard reagents to acetophenone and a subsequent Williamson etherification of the resulting tertiary alcohol, resulted in the formation of PKR 1,6 enyne **172** in 51% overall yield (Scheme 2.36).



Scheme 2.36. *Synthesis of PKR precursor **172***

Unfortunately, preliminary results indicated that tetraMe-BITIOP and BITIANP are not suitable ligands for the development of an enantioselective version of the Co-catalyzed PKR starting from enyne-ethers. Indeed, while running carbonylations in toluene, at 110 °C, using 10 mol% of $Co_2(CO)_8$, 10 mol % of chiral ligand and an ambient pressure of carbon monoxide, only racemic product **173** could be isolated in moderate yields (Table 2.6, entries 2-4).



Entry	L*	Yield (%)	*ee* (%)
1	/	36	0
2	BINAP	29	12
3	tetraMe-BITIOP	26	0
4	BITIANP	26	0

Table 2.6. *Asymmetric Co-catalyzed PKR*

Despite the last displeasing results, tetraMe-BITIOP and BITIANP resulted to be very successful ligands for enantioselective Rh-catalyzed hydogenations of prostereogenic functionalized ketonic and olefinic double bonds.[51] For this reason, the application of chiral biheteroaromatic diphosphine ligands in Rh-catalyzed PKR is currently under investigation in our laboratory.

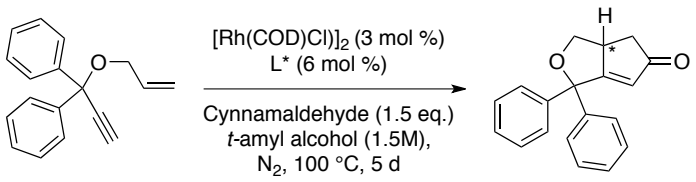
2.3. CONCLUSIONS AND FUTURE DEVELOPMENTS

There are really few organic transformations that add so much molecular complexity in one step as the Pauson–Khand reaction. The process yields cyclopentenones, which can be easily transformed into different functionalised cyclopentanes, present in the structure of many natural products. This reaction had its main drawback in the limited scope, low yields and lack of efficient catalytic procedures. The intramolecular PKR is now successfully used to obtain five-, six- and sometimes seven-membered rings. Disubstituted and electronically poor olefin fragments are frequently reactive and allenes act efficiently as the olefinic part. The intermolecular version is still quite limited, as unstrained olefins scarcely react, but the use of traceless tethers or directing groups like pyridyl silyl have circumvented this problem, also avoiding the formation of regioisomeric mixtures. There are a wide variety of catalytic protocols available to effect this reaction, some of them under mild conditions. Nevertheless the catalytic PKR is not a completely solved problem.

We have applied PKRs to the synthesis of oxygen-containing 5,5- and 6,5- bicyclic compounds. Electron poor and electron rich 1,*n*-enynes were employed in Co-catalyzed carbonylation reactions with almost no influence in terms of yield and ease of isolation. The relative position of the aromatic substituent and the alkene moiety of the starting material was found to play a crucial role in the control of the stereo-outcome of the reaction.

In collaboration with Sannicolò and co-workers (University of Milan), we also examined the activity of chiral biheteroaromatic diphosphine ligands in the Co-catalyzed PKR. TetraMe-BITIOP and BITIANP, however, turned out to be unsuitable ligands for the development of an enantioselective version of the Co-catalyzed PKR starting from enyne-ethers.

In the next future we will apply biheteroaromatic diphosphine ligands in enantioselective Rh-catalyzed PKR, with the aim to evaluate any eventual relation between the enantioselectivity and the electronic density on the phosphorus ligand employed. In this direction, encouraging preliminary results have been obtained while submitting substrate **172** to Chan's reaction conditions (Table 2.7, entries 1-3).[52]



172 **173**

Entry	L*	Yield (%)	*ee* (%)
2	BINAP	37	74
3	tetraMe-BITIOP	35	51
4	BITIANP	36	72

Table 2.2. *Asymmetric Rh-catalyzed PKR*

The optimization of the Rh-catalyzed PKR, as well as the screening of diverse catalysts and chiral biheteroaromatic diphosphine ligands, are currently under investigation and will be reported in due course.

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Chapter 3

Transition metal-catalyzed electrophilic activation of alkynes

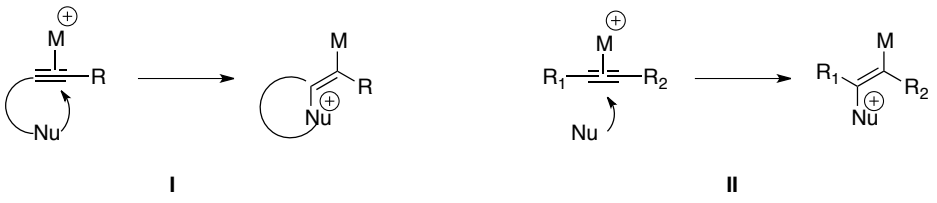
Synthesis of oxabicycle[2.2.1]heptanes and azabicycle[4.1.0.]heptenes

3.1. INTRODUCTION

The transition metal-catalyzed electrophilic activation of alkynes toward a variety of nucleophiles is among the most important strategies for the synthesis of cyclic and acyclic scaffolds, useful to obtain natural and non-natural products.[1] The significance of this process stems from the rapid increase in structural complexity starting from relatively simple acyclic subunits. Moreover, the reactions usually require mild conditions to generate products with excellent chemoselectivity and high synthetic efficiency.

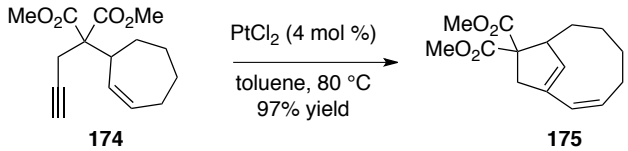
Among a range of transition metal complexes capable of alkyne activation, Pt and Au (gold(III) and cationic gold(I)) have shown an exceptional ability to promote a variety of organic transformations, delivering a diverse array of cyclic products.[2]

These processes result from the π-Lewis acidic properties of platinum and gold complexes. Indeed, the alkynophilic character of these soft metals and the π-acid activation of unsaturated groups promote the intra- (**I**) or intermolecular (**II**) attack of a nucleophile (Scheme 3.1).



Scheme 3.1. *Simplified nucleophilic attack on the M^+-activated alkyne*

The pioneering efforts in this area in the early 1990s utilized simple metal salts,[3] such as halides ($PtCl_2$ and $AuCl_3$, Scheme 3.2).



Scheme 3.2. *A pioneering example of platinum-catalyzed cycloisomerization*

Because the activation process invokes electrophilicity enhancement, a move toward cationic metal templates, which may be stabilized by a suitable spectator ligand, then resulted in increased activity. Indeed, Au(I) cationic species, such as Echavarren's and Gagosz's catalysts (Figure 3.1) recently proved to be versatile catalysts for both carbon-carbon and carbon-heteroatom bond formations.

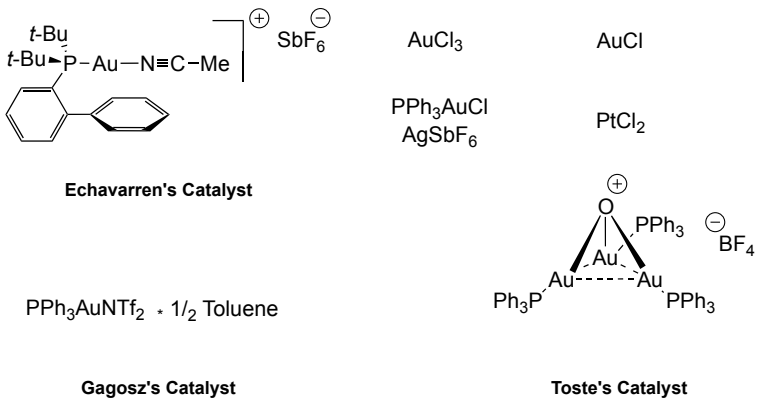


Figure 3.1. *Pt- and Au-based complexes commonly use for the electrophilic activation of alkynes*

Platinum- and gold-catalyzed reactions have many advantageous qualities: they are operationally safe, simple, and practical to perform, even if they generally require inert reaction conditions.[4] Moreover, they exhibit excellent chemoselectivity towards C-C π systems, thus leaving a diverse range of other functional groups untouched.

The ability to transform simple and robust units obviates the handling of highly reactive groups and therefore simplifies the wider synthetic routes that can employ this approach. These beneficial properties impart step-economy in the context of target-oriented synthesis.[5]

In this chapter we present the diverse range of transformations that have resulted from the π-acid activation of alkynes by grouping them according to the nucleophilic component of the reaction. Furthermore, since the catalytic activation of π systems toward nucleophiles have started to be used in the syntheses of natural products, representative examples are also discussed in the following sections.

3.1.1. Structural aspects of "π-acidity" and "alkynophilicity"

Any metal fragment that binds to a carbon–carbon multiple bond, and thereby deprives it of part of its electron density, could be defined as a "π acid".

The bonding situation in transition-metal complexes with alkynes as π ligands is usually discussed within the framework of the Dewar–Chatt–Duncanson (DCD) model,[6] which considers the bond as a donor–acceptor interaction between two closed-shell fragments.[7]

In general the DCD model assumes that a σ bond is formed by overlap of the π system of the ligand with an empty metal orbital of suitable symmetry. A π-interaction then results through back-donation of electron density from a filled metal d orbitals into an antibonding π* orbital

of the alkene or alkyne. This interpretation was rapidly accepted by the scientific community after its introduction in the early 1950s,[6] and most of the subsequent debate has been devoted to appraise the relative magnitudes of the synergistic σ and π interactions, as well as the choice of metal orbitals employed in bonding. In such a discussion, however, one must not overlook the electrostatic interactions that also come into play between a ligand and metal template. In fact, computational analyses for $[M^+(C_2H_4)]$ and $[M^+(C_2H_2)]$ (M = Cu, Ag, Au) at very advanced levels of theory indicate that approximately half of the total bonding force is actually electrostatic in nature.[8]

There are four principle components that can contribute to the bonding of alkynes as ligands (Figure 3.2). The in-plane π∥ orbitals are responsible for a σ-symmetric M←L donation as well as for the π-symmetric M→L back-donation referred to above. The orthogonal, out-of-plane π⊥ orbitals can engage in M←L π donation (an interaction of importance in alkyne complexes in which the ligand serves as a four-electron donor), while mixing of an occupied d orbital of the metal and the empty π*⊥ orbital of the alkyne can result in an additional component of M→L back-donation. This latter interaction, however, has δ symmetry, which results in only a weak overlap, and therefore leads to a minute contribution to the bonding.

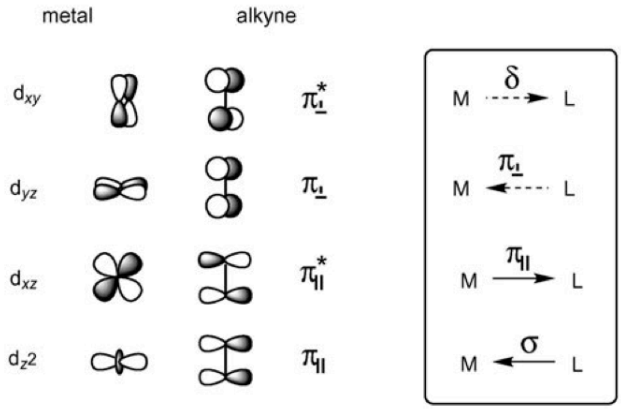


Figure 3.2. *Qualitative orbital diagram of the interaction between transition metals and alkynes*

This qualitative picture applies well to the d^8-platinum and d^{10}-gold complexes. The contributions of the individual terms have been analyzed in a more quantitative fashion by using high-level computational methods. For the parent Au^+–acetylene complex $[Au^+(C_2H_2)]$, the σ interaction accounts for the largest contribution to the orbital term (ca. 65 %), followed by the in-plane π∥ back-donation (ca. 27 %), whereas the effect of the orthogonal π⊥ term is small (ca. 7%) and that of the d bond can be ignored (ca. 1 %). Thus, one may conclude that alkynes are strong two-electron σ donors but fairly weak π acceptors toward Au(I) (as well as Pt(II)), although some back-donation does occur and cannot be neglected.[9] Structural

characteristics of representative metal-alkyne complexes resulted in line with theoretical predictions.[10]

Worthy of note, high-level computational studies of the bonding situation in Au^+–alkyne complexes showed that ethylene is a slightly better σ donor than acetylene.[8] Hence it is unlikely that this cation will distinguish between the different π systems of polyunsaturated substrates, such as enynes, to any appreciable extent, and even if it does, will rather disfavor the alkyne unit. The high selectivity observed in many of the Au(I)- and Pt(II)-catalyzed processes, which are usually triggered at the alkyne site, is therefore supposedly kinetic in origin. In other words, the pronounced "alkynophilicity" of the late-transition-metal catalysts likely reflects the preference of the incoming nucleophile for attack at the coordinated triple bond.

3.1.2. Reactivity of π-acidic systems

Numerous electrophiles other than Pt(II) and Au(I) fall under the definition of "π acids" given above. However, complexation and activation of a multiple bond constitutes just the very first step of a (catalytic) chemical transformation.

At first sight, the isolobal relationship between H^+ and LAu^+, as well as a certain analogy in their chemical behavior, may suggest that noble metal templates should be viewed merely as expensive equivalents of a proton with increased carbophilic character. This simplistic view, however, misses some of the most intriguing properties of these catalysts that are evident from high-level computational studies together with clear-cut structural data.

Ab initio calculations of a large set of bare $[M{=}CH_2]^+$ entities have shown that carbenes of the 5d transition metals are distinguished by particularly high bond energies, which peak at Pt.[11] If seen within the framework of the Dewar–Chatt–Duncanson model, the overlap between a lone pair of electrons on a singlet methylene entity with an empty (hybrid) orbital on the metal has σ symmetry. This dative bond is counterbalanced by overlap of a metal d_{xz} orbital with the empty p_x orbital of the ligand to form the π bond (Figure 3.3). In other words, Au as well as Pt can engage in electron back-donation from the metal atom to a carbene ligand. It is important to recognize that this effect contrasts the reluctance of the very same metal templates to back-donate into the π* orbital of an alkyne (see above).

Hence, gold and platinum fragments activate a C-C triple bond toward nucleophilic attack yet are able to stabilize incipient "carbene intermediates"; other late 5d elements may also display a similar behavior.[11]

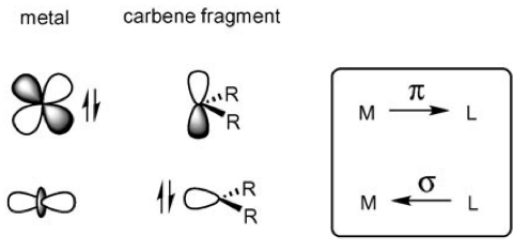
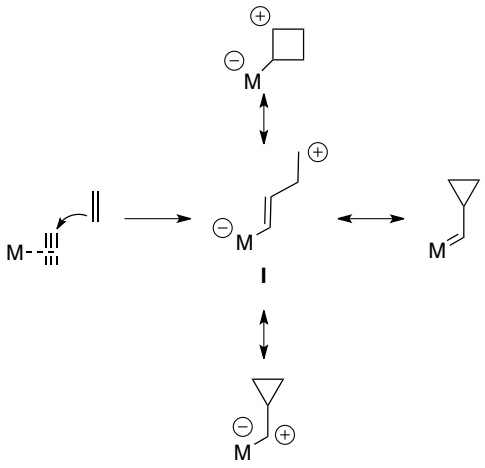


Figure 3.3. *Dominant orbital interactions in a Fischer-type carbene complex*

"Carbene" complexes have been invoked in many catalytic transformations effected by gold and platinum templates that were discovered during the last decade. If an alkyne unit activated by such a π acid is attacked, for example, by an alkene as the nucleophile, it formally evolves into a "carbene" substituted by a cyclopropyl group (Scheme 3.3).



Scheme 3.3. *Attack of an alkene onto an alkyne activated with a π-acidic metal template: formation of a metal–cyclopropyl carbenoid endowed with considerable "nonclassical" carbocation character.*

Two seemingly conflicting views have been used in the literature to interpret the behavior of these putative intermediates, depending on whether one prefers the "carbene" nomenclature or interprets reactive intermediates of this type as metal-stabilized cations.[12] In the latter case, the link to the "nonclassical" carbocation problem is immediately apparent, because the mesomeric extremes of a "cyclopropylmethyl", "homoallyl", or "cyclobutyl cation" form will apply.[13]

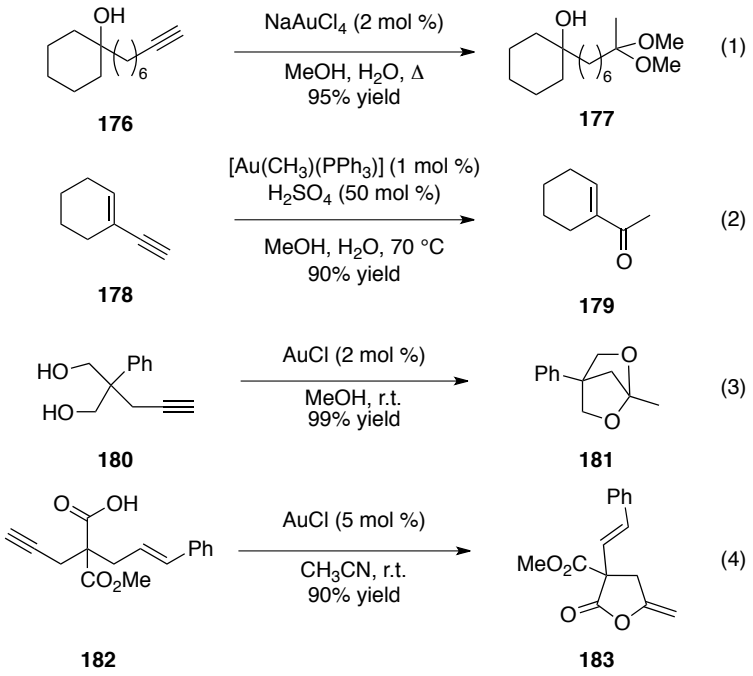
To the best of our knowledge, no such reactive species has been isolated and structurally characterized for M = Au or Pt, although analogous complexes are known for other metal fragments and have been thoroughly investigated.[13]

All the available data for the platinum and gold series suggest that a dogmatic approach to the

question of whether reactive intermediates of type **I** are "metal carbenes" or "metal-bound carbocations" is inappropriate. Even high-level computational studies do not provide an unambiguous answer, thereby leaving ample room for interpretation. Therefore, it is reasonable to assume that the purely cationic and the strict carbenoid descriptions are again nothing but the mesomeric extremes of a generic picture.[12] At the present level of understanding, one cannot help but conclude that such entities are "Janus-like" in character, and neither face can go without the other.

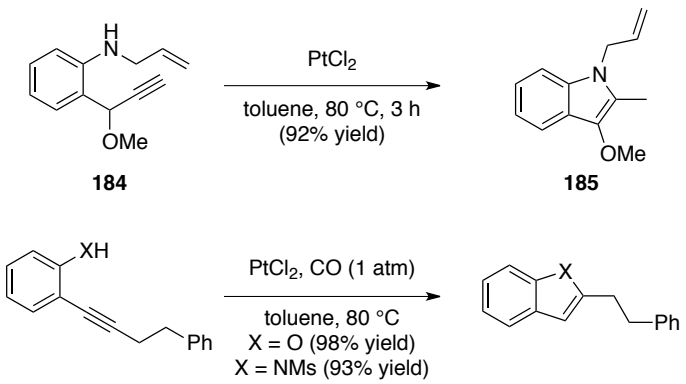
3.1.3. Heteroatom nucleophiles

The addition of heteroatoms to alkynes can be considered a direct way toward the synthesis of a wide variety of acyclic or cyclic molecules, according to the inter- or intramolecular mode of reaction, respectively. As the π system is only partially transformed during these reactions, valuable functional groups including ketones,[14] acetals,[15] enol ethers[16] or enol esters,[17] imines,[18] enamines, and enamides can be accessed (Scheme 3.4).



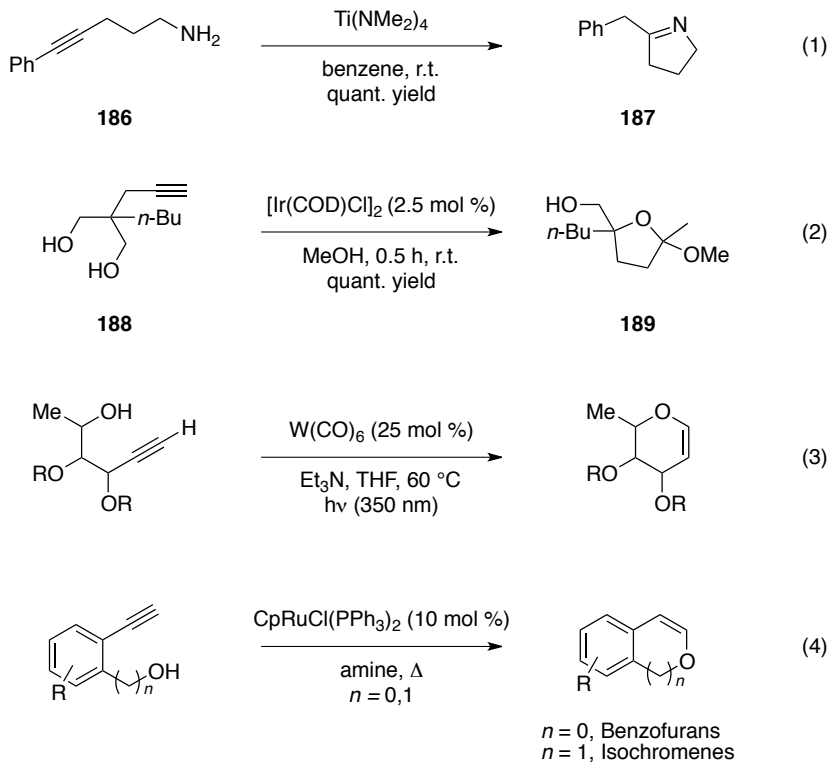
Scheme 3.4. *Intramolecular addition of heteroatoms to alkynes*

Moreover, intramolecular hydroaminations and hydroalkoxylations are readily amenable to the formation of heteroaromatic rings such as indoles and benzofurans, respectively (Scheme 3.5).[19] Low catalyst loadings are usually required to obtain near quantitative yields in many examples.



Scheme 3.5. *Platinum-catalyzed hydroamination and hydroxylation of alkynes*

Different transition metal complexes, other than Pt- and Au-speies, have been successfully employed to promote hydroaminations and hydroalkoxylations, but in this case higher catalyst loadings and the use of additives, such as bases,[20] are required to achieve quantitative conversions. Diverse products can be easily obtained depending upon the starting materials or the catalytic protocols employed (Scheme 3.6).[17,21]

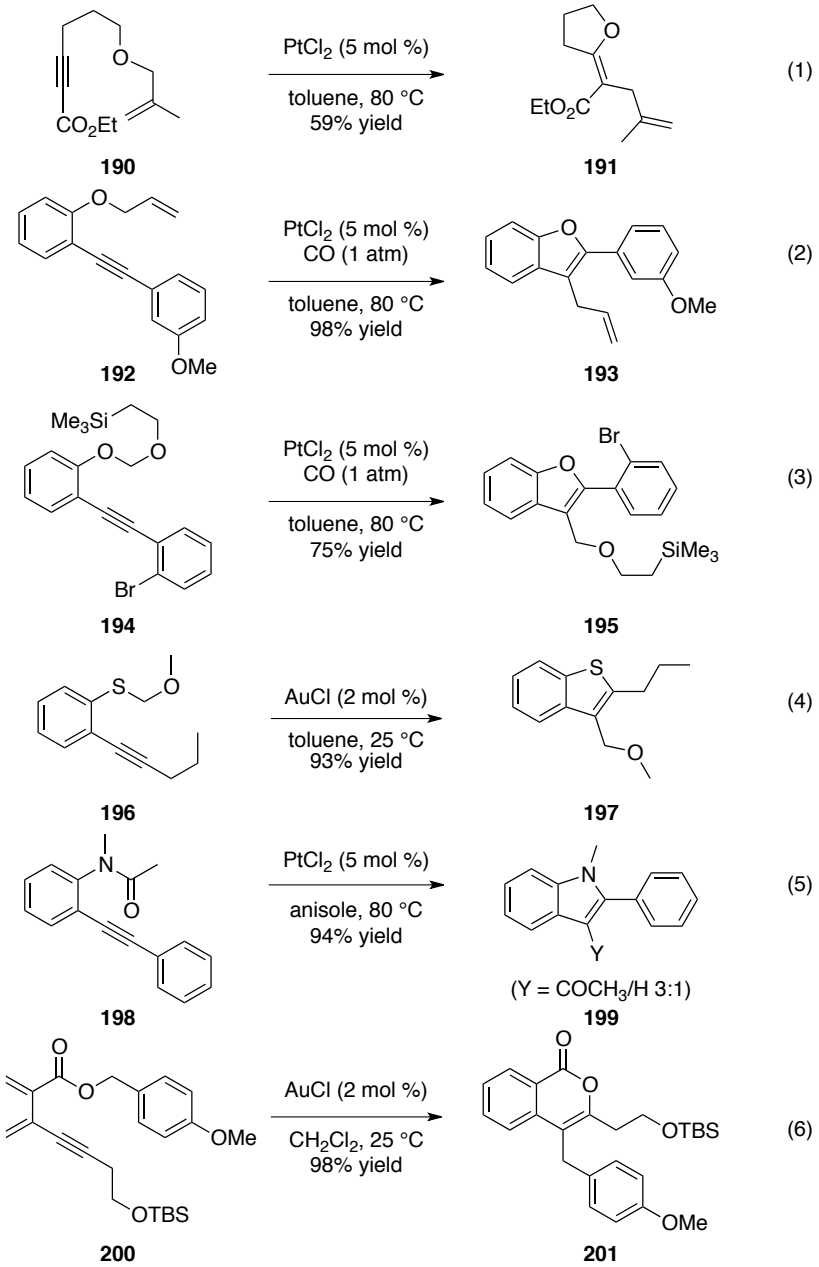


Scheme 3.6. *Transition metal-catalyzed hydroamination and hydroxylation of alkynes*

3.1.4. Carboalkoxylation Processes

Whilst the hydroamination and related reactions mimic classical π-activation chemistry, albeit with a vastly improved reaction profile, the use of nucleophiles with no proton attached demonstrates the further dimensions of these catalytic processes.

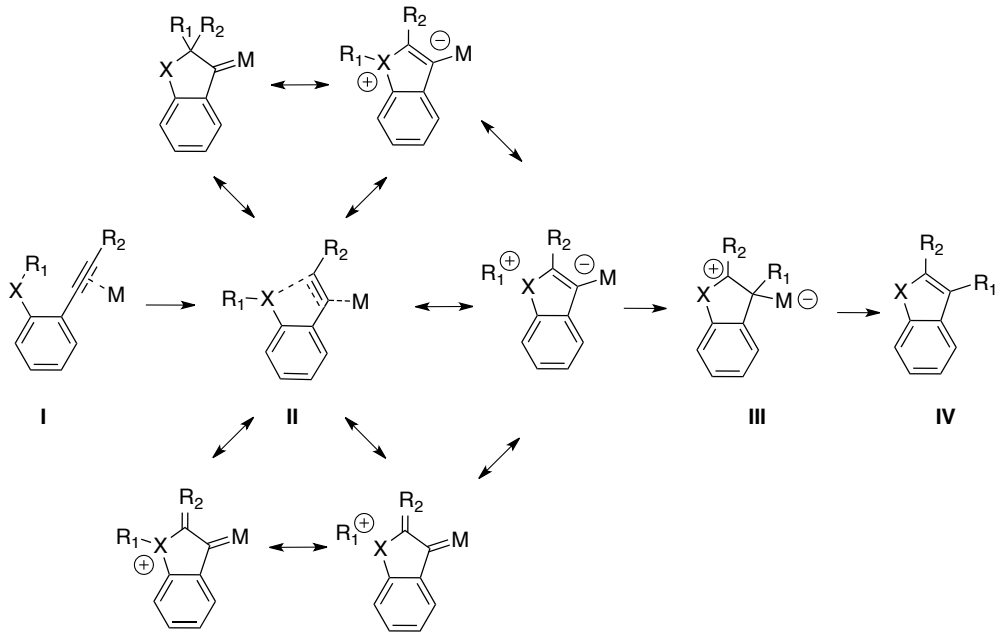
Mixed acetals and thioacetals, as well as allyl and benzyl ethers and amines, react with alkynes by this method, thus providing valuable heterocyclic scaffolds such as furans, benzofurans, benzothiophenes, indoles and cromanes (Scheme 3.7).[22]



Scheme 3.7. *Carboalkoxylation and carboamination of alkynes*

For maximum efficiency, the activity of the simple metal salts can be enhanced by the use of additives such as CO or olefins (cod, β-pinene, or benzoquinone).[23-25]

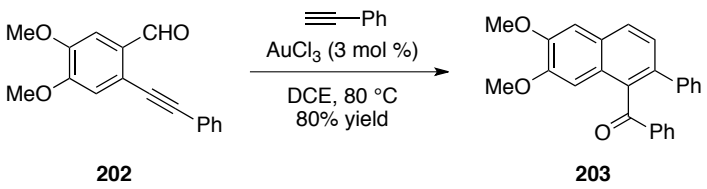
The proposed mechanistic scenario involves complexation of the nucleophilic heteroatom to the metal-activated alkyne to afford an onium intermediate (Scheme 3.8). Consequently, one of the heteroatom substituents transfers to the metalated position to effect an overall heteroatom-carbon shift. Although the mechanism for this carboalkoxylation process remains to be fully elucidated, it is the substituent that can best stabilize a developing positive charge that undergoes the shift.



Scheme 3.8. *Mechanism for the carboalkoxylation of alkynyl arenes*

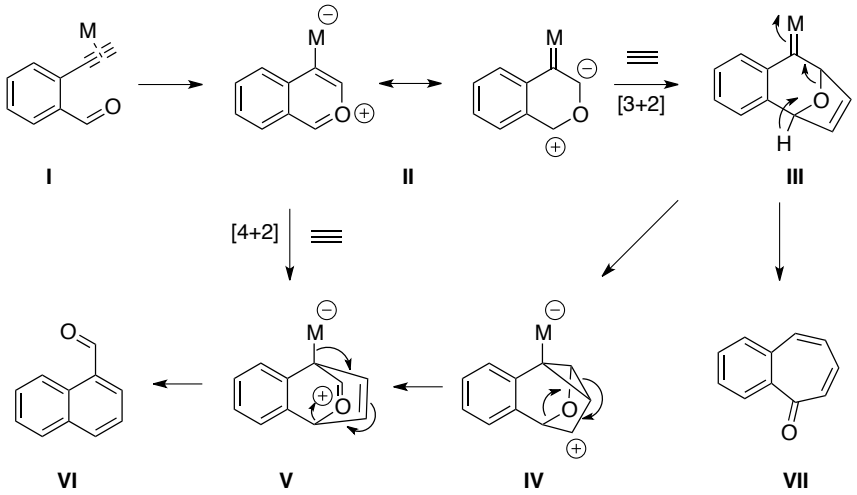
3.1.5. Platinum- and Gold-Catalyzed Cycloadditions

Whereas the previous examples have dealt with σ-bound nucleophiles, the use of π-bound systems (namely, carbonyl moieties) offers alternative reactivity. The further evolution of oxonium (iminium) species, generated from the nucleophilic attack of a carbonyl (imine) group onto a metal activated alkyne, makes this a powerful route to fused polycyclic materials (Scheme 3.9).



Scheme 3.9. *Benzannulation through a formal intermolecular [4+2] cycloaddition*

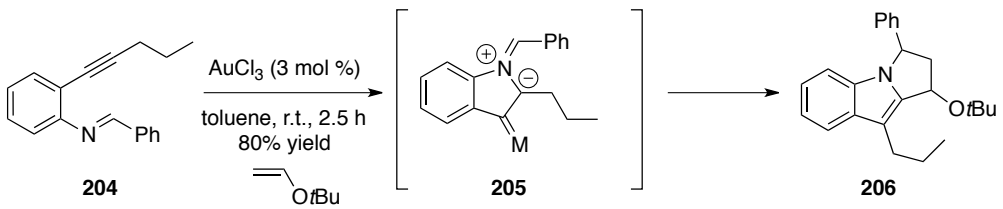
The coordination of the oxygen atom to the activated alkyne in substrates of type **I** affords a 1,3-dipole capable of reacting with an external or tethered alkyne unit to give benzannulated products after further rearrangement.[26] These processes were originally believed to proceed through a [4+2] mechanism, whereas recent theoretical calculations[27] suggest that a [3+2] cycloaddition with a subsequent rearrangement is more likely. However, experimental evidences suggest that the mechanistic outcome of the reaction might also be substrate- and catalyst-dependent.[28] Whatever the later stages of the mechanism, both routes arise from the same nucleophilic attack on an activated alkyne (Scheme 3.10).



Scheme 3.10. *[3+2] versus [4+2] mechanisms for nobel-metal-catalyzed benzannulation*

Computational studies showed that both Au(I) and Au(III) are equally capable of catalyzing this transformation, reiterating the equivalence of the formal cationic and carbene pathways.[27] Further mechanistic studies of such transformations is thus clearly desirable.

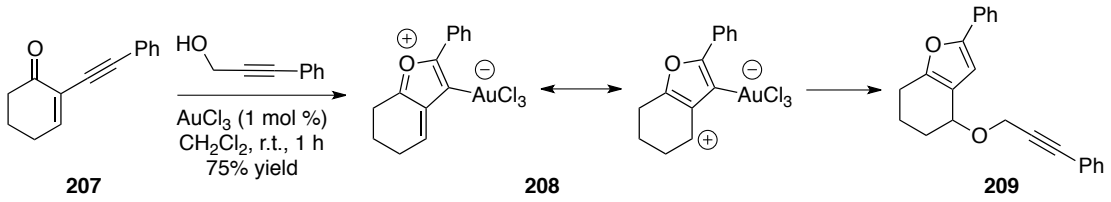
An interesting variation on the theme of [3+2] cycloaddition uses imines with inverse orientation relative to the alkyne. After activation with the catalyst, an azomethine ylide is generated which can be trapped with a suitable dipolarophile (Scheme 3.11).[29]



Scheme 3.11. *Cycloaddition via an azomethine ylide*

α-alkynyl enones also undergo transition-metal catalyzed reactions with a wide range of nucleophiles. The attack of the carbonyl unit onto the gold-activated alkyne generates a benzylic carbocation, which can be intercepted with various reagents such as alcohols, activated methylene compounds, and electron-rich arenes.

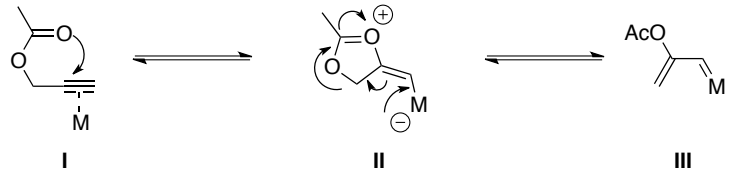
Overall, this process constitutes a highly flexible entry to polysubstituted furans (Scheme 3.12).[30]



Scheme 3.12. *Gold-catalyzed synthesis of furans*

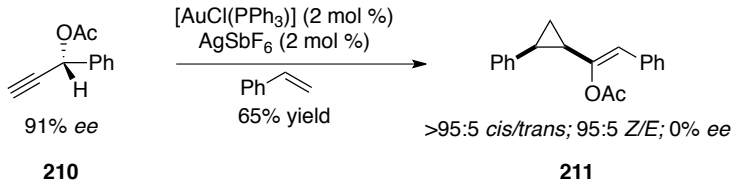
3.1.6. Reactions of Propargylic Carboxylates

A growing area concerns the use of propargylic carboxylates in catalytic processes. The carbonyl unit acts as a nucleophile onto the metal-activated alkyne; in doing so, its leaving-group ability at the incipient allylic position is enhanced to the extent that it is readily extruded on back-donation from the metal to the ligand. This process results in the formation of metal "carbenoid" **III** in which both the ester and the π system have migrated from their original positions (Scheme 3.13).



Scheme 3.13. *Metal-induced activation of propargyl acetates.*

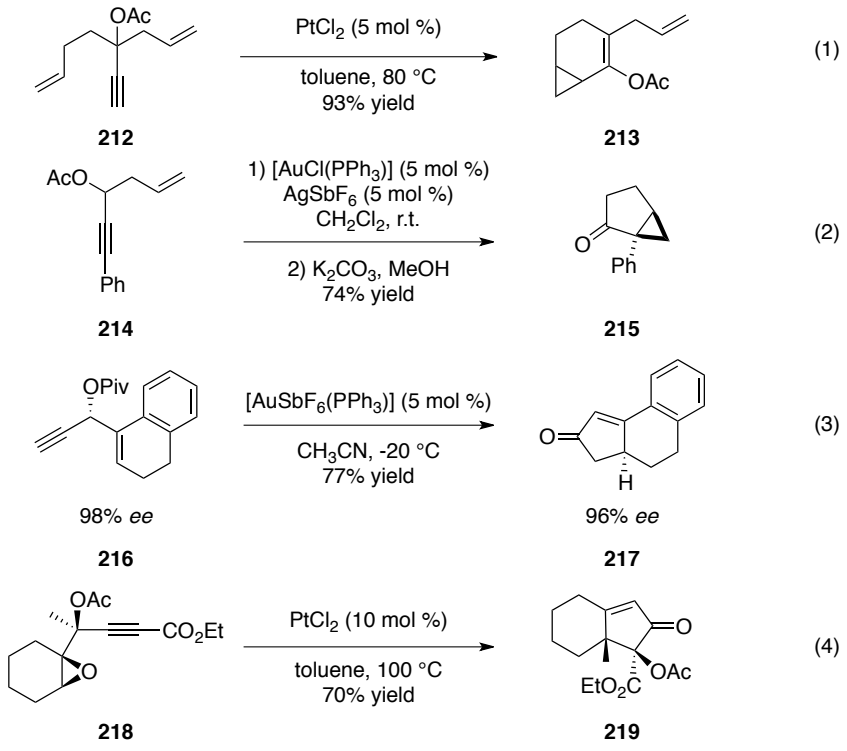
In essence, the carboxylate group serves to develop the metal–alkylidene species at the distal position of the alkyne. This mode of reactivity has been demonstrated in intermolecular reactions, by trapping with external alkenes, to afford vinylcyclopropanes such as **211** (Scheme 3.14).[31] The intermediacy of a planar alkylidene of type **III** is supported by the intermolecular reaction of enantiomerically enriched propargylic carboxylates with external alkenes, which afford racemic products (Scheme 3.14). [32]



Scheme 3.14. *Intermolecular rearrangement of propargylic carboxylates*

A higher level of complexity is seen in the intramolecular reactions of propargylic carboxylates with tethered alkene units (Scheme 3.15). The cyclization of 1,6-enynes [Scheme 3.15, Eq. (1)][33] showing propargylic carboxylate moieties is generally kinetically favored over those of 1,5-enynes,[34] even if the latter participate effectively and afford [3.1.0]-bicyclic structures under gold or platinum catalysis [Scheme 3.15, Eq. (2)].[35]

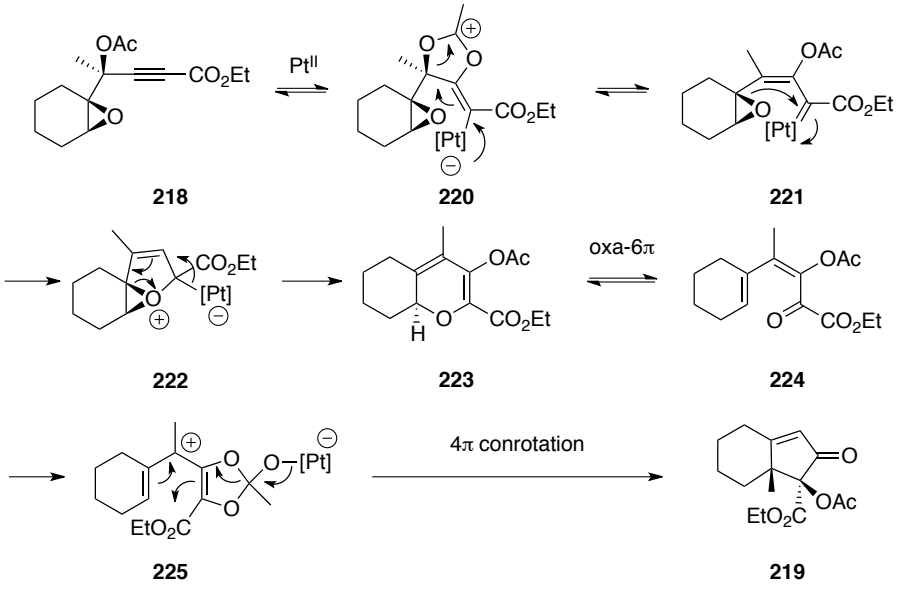
1,4-Enynes can be subjected to cycloisomerizations as well [Scheme 3.15, Eq. (3)]. Generally referred to as the Rautenstrauch reaction,[36] this last process offers an attractive route to cyclopentenones, alternative to classical transformations such as the Nazarov cyclization and the Pauson-Khand cyclocarbonylation.



Scheme 3.15. *Intramolecular cyclization of diverse propargylic carboxylates*

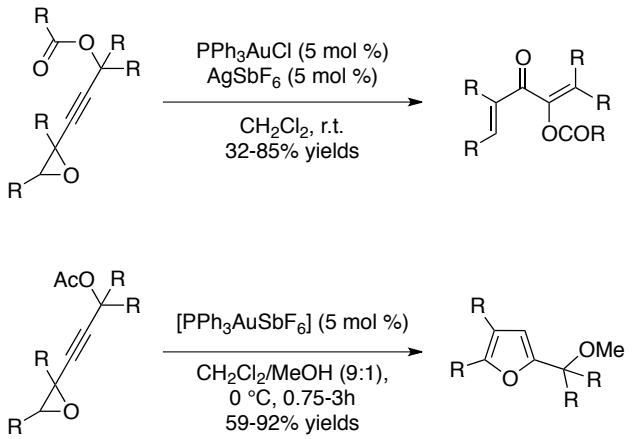
An interesting extension of this procedure has recently been outlined, in which an epoxide takes the role of the olefin [Scheme 3.15, Eq. (4)]. On interception of the putative platinum

carbenoid, a fragmentation cascade ensues, which leads to the formation of pyran **223**. This subsequently undergoes an electrocyclic ring opening to dienone **224**, which in turn converts into the functionalized cyclopentenone **219** (Scheme 3.16).[37]



Scheme 3.16. *Proposed mechanism for a platinum-catalyzed cyclopentenone synthesis*

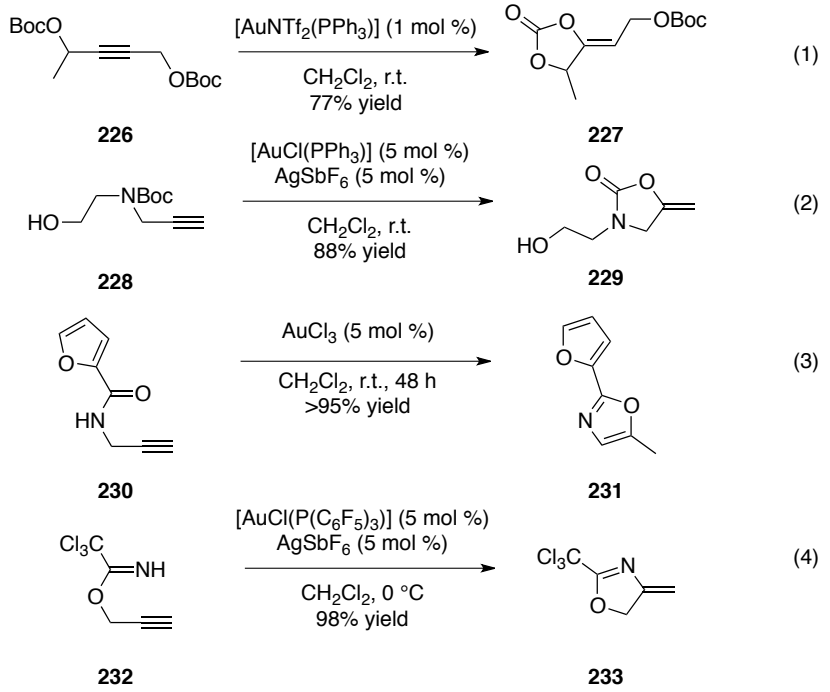
Different rearrangements of propargylic carboxylates containing epoxide moieties were also reported, as shown in Scheme 3.17.[38] In this case, gold-catalyzed reactions of acetoxylated alkynyloxiranes allowed various functionalized divinyl ketones and highly substituted furans to be formed efficiently under mild conditions.



Scheme 3.17. *Different rearrangements of propargylic carboxylates containing epoxide moieties*

The π-acid-induced rearrangement, seen with propargylic esters, is interrupted by

modification of the carboxylate group. The use of a *t*Bu-carbonate or *t*Bu-carbamate yields 1,3-dioxolan-2-ones[39] or oxazolidinones,[40] respectively, as a result of the elimination of isobutene and protonation at the vinylmetal species [Scheme 3.18, Eqs. (1) and (2)].[41] The structurally related *N*-propargylcarboxamides are similarly cyclized and form oxazoles on proton transfer and migration of the double bond, which is driven by the enthalpic gain of aromatization [Scheme 3.18, Eq. (3)].[42] However, this is no a prerequisite for the reaction to occur, as illustrated by the cyclization of propargylic and homopropargylic trichloroacetimidates to give non-aromatic heterocyclic products [Scheme 3.18, Eq. (4)].



Scheme 3.18. *Gold-catalyzed synthesis of heterocycles*

3.1.7. Enynes

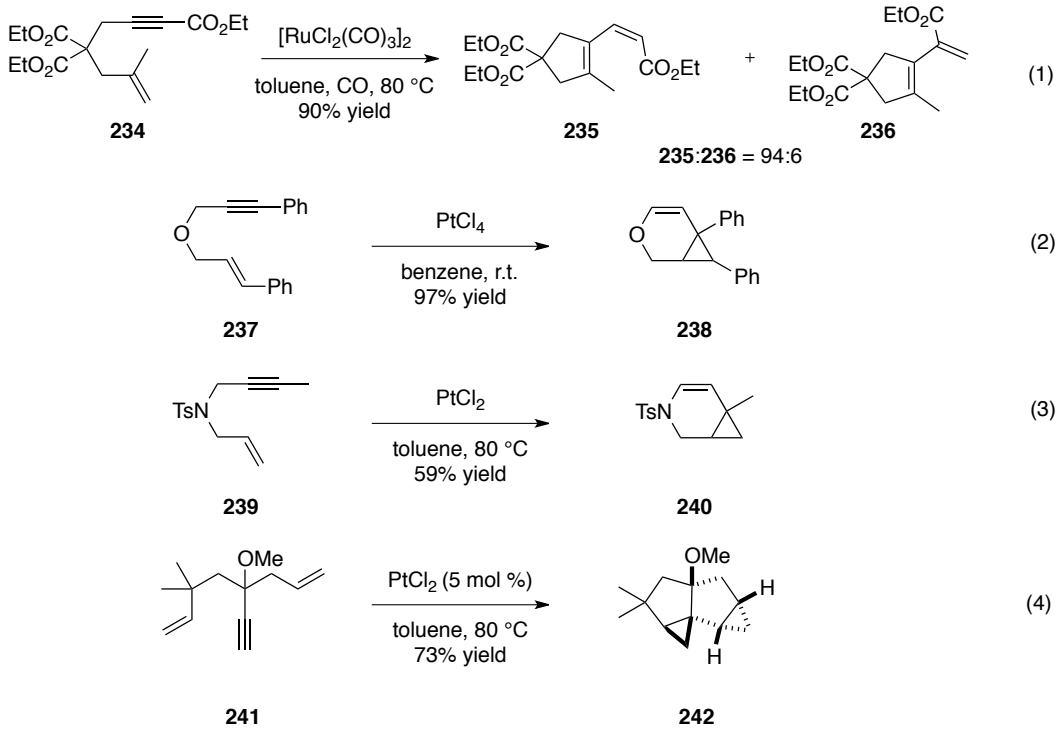
The reactivity of enynes (in particular 1,6-enynes) represents the most-widely studied substrate class in the field of cycloisomerizations.[43] Intense investigations over a number of decades have led to the development of numerous important transformations, which are distinguished examples of the concept of atom-economy in organic synthesis. Despite this impressive heritage, a new journey of chemical discovery was embarked upon when platinum, and later gold catalysts were employed.[44]

Early work by Murai, Chatani, and co-workers showed that enynes could be transformed into 1,3-dienes, by using ruthenium complexes and platinum salts, in a process formally resembling an enyne metathesis reaction. It soon became clear from the number of structurally

interesting products obtained, however, that the mechanism of these systems diverged from that accepted for already known metathesis or Alder–ene reactions.[45]

For example, the transformation of enyne **234** into two regioisomeric esters **235** and **236** cannot be rationalized by either the Alder–ene or metathesis-type reactivity. Similarly, the unprecedented [4.1.0]-bicyclic structures reported by Blum *et al.* at about the same time strongly suggested that an alternative explanation must be sought (Scheme 3.19).[45c]

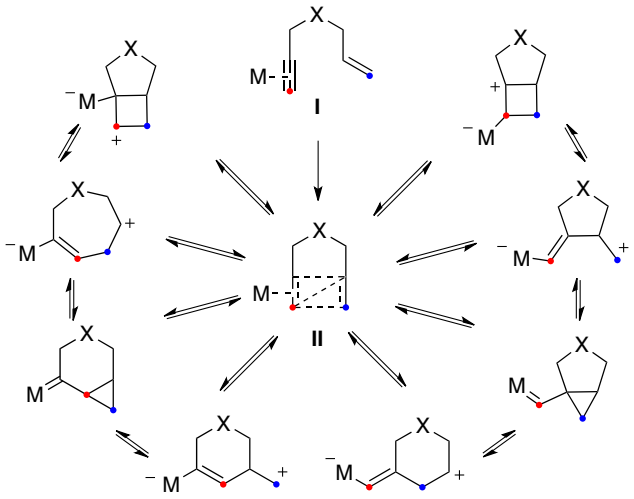
Recently, the Pt-catalyzed cycloisomerization of substrate **241** unequivocally illustrated the synthetic power of these transformation, since polycyclic derivative **242**, incorporating cyclopropyl ring systems, could be easily achieved in a full atom economy process.[46]



Scheme 3.19. *Examples of enyne-cycloisomerization reactions*

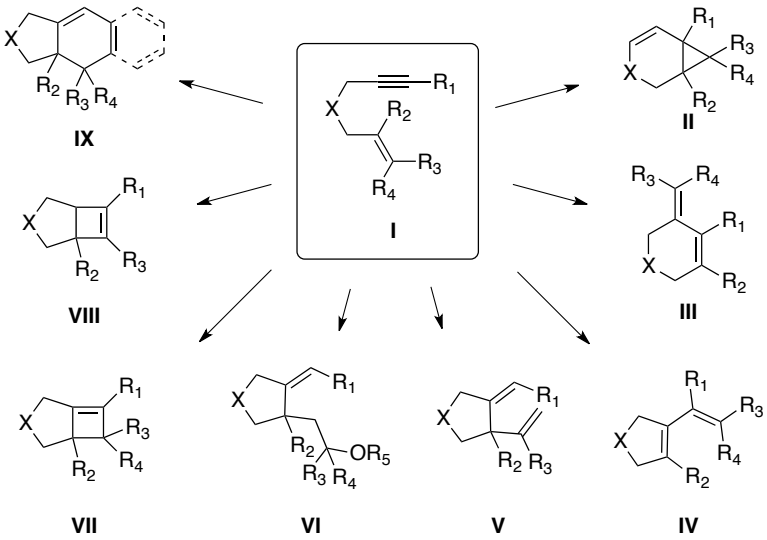
In Scheme 3.20 a mechanistic interpretation of metal-activated enynes is presented, which is able to explain the range of products isolated in transition metal catalyzed cycloisomerizations.[47] Simultaneous coordination of the alkene and the alkyne to the metal center is not essential, the reaction pathway requires only that the alkyne is coordinated to initiate. This proposal has been widely adopted and confirmed by numerous computational and experimental studies, which provide insights into the details of the reaction coordinates.[48] Whilst the carbene nature is perhaps the most appropriate description for the reactive intermediates in the platinum series, theoretical studies show that they should also be viewed as exhibiting considerable cationic character.

This view reflects the "split personality" displayed in the structure of the late-transition-metal "carbenes" previously discussed. The cationic nature appears to be more pronounced for the more-electrophilic gold species. It will be interesting to see whether the successful use of carbon monoxide in certain platinum-catalyzed transformations is due to an increase in the cationic nature of the intermediates.



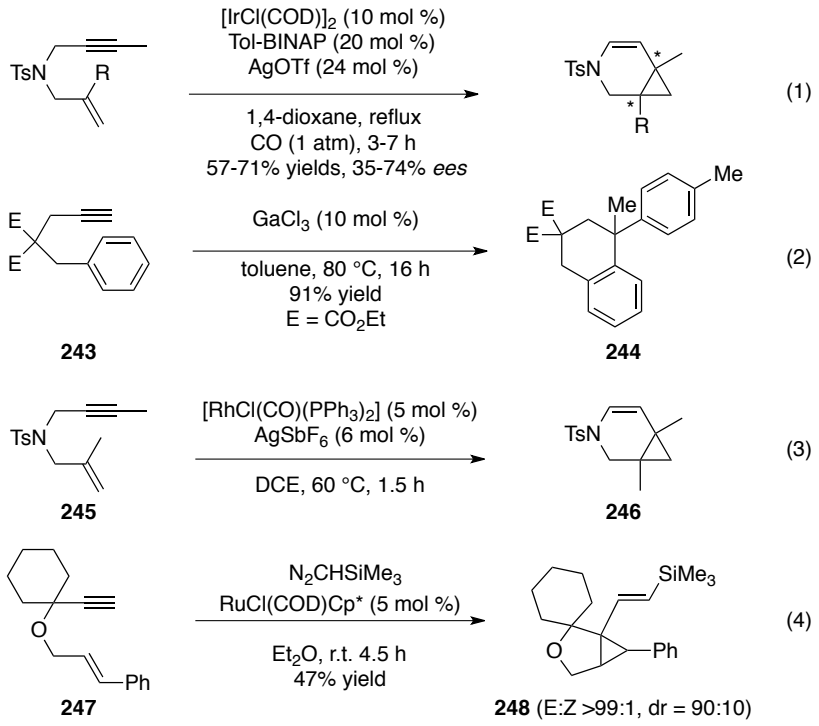
Scheme 3.20. *Interpretation of metal-activated enynes*

As this research field has developed, it is striking how the initial mechanistic hypothesis has been able to account for more and more diverse transformations by extension of the underlying principles (Scheme 3.21).



Scheme 3.21. *Observed reaction topologies in cycloisomerizations of 1,6-enynes.*

This hypothesis seems to hold true not only for gold and platinum, but also for a fairly diverse range of carbophilic catalysts that were successfully screened, most notably based on Ir(I),[49] Ga(III),[50] Rh,[51] and Ru[52] (Scheme 3.22).



Scheme 3.22. *Cycloisomerizations of 1,6-enynes catalyzed by Ir(I)-, Ga(III)-, Rh- and Ru-complexes*

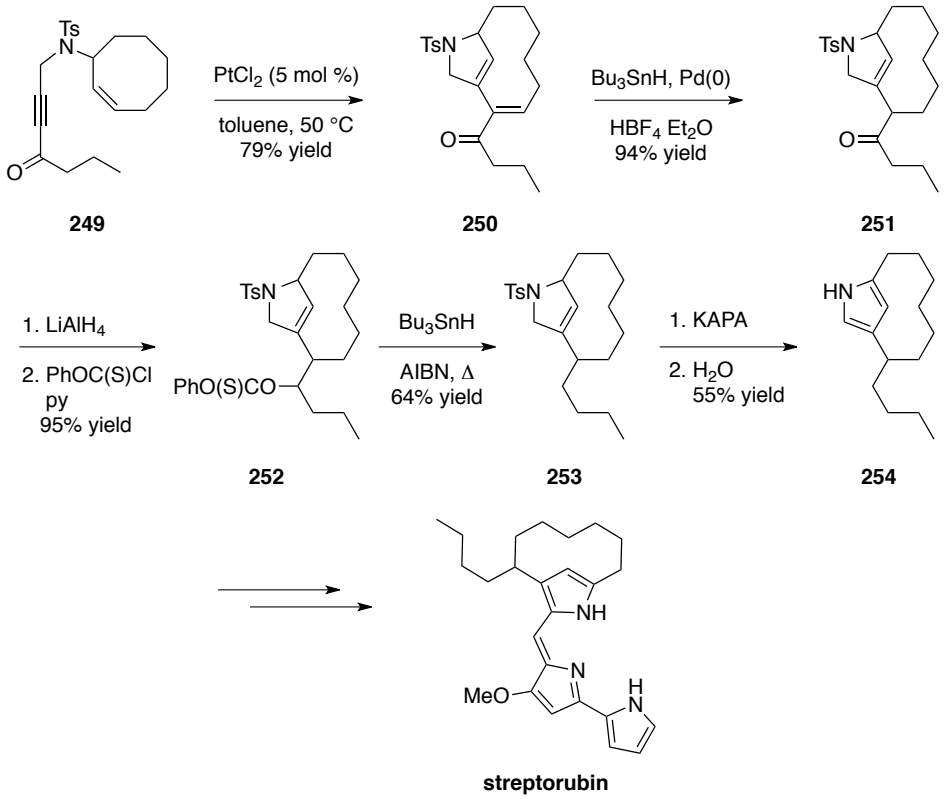
3.1.8. Selected applications in the total synthesis of natural products

The simplicity, mild conditions, and functional-group tolerance associated with platinum catalysis, and therefore its suitability for use within a natural product synthesis program were recognized at an early stage.

One of the first applications of the transition metal-catalyzed electrophilic activation of alkynes was the synthesis of the antibiotic streptorubin.[53] In this process, the enyne **249** underwent a smooth skeletal rearrangement, upon heating in the presence of catalytic amounts of $PtCl_2$ in toluene, to form the bicyclic product **250** in good yield on a multigram scale. (Scheme 3.23).

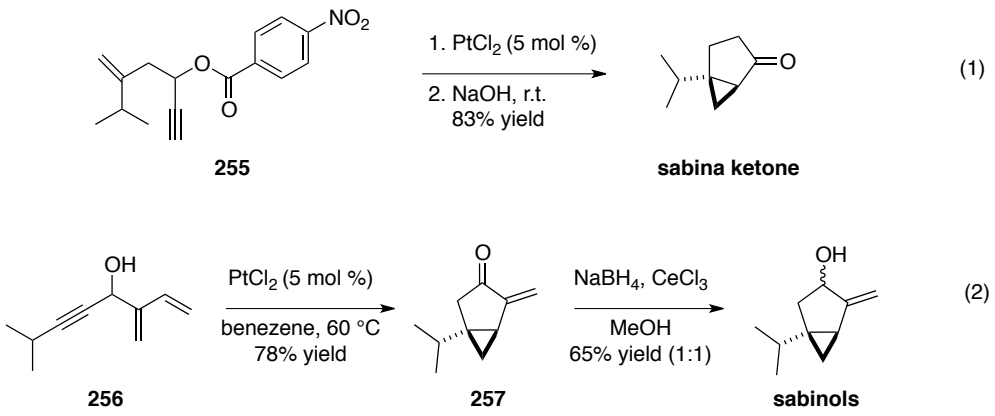
A range of platinum salts were shown to be capable of inducing this transformation ($PtCl_2$, $PtBr_2$, $PtCl_4$, $PtBr_4$), and even conventional Lewis and Brønsted acids ($ZnCl_2$, $TiCl_4$, $AlCl_3$, $SnCl_4$, $BF_3{\cdot}Et_2O$, HBF_4) can be used, but are somewhat less effective. A series of by-products could be isolated when the cycloisomerization was performed on a larger scale. Subsequent reduction of the enone unit followed by a deoxygenation, elimination, and rearrangement

strategy afforded the meta-bridged pyrrole core of **254** in nine steps from cyclooctene. This building block was then converted into the antibiotic by following literature methods.



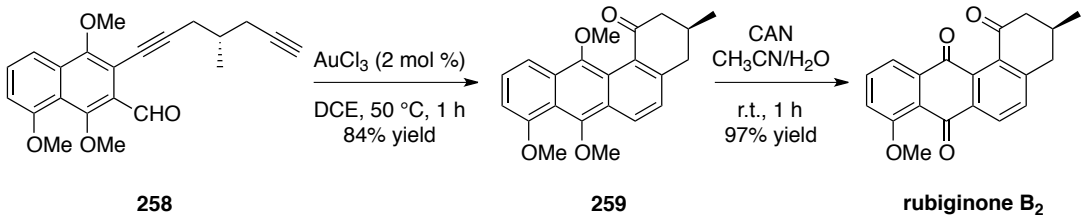
Scheme 3.23. *Synthesis of streptorubin by a platinum-catalyzed cycloisomerization*

In a different application, platinum-catalyzed cycloisomerizations of 1,5-enynes was successfully used in a concise synthesis of the sabina ketone, whereas the structurally similar sabinol terpenes were prepared by the reaction of enynol substrates (Scheme 3.24).[34]



Scheme 3.24. *Platinum-catalyzed synthesis of sabina ketone, sabinone and sabinols*

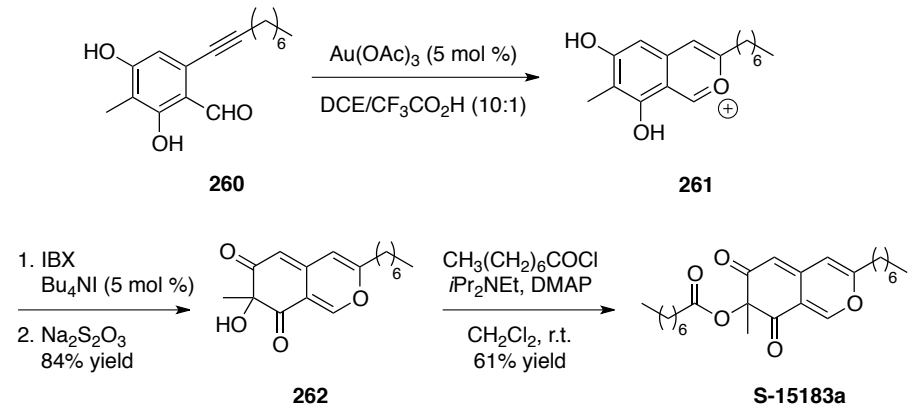
The total synthesis of rubiginone B_2 was accomplished by Yamamoto and co-workers, *via* an $AuCl_3$–catalyzed intramolecular [4+2] benzannulation reaction as the key step (Scheme 3.25).[54] After the efficient formation of the tetracyclic core, oxidation of the dihydrotetraphenone derivative **259** yielded the target natural product in excellent yield.



258 **259** **rubiginone B_2**

Scheme 3.25. *Synthesis of (+)-rubiginone B_2 by an $AuCl_3$-catalyzed benzannulation reaction*

Further applications of *o*-alkynylated benzaldehyde and aryl ketone cycloisomerizations were reported.[55] One example is the clever synthesis of azaphilones by isolation of the oxonium species **261** when the unprotected aldehyde **260** is treated with a gold catalyst in the presence of trifluoroacetic acid (Scheme 3.26).[56] Subsequent oxidation of **261** with IBX under phase-transfer conditions followed by esterification completed the synthesis of S-15183a, a potent sphingosine kinase inhibitor.



260 **261** **262** **S-15183a**

Scheme 3.26. *Synthesis of azaphilone S-15183a by a gold-catalyzed cyclization reaction*

As appears from the diverse range of transformation presented within this chapter, in the next future, the rapid increase in molecular complexity enabled by alkyne activation toward nucleophilic attack will result in many other applications of these catalytic processes in the area of complex molecule synthesis.

3.2. RESULTS AND DISCUSSION

As outlined in the previous section, the transition metal-catalyzed alkyne activation toward nucleophilic attack is a powerful method for accessing cyclic structures from acyclic precursors of substantially less molecular complexity.

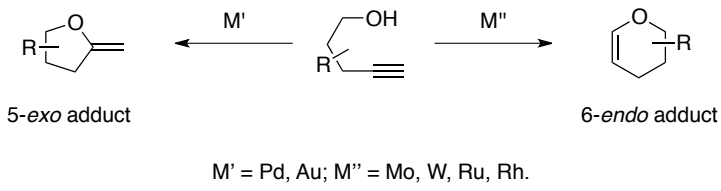
Although Pt and Au species have shown an exceptional ability to promote a variety of organic transformations, delivering a diverse array of cyclic products, the improvement of catalytic systems, involving different transition metal complexes, still remains an ongoing challenge.

With the perspective to expand our study on cycloisomerization reactions,[57] we recently envisaged to develop new catalytic processes, employing Ir(III)-species for the straightforward synthesis of oxygen- and nitrogen-containing bicyclic compounds.

In this section, we describe a new $[IrCp^*Cl_2]_2$-catalyzed cyclization of homopropargylic diols, which provided an efficient access to dioxabicyclo[2.2.1]ketals. The innovative catalyst also allowed the easy formation of azabicyclo[4.1.0]heptenes through the skeletal rearrangement of nitrogen-tethered 1,6-enynes. In particular, the selective synthesis of cyclopropane derivatives[58] is attracting the attention of many research groups, presumably due to their widespread occurrence as a subunit in natural products.[59]

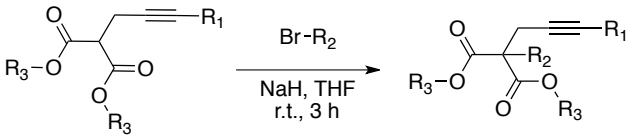
3.2.1. Synthesis of dioxabicyclo[2.2.1]ketals

In the course of our ongoing program concerning catalytic reactions with functionalized (poly)unsatured compounds, we became interested in the cyclization of bis-homopropargylic alcohols, which have shown challenging behaviors either in their *endo*- or *exo*-selective cyclizations in the presence of different transition-metal catalysts (Scheme 3.27).[15a,21b-e]



Scheme 3.27. *Metal-catalyzed cyclization of bis-homopropargylic alcohols*

Indeed, bis-homopropargilic alcohols **265a-i** were synthesized by a two-step procedure, involving an initial alkylation of commercially available malonic esters with different alkyl bromides (Table 3.1, entries 1-9).



263a-i **264a-i**

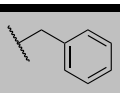
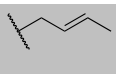
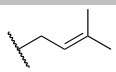
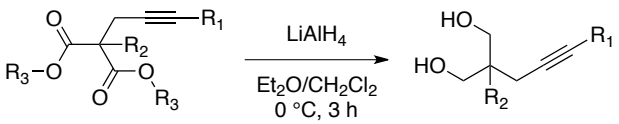
Entry	R_1	R_2	R_3	Reactant	Product	Yield (%)
1	H		Me	**263a**	**264a**	89
2	H	Me	Me	**263b**	**264b**	95
3	H		Et	**263c**	**264c**	97
4	H		Et	**263d**	**264d**	86
5	H		Me	**263e**	**264e**	53
6	H		Me	**263f**	**264f**	70
7	H		Me	**263g**	**264g**	88
8	H		Me	**263h**	**264h**	90
9	Me		Et	**263i**	**264i**	89

Table 3.1. *Synthesis of dialkyl malonates* ***264a-i***

In the second synthetic step, reduction of the dialkyl malonates **264a-i** with $LiAlH_4$ readily afforded the bis-homopropargilic alcohols **265a-i** in short reaction times and excellent yields (Table 3.2, entries 1-9).

After the desired substrates were synthesized, we turned our attention to investigate their cyclization in the presence of new catalysts. Thus, we began our investigation by using Ir(III)-based complexes.



264a-i **265a-i**

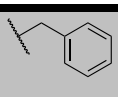
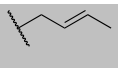
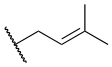
Entry	R_1	R_2	R_3	Reactant	Product	Yield (%)
1	H		Me	**264a**	**265a**	91
2	H	Me	Me	**264b**	**265b**	quant.
3	H		Et	**264c**	**265c**	quant.
4	H		Et	**264d**	**265d**	quant.
5	H		Me	**264e**	**265e**	95
6	H		Me	**264f**	**265f**	quant.
7	H		Me	**264g**	**265g**	89
8	H		Me	**264h**	**265h**	87
9	Me		Et	**264i**	**265i**	91

Table 3.2. *Synthesis of bis-homopropargilic alcohols* ***265a-i***

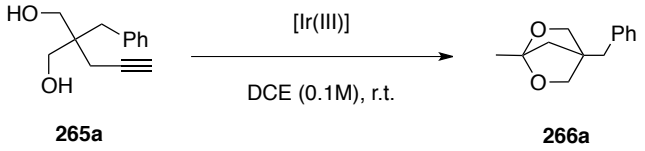
Unfortunately, initial attempts to effect the cyclization of precursor **265a** by using $IrCl_3$, $Ir(ppy)_3$, and $[Ir(ppy)_2dtbbpy]PF_6$ resulted in no conversion of the starting material (Table 3.3, entries 1-4).

Because of its ability to interact with alkynes in mild conditions,[60] commercially available $[IrCp^*Cl_2]_2$ appeared to be a suitable catalyst to promote the reaction. This complex had been frequently used to promote the oxidation of alcohols and their conversion into amides,[61] but it had never been tested before in cycloisomerization reactions.

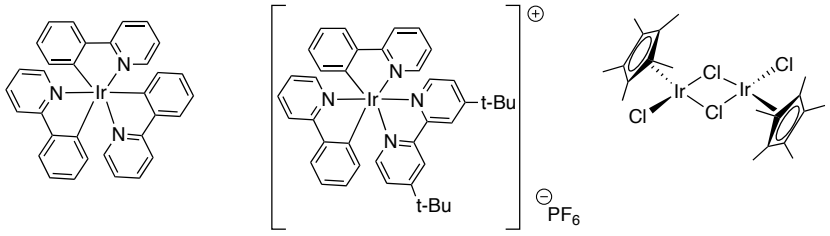
Gratifyingly, the preliminary work using 5 mol% of $[IrCp^*Cl_2]_2$ in dichloroethane (DCE), at room temperature, proceeded to the rapid formation of the bicyclic ketal **266a**, which was isolated in quantitative yield (Table 3.3, entry 5).[62] To the best of our knowledge, this is the first example of an Ir(III)-catalyzed cycloisomerization.[63]

Interestingly, whereas the reaction of bis-homopropargylic alcohols catalyzed by transition metals such as Rh, Ru, W, and Mo usually leads to 6-*endo* cyclization products,[21] the Ir(III)-catalyzed hydroalkoxylation was found to be 5-*exo*-selective, as no six-membered cyclic derivative was detected.

To our delight, catalyst loadings could be decreased to 1 mol% with no loss in yield, even if longer reaction times were required to achieve complete conversions of the starting material (Table 3.3, entries 6 and 7).



265a **266a**



$Ir(ppy)_3$ **$[Ir(ppy)_2dtbbpy]PF_6$** **$[IrCp^*Cl_2]_2$**

Entry	Catalyst	Catalyst loading (mol %)	t (h)	Yield (%)
1	$IrCl_3 \cdot 3H_2O$	10	1	0
2	$IrCl_3$	10	1	0
3	$Ir(ppy)_3$	5	1	0
4	$[Ir(ppy)_2dtbbpy]PF_6$	5	1	0
5	$[IrCp^*Cl_2]_2$	5	0.25	quant.
6	$[IrCp^*Cl_2]_2$	2.5	0.25	quant.
7	$[IrCp^*Cl_2]_2$	1	0.5	quant.

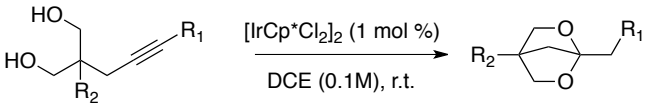
Table 3.3. *Optimization of the hydroalkoxylation reaction*

The substrate scope of this optimized cyclization was then examined starting from bis-homopropargylic alcohol **265b.** The expected hydroalkoxylation proceeded smoothly providing the corresponding adduct **266b** in 82% yield (Table 3.4, entry 1).

Substrates **265c-h**, containing different allylic moieties, underwent the cyclization as well. The reaction was found to be highly chemoselective towards alkynes, as no reactivity of the allylic chains was observed. These results further exemplified the synthetic potential of our method, since products **266c-h** were isolated in excellent yields (Table 3.4, entries 2-7).

Surprisingly, the isomerization of diol **265i**, showing an internal alkyne moiety, also generated the corresponding product **266i**, albeit in longer reaction times but still in good yield (Table 3.4, entry 8).

A plausible mechanism for hydroalkoxylations is outlined in Scheme 3.28. Despite $[IrCp^*Cl_2]_2$ is known to generate vinylidene complexes from alkynes in mild conditions,[64] the involvement of metal vinylidene species in the cycloisomerization process was excluded, since the formation of 6-*endo* cyclization products was not detected.



265a-i **266a-i**

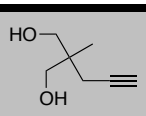
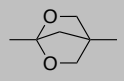
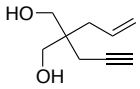
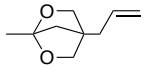
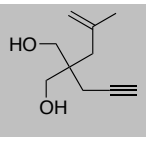
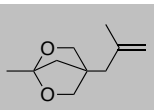
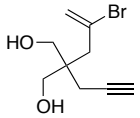
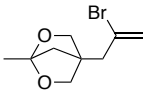
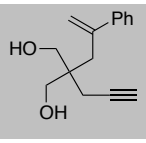
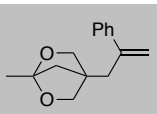
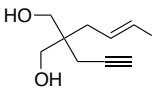
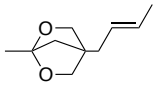
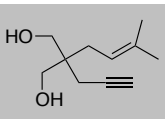
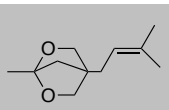
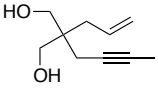
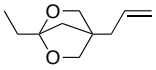
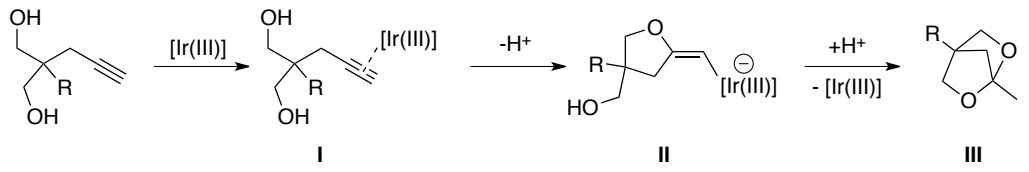
Entry	Reactant		Product		t (h)	Yield (%)
1	**265b**		**266b**		1	82
2	**265c**		**266c**		0.5	quant.
3	**265d**		**266d**		0.5	94
4	**265e**		**266e**		0.5	quant.
5	**265f**		**266f**		0.5	quant.
6	**265g**		**266g**		0.5	92
7	**265h**		**266h**		0.5	86
8	**265i**		**266i**		2	67

Table 3.4. *$[IrCp^*Cl_2]_2$ – catalyzed cycloisomerization of bis-homopropargylic alcohols*

In analogy with previously reported Au(I) and Ir(I)-catalyzed reactions, a mechanism based on the electrophilic activation of the alkyne seemed to be more consistent.[15a,21f]

An initial π-complexation of the triple bond to the Ir(III)-based catalyst would generate an electrophilic (η_2-alkyne)metal complex **I**.

Intramolecular nucleophilic *anti*-attack of the oxygen on the activated alkyne could then allow the formation of an enol vinyliridium intermediate **II**.[65] Protonolysis of **II** and subsequent addition of the remaining alcohol on the resulting vinyl ether would finally lead to the bicyclic ketal **III**.

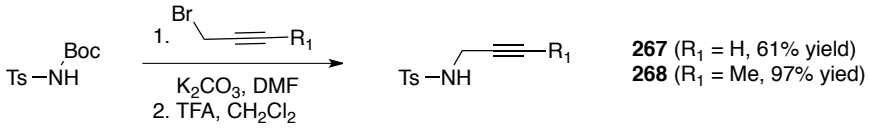


Scheme 3.28. *Proposed mechanism for the Ir(III)-catalyzed hydroalkoxylation reaction*

3.2.2. Synthesis of azabicyclo[4.1.0]heptenes

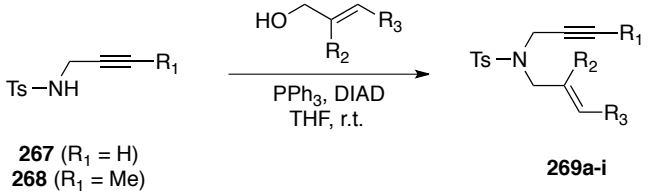
The high yield and mild conditions of $[IrCp^*Cl_2]_2$-catalyzed hydroalkoxylations encouraged us to examine other cycloisomerization reactions to form different heterocyclic compounds. The application of our catalytic system to nitrogen- and oxygen-tethered 1,6-enynes was thought to be the most exciting while considering the possibility to induce different skeletal rearrangements, involving both alkene and alkyne moieties of the molecules.[66]

Thus, precursors **269a-i**, needed for this study, were prepared starting from *N*-Boc-*p*-toluenesulfonamide by initial alkylations reaction and subsequent Boc-deprotection of the nitrogen atom (Scheme 3.29).



Scheme 3.29. *Synthesis of tosil amides **267** and **268***

In a second time, a Mitsunobu reaction of the resulting tosil amides **267** and **268** with different substituted allylic alcohols afforded the desired substrates **269a-i** in good to excellent yields, after isolation by column chromatography over silica gel (Table 3.5, entries 1-9).



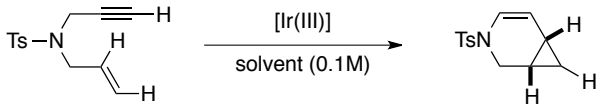
Entry	R_1	R_2	R_3	Reactant	Product	Yield (%)
1	H	H	H	**267**	**269a**	75
2	H	Me	H	**267**	**269b**	81
3	H	H	Me	**267**	**269c**	74
4	H	H	Ph	**267**	**269d**	88

5	Me	H	H	**268**	**269e**	79
6	Me	Me	H	**268**	**269f**	60
7	Me	H	Me	**268**	**269g**	73
8	Me	Ph	H	**268**	**269h**	65
9	Me	H	Ph	**268**	**269i**	82

Table 3.5. *Synthesis of nitrogen-tethered 1,6-enynes* ***269a-i***

With the required precursors in hand, we next turned our attention to the optimization of the cyclization conditions. Unluckily, the treatment of substrate **269a** in DCE at room temperature using 1 mol% of catalyst turned out in the recovery of the starting material (Table 3.6, entry 1).

A set of different reaction conditions were screened and $[IrCp^*Cl_2]_2$ was found to promote the cyclization in DCE at reflux, allowing the cyclopropane derivative **270a** to be isolated in 55% yield (Table 3.6, entries 2-4). A similar result was obtained when toluene was employed as solvent (Table 3.6, entry 5).



269a **270a**

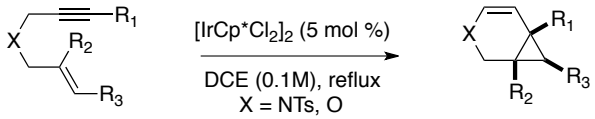
Entry	Catalyst loading (mol %)	Solvent	T (°C)	t (h)	Yield (%)
1	1	DCE	r.t.	24	0
2	2.5	DCE	r.t.	24	0
3	5	DCE	r.t.	24	30
4	5	DCE	reflux	3	55
5	5	toluene	reflux	3	53

Table 3.6. *Optimization of the cyclopropanation reaction*

The optimized cyclopropanation could be applied to a large variety of nitrogen-tethered 1,6-enynes, giving rise to the bicyclic products **270b-i** as single diastereomers (Table 3.7).[67] Both aryl and alkyl groups were tolerated on the alkene moiety of the molecules (Table 3.7, entries 1-3). The new catalytic protocol also led to successful isomerizations of precursors **269e-i**, possessing internal alkyne moieties, even if, in these cases, longer reaction times were needed to isolate the corresponding products in good yields (Table 3.7, entries 4-8).

Unlike *N*-containing precursors, oxygen-tethered 1,6-enynes showed poor reactivity towards the Ir(III) catalyst, as pointed out by the low yield of cyclized product **272** obtained when substrate **271** was submitted to the reaction conditions (Table 3.7, entry 9).[68]

Despite the last displeasing result, $[IrCp^*Cl_2]_2$ was found to be effective in low catalytic loadings and in absence of any other additive. Thus, the protocol we developed seems to have valuable applicability, especially if compared to previously reported Ir(I)-catalyzed cyclizations.[49]



269b-i, **271** **270b-i**, **272**

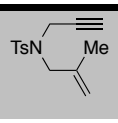
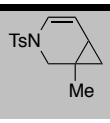
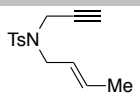
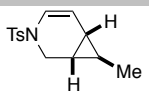
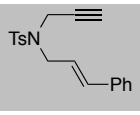
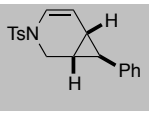
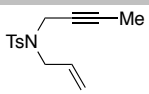
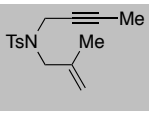
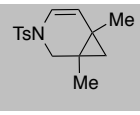
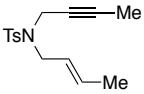
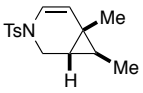
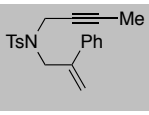
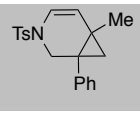
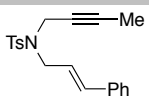
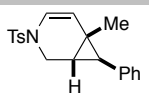
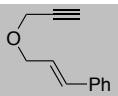
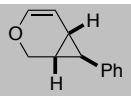
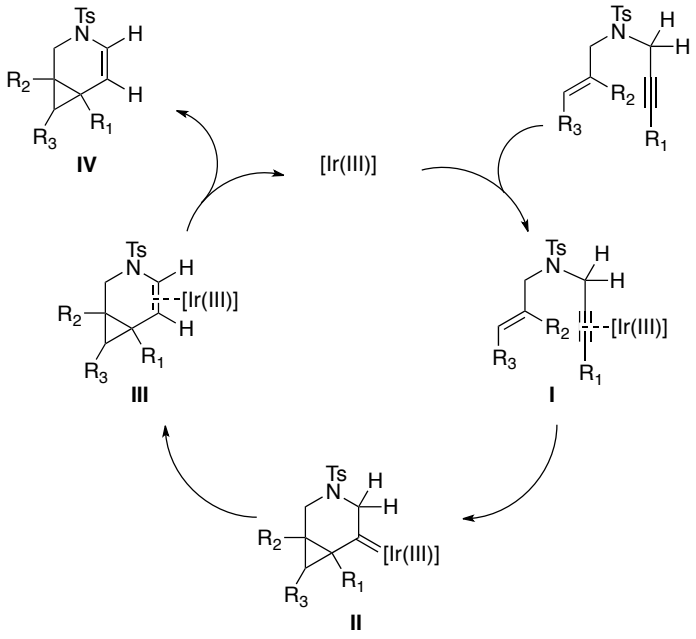
Entry	Reactant		Product		t (h)	Yield (%)
1	**269b**		**270b**		3	82
2	**269c**		**270c**		3	61
3	**269d**		**270d**		3	60
4	**269e**		**270e**		24	35
5	**269f**		**270f**		24	84
6	**269g**		**270g**		24	64
7	**269h**		**270h**		24	80
8	**269i**		**270i**		24	58
9	**271**		**272**		24	15

Table 3.7. *$[IrCp^*Cl_2]_2$ – catalyzed cycloisomerization of nitrogen- and oxygen-tethered 1,6 enynes*

On the basis of our results and previous studies,[69] the mechanism of cyclopropanations was supposed to involve an Ir(III) electrophilic activation of alkynes and the formation of carbene complexes, stabilized by donor heteroatoms. Indeed an initial π-complexation of the alkyne to the Ir(III) entity (**I**) would trigger an *endo-dig* cyclization to form a cyclopropyl metallacarbenoid **II**. Subsequent [1,2]-hydrogen shift and metal elimination would afford the observed cyclopropane **IV** (Scheme 3.30). The presence of a heteroatom at the propargylic site favors this process due to the stabilization of the intermediates by the heteroatom lone pair.



Scheme 3.30. *Proposed mechanism for Ir(III)-catalyzed cyclization of nitrogen-tethered 1,6-enynes*

In the next future, the high catalyst activity of $[IrCp^*Cl_2]_2$, along with the very mild reaction conditions, would probably allow further applications toward the synthesis of natural products and other structurally original polycyclic heterocycles.

3.3. CONCLUSIONS AND FUTURE DEVELOPMENTS

Transition metals exhibit significant efficacy in catalyzing the formation of carbon-carbon and carbon-heteroatom bonds, and in particular, Pt and Au (gold(III) and cationic gold(I)) show an exceptional capacity to promote a growing variety of organic transformations of unsaturated precursors.

The intriguing activity of platinum and gold species derives from their unique ability to activate carbon-carbon multiple bonds as soft, carbophilic Lewis acids, thus promoting the intra- or intermolecular attack of a nucleophile.

The rapid increase in molecular complexity enabled by alkyne activation toward nuclephiles resulted in many applications of Pt- and Au-catalyzed processes in the area of complex molecule synthesis of natural and unnatural products.

Whilst gold and platinum catalysts are similarly efficacious in many cases, in other examples there is a clear preference for one over the other. This finding ensures that the choice of catalyst is essential for the successful outcome of the reaction. In this context, the improvement of catalytic systems still remains an ongoing challenge.

With the perspective to expand our study on cycloisomerization reactions,[54] we envisaged to develop new catalytic processes, employing Ir(III)-species for the synthesis of oxygen and nitrogen containing bicyclic compounds. $[IrCp^*Cl_2]_2$ proved to be a novel powerful catalyst for the straightforward cycloisomerization of different functionalized 1,6-enynes.

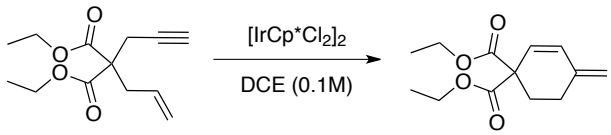
In particular, we have found that $[IrCp^*Cl_2]_2$ catalyst promote a highly efficient cycloisomerization of bis-homopropargylic alcohols under very mild conditions and in extremely short time. This process, starting from easily accessible materials, was shown to be general and atom-economical, leading to functionalized strained bicyclic ketals. Moreover, the reaction conditions were compatible with various functional groups and also allowed the isomerization of precursors possessing internal alkyne moieties. The mechanism was proposed and presumably involves a Lewis acid-type activation, followed by two intramolecular cyclizations.

The application of our catalytic system to nitrogen- and oxygen-tethered 1,6-enynes was also explored, in the aim to induce different skeletal rearrangements, involving both alkene and alkyne moieties of the molecules. Indeed, the formation of azabicyclo-[4.1.0]-heptenes was achieved by using $[IrCp^*Cl_2]_2$ in absence of any other additive. For this reason, the process we developed seems to have valuable applicability, especially if compared to previously reported Ir(I)-catalyzed cyclizations.[49]

The mechanism of cyclopropanations was supposed to involve an Ir(III) electrophilic activation of alkynes and the formation of carbene complexes, stabilized by donor heteroatoms.

Further studies on the scope and mechanism of Ir(III)-catalyzed cyclizations are currently under investigation in our laboratory.

Note-worthily, preliminary applications of our $[IrCp^*Cl_2]_2$-based catalytic system to the cycloisomerization of malonate-tethered 1,6-enyne **264c** resulted in the formation of the unprecedented compound **273**, albeit in low but encouraging 36% yield (Table 3.8, entry 4).

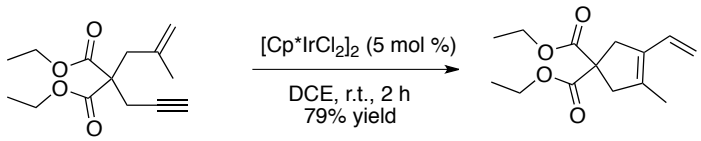


264c **273**

Entry	Catalyst loading (mol %)	Conditions	T (°C)	t (h)	Yield (%)
1	5	/	r.t.	24	0
2	10	/	reflux	24	traces
3	10	MW	150	0.20	complex mixture of products
4	10	sealed tube	100	2	36

Table 3.8. *$[IrCp^*Cl_2]_2$ – catalyzed cycloisomerization of compound **264c***

On the contrary, precursor **264d** smoothly reacted with 5 mol% of Ir(III)-catalyst, in DCE at room temperature, giving rise to the classical metathesis-type product **274** in short reaction times and 79% yield (Scheme 3.31).

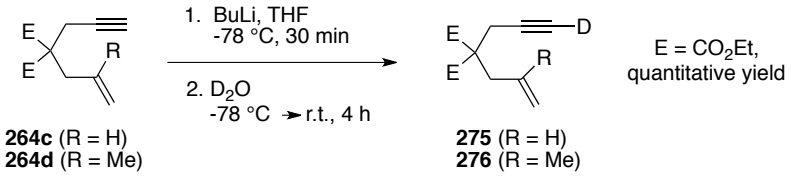


264d **274**

Scheme 3.31. *$[IrCp^*Cl_2]_2$ – catalyzed cycloisomerization of compound **264d***

To gain insight into the mechanism of cycloisomerization catalyzed by $[IrCp^*Cl_2]_2$, deuterium-labeling experiments were carried out. Indeed, compounds **275** and **276**, easily

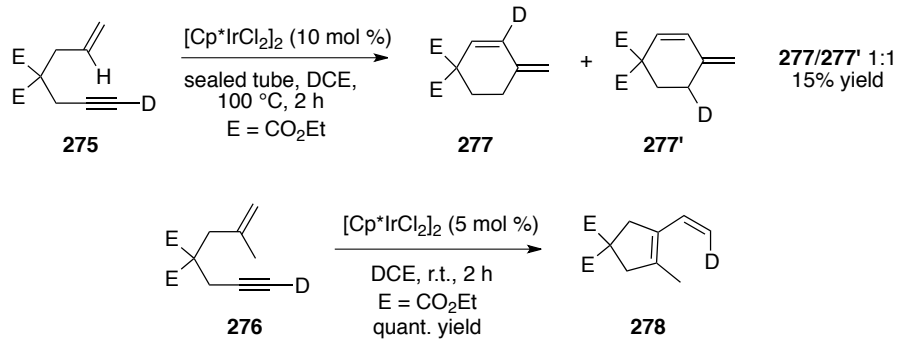
prepared starting from the corresponding malonate-tethered 1,6-enyne by the treatment with *n*BuLi and D_2O (Scheme 3.32), were submitted to the reaction conditions.



Scheme 3.32. *Synthesis of deuterated compound **275** and **276***

On one hand, the alkynyl deuterium of substrate **276** was transferred exclusively to the terminus of the exocyclic vinyl group, which characterizes product **278** (Scheme 3.33), therefore indicating a plausible analogy with Pt-catalyzed cycloisomerizations.

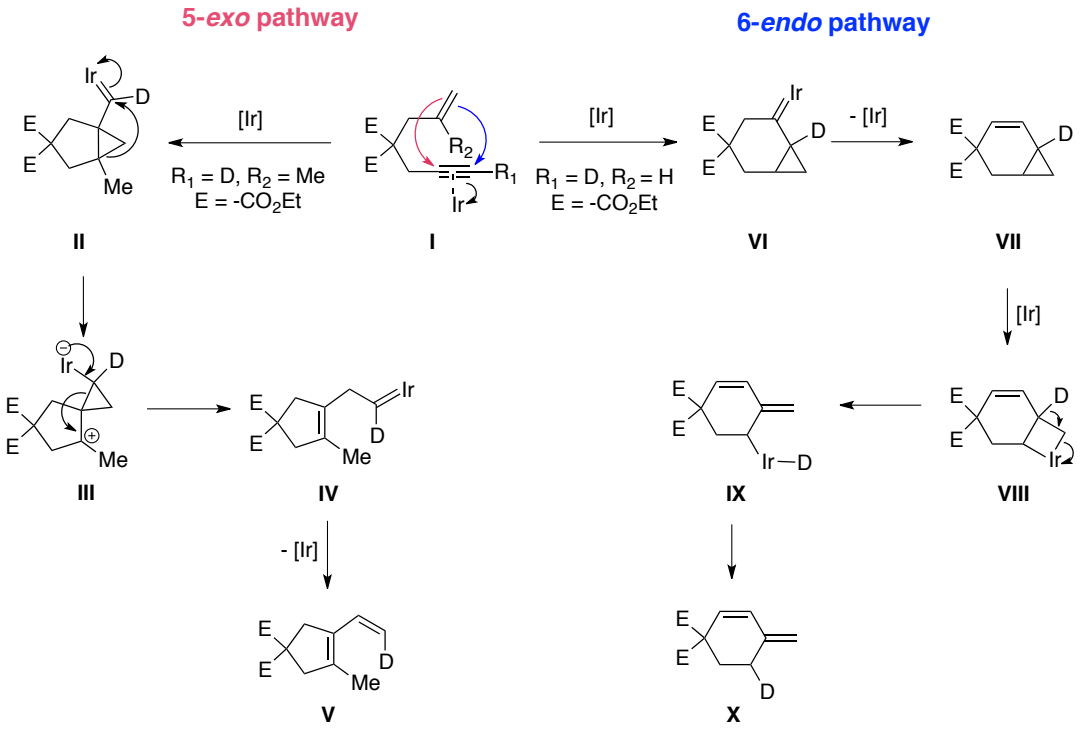
On the other hand, a 1:1 regioisomeric mixture of substrates **277** and **277'** was formed by the cyclization of precursors **275** (Scheme 3.33).



Scheme 3.33. *Deuterium-labeling experiments*

A double skeletal rearrangement of precursor **276** was supposed to occur in the presence of $[IrCp^*Cl_2]_2$ (Scheme 3.34, 5-*exo* pathway).[70] Indeed, the electrophilic interaction of the alkyne in **I** with Ir(III) would generate a cyclopropyl rhodium carbenoid **II**, which, in turn, would undergo rearrangement to give the spiro intermediate **III**. Depending on the substitution pattern, the spiro intermediate **III** would suffer a fragmentation to give the carbenoid **IV**. A [1,2]-H shift and the elimination of Ir(III) from **IV** would finally give rise to the observed *cis*-configured product **V**. The selective formation of product **278** from precursor **276** could finally be rationalized by the fact that the methyl group stabilizes the tertiary cation in **III**, leading to the selective generation of intermediate **IV**.

The involvement of a carbene complex **VI**, generated from **I** via the 6-*endo* pathway, is inferred based on the formation of a 2-aza-bicyclo[4.1.0]heptene derivatives **270a-i**.



Scheme 3.34. *Proposed mechanism for Ir(III)-catalyzed cycloisomerization of precursors* ***275*** *and* ***276***

Carbenes **II** and **VI** are presumably in rapid equilibrium. The course of the reaction is determined by the relative rate of conversion from **II** or **VI** or the stability of intermediates generated from **II** or **VI**. This would explain the observation that enynes react *via* either the 5-*exo* and 6-*endo* pathways, depending on their structure and on the metal employed to promote the cyclization. For these reasons, one could imagine that the 6-*endo* pathway is favored in the $[IrCp^*Cl_2]_2$-catalyzed cycloisomerization of compound **275** (Scheme 3.34). The cyclopropane derivative **VII** that results, unstable in the reaction condition, would then undergo an oxidative insertion of the iridium catalyst, followed by β-hydride elimination (**IX**) and reductive elimination, to afford the unprecedented product **X**. This mechanistic proposal, however, is able to explain the formation of only one of the two deuterated products, which were isolated when compound **275** was subjected to the reaction conditions (Scheme 3.33).

In the next future more detailed deuterium- and ^{13}C-labeling studies, as well as DFT calculations, will be conducted to get deeper insights in the mechanism of $[IrCp^*Cl_2]_2$-catalyzed cycloisomerizations. Finally, the scope of malonate-tethered 1,6-enyne cyclization will be better examined as well as the possibility to apply Ir(III)-catalytic system to the synthesis of natural or biologically active complex molecules.

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Chapter 4

Gold-catalyzed cycloisomerizations of allenes

Synthesis of multisubstituted N-amino pyrroles

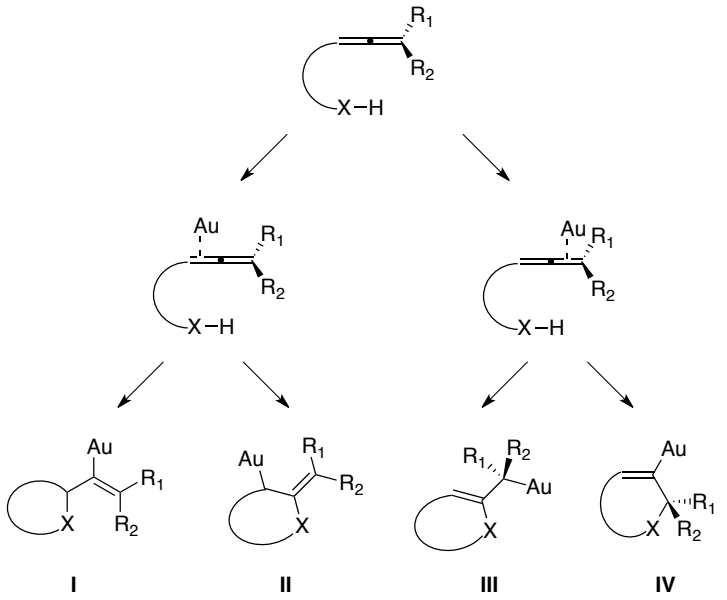
4.1. INTRODUCTION

Homogeneous gold catalysis is an emerging area of transition-metal mediated reactions with tremendous potential for organic synthesis.[1] As outlined in Chapter 3, both gold(I) and gold (III) salts are soft carbophilic Lewis acids and can activate C–C multiple bonds for an inter- or intramolecular attack of a nucleophile, to form new C–C or C–heteroatom bonds.

Among various substrates amenable to activation, alkynes play a dominant role, whereas gold-catalyzed reactions of alkenes or allenes have been studied less frequently.

From our point of view, allenes are particularly attractive starting materials since they combine high reactivity with axial chirality and therefore offer the opportunity to obtain new products in a stereoselective fashion by chirality transfer.

Gold catalysts[2] are particularly well suited for the selective activation of allenes in the presence of other reactive functionalities.[3] While intermolecular additions have been rarely investigated, intramolecular gold-catalyzed cyclizations of allenes have received much more attention. In this case, the gold catalyst can coordinate to either allenic double bond, and the regioselectivity of the subsequent nucleophilic attack depends on the structure of the substrate, in particular on the length of the tether connecting allene and on the characteristics of the nucleophile (Scheme 4.1).



Scheme 4.1. *Gold-catalyzed nucleophilic cyclizations of functionalized allenes*

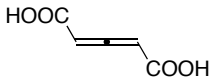
Hence, four different *endo*- or *exo*-cyclization products can be obtained. The formation of five- or six- membered rings *via* gold species **I** or **IV** (Scheme 4.1), by nucleophilic attack at a terminal allenic carbon atom, is favored in most cases, whereas products arising from

nucleophilic attack at the central allenic carbon atom (via intermediates **II** and **III**) are quite rare. In most cases, the cyclization products are chiral and can be accessed in a stereoselective manner either from chiral allenes by axis-to-center chirality transfer or from achiral allenes utilizing chiral gold catalysts.

In this chapter, we describe gold-catalyzed cyclizations of allenes by attack of heteroatom or carbon nucleophiles, with particular emphasis on the synthesis of multisubstituted pyrroles, ubiquitous constituent in natural and pharmaceutical products.

4.1.1. Structural properties of allenes

Compounds which contain the >C=C=C< groups are known as allenes.[4] Unlike conjugated dienes, they have only recently attracted the attention of chemists, in spite of the fact that the earliest authentic syntheses of allenes were reported nearly a century ago (Figure 4.1).[5]



I

Figure 4.1. *Penta-2,3-dienedioic acid **I**, one of the first synthesized allenes*

As a result of their tedious methods of preparation and the mistaken belief that the cumulated double-bond system would prove to be relatively unstable, allenes came to be regarded as chemical curiosities, mainly of interest for their unusual stereochemistry, which van't Hoff successfully predicted as long ago as 1875.

In the last 20 years this situation has entirely changed. Several convenient methods have been devised for the synthesis of allenes, and an ever-growing volume of publications is unfolding their interesting properties. The industrial potential of such compounds is being examined, and numerous patents cover the use of allenes as dyes, drugs, antioxidants, polymers or copolymers.

Proof that natural organisms produce compounds containing the allene bond system was first obtained in 1952. Since then, numerous other examples of natural allenes have come to light (Figure 4.2), giving irrevocably importance to the development of the allene chemistry.

With respect to structural features, the central carbon of the 1,2-diene system is sp-hybridized, leaving two orthogonal p-orbitals for π-bonding with the terminal sp^2-hybridized carbon atoms of the allene.

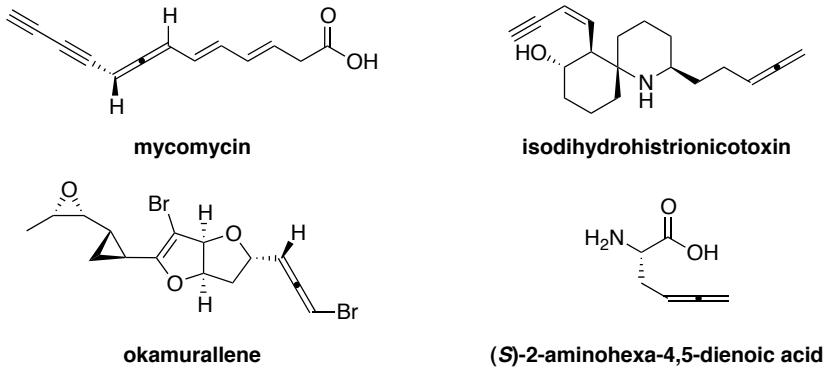


Figure 4.2. *Examples of naturally occurring allenes*

Maximum overlap results in two orthogonal π-bonds, which cannot rotate freely (Figure 4.3).

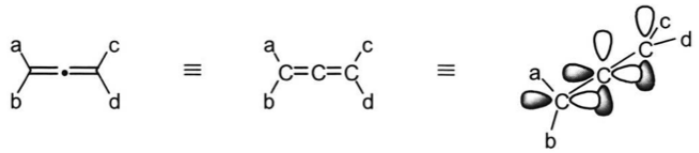


Figure 4.3. *Orthogonal bonding in allene*

Because of this structural constriction, axially chiral allenes can be prepared.[7a] Assignment of the absolute configuration is based on the Cahn, Ingold and Prelog convention (Figure 4.4).

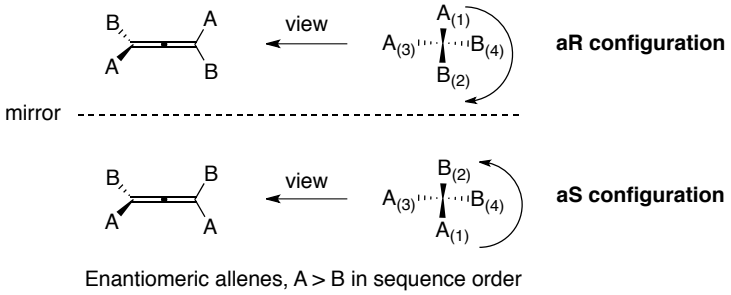


Figure 4.4. *Axially chiral allenes*

4.1.2. Gold complexes

Simple AuCl or $AuCl_3$ are sufficiently carbophilic to catalyze many reactions of the more reactive allenes. However, for many gold-catalyzed transformations, the most convenient catalysts are cationic complexes generated by chloride abstraction from [$AuCl(PPh_3)$] or similar phosphine complexes, using an equivalent of a silver salt with a non-coordinating

anion to generate the corresponding cationic species [Au(S)(PPh_3)]X (S = solvent or substrate molecule) *in situ*.[8] Similar cationic complexes can be obtained by cleavage of the Au-Me bond in [AuMe(PPh_3)] using a protic acid.[8,9]

Figure 4.5 shows a number of different gold complexes that act as catalysts or precatalysts. The gold(I) complexes **279a-c** and **280** bearing bulky, biphenyl-based phosphine ligands, which have been shown to be excellent ligands for Pd-catalyzed reactions,[10] yield very active catalysts when mixed with Ag(I) salts. More convenient are the cationic complexes **281** and **283**, which are stable crystalline solids that can be handled under ordinary conditions yet are very reactive as catalysts in a variety of transformations.[11]

The structures of **279a-c**, **280**, **281**, and **283** have been confirmed by X-ray crystallography.[12] The related complexes **282a** and **282b** containing weakly coordinated bis(trifluoromethanesulfonyl)amide (NTf_2) have also been prepared.[13]

Cationic complexes or those with NTf_2 ligands lead to cleaner reactions in the absence of Ag(I) salts.

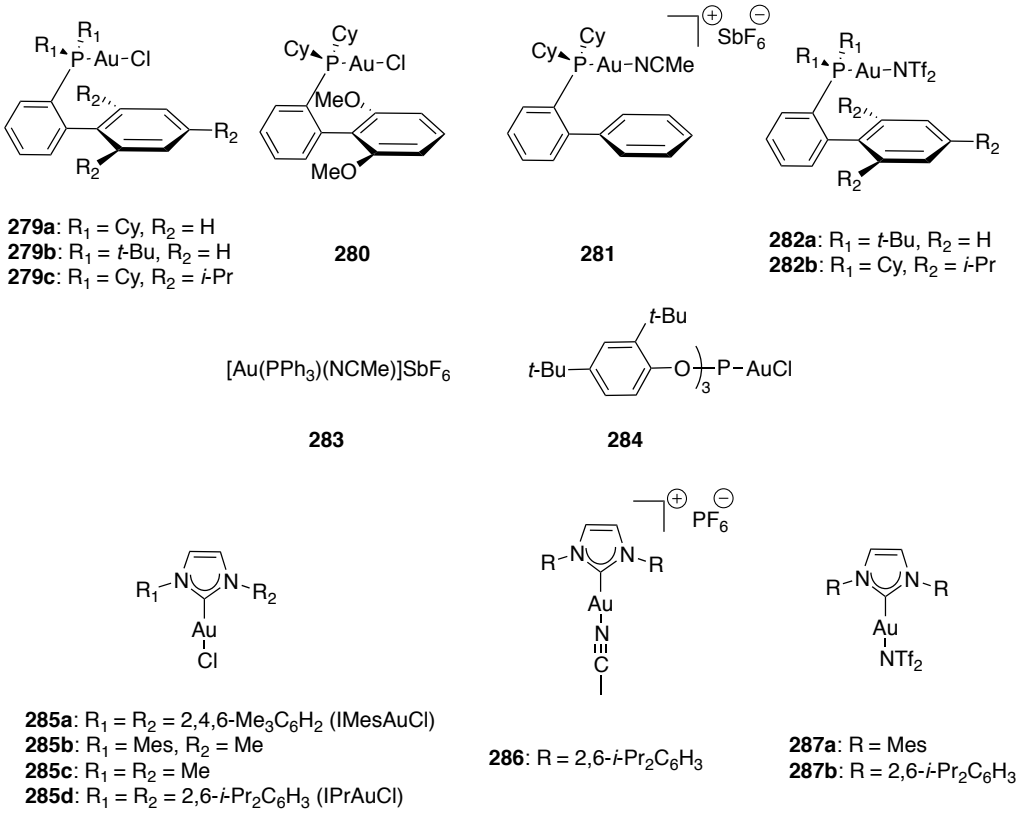


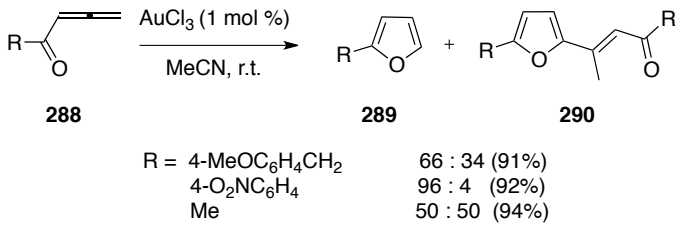
Figure 4.5. *Gold catalysts or precatalysts for allene cycloisomerizations*

Gold(I) complex **284** bearing tris(2,6-di-*tert*-butylphenyl)phosphite as a bulky ligand leads to a highly electrophilic cationic Au(I) catalyst in situ upon chloride abstraction with $AgSbF_6$.[14]

Gold complexes such as **285a-d** that contain strongly donating NHC ligands are also good precatalysts.[15] Cationic complexes bearing NHC ligands (such as **286**, which shows moderate stability at room temperature)[16] and those with NTf_2 ligands (**287a** and **287b**) have also been reported.[17]

4.1.3. Cyclization of allenes by attack of oxygen nucleophiles

The first gold-catalyzed addition of a heteroatom nucleophile was accomplished by Hashmi et al.,[18] who reported the cycloisomerization of α-allenyl ketones **288** to the corresponding substituted furans **289** (Scheme 4.2). Even if previous literature reports showed other transition metals (silver[19] or palladium[20]) to be employed for cycloisomerization reactions of this type, the use of gold entails a number of advantages such as shorter reaction times, milder conditions, and/or lower catalyst loadings. The reaction times decrease from one week (silver) to one hour (palladium) to one minute when gold catalysts were applied. On the other hand, variable amounts of the dimerization product **290** were obtained. In particular, product **290** was generated by a subsequent Michael addition of the newly formed furan to unconsumed allenic ketone.

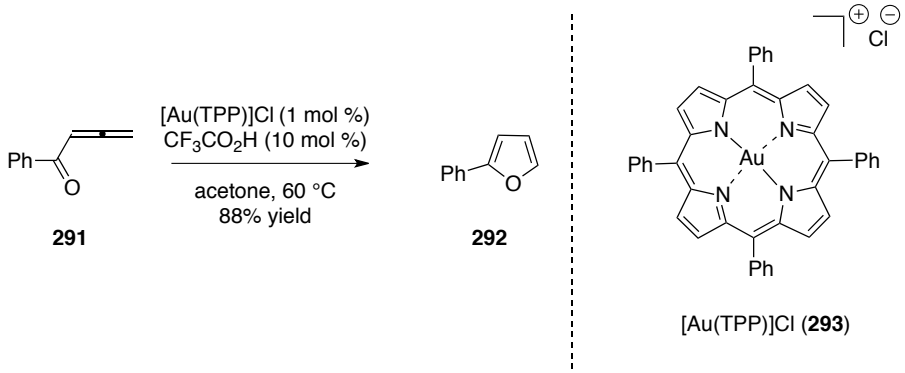


Scheme 4.2. *Gold-catalyzed cycloisomerization of allenic ketones to furans*

The side reaction can be prevented by using a modified gold catalyst as demonstrated by Che and co-workers,[21] who employed the cationic gold(III) porphyrin complex **293** for the cyclization of ketone **291** to the corresponding furan **292** (Scheme 4.3). Under these conditions, no dimer could be detected, but the presence of trifluoroacetic acid and elevated temperatures were essential, leading to problems with acid-labile substrates.

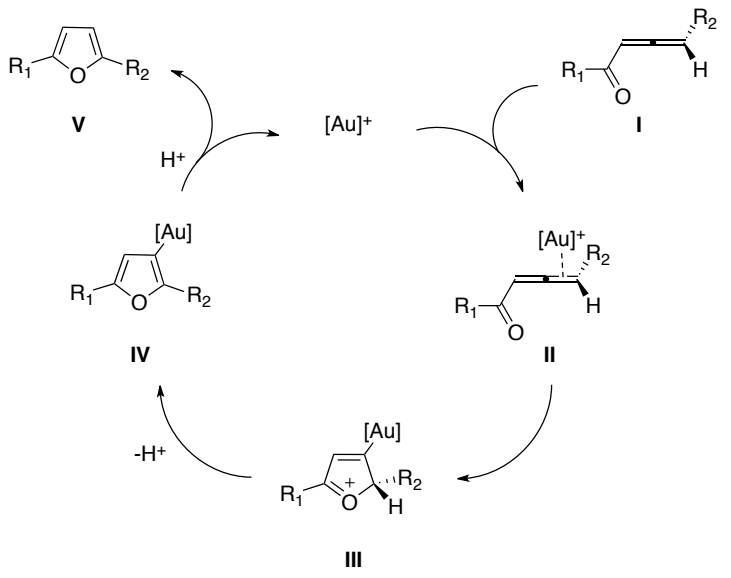
The Au(III) catalyst **293** resulted to be highly reactive (the catalyst loading can be decreased to 0.1 mol%), it could be recovered and reused in up to nine consecutive runs with no appreciable loss of reactivity or decrease of yield.

A proposed mechanism for the cycloisomerization of allenic ketones with $AuCl_3$ or [Au(TPP)]Cl is reported in Scheme 4.4.



Scheme 4.3. *Cycloisomerization of allenic ketones catalyzed by the porphyrin complex* ***293***

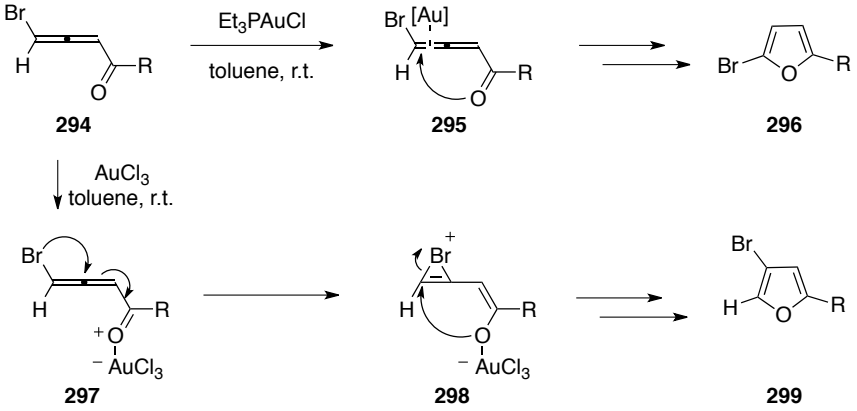
The active gold species coordinates to the "distal" double bond of the allene and induces a nucleophilic attack of the oxygen atom, furnishing the cationic intermediate **III**. After deprotonation to form the furyl-gold species **IV**, a protodeauration (which is facilitated in the presence of an external proton donor like CF_3CO_2H) leads to the furan **V** and releases the gold catalyst into the catalytic cycle. Widenhoefer and co-workers recently gained experimental support for this model through the isolation of a gold π-allene complex.[22]



Scheme 4.4. *Mechanistic model for the gold-catalyzed cycloisomerization of allenic ketones*

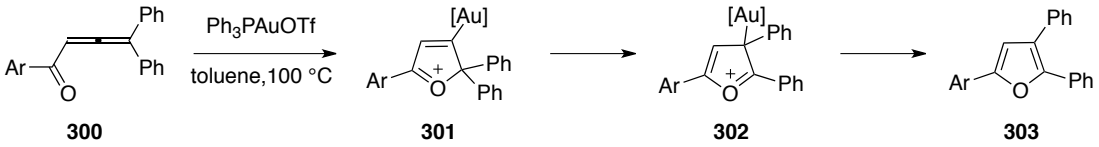
Besides alkyl- and aryl-substituted furans, halogenated furans are also considered molecules of great interest since they can undergo a large variety of transformations. These functionalized heterocycles were synthetized by the gold-catalyzed cycloisomerization of bromoallenones **294**, as shown in Scheme 4.5. Gevorgyan and co-workers[23] demonstrated that

the structure of the product is highly dependent on the gold catalyst. When a carbophilic Au(I) species (e.g., Et_3PAuCl) was used, the cycloisomerization led to the expected 5-bromofuran **296**, whereas the more oxophilic gold(III) chloride preferentially generated 4-bromofuran **299**. This remarkable result can be explained by formation of a bromoirenium ion **298** arising from the coordination of the oxophilic Au(III) catalyst to the carbonyl oxygen atom.



Scheme 4.5. *Gold-catalyzed cycloisomerization of bromoallenones*

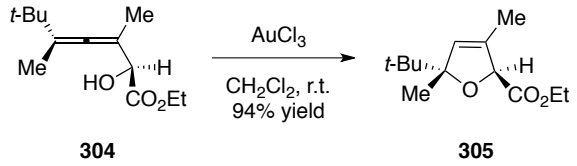
The driving force for the cycloisomerization of allenones is the formation of aromatic heterocycles. This is even possible with allenones bearing two carbon substituents in the γ-position if one of the substituents has a pronounced tendency to migrate (Scheme 4.6).[24] Indeed, while heating allenyl ketones **300** in the presence of $Ph_3PAuOTf$, furans **303** were formed *via* intermediates **301** and **302**, by ring closure and subsequent [1,5]-phenyl shift.



Scheme 4.6. *Gold-catalyzed cycloisomerization of allenones **300***

As demonstrated by the previous examples, the gold-catalyzed cycloisomerization of allenones offers an efficient and convenient access to various substituted furans. These products, however, are achiral and no advantages result while considering the possibility to employ chiral allenes as cyclization precursors. In contrast, replacing the carbonyl group with a hydroxy group allows the formation of chiral heterocycles.

Shortly after the first account on the gold-catalyzed cycloisomerization of allenones,[18] Krause and co-workers[25] reported the synthesis of chiral 2,5-dihydrofuran **305** by treatment of α-hydroxyallene **304** with catalytic amounts of $AuCl_3$ in CH_2Cl_2 (Scheme 4.7).

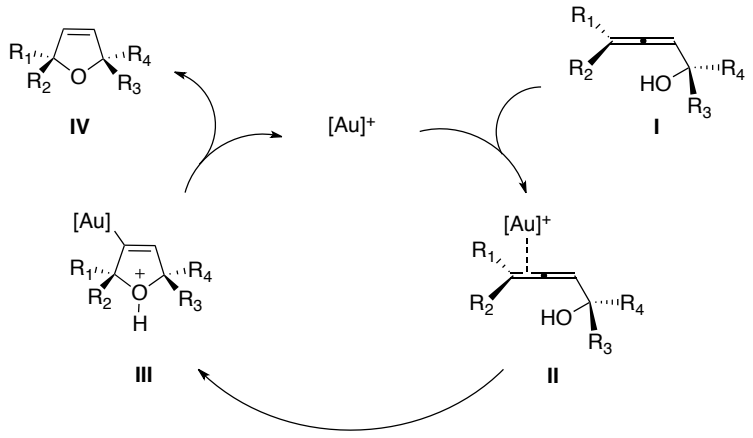


304 **305**

Scheme 4.7. *Gold-catalyzed cycloisomerization of α-hydroxyallenes*

Many functionalities (e.g., carbonyl groups, free alcohols, acid-sensitive protecting groups) were tolerated under these conditions. In the case of chiral allenes bearing alkyl substituents, the stereochemical information of the chirality axis was completely transferred to the newly formed stereogenic center.[26]

The proposed mechanistic model for the gold-catalyzed cycloisomerization of α-hydroxyallenes is similar to that of allenones (Scheme 4.8). Thus, coordination of the carbophilic gold catalyst to the allenic double bond distal to the hydroxy group affords π-complex **II**, which undergoes a 5-*endo*-cyclization to the zwitterionic σ-gold species **III**. Protodeauration leads to the dihydrofuran **IV** and regenerates the gold catalyst.

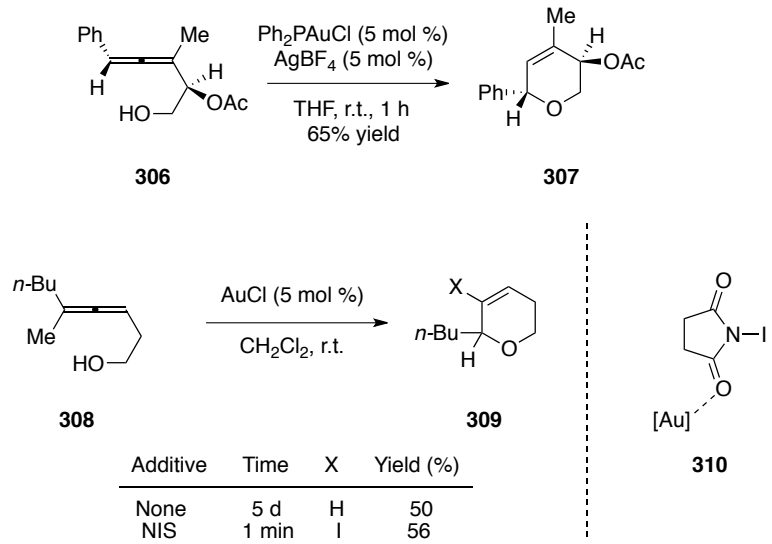


Scheme 4.8. *Mechanistic model for the gold-catalyzed cycloisomerization of α-hydroxyallenes*

Since the cyclization is accelerated in the presence of external proton donors (water, methanol), the protodeauration of **III** is thought to be the rate-limiting step of the reaction.

6-*endo*-trig cyclization can also be achieved by gold catalysis. Indeed, β-hydroxyallene **306** is converted to the corresponding 5,6-dihydro-2H-pyran **307** in the presence of a cationic gold catalyst formed in situ from Ph_3PAuCl and $AgBF_4$ (Scheme 4.9).[27]

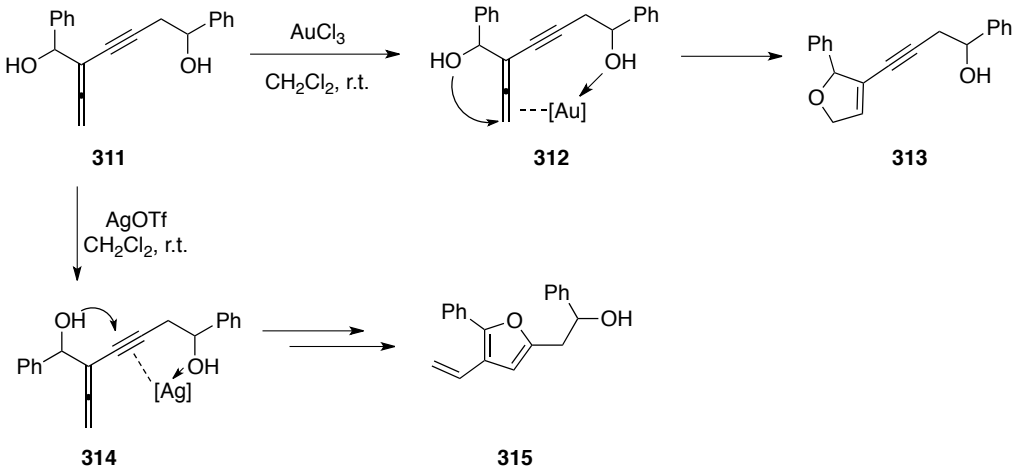
These cyclizations are often very slow, resulting in reaction times of several days. For example, treatment of β-hydroxyallene **308** with 5 mol% of AuCl in dichloromethane at room temperature required five days for complete conversion to dihydropyran **309** (X = H). However, addition of *N*-iodosuccinimide (NIS) to the reaction mixture induced a tremendous acceleration, leading to the formation of the corresponding iodinated dihydropyran within 1 min at room temperature.[28] This effect was probably caused by a very rapid iododeauration of a σ-gold intermediate (cf. **III** in Scheme 4.8) by NIS, which was activated by the gold catalyst (species **310**).[29]



Scheme 4.9. *Gold-catalyzed cycloisomerization of β-hydroxyallenes*

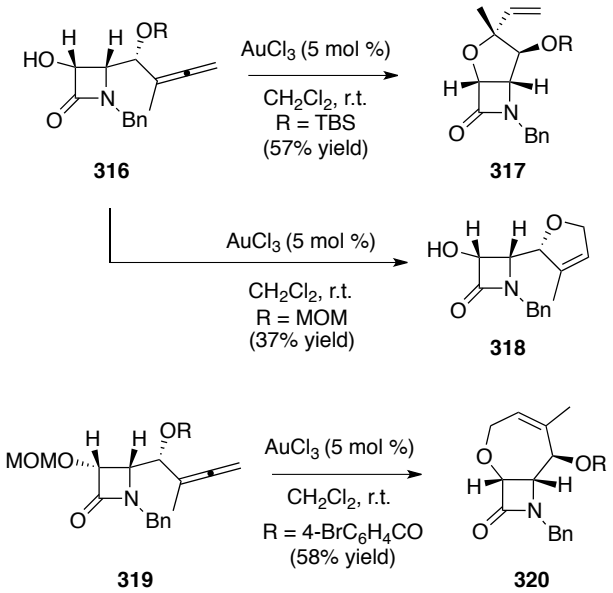
An interesting example of a chemoselective gold-catalyzed transformation was reported by Kim and Lee.[30] In this case, the diol **311** bearing both an alkyne and an allene moiety afforded different products depending upon the catalyst employed to promote the cyclization (Scheme 4.10). Whereas gold(III) chloride activated the allene and gave dihydrofuran **313** *via* intermediate **312**, treatment of **311** with silver triflate yielded furan **315** by activation of the triple bond (intermediate **314**).[31]

Besides *endo*-cyclizations, functionalized allenes can also undergo gold-catalyzed *exo*-selective attack, in particular if the distance between the nucleophilic group and the allene moiety is large.



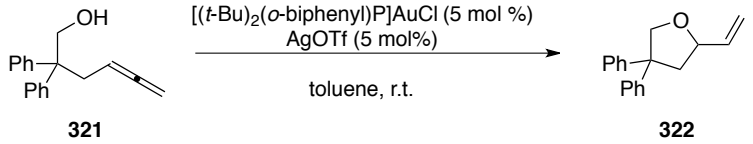
Scheme 4.10. *Cycloisomerization of diol* ***311***

Alcaide *et al.*[32] examined different gold-catalyzed transformations of β-lactams **316** containing an α,γ-dihydroxyallene structure and observed the formation of three different cyclization products (Scheme 4.11). Whereas treatment of the TBS-protected substrate with $AuCl_3$ afforded tetrahydrofuran derivative **317**, resulting from 5-*exo*-attack of the γ-hydroxy group, the corresponding methoxymethyl (MOM)-protected starting material underwent deprotection and 5-*endo*-trig cyclization to yield the 2,5-dihydrofuran **318** under the same conditions. Moving the MOM group to the γ-position (substrate **319**) led to the formation of the unusual product **320** by gold-catalyzed deprotection and 7-*endo*-trig cycloisomerization.



Scheme 4.11. *Different cyclization modes of allene* ***316*** *and* ***319***

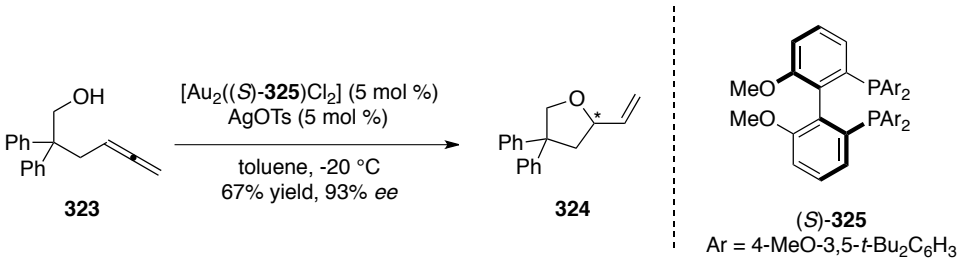
Another example for a gold-catalyzed *exo*-selective cyclization is the transformation of γ-allenol **321** into tetrahydrofuran **322**, which was reported by Widenhoefer and co-workers[33] (Scheme 4.12). The corresponding 6-*exo*-dig cycloisomerization leading to a dihydropyran did not take place under these conditions but rather in the presence of a platinum catalyst. Application of this method to axially chiral allenols afforded the corresponding tetrahydrofurans with high levels of chirality transfer.



321 **322**

Scheme 4.12. *Exo-selective cycloisomerization of allenol* ***321***

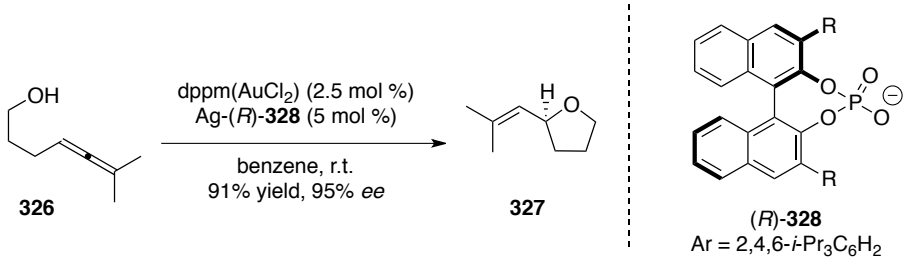
The same research group extended this methodology to the synthesis of the enantiomerically enriched tetrahydrofuran **324** by using chiral phosphine ligands on the gold catalyst (Scheme 4.13).[34] In the presence of biphep derivative (*S*)-**325**, the attack of the oxygen atom was directed to the Si-side of the allene.



323 **324**

Scheme 4.13. *Enantioselective cycloisomerization of allenols*

An alternative catalytic system, reported by Toste and co-workers[35], took advantage of a chiral counterion, which was introduced into the catalyst as a silver salt (Scheme 4.14).



326 **327**

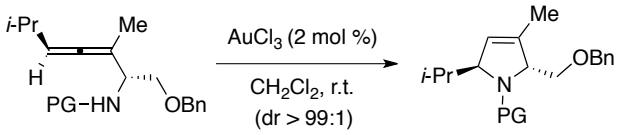
Scheme 4.14. *Use of a chiral counterion in enantioselective cycloisomerizations of allenols*

Thus, treatment of γ-allenols **326** with catalytic amounts of an achiral gold precatalyst and the chiral silver salt Ag-(*R*)-**328** afforded heterocycle **327** with high yield and excellent enantioselectivity.

4.1.4. Cyclization of allenes by attack of nitrogen nucleophiles

In 2004, Morita and Krause[36] reported the first intramolecular *endo*-selective hydroamination of various α-aminoallenes, which were converted to the corresponding 3-pyrrolines **330** with high levels of chirality transfer (Scheme 4.15).

Whereas short reaction times (30 min) were observed for protected aminoallenes, five days at room temperature were required for full conversion of the corresponding unprotected compound. The diminished reactivity is probably due to deactivation of the gold catalyst by the Lewis-basic amino group. By using gold(I) chloride instead of $AuCl_3$, the reaction time was decreased to several hours at room temperature.[37] The same method was applied by Lee and co-workers,[38] who used gold(III) chloride in dichloromethane to obtain bicyclic β-lactams, as well as by Reissig and co-workers[39] in a synthesis of tricyclic pyrroloisoindolones. Analogous to β-hydroxyallenes (Scheme 4.9), β-aminoallenes underwent a slow gold-catalyzed 6-*endo*-cycloisomerizion to the corresponding tetrahydropyridins.[27]



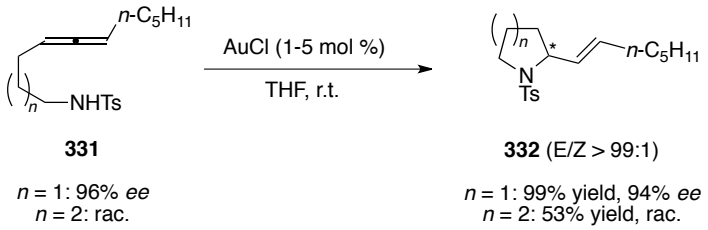
329 **330**

PG	Time	Yield (%)
Ms	30 min	77
Ts	30 min	93
Ac	30 min	80
Boc	30 min	69
H	5 d	74

Scheme 4.15. *Gold-catalyzed cycloisomerization of α-aminoallenes*

In analogy to the corresponding allenols, γ- or δ-aminoallenes also reacted through an *exo*-selective hydroamination reactions in the presence of gold catalysts.[40] Thus, Yamamoto and co-workers[41] obtained 2-vinylpyrrolidines or 2-vinylpiperidines **332** by treatment of aminoallenes **331** with gold(I) chloride (Scheme 4.16).

The low catalyst loading of 1 mol % was used when γ-aminoallenes were submitted to the reaction conditions revealed a high reactivity of these substrates toward the gold catalyst, whereas the formation of the six-membered ring required 5 mol% and longer reaction times (24 h at room temperature compared to 3 h for the 5-*exo*-trig cyclization).



331

n = 1: 96% *ee*
n = 2: rac.

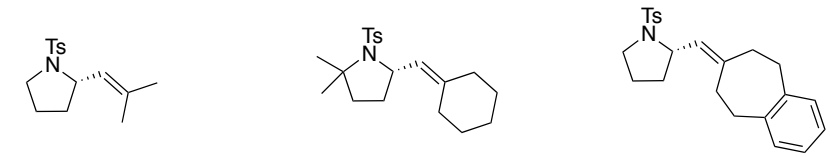
332 (E/Z > 99:1)

n = 1: 99% yield, 94% *ee*
n = 2: 53% yield, rac.

Scheme 4.16. *Gold-catalyzed exo-cycloisomerization of aminoallenes*

In the case of the enantiomerically enriched γ-aminoallene **331**, axis-to-center chirality transfer was observed, leading to pyrrolidine **332** with high enantioselectivity. Widenhoefer and co-workers[33] obtained analogous results using a phosphine-stabilized gold complex and silver triflate in dioxane at room temperature.

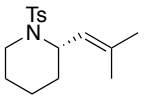
Higher levels of chiral induction were achieved by Toste and co-workers[42] using (*R*)-xylyl-BINAP(Au-*p*-nitrobenzoate)$_2$ or (*R*)-ClMeOBIPHEP(Au-*p*-nitrobenzoate)$_2$ as catalyst. These complexes allowed the smooth formation of chiral the heterocycles **333a-f** with up to 99% *ee* and high chemical yield from the corresponding trisubstituted tosyl-protected aminoallenes (Figure 4.6).



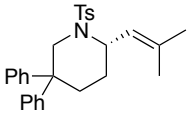
333a
98% yield, 99% *ee*

333b
76% yield, 96% *ee*

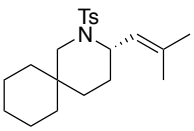
333c
80% yield, 98% *ee*



333d
88% yield, 81% *ee*



333e
70% yield, 88% *ee*



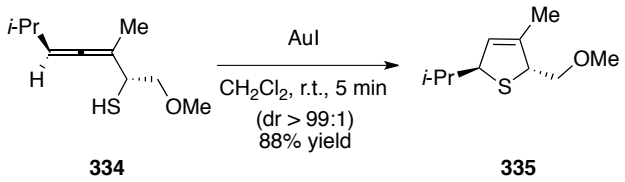
333f
66% yield, 97% *ee*

Figure 4.6. *Products obtained by enantioselective cycloisomerization of γ- or δ-aminoallenes*

Similar to the cycloisomerization of γ-hydroxyallenes (Scheme 4.14), gold catalysts with a chiral counterion could also be employed for the highly enantioselective intramolecular *exo*-hydroamination of aminoallenes.[35]

4.1.5. Cyclization of allenes by attack of sulfur nucleophiles

The gold-catalyzed addition of a sulfur nucleophile to an allene may be considered rather exotic. After all, sulfides are known to be potent poisons for transition metal catalysts, and because of the strong Au-S bonds, gold is no exception to this rule. Nevertheless, in 2006 Morita and Krause[43] reported the gold-catalyzed cycloisomerization of α-thioallenes (e.g., **334**) to the corresponding 2,5-dihydrothiophenes of type **335** (Scheme 4.17), which, at the time, was the first example of a gold-catalyzed carbon-sulfur bond formation.

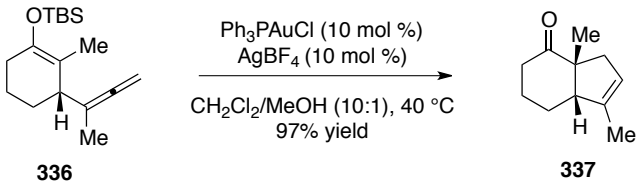


Scheme 4.17. *Gold-catalyzed cycloisomerization of α-thioallenes*

In this transformation, gold(I) catalysts showed a higher reactivity and gave better yields than gold(III) chloride. Independent of the catalyst used, complete axis-to-center chirality transfer was observed in the cycloisomerization of α-thioallenes.[44]

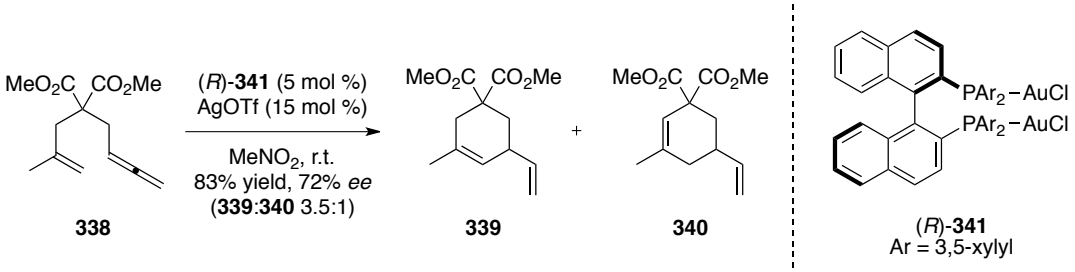
4.1.6. Cyclization of allenes by attack of carbon nucleophiles

Addition reactions of carbon nucleophiles to allenes have been first disclosed in 2006, and the number of reported examples is still rather small. Toste and co-workers[45] used acetylenic and allenic silyl enol ethers for the gold-catalyzed intramolecular C-C bond formation. For example, substrate **336** underwent a 5-*endo*-trig cyclization to hexahydroindenone derivative **337** in the presence of a cationic gold catalyst (Scheme 4.18). In these transformations, water or methanol was used as external proton source for protodeauration of intermediate vinylgold species.



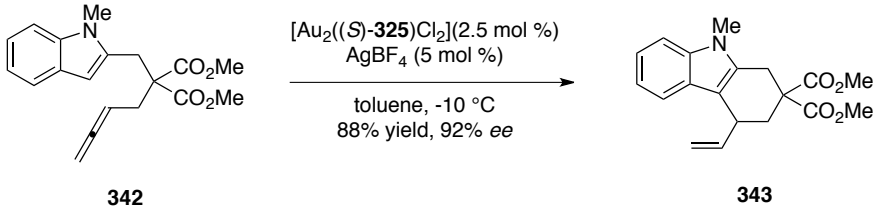
Scheme 4.18. *Gold-catalyzed cycloisomerization of allenic silyl enol ether* ***336***

Gold-catalyzed cyclization reactions of allenenes and allenynes usually proceed *via* non-nucleophilic pathways, different from those outlined in Scheme 4.1.[46] Exceptions involve the cycloisomerization of allenenes of the type **338** in the presence of chiral gold precatalyst (*R*)-**341** and silver triflate, which resulted in a mixture of chiral vinylcyclohexenes **339/340** with high yield and good enantioselectivity (Scheme 4.19).[47] The formation of these products is rationalized by nucleophilic attack of the olefinic double bond at the activated allene, followed by deprotonation and protodeauration of the resulting cyclohexyl cation.



Scheme 4.19. *Gold-catalyzed cycloisomerization of allenenes*

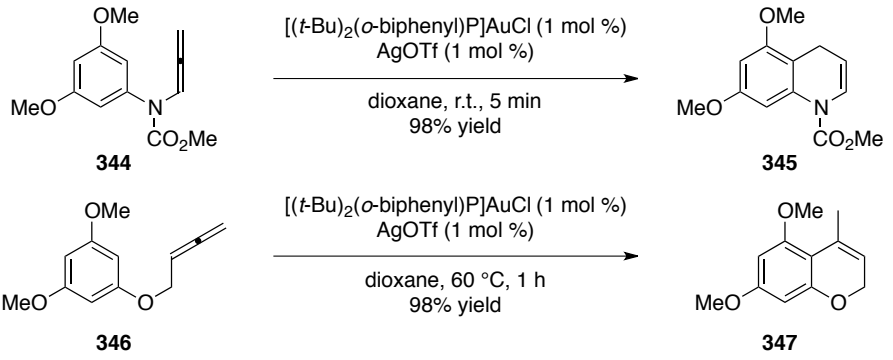
Electron-rich heteroaromatics like indoles can be used as nucleophiles in gold-catalyzed hydroarylations. As in the case of *exo*-selective hydroalkoxylations and hydroaminations, Widenhoefer[33] reported the synthesis of tetrahydrocarbazoles and related heterocycles from allenyl indoles. Starting from achiral allene **342**, the hydroarylation product **343** was obtained with high *ee* by using chiral gold precatalyst [Au_2{(*S*)-**325**}Cl_2] (cf. Scheme 4.13) and silver tetrafluoroborate (Scheme 4.20). Interestingly, this method also allowed the formation of seven-membered carbocycles.[48] Recently, *endo*-selective gold-catalyzed cycloisomerizations of *N*-(2,3-butadienyl)-substituted indol derivatives were described as well.[49]



Scheme 4.20. *Intramolecular hydroarylation of allenyl indoles*

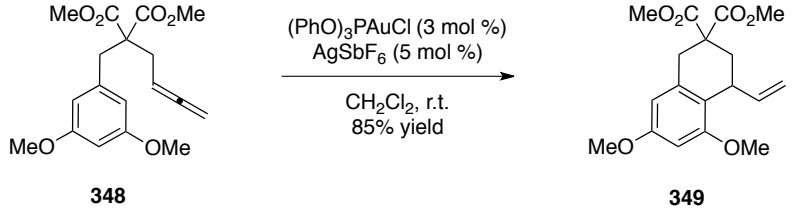
Electron-rich phenyl rings are also good nucleophiles for the intramolecular gold-catalyzed hydroarylation of allenes. An effcient route to dihydroquinoline and chromene derivatives was developed by Fujii, Ohno, and co-workers,[50] who exposed allenic anilines or allenic arylethers to a cationic gold catalyst (Scheme 4.21). Depending on the structure of the

substrate, the C-C bond was formed at the terminal or central allenic carbon atom. Thus, allenamide **344** delivered dihydroquinoline **345** with 96% yield by 6-*endo*-attack, whereas substrates **346**, with an extended tether between the allene and the aryl ring, underwent 6-*exo*-cyclization. Because of the lower reactivity of allene **346**, heating and longer reaction times were required to obtain the hydroarylation product **347** in synthetically relevant yields.



Scheme 4.21. *Intramolecular hydroarylation of arylallenes*

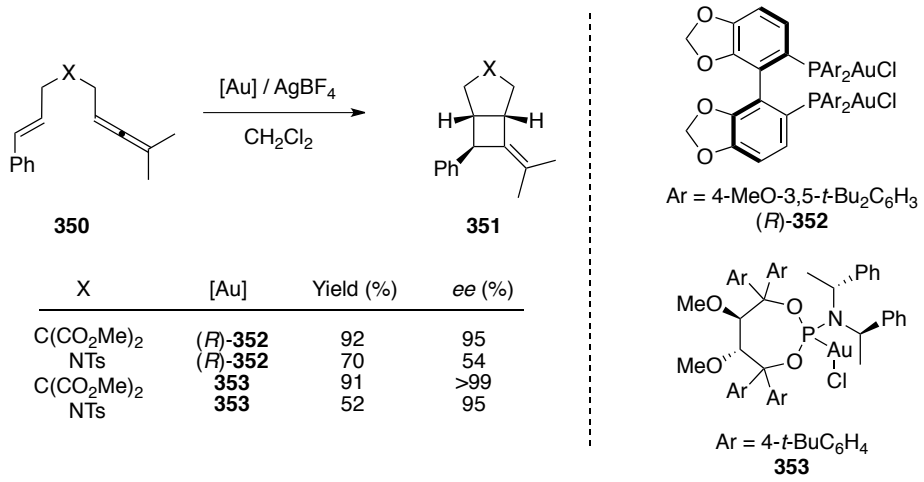
Gagné and co-workers[51] applied this method to arylallenes of the type **348**, bearing an extended all-carbon linker between the reactive sites. In this case, a 6-*exo*-trig cyclization was induced by a mixture of triphenylphosphite gold(I) chloride (3 mol%) and silver hexafluoroantimonate (5 mol%), giving the tetralin derivative **349** in high yield (Scheme 4.22). Extensive mechanistic studies revealed a diaurated species as resting state of the catalyst, which turned out to be activated by the silver salt.[52]



Scheme 4.22. *Intramolecular hydroarylation of arylallene **348***

Another possibility to use the activation of allenes by gold catalysts for C-C bond formation is their participation in cycloadditions.[53] Intramolecular [2+2]-cycloadditions of allenenes **350** were studied by Toste and co-workers,[54] who obtained the bicyclic cycloadducts **351** with moderate to high enantioselectivities by using chiral biarylphosphinegold(I) catalyst (*R*)-**352** together with silver tetrafluoroborate (Scheme 4.23). Even better results were reported recently by Fürstner and co-workers,[55] who employed the chiral TADDOL-derived gold

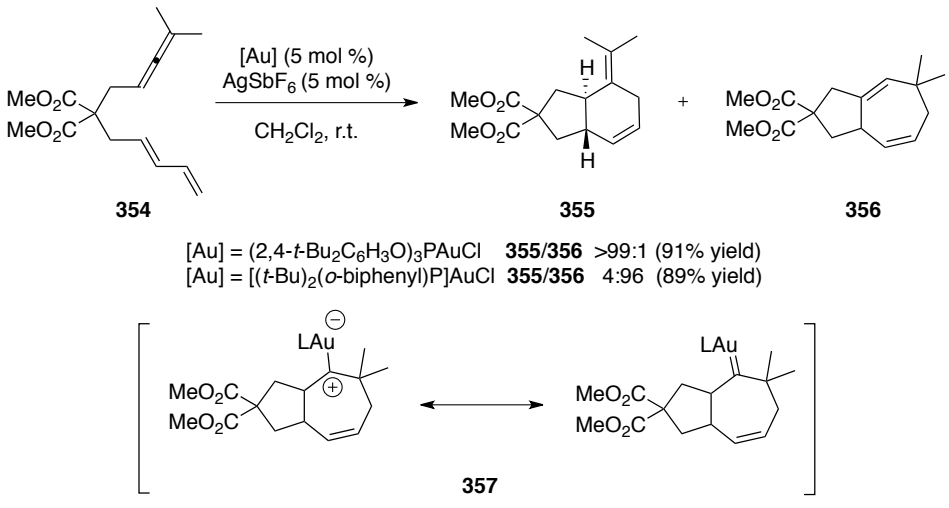
complex **353**. By using electron-rich NHC-gold catalysts, an alternative pathway toward [3+2]-cycloaddition products can be favored.[56]



X	[Au]	Yield (%)	*ee* (%)
$C(CO_2Me)_2$	(*R*)-**352**	92	95
NTs	(*R*)-**352**	70	54
$C(CO_2Me)_2$	**353**	91	>99
NTs	**353**	52	95

Scheme 4.23. *Gold-catalyzed intramolecular [2+2]-cycloaddition of allenenes*

Precatalyst **353** and related gold phosphoramidite complexes also promote enantioselective intramolecular [4+2]-cycloadditions of allenic dienes.[55,57] This transformation was previously studied by Shapiro and Toste,[53,58] who obtained Diels-Alder adduct **355** from tetraene **354** in the presence of cationic gold species formed from arylphosphite gold chlorides and silver hexafluoroantimonate (Scheme 4.24). In contrast to this, the [4+3]-cycloaddition product **356** was formed almost exclusively with gold catalysts bearing electron-rich σ-donor ligands. This was attributed to a stabilization of the gold carbenoid intermediate **357** formed in the [4+3]-cycloaddition.[56,58,59]

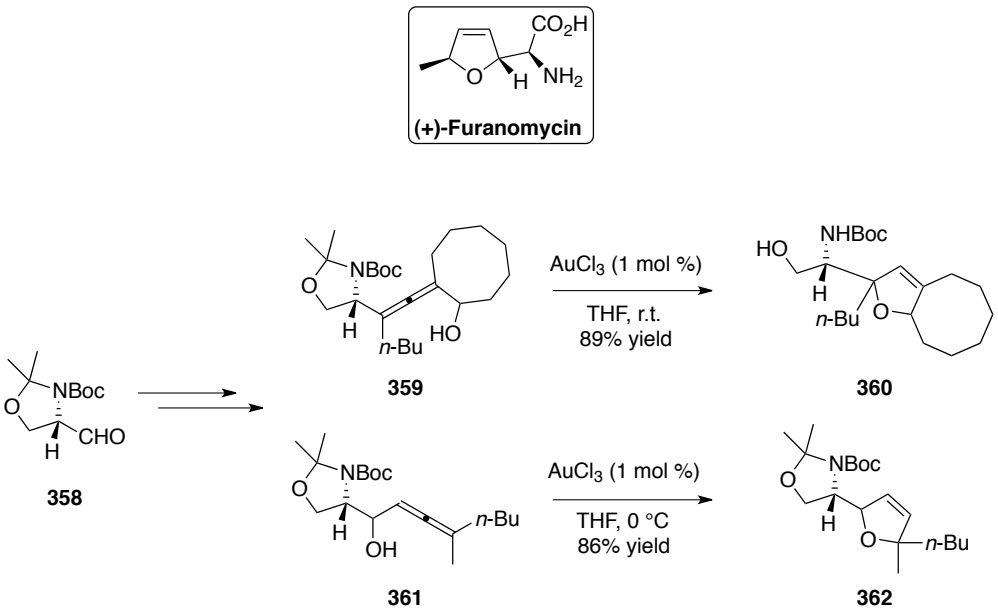


Scheme 4.24. *Gold-catalyzed intramolecular [4+2]- and [4+3]-cycloaddition of allenic diene **354***

4.1.7. Selected applications of allene cycloisomerizations in target-oriented synthesis

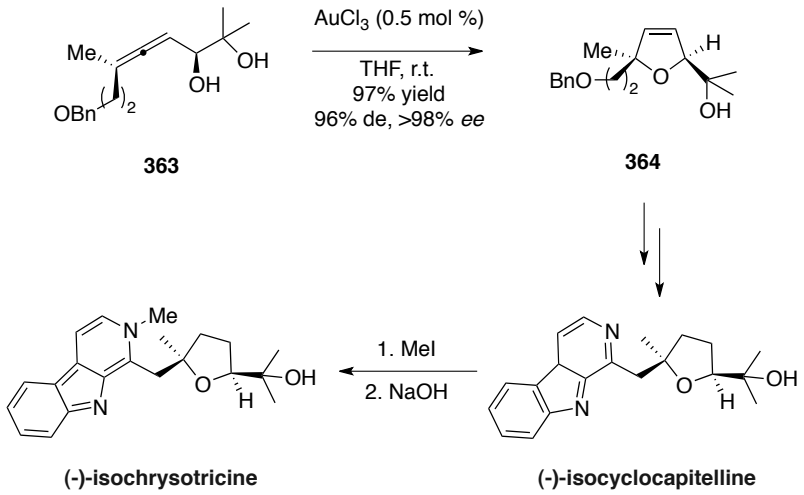
Gold(III) chloride in tetrahydrofuran (THF) resulted to be an efficient catalyst for the cycloisomerization of various functionalized allenols like α-hydroxyallenamides,[60] α,α'-bishydroxyallenes,[61] methoxyallenols,[62] and arylallenes,[63] and several applications in target-oriented synthesis have been disclosed. In a recent example published by Erdsack and Krause,[64] Garner's aldehyde **358** was used as precursor for α-hydroxyallenes **359** and **361**, which, upon treatment with 1 mol % of gold(III) chloride in THF, underwent cycloisomerization to the dihydrofurans **360** and **362** (Scheme 4.25).

In the case of allene **359**, the cyclization was accompanied by acetal cleavage, apparently due to the higher reaction temperature (room temperature instead of 0 °C). Subsequent removal of the protecting groups and oxidation afforded analogues of the antibiotic amino acid furanomycin.[65]



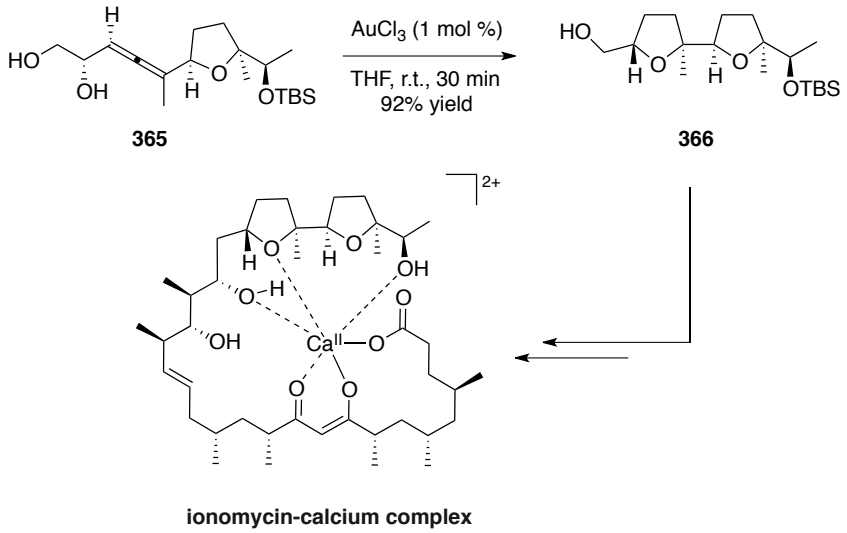
Scheme 4.25. *Synthesis of furanomycin analogues*

In the same year, Volz and Krause[65] reported the first total synthesis of the β-carboline alkaloids (-)-isocyclocapitelline and (-)-isochrysotricine by Pictet-Spengler reaction of a chiral tetrahydrofuran with tryptamine (Scheme 4.26). Key intermediate **364** was obtained from the corresponding α,β-dihydroxyallene **363** with complete axis-to-center chirality transfer, by the use of only 0.05 mol % of gold(III) chloride in THF. Hydrogenation of the double bond, oxidation, and carbolin formation led to the enantiomerically pure natural products.



Scheme 4.26. *Synthesis of β-carboline alkaloids*

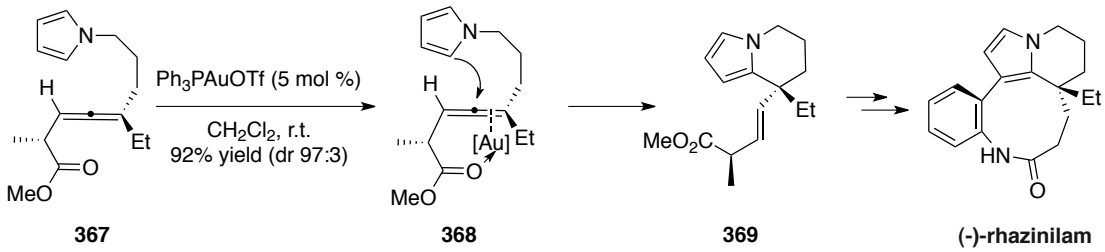
An analogous gold-catalyzed cycloisomerization of dihydroxyallene **365** to 2,5-dihydrofuran **366** was employed recently by Kocienski and co-workers[66] in their synthesis of the ionomycin-calcium complex (Scheme 4.27).



Scheme 4.27. *Synthesis of the ionomycin-calcium complex*

Most reports on the gold-catalyzed intramolecular C-C bond formation of allenes take advantage of electron-rich aromatics or heteroaromatics as the nucleophile.[67] Interestingly, this hydroarylation has been utilized in natural product synthesis even before the method was studied extensively. Thus, Nelson and co-workers[68] used a cationic gold catalyst to activate allene **367** for nucleophilic attack of the pyrrole ring, which delivered tetrahydroindolizine **369** (a precursor of the alkaloid (-)-rhazinilam) with high yield and excellent chirality transfer

(Scheme 4.28). It seems reasonable to assume that coordination of the Lewis acidic gold catalyst to the carbonyl group (intermediate **368**) is key to the high diastereoselectivity. In contrast to this, palladium or silver catalysts either failed to deliver the desired cyclization product or gave poor stereoselectivities.



Scheme 4.28. *Gold-catalyzed cycloisomerization of allenic pyrrol derivative* ***367***

These selected examples and several other applications in target-oriented synthesis demonstrate that gold-catalyzed cyclization of allenes is a convenient tool for the rapid generation of molecular complexity.

4.2. RESULTS AND DISCUSSION

Interest in the catalytic chemistry of Au(I) and Au(III) complexes has undergone a marked increase. Although traditionally undeveloped as homogeneous catalysts, such species have recently been employed in a great number of organic transformations. In particular, gold-catalyzed reactions of allenes have attracted tremendous attention in recent years, as pointed out in the previous section. The Lewis acidity of gold complexes, coupled with their potential to stabilize cationic reaction intermediates, imparts unique reactivity to such catalysts, which has been exploited in the development of new synthetic methods to achieve the formation of complex molecules.

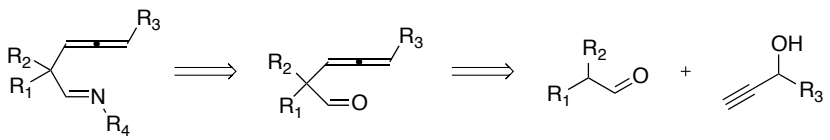
Recently, we envisaged to develop straightforward gold-catalyzed procedures, employing functionalized allenes for the synthesis of heterocyclic compounds. In particular, we focused our attention on highly substituted pyrroles. These compounds are important heterocycles broadly used in material science[69] and found in naturally occurring[70] and biologically important molecules.[71]

Several groups are currently investigating the transition metal-catalyzed synthesis of such heteroaromatic substrates.[72] Many processes, however, still present limitations in term of substituents and consequently exhibit a narrow substrate scope. For this reason, the development of versatile methods for the direct access to functionalized pyrroles is highly desirable.

In this section, we report new gold(I)-catalyzed cycloisomerizations of β-allenylimines and β-allenylhydrazones, which allowed the formation of 2,3,5-substituted pyrroles. Selective intramolecular 1,2-alkyl or -aryl migrations were observed, expanding the scope of this reaction.

4.2.1. Synthesis of β-allenylimines and β-allenylhydrazones

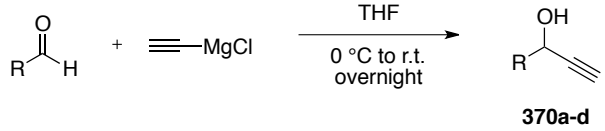
We began our investigations by developing a suitable strategy to access the desired cyclization precursors. A retrosynthetic pathway is reported in Scheme 4.29.



Scheme 4.29. *Retrosynthetic pathway to obtain β-allenylimines and β-allenylhydrazones*

β-allenylimines and β-allenylhydrazones can be obtained starting from the corresponding β-allenic aldehydes, which, in turn, came from the reaction between propargylic alcohols and enolizable adehydes.

If not commercially available, propargylic alcohols were synthetized starting from aldehydes upon the addition of ethynyl magnesium bromide (Table 4.1, entries 1-4).

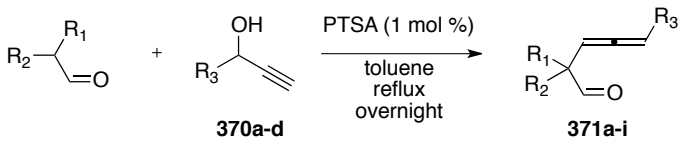


370a-d

Entry	R	Product	Yield
1	Me	**370a**	commercially available
2	*n*-Bu	**370b**	commercially available
3	Ph	**370c**	quantitative
4	4-Br-C_6H_4	**370d**	quantitative

Table 4.1. *Synthesis propargilic alcohols **370a-d***

β-Allenic aldehydes **371a-i** were obtained in a single synthetic step through the reaction between an enolizable aldehyde and the previously described propagylic alcohols **370a-d** (Table 4.2, entries 1-9). The process needed a catalytic amount of PTSA as well as thermal activation.

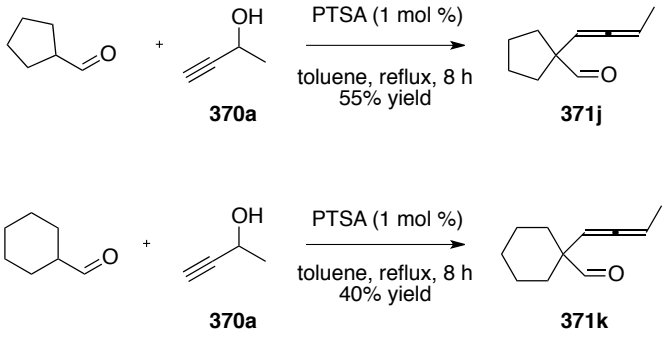


370a-d **371a-i**

Entry	R_1	R_2	R_3	Product	t (h)	Yield (%)
1	Me	Me	Me	**371a**	24	71
2	Me	Me	*n*-Bu	**371b**	24	80
3	Me	Me	Ph	**371c**	48	56
4	Me	Me	4-Br-C_6H_4	**371d**	24	64
5	Ph	Ph	Me	**371e**	8	41
6	Et	Me	Me	**371f**	8	67
7	Et	Me	Ph	**371g**	24	39
8	Et	Me	4-Br-C_6H_4	**371h**	12	31
9	Ph	Me	Me	**371i**	24	55

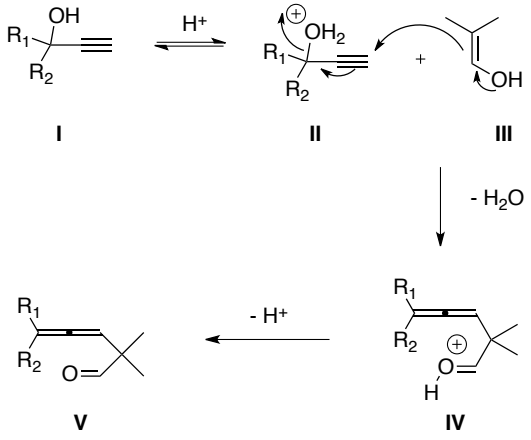
Table 4.2. *Synthesis β-allenic aldehydes **371a-i***

By using this convenient protocol, cyclic β-allenic aldehydes **371j** and **371k** were synthetized as well in satisfying yields (Scheme 4.30).



Scheme 4.30. *Synthesis β-allenic aldehydes **371j** and **371k***

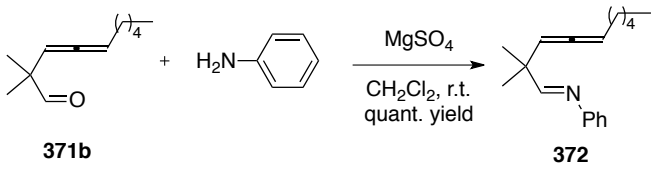
A proposed mechanism for the synthesis of β-allenic aldehydes is reported in Scheme 4.31. An initial protonation of alcohol **I** would generate the cation intermediate **II**. This species would then undergo a nucleophilic attack by the tautomeric form of the aldehyde (**III**), to yield the intermediate **IV**. Regeneration of the H^+ catalyst would finally afford the observed product **V**. [73]



Scheme 4.31. *Proposed mechanism for the synthesis of β-allenic aldehydes*

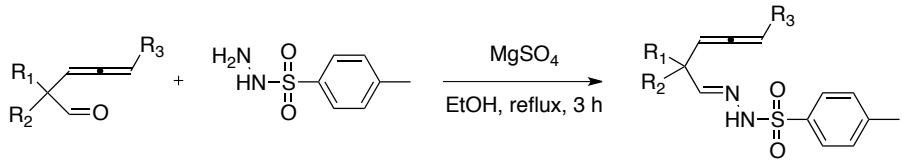
After the synthesis of β-allenic aldehydes, a condensation reaction between substrate **371b** and aniline afforded β-allenylimine **372**, which was obtained under mild conditions and in quantitative yield (Scheme 4.32).

In terms of mechanism, such reaction proceeds *via* nucleophilic addition of the amine to the carbonyl group giving a hemiaminal intermediate, followed by elimination of water to yield the imine. The equilibrium in this reaction usually favors of the carbonyl compound and the amine, so that azeotropic distillation or use of a dehydrating agent such as $MgSO_4$ is required to push the process in favor of the imine formation.



Scheme 4.32. *Synthesis of β-allenylimine **372***

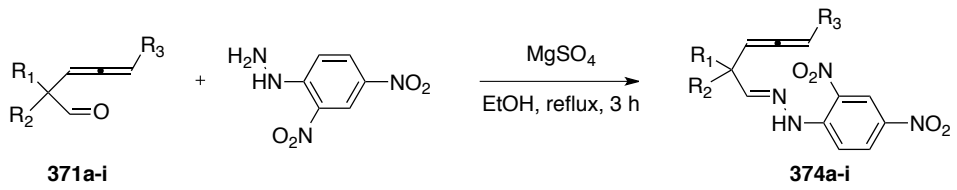
Using an analogous reaction, a set of diverse β-allenylhydrazones was obtained by the condensation of β-allenic aldehydes with two different hydrazines: tosyl hydrazine (Table 4.3, entries 1-8) and 2,4 dinitrophenylhydrazine (Table 4.4, entries 1-8).



Entry	R_1	R_2	R_3	Reactant	Product	Yield (%)
1	Me	Me	Me	**371a**	**373a**	72
2	Me	Me	*n*-Bu	**371b**	**373b**	71
3	Me	Me	Ph	**371c**	**373c**	55
4	Me	Me	4-Br-C_6H_4	**371d**	**373d**	72
5	Ph	Ph	Me	**371e**	**373e**	59
6	Et	Me	Me	**371f**	**373f**	64
7	Et	Me	Ph	**371g**	**373g**	79
8	Ph	Me	Me	**371i**	**373i**	41

Table 4.3. *Synthesis of β-allenylhydrazones **373a-i***

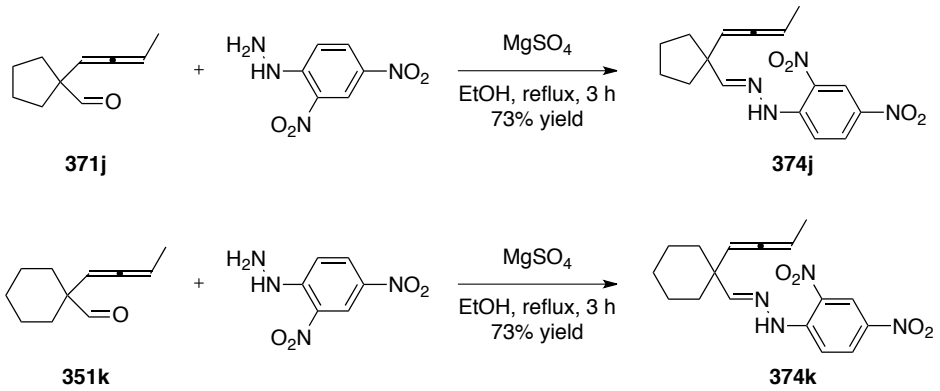
While imine **372** was difficult to isolate due to its sensitivity to hydrolysis, β-allenylhydrazones were easily purified over silica gel chromatography and were obtained in moderate to good yields.



Entry	R_1	R_2	R_3	Reactant	Product	Yield (%)
1	Me	Me	Me	**371a**	**374a**	60
2	Me	Me	*n*-Bu	**371b**	**374b**	88
3	Me	Me	Ph	**371c**	**374c**	44
4	Me	Me	4-Br-C_6H_4	**371d**	**374d**	67
5	Ph	Ph	Me	**371e**	**374e**	51
6	Et	Me	Me	**371f**	**374f**	72
7	Et	Me	4-Br-C_6H_4	**371g**	**374h**	64
8	Ph	Me	Me	**371i**	**374i**	45

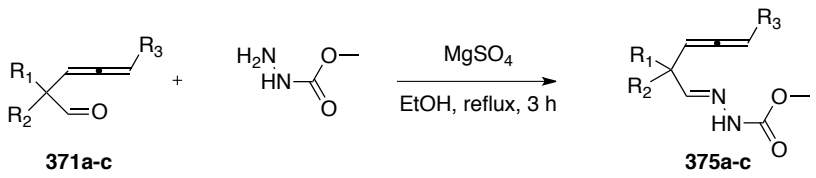
Table 4.4. *Synthesis of β-allenylhydrazones **374a-i***

Starting from cyclic β-allenic aldehydes **371j** and **371k**, only 2,4-dinitrophenylhydrazones **374j** and **374k** were synthetized (Scheme 4.33).



Scheme 4.33. *Synthesis of β-allenylhydrazones **374j** and **374k***

Three last examples of β-allenylhydrazones were finally obtained by the condensation reaction between aldehydes **371a-c** and methoxyhydrazino carboxylate (Table 4.5, entries 1-3).

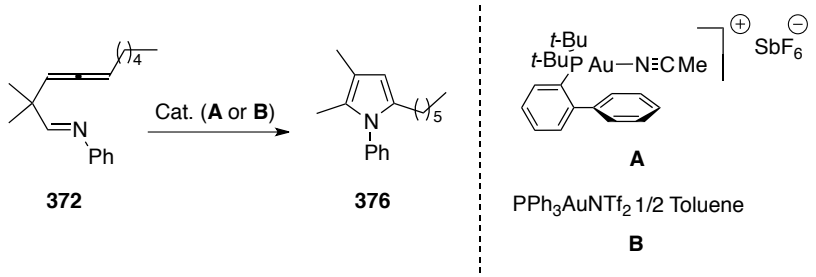


Entry	R_1	R_2	R_3	Reactant	Product	Yield (%)
1	Me	Me	Me	**371a**	**375a**	65
2	Me	Me	*n*-Bu	**371b**	**375b**	61
3	Me	Me	Ph	**371c**	**375c**	63

Table 4.5. *Synthesis of β-allenylhydrazones 375a-c*

4.2.2. Synthesis of multisubstituted N-amino pyrroles

To probe the viability of the cycloisomerization process, we first investigated the reactivity of β-allenylimine **372** as model. Treatment of this compound with 5 mol% of AuCl, $AuCl_3$, catalysts **A** or **B** respectively (Scheme 4.34), in CH_2Cl_2 at room temperature resulted in no conversion of the starting material.

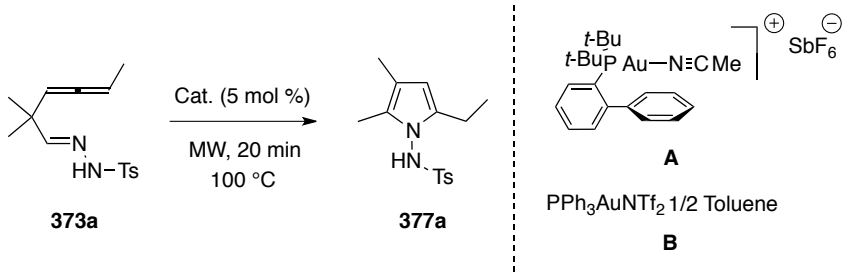


Scheme 4.34. *Synthesis of pyrrole derivative 376*

A set of different reaction conditions were screened and catalyst **A** was found to promote the desired cycloisomerization in DCE, at 100 °C under microwave irradiation (30W) within 20 minutes. Under these conditions, pyrrole **376** could be isolated as the only product, in 15% yield.

The reduced nucleophilicity and stability of β-allenylimines prompted us to examine the gold(I)-catalyzed cycloisomerization of β-allenylhydrazones.[74] The proposed cycloisomerization was explored using *β*-allenylhydrazone **373a** under microwave conditions, in dichloroethane (DCE), at 100 °C for 20 minutes, with 5 mol% of Echavarren's catalyst (**A**). Gratifyingly, the expected cycloisomerization/1,2-alkyl migration proceeded smoothly to give the corresponding pyrrole **377a** in 57% yield (Table 4.6, entry 1).

Other catalysts known to induce isomerization processes (Au(I), Au(III) Ag(I),[75] Cu(I),[76] Cu(II), Fe(III)[77]) were screened and catalysts **A** and **B** turned out to be the most effective (Table 4.6, entries 1 and 4) to promote the reaction.



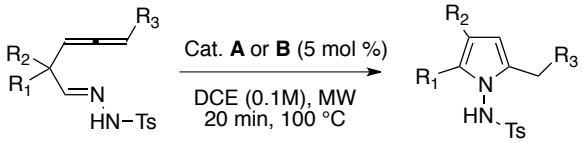
Entry	Catalyst	Solvent	Product
1	**A**	DCE	57%
2	$AuCl_3$	DCE	SM
3	AuCl	DCE	SM
4	**B**	DCE	55%
5	$AgNO_3$	DCE	SM
6	$AgSbF_6$	DCE	traces
7	AgOTf	DCE	SM
8	CuI	DCE	SM
9	$Cu(OTf)_2$	DCE	SM
10	$FeCl_3$	DCE	SM
11	TfOH	DCE	SM
12	$HN(OTf)_2$	DCE	SM

Table 4.6. *Catalysts screening*

These promising results incited us to explore the scope of the cyclization using various *β*-allenylhydrazones (Table 4.7). Under the optimized conditions, isomerization of *β*-allenylhydrazones **373b-i** afforded the desired pyrroles **377b-i** in good to excellent yields.

A variety of aryl and alkyl groups were tolerated at the allenyl terminus position. Interestingly, selective 1,2-migration of ethyl group over methyl group occurred both in *β*-allenylhydrazones **373f** and **373g** to give products **377f** and **377g** in 94% and 71% yields, respectively (Table 4.7, entries 5 and 6).

An analogous selective 1,2-migration of phenyl group over methyl group was also observed in the cyclization of *β*-allenylhydrazone **373i**, which is in accordance with the results of Gevorgyan (Table 4.7, entry 7).[78]



373b-i **377b-i**

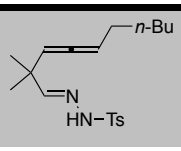
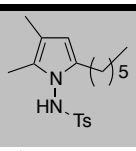
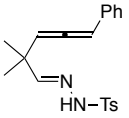
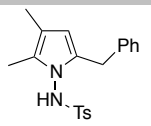
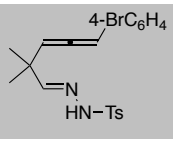
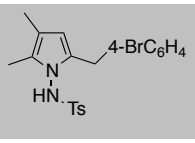
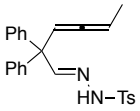
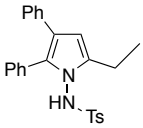
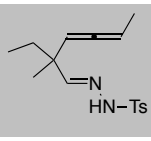
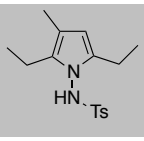
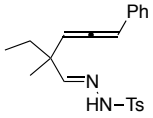
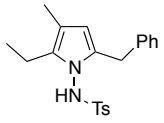
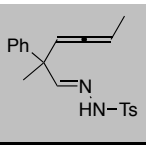
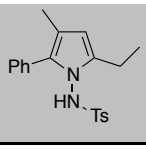
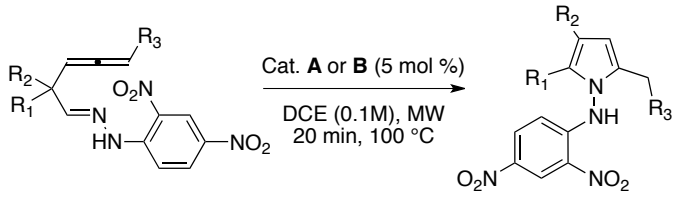
Entry	Reactant		Product		Cat.	Yield (%)
1	**373b**		**377b**		**A**	61
2	**373c**		**377c**		**A**	67
3	**373d**		**377d**		**B**	70
4	**373e**		**377e**		**A**	69
5	**373f**		**377f**		**B**	94
6	**373g**		**377g**		**B**	71
7	**373i**		**377i**		**B**	quant.

Table 4.7. *Synthesis of N-amino pyrroles **377b-i***

Substitution influence at the nitrogen atom was then examined with *β*-allenyl-2,4-dinitrophenylhydrazones **374a-i** as shown in Table 4.8. In this case, the cyclization took place to produce **378a-i** in excellent yields.

Once again, selective 1,2-migration of the ethyl and phenyl groups over the methyl group yielded pyrroles **378f, 378h** and **378i** in very high yields from the corresponding *β*-allenylhydrazones **374f, 374h** and **374i** (Table 4.8, entries 6-8).

Clear NOE correlations between the aromatic proton of the pyrrole ring and the methyl group confirmed the regiochemistry of compounds **378f** and **378i**.[79]



374a-i **378a-i**

Entry	Reactant	Product	Cat.	Yield (%)
1	**374a**	**378a**	**B**	93
2	**374b**	**378b**	**B**	92
3	**374c**	**378c**	**B**	quant.
4	**374d**	**378d**	**B**	quant.
5	**374e**	**378e**	**A**	90
6	**374f**	**378f**	**B**	quant.
7	**374h**	**378h**	**A**	89
8	**374i**	**378i**	**B**	quant.

Table 4.8. *Synthesis of N-amino pyrroles* ***378a-i***

The structure of pyrrole **378d** was confirmed by X-ray crystallographic analysis (Figure 4.7).[80] Interestingly, a π-stacking interaction between the two phenyl rings was found to characterize the molecule.

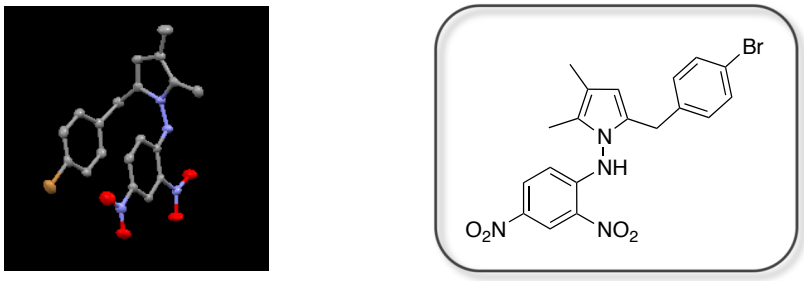
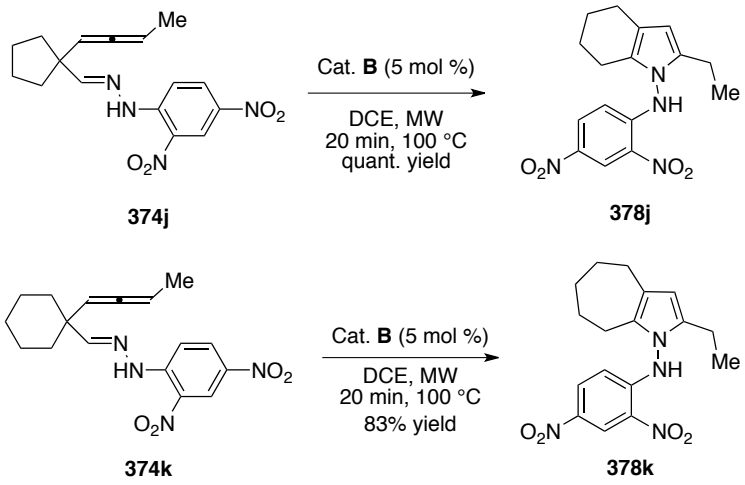


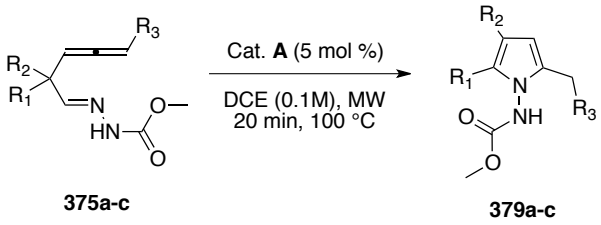
Figure 4.7. *X-ray crystallographic analysis of* ***378d***

To our delight, cyclization and subsequent ring expansion of cyclopentylallenyl hydrazone **374j** provided fused pyrrole **378j** in quantitative yield. Cyclohexylallenyl hydrazone **374k** was also employed affording the desired fused bicyclic product **378k** in 83% yield (Scheme 4.35).



Scheme 4.35. *Synthesis of pyrrole derivatives* ***378j*** *and* ***378k***

We then demonstrated the feasibility of this cycloisomerization process using *β*-allenylmethyl hydrazone carboxylates **375a-c**, that would constitute an interesting atom economical approach to this convenient pyrrole synthesis. Under the optimized conditions, isomerization proceeded smoothly to yield pyrroles **379a-c** with good reaction efficiency (Table 4.9, entries 1-3).



375a-c

379a-c

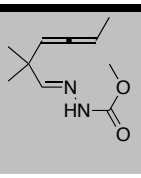
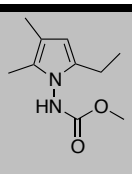
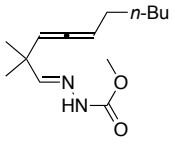
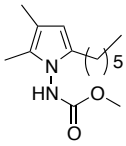
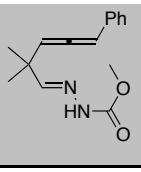
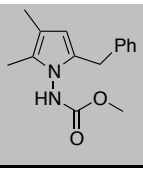
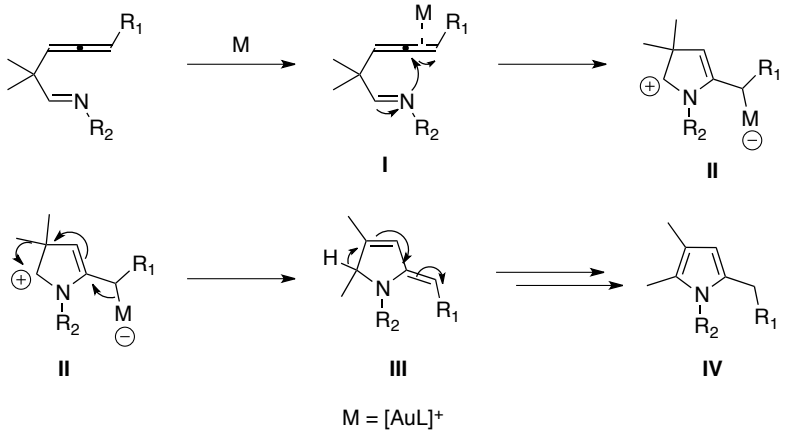
Entry	Reactant		Product		Yield (%)
1	375a		379a		61
2	375b		379b		51
3	375c		379c		67

Table 4.9. *Synthesis of N-amino pyrroles* ***379a-c***

A possible mechanism for the gold(I)-catalyzed cyloisomerizations of β-allenylhydrazones is outlined in Scheme 4.36. An initial π-complexation of the allene moiety to the Au(I) entity would trigger the nitrogen nucleophilic attack at the central atom of the allene. This would lead to the reactive zwitterion **II** which would then evolve to the formation of **III** through a [1,2] alkyl or aryl shift.[81] Final rearomatization of intermediate **III** would provide the observed pyrrole **IV**.



Scheme 4.36. *Mechanism for gold(I)-catalyzed cycloisomerizations of β-allenylhydrazones*

Because of the very mild reaction conditions, the low catalyst loading and the short reaction times, we expect that our methodology will be applied, in the next future, to the synthesis of natural products or biologically active molecules.

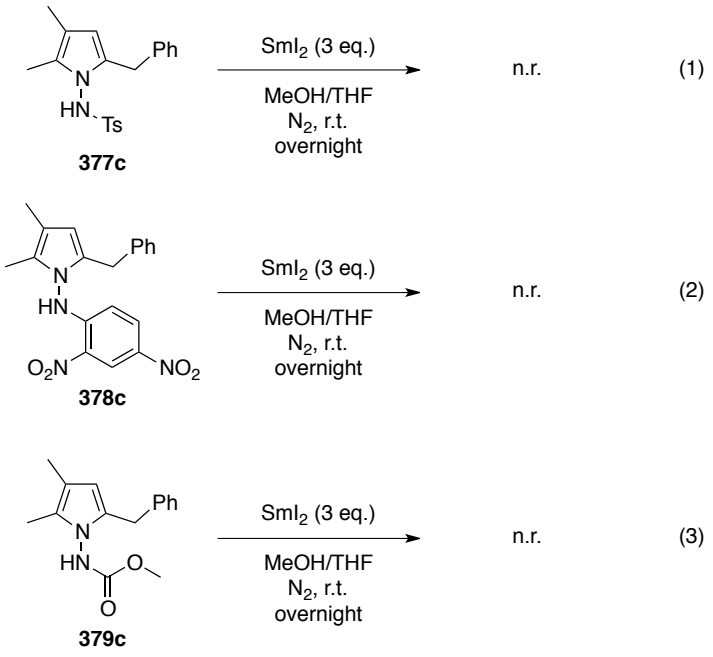
4.2.3. N-N bond cleavage

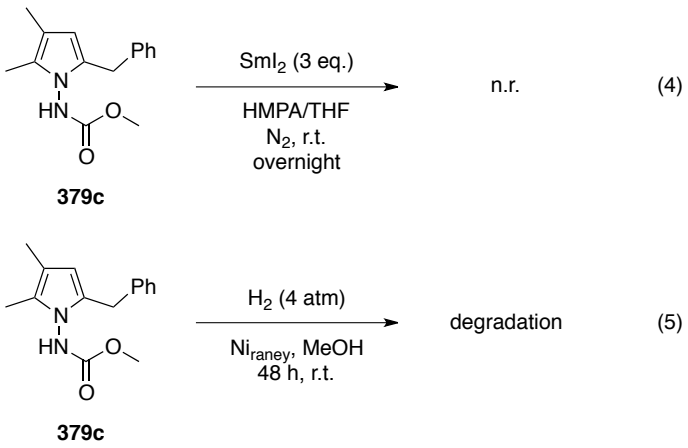
Different synthetic approaches to break the N–N bond of N-amino pyrroles and to trigger off the formation of the corresponding NH free compounds were investigated.

Several reductive methods have been disclosed for this chemical transformation. The most widely used technique hinges upon catalytic hydrogenolysis over Raney nickel,[82] platinium-[83] or palladium-based catalysts.[84] Alternative methods have been established, involving an electron transfer from metals, for example Na or Li/NH_3.[85] Furthermore, N–N bond cleavage has been observed upon treatment with SmI_2 and HMPA[86] or diborane.[87]

To circumvent limitations and difficulties related to the strong reducing conditions that are incompatible with a number of functionalities or protecting groups, oxidative methods, which involve peracids, have also been recently developed by J. M. Lassaletta and co-workers.[88]

Our initial attempts to achieve the reductive cleavage of N-N-bonds are summarized in Scheme 4.37. Unfortunately, treatment of substrates **377c**, **378c** and **379c** with freshly prepared SmI_2 or H_2/Ni_{raney} resulted in the recovery or in the degradation of the starting material after the reaction.





Scheme 4.37. *Initial attempts to cleave N-N-bonds*

In the future, different reductive conditions, as well as oxidative methods, will be evaluated in the aim to achieve the efficient formation of NH free derivatives.

On the other hand, according to the literature,[89] N-amino pyrroles could possess a valuable antitubercular activity. For this reason, the study of N-N-bond cleavage will be further focused after analyzing the biological and potential pharmacological activities of the molecules currently produced.

4.3. CONCLUSIONS AND FUTURE DEVELOPMENTS

The activation of allenes with homogeneous gold catalysts sets the stage for cyclization by intramolecular attack of various nucleophiles, affording highly useful hetero- or carbocyclic products by formation of new C-O, C-N, C-S, or C-C bonds. In many transformations of this type, the stereochemical information of the allene can be efficiently transferred to the product by axis-to-center chirality transfer, or it can be introduced into the product with the aid of chiral gold catalysts. A fine-tuning of the reactivity, catalyst stability, and stereoselectivity are possible by using σ-donors ligands to gold and/or weakly coordinating solvents like THF. Several applications in target-oriented synthesis demonstrate that homogenous gold catalysis is a perfect tool for the rapid generation of molecular complexity.

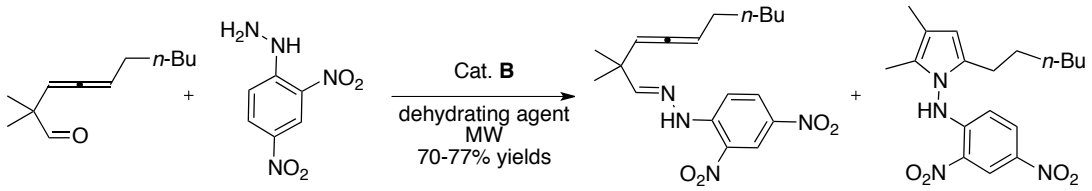
In the aim to disclose new gold-catalyzed procedures, we recently envisaged to employ functionalized allenes for the synthesis of nitrogen-containing heterocyclic compounds.

In this context, we reported an original and easy to handle gold(I)-catalyzed cycloisomerization of β-allenylhydrazones for the synthesis of functionalized pyrroles. These molecules are ubiquitous constituents in pharmaceuticals or natural products and are also frequently used as subunits in material sciences.

β-Allenylimines and β-allenylhydrazones, readily available from the corresponding β-allenic aldehydes, resulted to be suitable precursors for the reaction.

The protocol tolerated both alkyl and aryl groups at the terminal allenyl atom and was effective for a broad range of *N*-substituted precursors, some of which could possess a valuable antitubercular activity. Moreover, selective intramolecular 1,2-alkyl or -aryl migrations were observed throughout the cyclizations, extending the general scope of our method.

The development of a convenient one-pot reaction for the rapid conversion of readily available β-allenic aldehydes into multisubstituted pyrroles is currently under investigation in our laboratory. In this direction, a set of different reaction conditions were screened (Table 4.10, entries 1-7) and a preliminary result was obtained under microwaves conditions, in dichloroethane (DCE), at 100 °C for 20 minutes, with 10 mol% of Gagosz's catalyst and $MgSO_4$ as dehydrating agent (Table 4.10, entry 3).

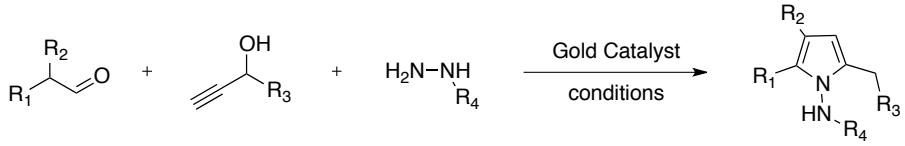


371b **374b** **378b**

Entry	Catalyst loading (mol %)	Dehydrating agent	Solvent	T (°C)	t (min)	374b : 378b
1	5	$MgSO_4$	DCE	100	20	5 : 1
2	5	$MgSO_4$	DCE	100	60	2.2 : 1
3	10	$MgSO_4$	DCE	100	20	0 : 1
4	5	$MgSO_4$	DCE	150	20	4.2 : 1
5	5	$MgSO_4$	THF	100	20	1 : 0
6	5	/	DCE	100	20	2.3 :1
7	5	Na_2SO_4	DCE	100	20	3.6 : 1

Table 4.10. *One-pot reaction for the conversion of β-allenylaldehydes into pyrroles*

Improvements of this procedure are still highly desirable. In particular, catalyst loadings lower then 10 mol% are essential to achieve a convenient and economical process.
A multicomponent reaction for the direct transformation of enolizable aldehydes, propargylic alcohols and hydrazines into pyrroles (Scheme 4.38) is also under investigation and will be reported in due course.



Scheme 4.38. *Multicomponent reaction for the direct transformation of enolizable aldehydes, propargylic alcohols and hydrazines into pyrroles*

4.4. REFERENCES

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Chapter 5

Experimental section

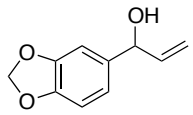
5.1. RING-CLOSING METATHESIS REACTIONS

5.1.1. General Remarks

All metathesis reactions were carried out under nitrogen or ethylene in oven-dried glassware. All substituted anilines and aldehydes were purchased from Sigma–Aldrich Chemical Co. and were employed without further purification. Distilled solvents were used for all reactions. Thin-layer chromatography (TLC) was performed on Macherey-Nagel polygram silica gel with fluorescent indicator UV_{254}. Carlo Erba reagents silica gel 60A (70-200 μm) was employed for column chromatography. The melting points reported were measured with a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded at 298K in $CDCl_3$ solutions (unless otherwise stated) on a Bruker Avance 400 MHz spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C NMR. Chemical shifts are given in parts per million, referenced to the residual proton resonance of the solvents (δ = 7.26 ppm for $CDCl_3$) or to the residual carbon resonance of the solvent (δ = 77.16 ppm for $CDCl_3$). When possible, ^1H and ^{13}C signals were assigned mostly on the basis of DEPT and 2D NMR (COSY, HMBC) experiments. The terms m, s, d, t, q represent multiplet, singlet, doublet, triplet, quadruplet, respectively, the term br means a broad signal. GC–MS analyses were run on Shimadzu GC-MS-QP5000. IR spectra were obtained using the Nicolet Magna-IR Spectrometer 550. Chemical ionization mass spectra (+ve mode) (CI+-MS) were performed on a Finnigan-MAT TSQ70 with isobutane as the reactant gas.

5.1.2. Synthesis of benzylic alcohols

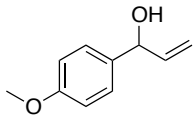
*5.1.2.1. Representative procedure (**RP1**). Synthesis of 1-benzo-[1,3]dioxol-5-yl-prop-2-en-1-ol (**55a**)*



Piperonal (3 g, 20 mmol) was placed in a three-necked 250 mL round bottomed flask, under nitrogen atmosphere, and was dissolved in THF (80 mL). The mixture was cooled to -78 °C and vinylmagnesium chloride (14 mL, 24 mmol) was added dropwise over 30 minutes. The mixture was then stirred at room temperature for 2 hour. The product formation was controlled with TLC analysis, using *n*-hexane/AcOEt (8:2) as eluent. At the end of the reaction, the mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (50 mL). The resulting organic phase was washed with saturated NH_4Cl aqueous solution (3 X 80 mL) and then dried on Na_2SO_4. The solvent was removed under reduced pressure. The desired product was obtained as a yellow oil that can be used without further purification (quantitative yield). IR (neat): ν 3369,

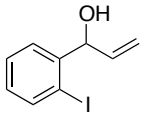
3077, 3011, 2979, 2778, 1855, 1641, 1609, 1503, 1488, 1443, 1374, 1247, 1185, 1125, 1093, 1040, 990, 933, 811, 794 cm^{-1}. ^{1}H NMR: δ 6,78 – 6,88 (m, 3H), 6.05 – 5.97 (m, 1H), 5,95 (s, 2H), 5,34 (d, *J* = 17,1 Hz, 1H), 5,19 (d, *J* = 10,3 Hz, 1H), 5,12 (d, *J* = 5,7 Hz, 1H), 2,08 (br, 1H). ^{13}C NMR: δ 147.7 (C), 146.9 (C), 140.3 (CH), 136.8 (C), 119.8 (CH), 114.8 (CH_2), 108.1 (CH), 107.0 (CH), 101.1 (CH_2), 74.8 (CH). GC-MS (EI): *m/z* 178, 149, 135, 121, 119, 91, 63. The spectral data for this compound correspond to previously reported data.[1]

*5.1.2.2. Synthesis of 1-(4-methoxy-phenyl)-prop-2-en-1-ol (**55b**)*



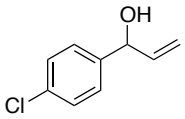
Substrate **55b** was synthesized from 4-methoxybenzaldehyde and vinylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3400, 3076, 3003, 2956, 1610, 1513, 1284, 1105, 991, 925 cm^{-1}. ^{1}H NMR: δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.11 – 6.01 (m, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.3 Hz, 1H), 5.17 (d, *J* = 6.2 Hz, 1H), 3.82 (s, 3H), 2.04 (br, 1H). ^{13}C NMR: δ 159.4 (C), 140.6 (CH), 135.1 (C), 127.9 (2CH), 115.0 (CH_2), 114.1 (2CH), 75.1 (CH), 55.5 (CH_3). GC-MS (EI): *m/z* 164, 148, 135, 121, 109, 94, 91, 77, 55. The spectral data for this compound correspond to previously reported data.[2]

*5.1.2.3. Synthesis of 1-(2-iodo-phenyl)-prop-2-en-1-ol (**55c**)*



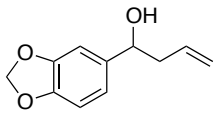
Substrate **55c** was synthesized from 2-iodobenzaldehyde and vinylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR: δ 7.83 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.98 (dt, *J* = 7.8, 1.6 Hz, 1H), 6.05 – 5.97 (m, 1H), 5.49 – 5-41 (m, 2H), 5.25 (d, *J* = 10.4 Hz, 1H), 2.32 (br, 1H). ^{13}C NMR: δ 145.1 (C), 135.8 (CH), 132.3 (CH), 129.1 (CH), 128.5 (CH), 127.7 (CH), 115.5 (CH_2), 86.3 (C), 79.9 (CH). The spectral data for this compound correspond to previously reported data.[3]

*5.1.2.4. Synthesis of 1-(4-chloro-phenyl)-prop-2-en-1-ol (**55d**)*



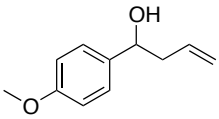
Substrate **55d** was synthesized from 4-chlorobenzaldehyde and vinylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR: δ 7.39 – 7.29 (m, 4H), 6.10 – 5.81 (m, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 5.17 (d, *J* = 6.0 Hz, 1H), 2.30 (br, 1H). ^{13}C NMR: δ 135.1 (C), 132.8 (CH), 130.7 (C), 129.1 (2CH), 127.7 (2CH), 115.5 (CH_2), 73.5 (CH). GC-MS (EI): *m/z* 168, 149, 139, 133, 115, 105, 91, 77, 55. The spectral data for this compound correspond to previously reported data.[4]

*5.1.2.5. Synthesis of 1-(3,4-dimethoxy-phenyl)-but-3-en-1-ol (**56a**)*



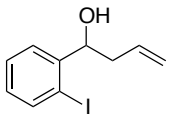
Substrate **56a** was synthesized from piperonal and allylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3386, 3075, 1640 cm^{-1}. ^{1}H NMR: δ 6.88 (s, 1H), 6.76 – 6.81 (m, 2H), 5.96 (s, 2H), 5.83 – 5.71 (m, 1H), 5.12 – 5.18 (m, 2H), 4.64 (t, *J* = 4.6 Hz, 1H), 3.73 - 376 (m, 2H), 3.75 (br, 1H). ^{13}C NMR: δ 147.9 (C), 147.1 (C), 138.2 (CH), 134.6 (C), 119.4 (CH), 118.5 (CH_2), 108.2 (CH), 106.6 (CH), 101.2 (CH_2), 73.4 (CH), 44.0 (CH_2). GC-MS (EI): *m/z* 192, 174, 151, 135, 123, 115, 93, 91, 65, 63. The spectral data for this compound correspond to previously reported data.[5]

*5.1.2.6. Synthesis of 1-(4-methoxy-phenyl)-but-3-en-1-ol (**56b**)*



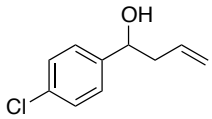
Substrate **56b** was synthesized from 4-methoxybenzaldehyde and allylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3418, 3074, 640 cm^{-1}. ^{1}H NMR: δ 7.31 – 7.27 (m, 2H), 6.92 – 6.87 (m, 2H), 5.83 – 5.79 (m, 1H), 5.14 (dd, *J* = 16.7, 1.5 Hz, 1H), 5.07 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.71 (t, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 2.65 – 2.58 (m, 1H), 2.55 – 2.49 (m, 1H), 2.21 (br, 1H). ^{13}C NMR: δ 159.2 (C), 136.2 (C), 134.8 (CH), 127.3 (2CH), 118.4 (CH_2), 114.0 (2CH), 73.2 (CH), 55.5 (CH_3), 43.9 (CH_2). GC-MS (EI): *m/z* 178, 161, 137, 121, 109, 94, 78, 77, 51. The spectral data for this compound correspond to previously reported data.[5]

*5.1.2.7. Synthesis of 1-(2-iodo-phenyl)-but-3-en-1-ol (**56c**)*



Substrate **56c** was synthesized from 2-iodobenzaldehyde and allylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3332, 3227, 988, 920 cm^{-1}. ^{1}H NMR: δ 7.83 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 6.99 (td, *J* = 7. 8, 1.7 Hz, 1H), 5.95 – 5.86 (m, 1H), 5.27 – 5.19 (m, 2H), 4.94 (dd, *J* = 8.6, 3.6 Hz, 1H), 2.66 – 2.61 (m, 1H), 2.35 – 2.31 (m, 1H), 2.08 (br, 1H).^{13}C NMR: δ 145.4 (C), 139.2 (CH), 134.2 (CH), 129.1 (CH), 128.4 (CH), 126.9 (CH), 118.6 (CH_2), 97.3 (C), 76.2 (CH), 42.7 (CH_2). GC-MS (EI): *m/z* 274, 257, 233, 231, 203, 165, 153, 127, 155, 105, 78, 77, 51. The spectral data for this compound correspond to previously reported data.[6]

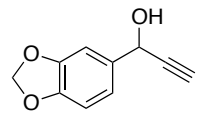
*6.1.2.8. Synthesis of 1-(4-chloro-phenyl)-but-3-en-1-ol (**56d**)*



Substrate **56d** was synthesized from 4-chlorobenzaldehyde and allylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3383, 3077, 1641 cm^{-1}.

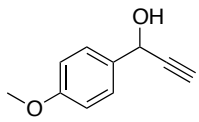
^{1}H NMR: δ 7.34 – 7.28 (m, 4H), 5.79 – 5.75 (m, 1H), 5.17 – 5.13 (m, 2H), 4.70 (dd, *J* = 7.4, 5.4 Hz, 1H), 2.49 – 2.45 (m, 2H), 2.29 (br, 1H). ^{13}C NMR: δ 142.4 (C), 134.0 (CH), 133.0 (C), 128.4 (2CH), 127.3 (2CH), 118.6 (CH_2), 72.7 (CH), 43.6 (CH_2). GC-MS (EI): *m/z* 182, 165, 141, 113, 77. The spectral data for this compound correspond to previously reported data.[5]

*5.1.2.9. Synthesis of 1-benzo-[1,3]dioxol-5-yl-prop-2-yn-1-ol (**57a**)*



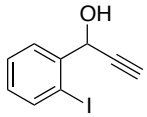
Substrate **57a** was synthesized from piperonal and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3351, 3288, 2290 cm^{-1}. ^{1}H NMR: δ 7.04 – 6.99 (m, 1H), 6.84 – 6.78 (m, 2H), 5.96 (s, 2H), 4.58 (s, 1H), 2.66 (s, 1H), 2.49 (br, 1H). ^{13}C NMR: δ 147.7 (C), 147.6 (C), 133.4 (C), 120.2 (CH), 108.1 (CH), 107.2 (CH), 101.2 (CH_2), 83.4 (C), 74.7 (CH), 64.2 (CH). The spectral data for this compound correspond to previously reported data.[7]

*5.1.2.10. Synthesis of 1-(4-methoxy-phenyl)-prop-2-yn-1-ol (**57b**)*



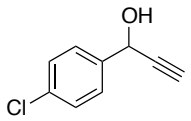
Substrate **57b** was synthesized from 4-methoxybenzaldehyde and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3438, 3003, 2935, 2837, 1892, 1512, 1442, 1173, 948, 768 cm^{-1}. ^{1}H NMR: δ 7.47 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6, 2H), 5.41 (s, 1H), 3.81 (s, 3H), 2.65 (d, *J* = 1.6 Hz, 1H), δ 2.45 (br, 1H). ^{13}C NMR: δ 159.8 (C), 132.4 (C), 128.1 (2CH), 114.0 (2CH), 83.7 (CH), 74.7 (C), 64.0 (CH), 55.4 (CH_3). GC-MS (EI): *m/z* 162, 161, 145, 131, 109, 102, 91, 77, 53. The spectral data for this compound correspond to previously reported data.[8]

*5.1.2.11. Synthesis of 1-(2-iodo-phenyl)-prop-2-yn-1-ol (**57c**)*



Substrate **57c** was synthesized from 2-iodobenzaldehyde and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a yellow oil. IR (neat): ν 3292, 1437, 1011, 952, 752, 665, 639 cm^{-1}. ^{1}H NMR: δ 7.83 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.75 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 (td, *J* = 7.6, 0.9 Hz, 1H), 7.01 (td, *J* = 7.7, 1.6 Hz, 1H), 5.65 (d, *J* = 2.3 Hz, 1H), 2.82 (br, 1H), 2.66 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR: δ 141.9 (C), 139.6 (CH), 130.2 (CH), 128.8 (CH), 128.0 (CH), 98.0 (C), 82.6 (C), 75.2 (CH), 68.1 (CH). GC-MS (EI): *m/z* 258, 240, 203, 176, 165, 152, 139, 131, 113, 103, 78, 77, 53. The spectral data for this compound correspond to previously reported data.[9]

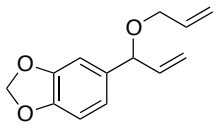
*5.1.2.12. Synthesis of 1-(4-chloro-phenyl)-prop-2-yn-1-ol (**57d**)*



Substrate **57d** was synthesized from 4-chlorobenzaldehyde and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR: δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.43 (d, *J* = 3.5 Hz, 1H), 2.78 (br, 1H), 2.67 (s, 1H). GC-MS (EI): *m/z* 166, 149, 139, 131, 111, 103, 85, 75, 55. The spectral data for this compound correspond to previously reported data.[9]

5.1.3. Synthesis of benzylic ethers

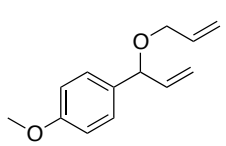
*5.1.3.1. Representative procedure (**RP2**). Synthesis of 5-(1-allyloxy-allyl)-benzo[1,3]dioxole (**58a**)*



Sodium hydride (0.13 g, 60% dispersion in mineral oil, 5.6 mmol) was placed in a two-necked 100 mL round bottomed flask, under nitrogen atmosphere, and was dissolved in THF (10 mL). The solution was stirred at room temperature for 5-10 minutes and then was cooled to 0 °C. 1-Benzo-[1,3]dioxol-5-yl-prop-2-en-1-ol (1.00 g, 5.5 mmol) was dissolved in THF/Et_2O (1:1, 20 mL) and was added dropwise to the sodium hydride solution over 30 minutes. After that, allyl bromide (0.81 g, 0.71 mL, 6.7 mmol) was added and the mixture was stirred at room temperature for 24 hours. The product formation was controlled with TLC analysis, using *n*-hexane/AcOEt (8:2) as eluent. At the end of the reaction, the mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (40 mL). Water (30 mL) was added and the resulting aqueous mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic extract was washed with brine (3 x 60 mL), dried on Na_2SO_4 and the solvent was removed *in vacuo*. The oil residue was purified by column chromatography using *n*-hexane/CH_2Cl_2 (3:7) as eluent. The required pure product was obtained as a yellow oil (58 % yield). IR (neat): ν 2837, 1613, 1515, 1245, 1077, 1033, 924, 829 cm^{-1}. ^{1}H NMR: δ 6.87 (s, 1H), 6.81 – 6.77 (m, 2H), 5.95 (s, 2H), 5.93 – 5.89 (m, 2H), 5.27 – 5.23 (m, 4H), 4.72 (d, *J* = 6.4 Hz, 1H), 3.97 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR: δ 147.8 (C), 147.1 (C), 138.9 (CH), 135.0 (C), 134.8 (CH), 120.4 (CH), 116.8 (CH_2), 116.0 (CH_2), 108.1 (CH), 107.3 (CH), 100.9 (CH_2), 81.7 (CH), 69.1 (CH_2). GC-MS (EI): *m/z* 218, 207, 191, 177, 162, 149, 135, 131, 119, 103, 91, 77, 55.

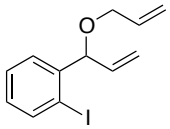
*5.1.3.2. Synthesis of 5-(1-allyloxy-allyl)-benzo[1,3]dioxole (**58b**)*

Substrate **58b** was synthesized from **55b** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 60% yield) as a yellow oil. IR (neat): ν 2836, 1611, 1512, 1247, 1071, 1036, 924, 829 cm^{-1}. ^{1}H NMR: δ 7.27 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.1 Hz,



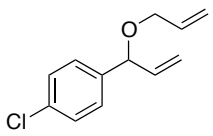
2H), 5.97 – 5.93 (m, 2H), 5.27 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.21 – 5.17 (m, 3H), 4.77 (d, *J* = 6.4 Hz, 1H), 3.99 – 3-55 (m, 2H), 3.81 (s, 3H). ^{13}C NMR: δ 159.2 (C), 139.1 (CH), 134.9 (CH), 133.1 (C), 128.2 (2CH), 116.7 (2CH), 115.9 (CH_2), 113.8 (CH_2), 81.6 (CH), 69.1 (CH_2), 55.3 (CH_3). GC-MS (EI): *m/z* 204, 203, 177, 163, 148, 135, 121, 115, 103, 91, 77, 55. The spectral data for this compound correspond to previously reported data.[10]

*5.1.3.3. Synthesis of 1-(1-allyloxy-allyl)-2-iodo-benzene (**58c**)*



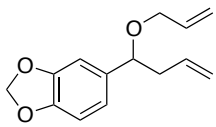
Substrate **58c** was synthesized from **55c** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 44% yield) as a yellow oil. IR (neat): ν 2839, 1615, 1510, 1251, 1011, 924, 829, 737 cm^{-1}. ^{1}H NMR: δ 7.83 (dd, *J* = 7.9,1.0 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38 (td, *J* = 7.3, 0.8 Hz, 1H), 6.99 (td, *J* = 7.7, 1.8 Hz, 1H), 5.95 – 5.91 (m, 2H), 5.42 – 5.38 (m, 4H), 5.11 (d, *J* = 6.0 Hz, 1H), 4.01 – 3.97 (m, 2H). ^{13}C NMR: δ 144.1 (C), 139.2 (CH), 133.6 (CH), 134.5 (CH), 129.2 (CH), 128.5 (CH), 127.6 (CH), 117.1 (CH_2), 116.4 (CH_2), 98.6 (C), 83.8 (CH), 71.2 (CH_2). MS (CI): *m/z* 301 (M+1). The spectral data for this compound correspond to previously reported data.[11]

*5.1.3.4. Synthesis of 1-(1-allyloxy-allyl)-4-chloro-benzene (**58d**)*



Substrate **58d** was synthesized from **55d** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 31% yield) as a yellow oil. IR (neat): ν 3298, 3082, 2857, 1490, 1259, 1076, 931, 820 cm^{-1}. ^{1}H NMR: δ 7.32 – 7.26 (m, 4H), 5.95 – 5.89 (m, 2H$_8$), 5.29 – 5.24 (m, 4H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.03 – 3.94 (m, 2H). ^{13}C NMR: δ 139.6 (C), 138.4 (CH), 134.6 (CH), 133.3 (C), 128.6 (2CH), 128.2 (2CH), 117.0 (CH_2), 116.7 (CH_2), 81.3 (CH), 69.2 (CH_2). GC-MS (EI): *m/z* 208, 190, 181, 167, 151, 139, 125, 115, 103, 89, 77, 55.

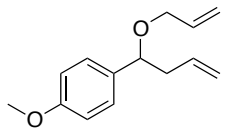
*5.1.3.5. Synthesis of 5-(1-allyloxy-but-3-enyl)-benzo-[1,3]dioxole (**59a**)*



Substrate **59a** was synthesized from **56a** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 39% yield) as a yellow oil. IR (neat): ν 3076, 2896, 1642, 1487, 1442, 1244, 1079, 1040, 921, 812 cm^{-1}. ^{1}H NMR: δ 6.38 (s, 1H), 6.77 – 6.73 (m, 2H), 5.95 (s, 2H), 5.81 – 5.87 (m, 1H), 5.77 – 5.73 (m, 1H), 5.24 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 5.03 – 4.99 (m, 2H), 4.25 (t, *J* = 6.7 Hz, 1H), 3.94 – 3.90 (m, 1H), 3.76 – 3.72 (m, 1H), 2.57 – 2.53 (m, 1H), 2.41 – 2.37 (m, 1H). ^{13}C NMR: δ 147.8 (C), 146.9 (C), 135.9 (CH), 134.9 (C), 134.8 (CH), 120.4 (CH), 116.8 (CH_2), 116.7 (CH_2), 107.9 (CH), 106.9 (CH), 100.9 (CH_2), 80.9 (CH), 69.2

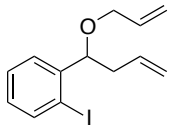
(CH_2), 42.6 (CH_2). GC-MS (EI): *m/z* 232, 207, 191, 189, 163, 149, 135, 121, 115, 105, 91, 63. The spectral data for this compound correspond to previously reported data.[12]

*5.1.3.6. Synthesis of 1-(1-allyloxy-but-3-enyl)-4-methoxy-benzene (**59b**)*



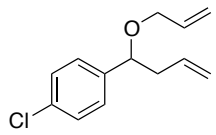
Substrate **59b** was synthesized from **56b** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 77% yield) as a yellow oil. IR (neat): ν 3075, 2934, 2908, 1611, 1512, 1247, 1079, 917, 831 cm^{-1}. ^1H NMR: δ 7.23 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.92 – 5.88 (m, 1H), 5.80 – 5.76 (m, 1H), 5.24 (d, *J* = 17.3 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 5.05 – 3.01 (m, 2H), 4.30 (t, *J* = 6.6 Hz, 1H), 3.94 – 3.90 (m, 1H), 3.82 (s, 3H), 3.78 – 3.74 (m, 1H), 2.63 – 2.59 (m, 1H), 2.45 – 2.41 (m, 1H). ^{13}C NMR: δ 159.1 (C), 135.0 (CH), 134.9 (CH), 133.9 (C), 127.9 (2CH), 116.7 (CH_2), 116.6 (CH_2), 113.7 (2CH), 80.7 (CH), 69.2 (CH_2), 55.2 (CH_3), 42.6 (CH_2). GC-MS (EI): *m/z* 218, 204, 190, 177, 162, 149, 135, 121, 108, 92, 91, 77, 51. The spectral data for this compound correspond to previously reported data.[13]

*5.1.3.7. Synthesis of 1-(1-allyloxy-but-3-enyl)-2-iodo-benzene (**59c**)*



Substrate **59c** was synthesized from **56c** and allylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 6:4, 92% yield) as a yellow oil. IR (neat): ν 3076, 2901, 1615, 1512, 1247, 1081, 831, 734 cm^{-1}. ^1H NMR: δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 5.92 – 5.88 (m, 2H), 5.26 (dd, *J* = 17.3 Hz, 10.4 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.10 – 5.06 (m, 2H), 4.64 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.93 (dd, *J* = 12.8, 5.1 Hz, 1H), 3.78 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.45 – 2.41 (m, 2H). ^{13}C NMR: δ 144.0 (C), 139.3 (CH), 134.6 (CH), 134.5 (CH), 129.2 (CH), 128.5 (CH), 127.6 (CH), 117.1 ($2CH_2$), 98.6 (C), 83.8 (CH), 69.9 (CH_2), 41.3 (CH_2). GC-MS (EI): *m/z* 314, 274, 273, 256, 232, 231, 217, 203, 177, 167, 153, 145, 129, 117, 104, 91, 76, 51.

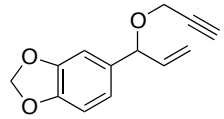
*5.1.3.8. Synthesis of 1-(1-allyloxy-but-3-enyl)-4-chloro-benzene (**59d**)*



Substrate **59d** was synthesized from **56d** and allylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 6:4, 77% yield) as a yellow oil. IR (neat): ν 3079, 2933, 1629, 1510, 1245, 917, 722 cm^{-1}. ^1H NMR: δ 7.32 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.91 – 5.87 (m, 1H), 5.76 – 5.72 (m, 1H), 5.24 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 5.06 – 5.02 (m, 2H), 4.32 (t, *J* = 6.6 Hz, 1H), 3.93 – 3.89 (m, 1H), 3.77 – 3.73 (m, 1H), 2.61 – 2.57 (m, 1H), 2.34 – 2.30 (m, 1H). ^{13}C NMR: δ 140.4 (C), 134.7 (CH), 134.3 (CH), 133.2 (C), 128.5 (2CH), 128.1 (2CH), 117.2 (CH_2), 116.9 (CH_2), 80.4 (CH), 69.5 (CH_2), 42.4 (CH_2). GC-MS (EI): *m/z* 222, 182, 165, 149,

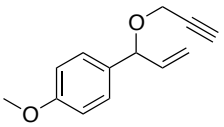
141, 129, 113, 105, 78, 77, 51. The spectral data for this compound correspond to previously reported data.[13]

*5.1.3.9. Synthesis of 5-(1-prop-2-ynyloxy-allyl)-benzo[1,3]dioxole (**60a**)*



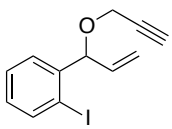
Substrate **60a** was synthesized from **55a** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 8:2, 49% yield) as a yellow oil. IR (neat): ν 3079, 2931, 2887, 1443, 1245, 810 cm^{-1}. ^1H NMR: δ 6.78 – 6.87 (m, 3H), 5.96 (s, 2H), 5.96 – 5.92 (m, 1H), 5.32 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.25 (d, *J* = 10.3 Hz, 1H), 4.96 (d, *J* = 6.5 Hz, 1H), 4.17 (dd, *J* = 15.7, 2.4 Hz, 1H), 4.08 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.45 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 147.9 (C), 147.3 (C), 137.9 (CH), 133.9 (C), 120.8 (CH), 116.9 (CH_2), 108.1 (CH), 107.5 (CH), 101.1 (CH_2), 80.9 (CH), 79.8 (C), 74.4 (CH), 55.1 (CH_2). MS (CI): *m/z* 217 (M+1).

*5.1.3.10. Synthesis of 1-methoxy-4-(1-prop-2-ynyloxy-allyl)-benzene (**60b**)*



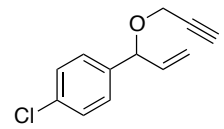
Substrate **60b** was synthesized from **55b** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 8:2, 70% yield) as a yellow oil. IR (neat): ν 3081, 2932, 2885, 1444, 1242, 810, 737 cm^{-1}. ^1H NMR: δ 6.84 (s, 1H), 6.76 – 6.78 (m, 2H), 5.98 (s, 2H), 5.77 – 5.73 (m, 1H), 5.02 – 5.10 (m, 2H), 4.52 (t, *J* = 7.0 Hz, 1H), 4.29 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.89 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.57 – 2.65 (m, 1H), 2.38 – 2.45 (m, 1H), 2.41 (t, *J* = 2.4Hz, 1H). ^{13}C NMR: δ 159.4 (C), 139.2 (CH), 132.1 (C), 128.8 (2CH), 116.7 (CH_2), 114.0 (2CH), 80.7 (CH), 80.1 (C), 74.5 (CH), 55.2 (CH_3), 55.1 (CH_2). MS (CI): *m/z* 203 (M+1). The spectral data for this compound correspond to previously reported data.[14]

*5.1.3.11. Synthesis of 1-iodo-2-(1-prop-2-ynyloxy-allyl)-benzene (**60c**)*



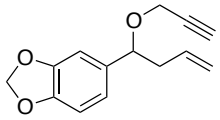
Substrate **60c** was synthesized from **55c** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 44% yield) as a yellow oil. IR (neat): ν 3079, 2982, 2888, 1487, 1442, 1243, 1040, 931, 809 cm^{-1}. ^1H NMR: δ 7.84 (d, *J*= 7.9 Hz, 1H), 7.44 (dd, *J*= 7.8, 1.6 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.00 (dt, *J* = 7.9, 1.8 Hz, 1H), 6.90 – 6.86 (m, 1H), 5.40 (d, *J* = 11.3 Hz, 1H), 5.29 – 5.25 (m, 2H), 4.20 (dd, *J* = 15.6, 2.4 Hz, 1H), 4.10 (dd, *J* = 15.6, 2.4 Hz, 1H), 2.47 (t, *J* = 2.3 Hz, 1H). ^{13}C NMR: δ 142.0 (C), 139.5 (CH), 136.4 (CH), 129.6 (CH), 128.7 (CH), 128.2 (CH), 117.7 (CH_2), 98.9 (C), 84.2 (CH), 74.7 (CH), 69.5 (C), 55.6 (CH_2). MS (CI): *m/z* 299 (M+1).

*5.1.3.12. Synthesis of 1-chloro-4-(1-prop-2-ynyloxy-allyl)-benzene (**60d**)*



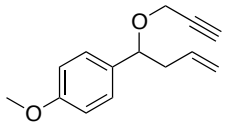
Substrate **60d** was synthesized from **55d** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 37% yield) as a yellow oil. IR (neat): ν 3298, 3082, 2929, 2118, 1686, 1489, 1083, 932, 824, 631 cm^{-1}. ^1H NMR: δ 7.34 – 7.30 (m, 4H), 5.92 – 5.88 (m, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.20 (dd, *J* = 15.8, 2.4 Hz, 1H), 4.12 (dd, *J* = 15.8, 2.4 Hz, 1H), 2.45 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 138.6 (C), 137.4 (CH), 133.6 (C), 128.7 (2CH), 128.5 (2CH), 117.8 (CH_2), 80.4 (CH), 79.6 (C), 74.6 (CH), 55.3 (CH_2). GC-MS (EI): *m/z* 206, 179, 167, 140, 115, 102, 89, 75, 63, 39, 27.

*5.1.3.13. Synthesis of 5-(1-prop-2-ynyloxy-but-3-enyl)-benzo[1,3]dioxole (**61a**)*



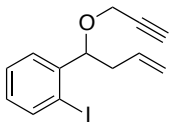
Substrate **61a** was synthesized from **56a** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 6:4, 41% yield) as a yellow oil. IR (neat): ν 3298, 2960, 2915, 2851, 1490, 1443, 1255, 1077, 1039, 737 cm^{-1}. ^1H NMR: δ 6.84 (s, 1H), 6.76 – 6.78 (m, 2H), 5.98 (s, 2H), 5.77 – 5.73 (m, 1H), 5.02 – 5.10 (m, 2H), 4.52 (t, *J* = 7.0 Hz, 1H), 4.29 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.89 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.57 – 2.65 (m, 1H), 2.38 – 2.45 (m, 1H), 2.41 (t, *J* = 2.4Hz, 1H). ^{13}C NMR: δ 147.9 (C), 147.3 (C), 136.9 (CH), 130.9 (C), 120.8 (CH), 116.9 (CH_2), 108.1 (CH), 107.2 (CH), 101.3 (CH_2), 89.1 (CH), 79.8 (C), 77.4 (CH), 57.3 (CH_2) 42.1 (CH_2). GC-MS (EI): *m/z* 230, 190, 189, 175, 149, 135, 131, 115, 103, 91, 63.

*5.1.3.14. Synthesis of 1-Methoxy-4-(1-prop-2-ynyloxy-but-3-enyl)-benzene (**61b**)*



Substrate **61b** was synthesized from **56b** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 8:2, 44% yield) as a yellow oil. IR (neat): ν 3287, 2961, 1736, 1513, 1243, 1030, 805 cm^{-1}. ^1H NMR: δ 7.26 (dd, *J* = 8.6, 2.1 Hz, 2H), 6.90 (dd, *J* = 8.6, 2.1 Hz, 2H), 5.78 – 5.74 (m, 1H), 5.02 – 5.10 (m, 2H), 4.51 (t, *J* = 6,8 Hz, 1H), 4.10 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.85 (dd, *J* = 15.7, 2.4 Hz, 1H), 3.83 (s, 3H), 2.65 – 2.61 (m, 1H), 2.48 – 2.44 (m, 1H), 2.41 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 159.4 (C), 134.6 (CH), 132.5 (C), 128.3 (2CH), 116.9 (CH_2), 113.9 (2CH), 79.9 (CH), 78.7 (C), 74.1 (CH), 55.2 (CH_2), 55.2 (CH_3), 42.1 (CH_2). GC-MS (EI): *m/z* 216, 176, 175, 161, 135, 132, 115, 92, 91, 77, 51.

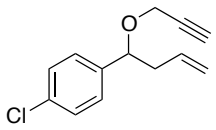
*5.1.3.15. Synthesis of 1-Iodo-2-(1-prop-2-ynyloxy-but-3-enyl)-benzene (**61c**)*



Substrate **61c** was synthesized from **56c** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 8:2, 44% yield) as a yellow oil. IR (neat): ν 3296, 3070, 2903, 2118, 1434, 1082, 1010, 918, 756, 630 cm^{-1}.

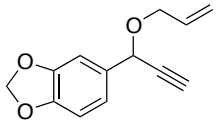
^{1}H NMR: δ 7.83 (d, *J* = 7.8 Hz, 1H), δ 7.37 – 7.44 (m, 2H), 7.00 (td, *J* = 7.4, 2.1 Hz, 1H), 5.86 – 5.96 (m, 1H), 5.07 – 5.15 (m, 2H), 4.86 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.13 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.92 (dd, *J* = 15.6, 2.4 Hz, 1H), 2.57 – 2.53 (m, 3H). ^{13}C NMR: δ 142.9 (C), 139.5 (CH), 134.1 (CH), 129.5 (CH), 128.7 (CH), 127.5 (CH), 117.5 (CH_2), 98.9 (C), 83.4 (CH), 79.7 (C), 74.9 (CH), 56.2 (CH_2), 41.2 (CH_2). GC-MS (EI): *m/z* 312, 274, 271, 232, 231, 201, 144, 128, 116, 104, 89, 76, 51.

*5.1.3.16. Synthesis of 1-Chloro-4-(1-prop-2-ynyloxy-but-3-enyl)-benzene (**61d**)*



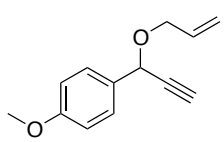
Substrate **61d** was synthesized from **56d** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 51% yield) as a yellow oil. IR (neat): ν 3298, 2965, 2915, 1447, 1251, 1077, 735 cm^{-1}. ^{1}H NMR: δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 5.76 – 5.72 (m, 1H), 5.03 – 4.99 (m, 2H), 4.55 (t, *J* = 5.9 Hz, 1H), 4.12 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.87 (dd, *J* = 15.8, 2.4 Hz, 1H), 2.61 – 2.57 (m, 1H), 2.44 – 2.40 (m, 2H). ^{13}C NMR: δ 139.3 (C), 133.9 (CH), 133.6 (C), 128.7 (2CH), 128.4 (2CH), 117.5 (CH_2), 79.6 (CH), 78.5 (C), 74.6 (CH), 55.6 (CH_2), 42.0 (CH_2). MS (CI): *m/z* 221 (M+1).

*5.1.3.17. Synthesis of 1-(1-allyloxy-prop-2-ynyl)-benzo[1,3]-dioxole (**62a**)*



Substrate **62a** was synthesized from **57a** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 36% yield) as a yellow oil. IR (neat): ν 3298, 3109, 2965, 2915, 1447, 1107, 1077, 737 cm^{-1}. ^{1}H NMR: δ 7.26 (s, 1H), 6.81 – 6.77 (m, 2H), 5.96 (s, 2H), 5.97 – 5.93 (m, 1H), 5.34 – 5.30 (m, 1H), 5.24 – 5.20 (m, 1H), 5.12 (s, 1H), 4.17 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.09 (dd, *J* = 12.4, 6.9 Hz, 1H), 2.64 (s, 1H). ^{13}C NMR: δ 148.2 (C), 147.1 (C), 134.1 (CH), 132.2 (C), 121.2 (CH), 117.9 (CH_2), 108.0 (CH), 107.9 (CH), 101.2 (CH_2), 81.8 (CH), 71.9 (C), 70.1 (CH), 69.0 (CH_2). GC-MS (EI): *m/z* 216, 201, 186, 175, 149, 135, 121, 115, 94, 91, 65, 63. The spectral data for this compound correspond to previously reported data.[15]

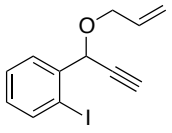
*5.1.3.18. Synthesis of 1-(1-allyloxy-prop-2-ynyl)-4-methoxy-benzene (**62b**)*



Substrate **62b** was synthesized from **57b** and allylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 31% yield) as a yellow oil. IR (neat): ν 3293, 3063, 2851, 2114, 1430, 1115, 930, 773 cm^{-1}. ^{1}H NMR: δ 7.45 (d, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 7.8 Hz, 2H), 5.97 – 5.93 (m, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 5.18 (s, 1H), 4.18 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.09 (dd, *J* = 12.4, 6.0 Hz, 1H), 3.82 (s, 3H), 2.67 (s, 1H). ^{13}C NMR: δ 159.8 (C), 134.2 (CH), 130.4 (C), 128.8 (2CH), 117.7 (CH_2), 113.9 (2CH), 82.9 (C), 75.4 (CH_2), 69.9 (CH), 68.9

(CH), 55.3 (CH_3). MS (CI): *m/z* 203 (M+1). The spectral data for this compound correspond to previously reported data.[16]

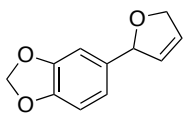
*5.1.3.19. Synthesis of 1-(1-allyloxy-prop-2-ynyl)-2-iodobenzene (**62c**)*



Substrate **62c** was synthesized from **57c** and allylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 31% yield) as a yellow oil. IR (neat): ν 3292, 3067, 2859, 2114, 1711, 1431, 1304, 1063, 930, 755, 645 cm^{-1}. ^1H NMR: δ 7.86 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.43 (td, *J* = 7.7, 0.7 Hz, 1H), 7.03 (td, *J* = 7.7, 1.6 Hz, 1H), 6.03 – 5.99 (m, 1H), 5.40 (dd, *J* = 16.8, 1.5 Hz, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.30 – 4.26 (m, 1H), 4.17 – 4.13 (m, 1H), 2.66 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR: δ 140.5 (C), 139.6 (CH), 133.9 (CH), 130.2 (CH), 128.9 (CH), 128.6 (CH), 118.2 (CH_2), 98.7 (C), 81.0 (C), 75.9 (CH), 74.3 (CH), 70.1 (CH_2). GC-MS (EI): *m/z* 297, 283, 268, 241, 231, 204, 203, 171, 153, 141, 128, 114, 102, 88, 76, 53.

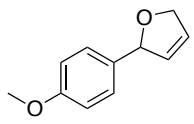
5.1.4. Synthesis of five- and six-membered cyclic ethers

*5.1.4.1. Representative procedure (**RP3**). Synthesis of 2-(2,3-metilendioxy-phenyl)-2,5-dihydro-furan (**63a**)*



Compound **58a** (0.2415 g, 1.1 mmol) was placed in a two-necked 50 mL round bottomed flask, under nitrogen atmosphere. The reactant was dissolved in toluene (11 mL) and Grubbs' catalyst **8** (0.030 g, 0.04 mmol) was added. The mixture was warmed to 50 °C and stirred for 1 h. The product formation was controlled with TLC analysis, using *n*-hexane/CH_2Cl_2 (3:7) as eluent. At the end of the reaction, the mixture was concentrated *in vacuo*. The oil residue (0.2546 g) was purified by column chromatography using *n*-hexane/AcOEt (7:3) as eluent to give the desired pure product as a brown oil (91% yield). IR (neat): ν 3432, 3076, 2851, 2781, 1608, 1486, 1443, 1254, 1038, 933, 795, 689 cm^{-1}. ^1H NMR: δ 6.89 – 6.75 (m, 3H), 6.12 – 6.01 (m, 1H), 5.94 (s, 2H), 5.89 – 5.79 (m, 1H), 5.75 – 5.69 (m, 1H), 4.90 – 4.79 (m, 1H), 4.76 – 4.69 (m, 1H). ^{13}C NMR: δ 147.9 (C), 147.3 (C), 136.0 (C), 129.9 (CH), 126.9 (CH), 120.1 (CH), 108.1 (CH), 107.0 (CH), 100.9 (CH_2), 87.7 (CH), 75.6 (CH_2). GC-MS (EI): *m/z* 190, 189, 171, 149, 135, 131, 119, 103, 91, 77, 51.

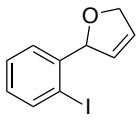
*5.1.4.2. Synthesis of 2-(4-methoxy-phenyl)-2,5-dihydro-furan (**63b**)*



Substrate **63b** was synthesized from **58b**, following the *RP3* and was isolated (*n*-hexane/AcOEt 8:2, quantitative yield) as a brown oil. IR (neat): ν 3451, 3002, 2839, 1605, 1512, 1246, 1173, 1061, 1033, 830,

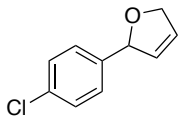
675 cm^{-1}. ^{1}H NMR: δ 7.25 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.12 – 5.90 (m, 1H), 5.90 – 5.85 (m, 1H), 5.77 (br, 1H), 4.92 – 4.89 (m, 1H), 4.82 – 4.69 (m, 1H), 3.81 (s, 3H). ^{13}C NMR: δ 159.4 (C), 134.2 (C), 130.0 (CH), 127.9 (2CH), 126.7 (CH), 113.9 (2CH), 87.5 (CH), 75.5 (CH_2), 55.3 (CH_3). GC-MS (EI): *m/z* 175, 160, 135, 131, 115, 103, 91, 77, 51. The spectral data for this compound correspond to previously reported data.[17]

*5.1.4.3. Synthesis of 2-(2-iodo-phenyl)-2,5-dihydro-furan (**63c**)*



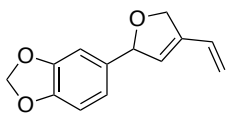
Substrate **63c** was synthesized from **58c**, following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 7:3 84% yield) as a brown oil. IR (neat): ν 3383, 2923, 2854, 1588, 1504, 1316, 1005, 742, 701 cm^{-1}. ^{1}H NMR: δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.49 – 7.32 (m, 2H), 7.12 – 6.79 (m, 1H), 6.22 – 6.01 (m, 1H), 5.99 – 5.85 (m, 1H), 5.02 – 4.89 (m, 1H), 4.85 – 4.75 (m, 1H), ^{13}C NMR: δ 144.1 (C), 139.3 (CH), 129.4 (CH), 129.0 (CH), 128.7 (CH), 127.4 (CH), 126.8 (CH), 96.6 (C), 91.2 (CH), 76.4 (CH_2). MS (CI): *m/z* 273 (M+1).

*5.1.4.4. Synthesis of 2-(4-chloro-phenyl)-2,5-dihydro-furan (**63d**)*



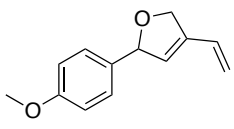
Substrate **63d** was synthesized from **58d**, following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 4:6, 85% yield) as a yellow oil. IR (neat): ν 3092, 2962, 2932, 1590, 1402, 1264, 1092, 1014, 737 cm^{-1}. ^{1}H NMR: δ 7.32 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.05 (d, *J* = 6.2 Hz, 1H), 5.98 – 5.79 (m, 1H), 5.77 – 7.67 (m, 1H), 4.87 (dd, *J* = 12.9, 6.0 Hz, 1H), 4.79 – 4.45 (m, 1H). ^{13}C NMR: δ 140.6 (C), 133.5 (C), 129.6 (CH), 128.6 (2CH), 127.8 (2CH), 127.0 (CH), 87.2 (CH), 75.8 (CH_2). GC-MS (EI): *m/z* 180, 163, 151, 139, 127, 115, 99, 89, 69, 50. The spectral data for this compound correspond to previously reported data.[18]

*5.1.4.5. Synthesis of 5-(4-vinyl-2,5-dihydro-furan-2-yl)-2-benzo[1,3]dioxole (**64a**)*



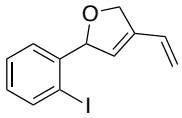
Substrate **64a** was synthesized from **60a**, following the *RP3* and was isolated (CH_2Cl_2, 28% yield) as a yellow oil. IR (neat): ν 3412, 2922, 1710, 1495, 1443, 1247, 1036, 932, 810, 734 cm^{-1}. ^{1}H NMR: δ 6.79 – 6.72 (m, 3H), 6.65 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.95 (d, *J*= 7.9 Hz, 1H), 5.83 – 5.79 (m, 2H), 5.78 – 5.76 (m, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.7 Hz, 1H), 4.97 (dd, *J*= 11.8, 3.6 Hz, 1H), 4.85 (dd, *J* = 11.8, 2.3 Hz, 1H). ^{13}C NMR: δ 147.9 (C), 147.3 (C), 138.9 (C), 135.8 (C), 129.3 (CH), 128.2 (CH), 120.1 (CH), 117.1 (CH_2), 108.1 (CH), 107.1 (CH), 101.0 (CH_2), 81.8 (CH), 74.1 (CH_2). GC-MS (EI): *m/z* 216, 187, 173, 157, 149, 129, 121, 115, 91, 77, 65, 51, 39, 27.

*5.1.4.6. Synthesis of 2-(4-methoxy-phenyl)-4-vinyl-2,5-dihydro-furan (**64b**)*



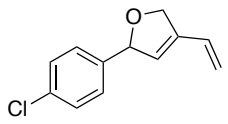
Substrate **64b** was synthesized from **60b**, following the *RP3* and was isolated (CH_2Cl_2, 36% yield) as a yellow oil. IR (neat): ν 3416, 3057, 2938, 2841, 1760, 1602, 1258, 1174, 1030, 834, 737 cm^{-1}. ^1H NMR: δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.58 (dd, *J* = 17.6, 10.8 Hz , 1H), 5.89 – 5.79 (m, 2H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 5.02 – 4.92 (m, 1H), 4.89 – 4.82 (m, 1H), 3.81 (s, 3H). ^{13}C NMR: δ 159.8 (C), 139.2 (C), 134.3 (C), 129.8 (CH), 128.8 (CH), 128.3 (2CH), 117.2 (CH_2), 114.6 (2CH), 88.4 (CH), 74.6 (CH_2), 55.7 (CH_3). MS (CI): *m/z* 203 (M+1).

*5.1.4.7. Synthesis of 2-(2-iodo-phenyl)-4-vinyl-2,5-dihydro-furan (**64c**)*



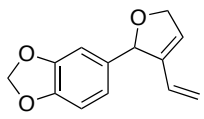
Substrate **64c** was synthesized from **60c**, following the *RP3* and was isolated (CH_2Cl_2, 32% yield) as a colorless oil. IR (neat): ν 3432, 3056, 2926, 2855, 1462, 1433, 1265, 1011, 738 cm^{-1}. ^1H NMR: δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.33 (m, 2H), 6.98 (td, *J*= 7.8, 1.8 Hz, 1H), 6.53 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.12 – 5.98 (m, 2H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.11 (d, *J* = 13.8 Hz, 1H), 5.15 – 4.99 (m, 1H), 4.98 – 4.75 (m, 1H). ^{13}C NMR: δ 143.8 (C), 139.3 (CH), 138.8 (C), 129.6 (CH), 129.4 (CH), 128.7 (CH), 127.5 (CH), 127.2 (CH), 117.2 (CH_2), 96.5 (C), 91.2 (CH), 75.0 (CH_2). MS (CI): *m/z* 299 (M+1).

*5.1.4.8. Synthesis of 2-(4-chloro-phenyl)-4-vinyl-2,5-dihydro-furan (**64d**)*



Substrate **64d** was synthesized from **60d**, following the *RP3* and was isolated (CH_2Cl_2, 26% yield) as a yellow oil. IR (neat): ν 3408, 3057, 2931, 1764, 1487, 1266, 1092, 829, 737 cm^{-1}. ^1H NMR: δ 7.35 – 7.32 (m, 2H), 7.29 – 7.21 (m, 2H), 6.56 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.85 – 5.79 (m, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.7 Hz, 1H), 5.10 – 4.95 (m, 1H), 4.91 – 4.86 (m, 1H). ^{13}C NMR: δ 140.8 (C), 139.5 (C), 134.0 (C), 129.5 (2CH), 129.1 (2CH), 128.2 (2CH), 117.7 (CH_2), 88.0 (CH), 74.9 (CH_2). GC-MS (EI): *m/z* 206, 177, 149, 139, 128, 115, 110, 95, 75, 65, 39, 27.

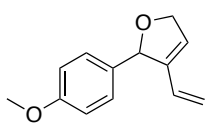
*5.1.4.9. Synthesis of 5-(3-vinyl-2,5-dihydro-furan-2-yl)-benzo[1,3]-dioxole (**65a**)*



Substrate **65a** was synthesized from **62a**, following the *RP3* and was isolated (*n*-hexane/AcOEt 8:2, 76% yield) as a yellow oil. IR (neat): ν 3422, 2962, 2902, 1645, 1487, 1260, 1039, 738 cm^{-1}. ^1H NMR: δ 6.82 – 6.76 (m, 3H), 6.41 (dd, *J* = 17.7, 11.1 Hz, 1H), 6.08 (s, 1H), 5.94 (s, 2H), 5.74 (br, 1H), 5.04 (d, *J* = 11.1 Hz, 1H), 4.99 (d, *J* = 17.7 Hz, 1H), 4.85 – 4.79 (m, 1H), 4.71 (d, *J* =

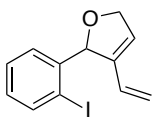
14.3 Hz, 1H). ^{13}C NMR: δ 148.0 (C), 147.6 (C), 140.2 (C), 135.1 (C), 128.9 (CH), 126.6 (CH), 121.4 (CH), 117.6 (CH_2), 108.1 (CH), 107.6 (CH), 101.0 (CH_2), 87.2 (CH), 74.6 (CH_2). GC-MS (EI): *m/z* 216, 201, 187, 173, 149, 135, 129, 115, 93, 91, 65, 51.

*5.1.4.10. Synthesis of 2-(4-methoxy-phenyl)-3-vinyl-2,5-dihydro-furan (**65b**)*



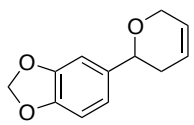
Substrate **65b** was synthesized from **62b**, following the *RP3* and was isolated (*n*-hexane/AcOEt 8:2, 71% yield) as a yellow oil. IR (neat): ν 3424, 2961, 2935, 2842, 1600, 1512, 1257, 1173, 1029, 735 cm^{-1}. ^{1}H NMR: δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.41 (dd, *J* = 17.8, 11.1 Hz, 1H), 6.08 (s, 1H), 5.79 (br, 1H), 5.03 (d, *J* = 11.1 Hz, 1H), 4.86 (d, *J* = 18.0 Hz, 2H), 4.73 (d, *J* = 17.8 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR: δ 159.6 (C), 140.3 (C), 133.3 (C), 129.0 (CH), 128.8 (2CH), 126.5 (CH), 117.6 (CH_2), 114.0 (2CH), 86.9 (CH), 74.5 (CH_2), 55.2 (CH_3). MS (CI): *m/z* 203 (M+1).

*5.1.4.11. Synthesis of 2-(2-iodo-phenyl)-3-vinyl-2,5-dihydro-furan (**65c**)*



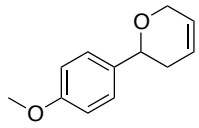
Substrate **65c** was synthesized from **62c**, following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 9:1, 64% yield) as a yellow oil. IR (neat): ν 3417, 3054, 2932, 1758, 1453, 1265, 1011, 738 cm^{-1}. ^{1}H NMR: δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.19 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.00 (td, *J* = 7.7, 1.7 Hz, 1H), 6.45 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.22 – 6.15 (m, 2H), 5.08 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 17.8 Hz, 1H), 4.82 – 4.76 (m, 2H). ^{13}C NMR: δ 142.6 (C), 140.8 (C), 140.1 (CH), 130.4 (CH), 129.1 (CH), 129.0 (CH), 129.0 (CH), 128.6 (CH), 118.8 (CH_2), 100.7 (C), 90.9 (CH), 75.2 (CH_2). GC-MS (EI): *m/z* 298, 280, 269, 254, 231, 203, 171, 153, 141, 128, 115, 95, 89, 76, 51.

*5.1.4.12. Synthesis of 5-(3,6-dihydro-pyran-2-yl)-benzo-[1,3]dioxole (**66a**)*



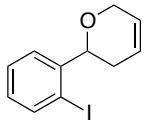
Substrate **66a** was synthesized from **59a**, following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 3:7, 92% yield) as a colorless oil. IR (neat): ν 3444, 3034, 2893, 2829, 1443, 1248, 1089, 933, 809, 661 cm^{-1}. ^{1}H NMR: δ 6.91 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 2H), 5.99 – 5.89 (m, 1H), 5.85 – 5.81 (m, 1H), 4.47 (dd, *J* = 10.2, 3.4 Hz, 1H), 4.35 – 4.31 (m, 2H), 2.37 – 2.33 (m, 1H), 2.25 – 2.16 (m, 1H). ^{13}C NMR: δ 147.7 (C), 146.8 (C), 136.7 (C), 126.4 (CH), 124.4 (CH), 119.3 (CH), 108.0 (CH), 106.7 (CH), 100.9 (CH_2), 75.4 (CH), 66.6 (CH_2), 32.9 (CH_2). GC-MS (EI): *m/z* 204, 202, 173, 150, 135, 121, 115, 103, 91, 63.

*5.1.4.13. Synthesis of 2-(4-methoxy-phenyl)-3,6-dihydro-pyran (**66b**)*



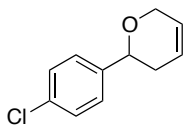
Substrate **66b** was synthesized from **59b**, following the *RP3* and was isolated (*n*-hexane/AcOEt 8:2, 90% yield) as a brown oil. IR (neat): ν 3445, 3029, 2896, 1441, 1249, 1085, 809, 661 cm^{-1}. ^{1}H NMR: δ 7.32 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.99 – 5.89 (m, 1H), 5.82 (d, *J* = 10.2 Hz, 1H), 4.52 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.39 – 4.32 (m, 2H), 3.81 (s, 3H), 2.41 – 2.36 (m, 1H), 2.28 – 2.22 (m, 1H). ^{13}C NMR: δ 159.0 (C), 134.8 (C), 127.2 (CH), 126.4 (2CH), 124.5 (CH), 113.8 (2CH), 75.3 (CH), 66.5 (CH_2), 55.2 (CH_3), 32.8 (CH_2). GC-MS (EI): *m/z* 190, 188, 172, 159, 136, 121, 107, 91, 77, 54. The spectral data for this compound correspond to previously reported data.[19]

*5.1.4.14. Synthesis of 2-(2-iodo-phenyl)-3,6-dihydro-2H-pyran (**66c**)*



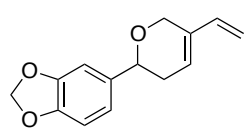
Substrate **66c** was synthesized from **59c**, following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 1:1, quantitative yield) as a yellow oil. IR (neat): ν 3434, 3025, 2891, 2821, 1248, 1077, 933, 737 cm^{-1}. ^{1}H NMR: δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.02 – 5.91 (m, 1H), 5.83 (d, *J* = 10.4, 1H), 4.71 (dd, J = 10.4, 3.0 Hz, 1H), 4.47 – 4.43 (m, 2H), 2.98 – 2.93 (m, 1H), 2.17 – 2.11(m, 1H). ^{13}C NMR: δ 144.7 (C), 139.1 (CH), 129.1 (CH), 128.7 (CH), 127.1 (CH), 126.3 (CH), 124.4 (CH), 97.4 (C), 79.1 (CH), 66.8 (CH_2), 31.9 (CH_2). GC-MS (EI): *m/z* 286, 257, 231, 232, 217, 203, 177, 158, 141, 128, 115, 104, 78, 76, 54.

*5.1.4.15. Synthesis of 6-(4-chloro-phenyl)-3,6-dihydro-pyran (**66d**)*



Substrate **66d** was synthesized from **59d**, following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 1:1, 93% yield) as a colorless oil. IR (neat): ν 3443, 3024, 2823, 1433, 1241, 1087, 938, 773, 661 cm^{-1}. ^{1}H NMR: δ 7.43 – 7.21 (m, 4H), 6.04 – 5.89 (m, 1H), 5.91 – 5.79 (m, 2H), 4.54 (dd, *J* = 9.7, 4.1 Hz, 1H), 4.35 (d, *J* = 0.9 Hz, 1H), 2.34 – 2.26 (m, 2H). ^{13}C NMR: δ 141.2 (C), 133.1 (C), 128.2 (CH), 127.2 (2CH), 126.4 (2CH), 124.6 (CH), 74.8 (CH), 66.5 (CH_2), 32.9 (CH_2). GC-MS (EI): *m/z* 194, 177, 165, 151, 139, 125, 111, 103, 89, 75, 54.

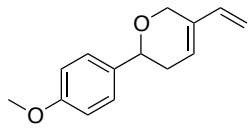
*5.1.4.16. Synthesis of 5-(5-vinyl-3,6-dihydro-2H-pyran-2-yl)- benzo[1,3]dioxole (**67a**)*



Substrate **67a** was synthesized from **61a** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 2:8, 62% yield) as a yellow oil. IR (neat): ν 3005, 2932, 1615, 1269, 1111, 1032, 737 cm^{-1}. ^{1}H NMR: δ 6.93 (s, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 7.9 Hz, 1H), 6.33 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.97 (s, 2H), 5.99 – 5.91 (m, 1H), 5.37 (t, *J* = 5.1 Hz, 1H), 5.02 (s, 1H), 4.98 (d, *J* = 9.2 Hz,

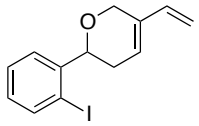
1H), 3.89 – 3.85 (m, 2H), 2.47 – 2.43 (m, 2H). ^{13}C NMR: δ 147.5 (C), 147.1 (C), 139.9 (C), 136.8 (C), 129.9 (CH), 128.5 (CH), 121.1 (CH), 118.1 (CH_2), 108.5 (CH), 107.2 (CH), 101.3 (CH_2), 80.4 (CH), 73.1 (CH_2), 35.2 (CH_2). MS (CI): *m/z* 231 (M+1).

*5.1.4.17. Synthesis of 2-(4-methoxy-phenyl)-5-vinyl-3,6-dihydro-2H-pyran (**67b**)*



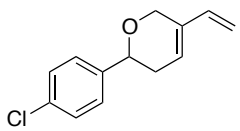
Substrate **67b** was synthesized from **61b** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 2:8, 81% yield) as a yellow oil. IR (neat): ν 3001, 2932, 2852, 1611, 1514, 1249, 1100, 1032, 827, 735 cm^{-1}. ^{1}H NMR: δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8. 7 Hz, 2H), 6.33 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.99 – 5.93 (m, 1H), 5.01 (t, *J* = 18.2 Hz, 1H), 4.97 (t, *J* = 7.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.54 – 4.46 (m, 2H), 3.82 (s, 3H), 2.47 – 2.43 (m, 2H). ^{13}C NMR: δ 159.1 (C), 135.8 (CH), 135.1 (C), 134.35 (C), 127.2 (2CH), 125.9 (CH), 113.8 (2CH), 111.1 (CH_2), δ 75.4 (CH), 66.02 (CH_2), 55.3 (CH_3), 33.1 (CH_2). MS (CI): *m/z* 217 (M+1).

*5.1.4.18. Synthesis of 2-(2-iodo-phenyl)-5-vinyl-3,6-dihydro-2H-pyran (**67c**)*



Substrate **67c** was synthesized from **61c** following the *RP3* and was isolated (CH_2Cl_2, 87% yield) as a yellow oil. IR (neat): ν 3444, 3054, 2983, 2924, 2853, 1466, 1264, 1083, 1011, 737, 704 cm^{-1}. ^{1}H NMR: δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.00 (td, *J* = 7.9, 1.7 Hz, 1H), 6.35 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.96 (br, 1H), 5.11 – 4.98 (m, 2H), 4.67 – 4.62 (m, 3H), 2.65 – 2.63 (m, 1H), 2.26 – 2.21 (m, 1H). ^{13}C NMR: δ 144.9 (C), 139.6 (CH), 136.1 (CH), 135.3 (C), 129.7 (CH), 129.1 (CH), 127.4 (CH), 126.1 (CH), 111.7 (CH_2), 97.8 (C), 79.7 (CH), 66.7 (CH_2), 32.2 (CH_2). MS (CI): *m/z* 313 (M+1).

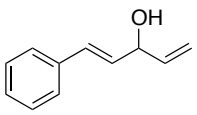
*5.1.4.19. Synthesis of 2-(4-chloro-phenyl)-5-vinyl-3,6-dihydro-2H-pyran (**67d**)*



Substrate **67d** was synthesized from **61d** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 3:7, 70% yield) as a yellow oil. IR (neat): ν 3055, 2923, 853, 1595, 1492, 1263, 1089, 1014, 820, 737 cm^{-1}. ^{1}H NMR: δ 7.39 – 7.32 (m, 4H), 6.35 (dd, *J* = 17.9, 11.2 Hz, 1H), 5.97 – 5.92 (m, 1H), 5.13 – 4.98 (m, 2H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.57 – 4.49 (m, 2H), 2.48 – 2.37 (m, 2H). ^{13}C NMR: δ 141.2 (C), 136.1 (CH), 135.5 (C), 133.6 (C), 128.9 (2CH), 127.6 (2CH), 125.8 (CH), 111.7 (CH_2), 75.4 (CH), 66.4 (CH_2), 33.6 (CH_2). MS (CI): *m/z* 221 (M+1).

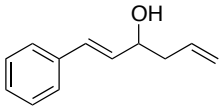
5.1.5. Synthesis of cyclic ethers starting from cynnamaldehyde

*5.1.5.1. Synthesis of (E)-1-phenyl-penta-1,4-dien-3-ol (**68**)*



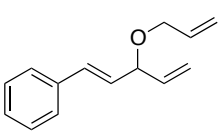
Substrate **68** was synthesized from cynnammaldehyde and vinylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR: δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 – 7.24 (m, 1H), 6.62 (d, *J* = 15.0 Hz, 1H), 6.24 (dd, *J* = 15.2, 6.4 Hz, 1H), 6.03 – 5.91 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.3 Hz, 1H), 4.81 (t, *J* = 5.8 Hz, 1H), 2.03 (br, 1H). ^{13}C NMR: δ 137.9 (CH), 136.4 (C), 134.7 (CH), 128.9 (2CH), 128.5 (2CH), 127.8 (CH), 126.6 (CH), 116.9 (CH_2), 79.1 (CH). MS (CI): *m/z* 161 (M+1).

*5.1.5.2. Synthesis of (E)-1-phenyl-hexa-1,5-dien-3-ol (**69**)*



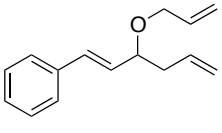
Substrate **69** was synthesized from cynnammaldehyde and allylmagnesium chloride, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR: δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.27 – 7.21 (m, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.91 – 5.79 (m, 1H), 5.23 – 5.15 (m, 2H), 4.36 – 4.32 (m, 1H), 2.44 – 2.40 (m, 2H), 2.01 (br, 1H). ^{13}C NMR: δ 136.4 (C), 134.4 (CH), 131.3 (CH), 129.9 (2CH), 128.6 (2CH), 127.5 (CH), 117.5 (CH_2), 79.7 (CH), 44.3 (CH_2). MS (CI): *m/z* 175 (M+1). The spectral data for this compound correspond to previously reported data.[21]

*5.1.5.3. Synthesis of ((E)-3-allyloxy-penta-1,4-dienyl)-benzene (**70**)*



Substrate **70** was synthesized from **68** and allylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 4:6, 59% yield) as a yellow oil. IR (neat): ν 3077, 2935, 2857, 1451, 1263, 1071, 747, 693 cm^{-1}. ^{1}H NMR: δ 7.42 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 – 7.25 (m, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.9 Hz, 1H), 5.98 – 5.93 (m, 2H), 5.34 (d, *J* = 17.3 Hz, 2H), 5.26 (d, *J* = 10.4 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.45 (t, *J* = 6.7 Hz, 1H), 4.07 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR: δ 137.7 (CH), 136.6 (C), 134.9 (CH), 131.9 (CH), 128.9 (2CH), 128.5 (2CH), 127.8 (CH), 126.6 (CH), 116.9 (CH_2), 116.8 (CH_2), 80.8 (CH), 68.9 (CH_2). GC-MS (EI): *m/z* 200, 189, 172, 159, 143, 131, 115, 105, 91, 77, 55.

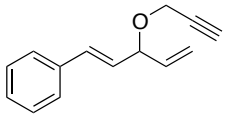
*5.1.5.4. Synthesis of ((E)-3-alyloxy-hexa-1,5-dienyl)-benzene (**71**)*



Substrate **71** was synthesized from **69** and allylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 51% yield) as a yellow oil. IR (neat): ν 3078, 2925, 2855, 1642, 1450, 1262, 1072, 917, 747, 694

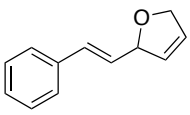
cm^{-1}. ^1H NMR: δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.28 – 7.24 (m, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.54 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.93 – 5.87 (m, 2H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dd, *J* = 10.3, 1.2 Hz, 1H), 5.13 – 5.08 (m, 2H), 4.15 – 4.08 (m, 1H), 3.96 – 3.92 (m, 2H), 2.51 – 2.46 (m, 1H), 2.43 – 2.39 (m, 1H). ^{13}C NMR: δ 136.6 (C), 134.5 (CH), 134.4 (CH), 132.3 (CH), 129.9 (2CH), 128.6 (2CH), 127.3 (CH), 126.5 (CH), 117.1 (CH_2), 116.7 (CH_2), 79.7 (CH), 69.2 (CH_2), 40.3 (CH_2). MS (CI): *m/z* 215 (M+1). The spectral data for this compound correspond to previously reported data.[22]

*5.1.5.5. Synthesis of ((E)-3-prop-2-ynyloxy-penta-1,4-dienyl)-benzene (**72**)*



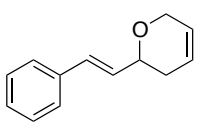
Substrate **72** was synthesized from **68** and propargylbromide, following the *RP2* and was isolated (*n*-hexane/CH_2Cl_2 7:3, 48% yield) as a yellow oil. IR (neat): ν 3076, 2927, 2851, 2111, 1644, 1454, 1262, 1072, 737 cm^{-1}. ^1H NMR: δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.29 – 7.23 (m, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.16 (dd, *J* = 16.0, 7.1 Hz, 1H), 5.92 – 5.87 (m, 1H), 5.38 (dd, *J* = 17.2, 0.6 Hz, 1H), 5.30 (dd, *J* = 10.3, 0.8 Hz, 1H), 4.65 (t, *J* = 6.8 Hz, 1H), 4.22 (d, *J* = 1.8 Hz, 2H), 2.46 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR: δ 136.8 (CH), 136.4 (C), 132.8 (CH), 128.6 (2CH), 127.9 (2CH), 127.8 (CH), 126.6 (CH), 117.7 (CH_2), 80.1 (CH), 79.1 (C), 74.3 (CH), 55.0 (CH_2). MS (CI): *m/z* 199 (M+1).

*5.1.5.6. Synthesis of 2-((E)-styril)-2,5-dihydro-furan (**73**)*



Substrate **73** was synthesized from **70** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 3:7, 87% yield) as a yellow oil. IR (neat): ν 3435, 3059, 2963, 2930, 1906, 1266, 1174, 1046, 783, 702 cm^{-1}. ^1H NMR: δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.29 – 7.25 (m, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 6.17 (dd, *J* = 15.8, 7.2 Hz, 1H), 6.03 – 5.97 (m, 1H), 5.86 – 5.83 (m, 1H), 5.40 (br, 1H), 4.79 – 4.75 (m, 1H), 4.74 – 4.69 (m, 1H). ^{13}C NMR: δ 136.7 (C), 130.9 (CH), 129.3 (CH), 128.8 (2CH), 128.5 (2CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 86.8 (CH), 75.3 (CH_2). MS (CI): *m/z* 173 (M+1). The spectral data for this compound correspond to previously reported data.[23]

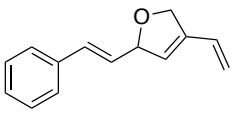
*5.1.5.7. Synthesis of 2-((E)-styryl)-3,6-dihydro-pyran (**74**)*



Substrate **74** was synthesized from **71** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 1:1, 27% yield) as a yellow oil. IR (neat): ν 3061, 3032, 2925, 1638, 1451, 1260, 1073, 699 cm^{-1}. ^1H NMR: δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.29 – 7.22 (m, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.29 (dd, *J* = 16.0, 5.9 Hz, 1H), 5.92 – 5.83 (m, 1H), 5.81 – 5.76 (m, 1H), 4.35 – 4.29 (m, 2H), 4.25 –

4.21 (m, 1H), 2.31 – 2.25 (m, 1H), 2.22 – 2.16 (m, 1H). ^{13}C NMR: δ 136.8 (C), 130.5 (CH), 129.9 (CH), 128.5 (2CH), 127.6 (2CH), 126.5 (CH), 126.3 (CH), 123.9 (CH), 73.8 (CH), 65.7 (CH_2), 31.1 (CH_2). MS (CI): *m/z* 187 (M+1). The spectral data for this compound correspond to previously reported data.[24]

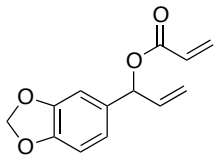
*5.1.5.8. Synthesis of 2-((E)-styryl)-4-vinyl-2,5-dihydro-furan (**75**)*



Substrate **75** was synthesized from **72** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 4:6, 79% yield) as a yellow oil. IR (neat): ν 3063, 2927, 1630, 1451, 1261, 1077, 699 cm^{-1}. ^{1}H NMR: δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), δ 7.27 – 7-23 (m, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.55 (dd, *J* = 17.7, 10,8 Hz, 1H), 6.17 (dd, *J* = 15.8, 7.3 Hz, 1H), 5.77 (br, 1H), 5.45 (br, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 5.06 (d, *J* = 17.7 Hz, 1H), 4.91 (dd, *J* = 11.6, 4.8 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR: δ 139.2 (C), 136.6 (C), 131.1 (CH), 129.4 (CH), 128.9 (CH), 128.5 (2CH), 127.7 (2CH), 127.2 (CH), 126.6 (CH), 116.9 (CH_2), 87.2 (CH), 73.9 (CH_2). GC-MS (EI): *m/z* 198, 183, 165, 155, 141, 131, 115, 103, 91, 77, 55.

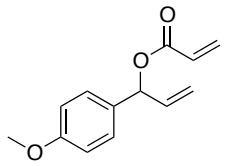
5.1.6. Synthesis of acrylic esters

*5.1.6.1. Representative procedure (**RP4**). Synthesis* of *acrylic acid 1-benzo[1,3]dioxol-5-yl-allyl ester (**76a**)*



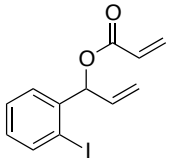
Compound **55a** (0.5051 g, 2.8 mmol) was placed in a one-necked 100 mL round bottomed flask and was dissolved in CH_2Cl_2 (20 mL). Et_3N (0.85 g, 1.16 mL, 8.4 mmol) and DMAP (0.034 g, 0.28 mmol) were added and the mixture was cooled to -30 °C. Acryloyl chloride (0.30 g, 0.27 mL, 3.4 mmol) was added dropwise over 15 minutes and the mixture was stirred at room temperature for 2 hours. The product formation was controlled with TLC analysis using *n*-hexane/AcOEt (8:2) as eluent. At the end of the reaction, the solution was washed with water (3 x 30 mL) and brine (2 x 30 mL), then dried on Na_2SO_4 and the solvent removed *in vacuo*. The oil residue was purified by column chromatography using *n*-hexane/AcOEt (8:2) as eluent to give the required pure product as a colorless oil (55% yield). IR (neat): ν 2957, 2839, 1723, 1511, 1247, 1177, 1030, 968 cm^{-1}. ^{1}H NMR: δ 6.89 – 6.84 (m, 2H), 6.79 – 6.73 (m, 1H), 6.45 (d, *J* = 17.3 Hz, 1H), 6.26 (d, *J* = 5.4 Hz, 1H), 6.17 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.11 – 5.99 (m, 1H), 5.95 (s, 2H), 5.85 (d, *J* = 10.4 Hz, 1H), 5.31 – 5.27 (m, 2H). ^{13}C NMR: δ 165.0 (C), 147.8 (C), 147.5 (C), 136.1 (CH), 132.7 (C), 131.1 (CH_2), 128.5 (CH), 121.0 (CH), 116.7 (CH_2), 108.2 (CH), 107.7 (CH), 101.2 (CH_2), 76.0 (CH). GC-MS (EI): *m/z* 232, 231, 204, 190, 178, 162, 160, 147, 131, 119, 103, 91, 77, 55.

5.1.6.2. Synthesis of *acrylic acid 1-(4-methoxy-phenyl)-allyl ester (**76b**)*



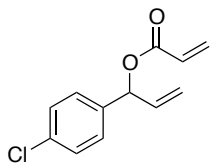
Substrate **76b** was synthesized from **55b**, following the *RP4* and was isolated (*n*-hexane/AcOEt 8:2, 69% yield) as a colorless oil. IR (neat): ν 3003, 2956, 2837, 1723, 1512, 1249, 1176, 1034, 967 cm^{-1}. ^{1}H NMR: δ 7.32 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.44 (d, *J* = 17.3 Hz, 1H), 6.31 (d, *J* = 5.4 Hz, 1H), 6.17 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.07 – 6.03 (m, 1H), 5.84 (d, *J* = 10.4 Hz, 1H), 5.29 – 5.25 (m, 2H), 3.80 (s, 3H). ^{13}C NMR: δ 165.2 (C), 159.5 (C), 136.3 (CH), 130.9 (CH_2), 128.7 (2CH), 120.8 (C), 116.6 (CH_2), 116.5 (CH), 113.9 (2CH), 75.8 (CH), 55.3 (CH_3). GC-MS (EI): *m/z* 218, 206, 190, 170, 163, 148, 131, 115, 103, 91, 77, 55.

5.1.6.3. Synthesis of *acrylic acid 1-(2-iodo-phenyl)-allyl ester (**76c**)*



Substrate **76c** was synthesized from **55c**, following the *RP4* and was isolated (*n*-hexane/AcOEt 9:1, 61% yield) as a colorless oil. IR (neat): ν 2963, 2924, 2856, 1723, 1260, 1011, 747 cm^{-1}. ^{1}H NMR: δ 7.86 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.00 (td, *J* = 7.9, 1.8 Hz, 1H), 6.53 (d, *J* = 5.5 Hz, 1H), 6.49 (dd, *J* = 17.4, 1.4 Hz, 1H), 6.21 (dd, *J* = 17.4, 10.4 Hz, 1H), 6.05 – 5.87 (m, 1H), 5.88 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.35 – 5.31 (m, 2H). ^{13}C NMR: δ 164.8 (C), 141.2 (C), 139.7 (CH), 134.7 (CH), 131.5 (CH_2), 129.8 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 117.7 (CH_2), 98.3 (C), 79.4 (CH). MS (CI): *m/z* 315 (M+1).

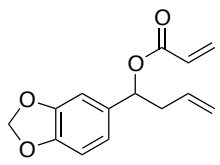
5.1.6.4. Synthesis of *acrylic acid 1-(4-chloro-phenyl)-allyl ester (**76d**)*



Substrate **76d** was synthesized from **55d**, following the *RP4* and was isolated (*n*-hexane/CH_2Cl_2 4:6, 43% yield) as a colorless oil. IR (neat): ν 3425, 2963, 1727, 1405, 1261, 1184, 1091, 808 cm^{-1}. ^{1}H NMR: δ 7.35 – 7.29 (m, 4H), 6.45 (d, *J* = 17.3 Hz, 1H), 6.31 (d, *J* = 5.8 Hz, 1H), 6.18 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.13 – 5.97 (m, 1H), 5.87 (d, *J* = 14.4 Hz, 1H), 5.37 – 5.25 (m, 2H). ^{13}C NMR: δ 164.9 (C), 137.3 (CH), 135.7 (CH), 134.1 (C), 131.3 (CH_2), 128.7 (2CH), 128.5 (2CH), 128.3 (C), 117.5 (CH_2), 75.5 (CH). GC-MS (EI): *m/z* 222, 207, 194, 187, 167, 150, 139, 125, 115, 103, 89, 75, 55. The spectral data for this compound correspond to previously reported data.[25]

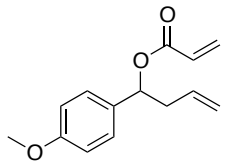
*5.1.6.5. Synthesis of acrylic acid 1-benzo[1,3]dioxol-5-yl-but-3-enyl ester (**77a**)*

Substrate **77a** was synthesized from **56a**, following the *RP4* and was isolated (*n*-hexane/CH_2Cl_2 2:8, 47% yield) as a colorless oil. IR (neat): ν 3070, 2951, 2836, 1723, 1515, 1251, 1037, 982, 830 cm^{-1}. ^{1}H NMR: δ 6.76 – 6.88 (m, 3H), 6.41 (d, *J* = 17.3 Hz, 1H), 6.13



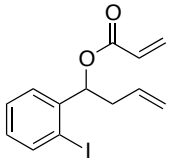
(dd, *J* = 17.3, 10.4 Hz, 1H), 5.95 (s, 2H), 5.87 – 5.78 (m, 2H), 5.73 – 5.48 (m, 1H), 5.11 – 5.03 (m, 2H), 2.69 – 5.65 (m, 1H), 2.57 – 5.53 (m, 1H). ^{13}C NMR: δ 165.3 (C), 147.7 (C), 147.3 (C), 133.8 (C), 133.2 (CH), 130.8 (CH_2), 128.5 (CH), 120.4 (CH), 118.1 (CH_2), 108.2 (CH), 107.0 (CH), 101.8 (CH_2), 75.2 (CH), 40.7 (CH_2). GC-MS (EI): *m/z* 246, 205, 203, 174, 144, 115, 91, 65, 55.

*5.1.6.6. Synthesis of acrylic acid 1-(4-methoxy-phenyl)-but-3-enyl ester (77**b**)*



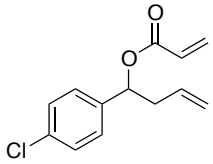
Substrate **77b** was synthesized from **56b**, following the *RP4* and was isolated (*n*-hexane/AcOEt 8:2, 88% yield) as a colorless oil. IR (neat): ν 3077, 3003, 2956, 2837, 1723, 1514, 1250, 1191, 1037, 982, 830 cm^{-1}. ^{1}H NMR: δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.41 (dd, *J* = 17.3, 1.0 Hz, 1H), 6.14 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.86 (d, *J* = 6.8 Hz, 1H), 5.86 (d, *J* = 10.7 Hz, 1H), 5.73 – 5.69 (m, 1H), 5.09 – 5.03 (m, 2H), 3.80 (s, 3H), 2.73 – 2.69 (m, 1H), 2.60 – 2.56 (m, 1H). ^{13}C NMR: δ 165.4 (C), 159.3 (C), 133.5 (CH), 132.1 (C), 130.6 (CH), 128.7 (CH_2), 128.0 (2CH), 118.0 (CH_2), 113.8 (2CH), 75.1 (CH), 55.2 (CH_3), 40.5 (CH_2). GC-MS (EI): *m/z* 232, 207, 191, 177, 161, 135, 129, 115, 91, 77.

*5.1.6.7. Synthesis of acrylic acid 1-(2-iodo-phenyl)-but-3-enyl ester (77**c**)*



Substrate **77c** was synthesized from **56c**, following the *RP4* and was isolated (*n*-hexane/AcOEt 8:2, 48% yield) as a colorless oil. IR (neat): ν 3074, 2962, 1728, 1404, 1263, 1183, 1013, 918, 806, 755 cm^{-1}. ^{1}H NMR: δ 7.85 – 7.81 (m, 1H), 7.37 – 7.33 (m, 2H), 6.94 – 6.90 (m, 1H), 6.46 (d, *J* = 17.3 Hz, 1H), 6.19 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.11 – 6.03 (m, 1H), 5.87 (d, *J* = 10.4 Hz, 1H), 5.84 – 5.78 (m, 1H), 5.11 – 5.07 (m, 2H), 2.65 – 2.60 (m, 2H). ^{13}C NMR: δ 165.0 (C), 142.6 (C), 139.5 (CH), 132.9 (CH), 131.2 (CH_2), 129.4 (CH), 128.4 (CH), 128.3 (CH), 126.9 (CH), 118.3 (CH_2), 97.5 (C), 78.6 (CH), 39.8 (CH_2). GC-MS (EI): *m/z* 328, 288, 287, 256, 231, 271, 201, 177, 147, 128, 115, 104, 76, 55.

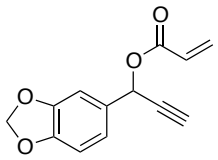
*5.1.6.8. Synthesis of acrylic acid 1-(4-chloro-phenyl)-but-3-enyl ester (77**d**)*



Substrate **77d** was synthesized from **56d**, following the *RP4* and was isolated (*n*-hexane/CH_2Cl_2 4:6, 41% yield) as a yellow oil. IR (neat): ν 3292, 3066, 2980, 1723, 1405, 1101, 806, 755 cm^{-1}. ^{1}H NMR: δ 7.35 – 7.29 (m, 4H), 6.43 (d, *J* = 17.3 Hz, 1H), 6.15 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.87 – 5.83 (m, 2H), 5.71 – 5.65 (m, 1H), 5.11 – 5.05 (m, 2H), 2.73 – 2.66 (m, 1H), 2.59 –

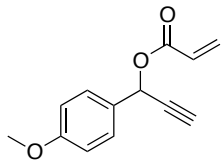
2.55 (m, 1H). ^{13}C NMR: δ 165.2 (C), 138.4 (C), 137.8 (C), 132.8 (CH), 131.1 (CH_2), 128.6 (2CH), 128.4 (CH), 127.9 (2CH), 118.5 (CH_2), 74.7 (CH), 40.6 (CH_2). GC-MS (EI): *m/z* 236, 207, 195, 181, 165, 149, 139, 129, 111, 101, 89, 77, 55.

*5.1.6.9. Synthesis of acrylic acid 1-(3,4-dimethoxy-phenyl)-prop-2-ynyl ester (**78a**)*



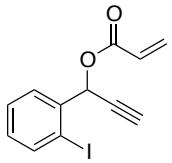
Substrate **78a** was synthesized from **57a**, following the *RP4* and was isolated (*n*-hexane/CH_2Cl_2 2:8, 35% yield) as a yellow oil. IR (neat): ν 3290, 3064, 2989, 2122, 1726, 1404, 1171, 1013, 755 cm^{-1}. ^{1}H NMR: δ 7.12 – 7.03 (m, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.49 – 6.45 (m, 2H), 6.15 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.98 (s, 2H), 5.88 (d, *J* = 10.4 Hz, 1H), 2.67 (d, *J* = 1.1 Hz, 1H). ^{13}C NMR: δ 164.8 (C), 148.3 (C), 147.9 (C), 131.9 (CH), 131.0 (CH_2), 128.3 (C), 121.9 (CH), 108.3 (CH), 108.2 (CH), 101.4 (CH_2), 80.2 (C), 75.4 (CH), 65.3 (CH). MS (CI): *m/z* 231 (M+1).

*5.1.6.10. Synthesis of acrylic acid 1-(4-methoxy-phenyl)-prop-2-ynyl ester (**78b**)*



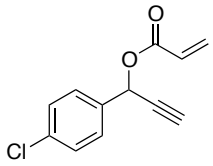
Substrate **78b** was synthesized from **57b**, following the *RP4* and was isolated (*n*-hexane/CH_2Cl_2 9:1, 45% yield) as a yellow oil. IR (neat): ν 3291, 3062, 2987, 2125, 1727, 1494, 1172, 1013, 754 cm^{-1}. ^{1}H NMR: δ 7.50 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.49 (d, *J*= 17.3 Hz, 1H), 6.44 (s, 1H), 6.14 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.86 (d, *J* = 10.4 Hz, 1H), 3.82 (s, 3H), 2.67 (s, 1H). ^{13}C NMR: δ 164.9 (C), 160.2 (C), 131.8 (CH), 129.3 (2CH), 128.6 (C), 127.9 (CH_2), 114.0 (2CH), 80.3 (C), 75.3 (CH), 66.2 (CH), 55.3 (CH_3). MS (CI): *m/z* 217 (M+1).

*5.1.6.11. Synthesis of acrylic acid 1-(2-iodo-phenyl)-prop-2-ynyl ester (**78c**)*



Substrate **78c** was synthesized from **57c**, following the *RP4* and was isolated (*n*-hexane/AcOEt 8:2, 47% yield) as a yellow oil. IR (neat): ν 3291, 3061, 2957, 2125, 1729, 1404, 1172, 1013, 754 cm^{-1}. ^{1}H NMR: δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 1.4 Hz, 1H), 6.50 (d, *J* = 17.3 Hz, 1H), 6.17 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.90 (d, *J* = 10.4 Hz, 1H), 2.71 (d, *J* = 1.4 Hz, 1H). ^{13}C NMR: δ 165.4 (C), 139.9 (CH), 138.6 (C), 132.3 (CH_2), 130.7 (CH), 129.2 (CH), 128.7 (CH), 127.5 (CH), 98.4 (C), 79.4 (C), 76.3 (CH), 69.5 (CH). MS (CI): *m/z* 313 (M+1).

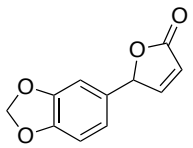
*5.1.6.12. Synthesis of acrylic acid 1-(4-chloro-phenyl)-prop-2-ynyl ester (**78d**)*



Substrate **78d** was synthesized from **57d**, following the *RP4* and was isolated (*n*-hexane/CH_2Cl_2 3:7, 45% yield) as a yellow oil. IR (neat): ν 3019, 2922, 2853, 1722, 1493, 1380, 1245, 1013, 815, 755 cm^{-1}. ^1H NMR: δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.50 (s, 1H), 6.48 (d, *J* = 17.9 Hz, 1H), 6.15 (dd, *J* = 17.9, 10.4 Hz, 1H), 5.90 (d, *J* = 10.4 Hz, 1H), 2.69 (s, 1H). ^{13}C NMR: δ 164.7 (C), 135.1 (C), 134.9 (CH), 132.2 (CH_2), 129.1 (2CH), 128.9 (2CH), 127.6 (C), 79.7 (C), 75.9 (CH), 64.7 (CH). MS (CI): *m/z* 221 (M+1).

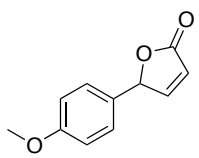
5.1.7. Synthesis of five- and six-membered lactones

*5.1.7.1. Synthesis of 5-benzo[1,3]dioxol-5-yl-5H-furan-2-one (**79a**)*



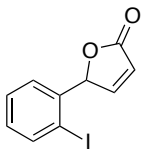
Substrate **79a** was synthesized from **76a** following the *RP3* and was isolated (*n*-hexane/AcOEt 1:1, 86% yield) as a brown oil. IR (neat): ν 3091, 1015, 2909, 1752, 1502, 1445, 1251, 1036, 813 cm^{-1}. ^1H NMR: δ 7.47 (d, *J* = 5.5 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.20 (d, *J* = 5.5 Hz, 1H), 5.98 (s, 2H), 5.92 (br, 1H). ^{13}C NMR: δ 172.9 (C), 155.6 (CH), 148.5 (C), 148.3 (C), 127.7 (C), 121.2 (CH), 120.8 (CH), 108.6 (CH), 106.8 (CH), 101.5 (CH_2), 84.3 (CH). GC-MS (EI): *m/z* 204, 175, 149, 121, 118, 102, 91, 63. The spectral data for this compound correspond to previously reported data.[26]

*5.1.7.2. Synthesis of 5-(4-methoxy-phenyl)-5H-furan-2-one (**79b**)*



Substrate **79b** was synthesized from **76b** following the *RP3* and was isolated (*n*-hexane/AcOEt 4:6, 93% yield) as a brown oil. IR (neat): ν 3084, 3008, 2962, 2840, 1754, 1513, 1254, 1172, 1029, 831 cm^{-1}. ^1H NMR: δ 7.49 (d, *J* = 5.5 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.21 (dd, *J* = 5.5, 1.2 Hz, 1H), 5.96 (br, 1H), 3.80 (s, 3H). ^{13}C NMR: δ 173.1 (C), 160.4 (C), 155.8 (CH), 128.2 (2CH), 126.3 (C), 121.1 (CH), 114.4 (2CH), 84.3 (CH), 55.3 (CH_3). GC-MS (EI): *m/z* 190, 176, 161, 135, 131, 107, 91, 77, 55. The spectral data for this compound correspond to previously reported data.[26]

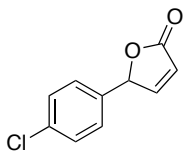
*5.1.7.3. Synthesis of 5-(2-iodo-phenyl)-5H-furan-2-one (**79c**)*



Substrate **79c** was synthesized from **76c** following the *RP3* and was isolated (*n*-hexane/AcOEt 6:4, 91% yield) as a brown oil. IR (neat): ν 3090, 2925, 1774, 1434, 1276, 1158, 1015, 895, 753 cm^{-1}. ^1H NMR: δ 7.88 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.67 (dd, *J* = 5.6, 1.7 Hz, 1H), 7.37 (td, *J* = 7.5, 1.0 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.5

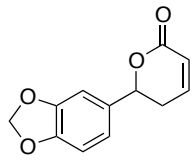
Hz, 1H), 7.07 (td, *J* = 7.7, 1.6 Hz, 1H), 6.31 (t, *J* = 1.7 Hz, 1H), 6.21 (dd, *J* = 5.6, 2.2 Hz, 1H). ^{13}C NMR: δ 173.1 (C), 155.5 (CH), 139.8 (CH), 136.6 (C), 130.7 (CH), 129.0 (CH), 126.6 (CH), 120.8 (CH), 96.7 (C), 87.4 (CH). MS (CI): *m/z* 287 (M+1).

*5.1.7.4. Synthesis of 5-(2-iodo-phenyl)-5H-furan-2-one (**79d**)*



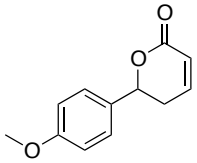
Substrate **79d** was synthesized from **76d** following the *RP3* and was isolated (*n*-hexane/AcOEt 1:1, 84% yield) as a brown oil. IR (neat): ν 3092, 2927, 1777, 1424, 1275, 1155, 1015, 890, 755 cm^{-1}. ^{1}H NMR: δ 7.49 (d, *J* = 5.5 Hz, 1H), 7.35 – 7.29 (m, 4H), 6.21 (dd, *J* = 5.5, 1.2 Hz, 1H), 6.15 (br, 1H). ^{13}C NMR: δ 168.3 (C), 164.4 (C), 155.8 (CH), 128.7 (2CH), 128.5 (2CH), 128.3 (C), 121.1 (CH), 84.3 (CH). MS (CI): *m/z* 195 (M+1). The spectral data for this compound correspond to previously reported data.[26]

*5.1.7.5. Synthesis of 6-benzo[1,3]dioxol-5-yl-5,6-dihydro-pyran-2-one (**80a**)*



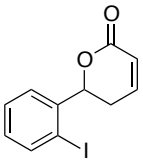
Substrate **80a** was synthesized from **77a** following the *RP3* and was isolated (*n*-hexane/AcOEt 7:3, 90% yield) as a brown oil. IR (neat): ν 3015, 2903, 1724, 1502, 1247, 1037, 814, 755 cm^{-1}. ^{1}H NMR: δ 6.99 – 6.95 (m, 1H), 6.92 (s, 1H), 6.19 – 6.17 (m, 2H), 6.12 (dd, *J* = 9.8, 2.3 Hz, 1H), 5.98 (s, 2H), 5.35 (dd, *J* = 4.2, 1.7 Hz, 1H), 2.57 – 2.53 (m, 2H). ^{13}C NMR: δ 164.0 (C), 147.9 (C), 144.8 (CH), 132.3 (C), 131.3 (C), 121.7 (CH), 119.9 (CH), 108.6 (CH), 106.8 (CH), 101.3 (CH_2), 79.2 (CH), 31.7 (CH_2). GC-MS (EI): *m/z* 218, 207, 188, 173, 150, 147, 115, 89, 68, 63.

*5.1.7.6. Synthesis of 6-(4-methoxy-phenyl)-5,6-dihydro-pyran-2-one (**80b**)*



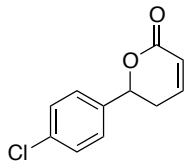
Substrate **80b** was synthesized from **77b** following the *RP3* and was isolated (*n*-hexane/AcOEt 6:4, 95% yield) as a brown oil. IR (neat): ν 3008, 2960, 2838, 1723, 1514, 1249, 1177, 1029, 817, 757 cm^{-1}. ^{1}H NMR: δ 7.34 (d, *J* = 8.7 Hz, 2H), 6.99 – 6.95 (m, 1H), 6.92 (d, *J* = 7.7 Hz, 2H), 6.13 (dd, *J* = 9.7, 2.2 Hz, 1H), 5.40 (dd, *J* = 11.8, 4.1 Hz, 1H), 3.82 (s, 3H), 2.71 – 2.67 (m, 1H), 2.58 – 5.54 (m, 1H). ^{13}C NMR: δ 164.3 (C), 159.8 (C), 144.9 (CH), 130.5 (C), 127.6 (2CH), 121.7 (CH), 114.0 (2CH), 79.1 (CH), 55.3 (CH_3), 31.5 (CH_2). GC-MS (EI): *m/z* 204, 202, 187, 173, 159, 135, 129, 108, 91, 68, 51. The spectral data for this compound correspond to previously reported data.[27]

*5.1.7.7. Synthesis of 6-(2-iodo-phenyl)-5,6-dihydro-pyran-2-one (**80c**)*



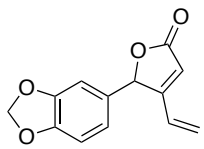
Substrate **80c** was synthesized from **77c** following the *RP3* and was isolated (*n*-hexane/AcOEt 6:4, quantitative yield) as a brown oil. IR (neat): ν 3438, 3060, 3016, 2917, 1724, 1379, 1243, 1061, 815, 756 cm^{-1}. ^{1}H NMR: δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.17 (dd, *J* = 9.7, 2.3 Hz, 1H), 5.61 (dd, *J* = 12.3, 3.7 Hz, 1H), 2.84 – 2.82 (m, 1H), 2.42 – 2.38 (m, 1H). ^{13}C NMR: δ 206.9 (C), 163.8 (C), 144.7 (CH), 139.5 (CH), 130.2 (CH), 128.9 (CH), 127.5 (CH), 121.6 (CH), 96.1 (C), 82.7 (CH), 30.6 (CH_2). GC-MS (EI): *m/z* 300, 281, 272, 231, 203, 173, 156, 144, 128, 115, 104, 78, 68, 51.

*5.1.7.8. Synthesis of 6-(4-chloro-phenyl)-5,6-dihydro-pyran-2-one (**80d**)*



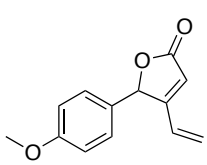
Substrate **80d** was synthesized from **77d** following the *RP3* and was isolated (CH_2Cl_2, quantitative yield) as a colorless oil. IR (neat): ν 3066, 3015, 2915, 1723, 1241, 1041, 815, 756 cm^{-1}. ^{1}H NMR: δ 7.37 – 7.29 (m, 4H), 6.99 – 6.95 (m, 1H), 6.14 (d, *J* = 9.7 Hz, 1H), 5.43 (t, *J* = 7.9 Hz, 1H), 2.65 – 2.59 (m, 2H). ^{13}C NMR: δ 165.2 (C), 144.7 (CH), 136.9 (C), 132.7 (C), 128.9 (2CH), 127.3 (2CH), 121.7 (CH), 78.4 (CH), 30.6 (CH_2). GC-MS (EI): *m/z* 208, 191, 178, 162, 149, 139, 128, 111, 103, 89, 68, 51.

*5.1.7.9. Synthesis of 5-benzo-[1,3]dioxol-5-yl-4-vinyl-furan-2-one (**81a**)*



Substrate **81a** was synthesized from **78a** following the *RP3* and was isolated (*n*-hexane/CH_2Cl_2 2:8, 27% yield) as a colorless oil. IR (neat): ν 3424, 2920, 1750, 1488, 1248, 1037, 754 cm^{-1}. ^{1}H NMR: δ 6.89 – 6.85 (m, 2H), 6.65 (s, 1H), 6.51 (dd, *J* = 18.0, 11.4 Hz, 1H), 6.14 (s, 1H), 5.90 (s, 2H), 5.89 (s, 1H), 5.55 – 5.48 (m, 2H). ^{13}C NMR: δ 164.5 (C), 148.8 (C), 148.8 (C), 135.1 (C), 131.0 (C), 127.2 (CH), 125.6 (CH), 122.2 (CH), 117.1 (CH_2), 108.6 (CH), 107.3 (CH), 101.5 (CH_2), 83.9 (CH). MS (CI): *m/z* 231 (M+1).

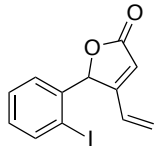
*5.1.7.10. Synthesis of 5-(4-methoxy-phenyl)-4-vinyl-furan-2-one (**81b**)*



Substrate **81b** was synthesized from **78b** following the *RP3* and was isolated (*n*-hexane/AcOEt 7:3, 35% yield) as a colorless oil. IR (neat): ν 3420, 3016, 2962, 1751, 1512, 1253, 1174, 1030, 755 cm^{-1}. ^{1}H NMR: δ 7.19 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.55 – 6.47 (m, 1H), 6.14 (s, 1H), 5.96 (s, 1H), 5.49 – 5.55 (m, 2H), 3.81 (s, 3H). ^{13}C NMR: δ 163.7 (C), 160.6

(C), 156.6 (C), 133.2(C), 129.2 (CH), 129.1 (2CH), 125.5 (CH), 117.0 (CH_2), 114.5 (2CH), 83.8 (CH), 55.3 (CH_3). MS (CI): *m/z* 217 (M+1).

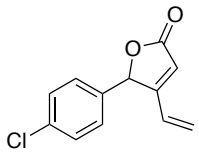
*5.1.7.11. Synthesis of 5-(2-iodo-phenyl)-4-vinyl-furan-2-one (**81c**)*



Substrate **81c** was synthesized from **78c** following the *RP3* and was isolated (*n*-hexane/AcOEt 7:3, 52% yield) as a colorless oil. IR (neat): ν 3490, 3018, 2926, 1756, 1466, 1217, 1160, 1006, 756 cm^{-1}. ^1H NMR: δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.3, 1H), 7.08 (t, *J* = 7.3, 1H), 7.01 (d, *J* = 9.4 Hz, 1H), 6.55 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.47 (s, 1H), 5.91 (s, 1H), 5.54 (d, *J* = 10.9 Hz, 1H), 5.44 (d, *J* = 17.6 Hz, 1H). ^{13}C NMR: δ 172.4 (C), 164.0 (C), 140.1 (CH), 137.3 (C), 131.3 (CH), 129.2 (CH), 128.0 (CH), 127.0 (CH), 126.2 (CH), 117.2 (CH_2), 100.5 (C), 87.3 (CH). MS (CI): *m/z* 313 (M+1).

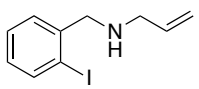
*5.1.7.12. Synthesis of 5-(4-chloro-phenyl)-4-vinyl-furan-2-one (**81d**)*

Substrate **81d** was synthesized from **78d** following the *RP3* and was isolated (*n*-hexane/AcOEt 1:1, 42% yield) as a yellow oil. IR (neat): ν 3432, 3020, 2928, 1755, 1491, 1260, 1091, 756 cm^{-1}. ^1H NMR: δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.51 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.18 (s, 1H), 5.97 (s, 1H), 5.53 (d, *J* = 7.3 Hz, 1H), 5.44 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR: δ 172.3 (C), 163.4 (C), 135.7 (C), 133.4 (C), 129.4 (2CH), 129.0 (2CH), 127.0 (CH), 125.4 (CH), 117.1 (CH_2), 83.1 (CH). MS (CI): *m/z* 221 (M+1).



5.1.7. Synthesis of *N*-benzylprop-2-en-1-amines

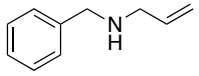
*5.1.7.1. <u>Representative procedure (**RP5**).</u> Synthesis of N-(2-iodobenzyl)prop-2-en-1-amine (**82a**)*



2-iodo-benzaldehyde (1.5 g, 6.5 mmol) was dissolved in $CHCl_3$ (15 mL) at room temperature. $MgSO_4$ (0.92 g, 7.7 mmol) and allylamine (0.44 g, 0.6 mL, 7.7 mmol) were added and the solution was stirred at room temperature for 3 h. At the end of the reaction, the mixture was filtered over a Buchner funnel and the solvent was removed under reduced pressure. The resulting yellow oil was dissolved in MeOH (30 mL) at 0 °C, $NaBH_3CN$ (0.6 g, 8.1 mmol) was added and the reaction was stirred at room temperature overnight. The solution was then diluted with AcOEt (20 mL), washed with water (40 mL) and the aqueous phase was extracted with AcOEt (3 x 20 mL). The combined organic layers were treated with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The required product was obtained as a yellow oil and was used

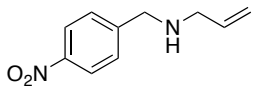
without further purification (quantitative yield). IR (neat): ν 3323, 3026, 2977, 2914, 2820, 1460, 1011, 749 cm^{-1}. ^{1}H NMR: δ 7.80 (dd, *J* = 8.6, 4.0 Hz, 1H), 7.41 – 7.24 (m, 2H), 6.92 (t, *J* = 6.7 Hz, 1H), 6.04 – 5.83 (m, 1H), 5.26 – 5.16 (m, 1H), 5.15 – 5.06 (m, 1H), 3.78 (s, 2H), 3.26 (dd, *J* = 7.3, 2.7 Hz, 2H), 1.63 (br s, 1H). ^{13}C NMR: δ 142.2 (C), 139.4 (CH), 136.7 (CH), 129.7 (CH), 128.8 (CH), 128.3 (CH), 116.2 (CH_2), 99.7 (C), 57.5 (CH_2), 51.6 (CH_2). GC-MS (EI): *m/z* 273, 258, 246, 230, 217, 203, 146, 118, 116, 89, 76, 70, 56, 41, 28. The spectral data for this compound correspond to previously reported data.[28]

*5.1.7.2. Synthesis of N-benzylprop-2-en-1-amine (**82b**)*



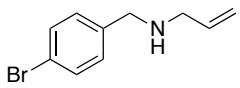
Substrate **82b** was synthesized, following the *RP5*, from benzaldehyde and was used without further purification (yellow oil, quantitative yield). IR (neat): ν 3324, 3064, 3028, 2919, 2810, 1452, 1109, 921, 740, 698 cm^{-1}. ^{1}H NMR: δ 7.46 – 7.19 (m, 5H), 5.98 – 5.89 (m, 1H), 5.26 – 5.08 (m, 2H), 3.80 (s, 1H), 3.59 (s, 1H), 3.49 (br, 1H), 3.32 – 3.25 (m, 2H). ^{13}C NMR: δ 140.2 (C), 136.5 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.9 (CH), 117.4 (CH_2), 54.5 (CH_2), 51.4 (CH_2). GC-MS (EI): *m/z* 148, 146, 132, 118, 104, 91, 77, 70, 65, 56, 41, 28. The spectral data for this compound correspond to previously reported data.[29]

*5.1.7.3. Synthesis of N-(4-nitrobenzyl)prop-2-en-1-amine (**82c**)*



Substrate **82c** was synthesized, following the *RP5*, from 4-nitrobenzaldehyde and was used without further purification (orange oil, quantitative yield). IR (neat): ν 3384, 3324, 3077, 2821, 1694, 1515, 1344, 1108, 922, 853, 738 cm^{-1}. ^{1}H NMR: δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 6.04 – 5.73 (m, 1H), 5.38 – 4.97 (m, 2H), 3.90 (s, 2H), 3.28 (dt, *J* = 6.0, 1.4 Hz, 2H). ^{13}C NMR: δ 148.1 (C), 147.2 (C), 136.3 (CH), 128.8 (2CH), 123.8 (2CH), 116.7 (CH_2), 52.4 (CH_2), 51.8 (CH_2). GC-MS (EI): *m/z* 192, 177, 165, 145, 136, 106, 89, 78, 56, 41, 28. The spectral data for this compound correspond to previously reported data.[30]

*5.1.7.4. Synthesis of N-(4-bromobenzyl)prop-2-en-1-amine (**82d**)*

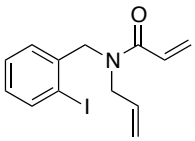


Substrate **82d** was synthesized, the following *RP5*, from 4-bromobenzaldehyde and was used without further purification (yellow oil, quantitative yield). IR (neat): ν 3077, 2978, 2819, 1486, 1403, 1361, 1099, 1070, 1010, 921, 804 cm^{-1}. ^{1}H NMR: δ 7.57 – 7.41 (m, 2H), 7.30 – 7.16 (m, 2H), 6.03 – 5.81 (m, 1H), 5.28 – 5.03 (m, 2H), 3.76 (s, 2H), 3.49 (br, s, 1H), 3.27 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR: δ 139.2 (C), 135.9 (CH), 131.5 (2CH), 130.4 (2CH), 121.4 (C), 116.7 (CH_2), 52.2 (CH_2), 51.4 (CH_2).

GC-MS (EI): *m/z* 226, 212, 198, 184, 171, 169, 146, 117, 89, 77, 70, 56, 41, 28. The spectral data for this compound correspond to previously reported data.[31]

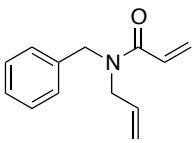
5.1.8. Synthesis of *N*-allyl-*N*-benzylacrylamides

*5.1.8.1. Representative procedure (**RP6**). Synthesis of N-allyl-N-(2-iodobenzyl)acrylamide (**83a**)*



Compound **83a** (0.48 g, 1.8 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C. Et_3N (0.27 g, 0.36 mL, 2.6 mmol) and acryloyl chloride (0.2 g, 0.17 mL, 2.1 mmol) were added, the solution was warmed at room temperature and stirred for 2 h. At the end of the reaction, the mixture was washed with water (40 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were treated with brine (2 x 30 mL), dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane 3:7) affording the desired product as a yellow oil (90% yield). IR (neat): ν 3305, 3062, 2983, 2926, 1652, 1615, 1434, 1221, 753 cm^{-1}. ^{1}H NMR: δ 7.89 – 7.77 (m, 1H), 7.41 – 7.22 (m, 1H), 7.22 – 7.06 (m, 1H), 6.98 (dt, *J* = 24.1, 7.5 Hz, 1H), 6.65 – 6.27 (m, 2H), 5.96 – 5.61 (m, 2H), 5.20 (dd, *J* = 28.1, 13.8 Hz, 2H), 4.69 (s, 1H), 4.47 (s, 1H), 4.07 (d, *J* = 6.3 Hz, 1H), 4.01 – 3.86 (m, 1H). ^{13}C NMR: δ 164.3 (C, I_A and C, I_B), 145.1 (C, I_A and C, I_B), 139.7 (CH, I_A), 139.4 (CH, I_B), 132.4 (CH, I_A), 132.1 (CH, I_B), 131.3 (CH, I_A), 130.9 (CH, I_B), 129.2 (CH_2, I_A), 129.0 (CH_2, I_B), 128.8 (CH, I_A), 128.7 (CH, I_B), 128.5 (CH, I_A), 128.3 (CH, I_B), 127.3 (CH, I_A), 126.9 (CH, I_B), 118.2 (CH_2, I_A), 117.2 (CH_2, I_B), 97.1 (C, I_A and C, I_B), 55.8 (CH_2, I_A), 53.8 (CH_2, I_B), 49.6 (CH_2, I_A), 48.9 (CH_2, I_B). GC-MS (EI): *m/z* 331, 284, 242, 255, 203, 171, 158, 144, 115, 103, 88, 76, 56, 41, 27. I_A and I_B refer to the major and minor rotamer, respectively.

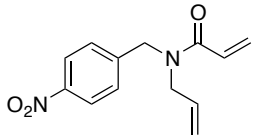
*5.1.8.2. Synthesis of N-allyl-N-benzylacrylamide (**83b**)*



Substrate **83b** was synthesized from compound **82b** and acryloyl chloride, following the *RP3* and was isolated (AcOEt/*n*-hexane 3:7, 48% yield) as a yellow oil. IR (neat): ν 3420, 2984, 1738, 1650, 1512, 1246, 1045, 755 cm^{-1}. ^{1}H NMR: δ 7.41 – 7.11 (m, 5H), 6.55 (dd, *J* = 16.7, 10.2 Hz, 1H), 6.43 (dd, *J* = 16.7, 2.2 Hz, 1H), 5.73 – 5.67 (m, 2H), 5.28 – 5.04 (m, 2H), 4.65 (s, 1H), 4.57 (s, 1H), 4.06 (d, *J* = 5.9 Hz, 1H), 3.94 – 3.80 (m, 1H). ^{13}C NMR: δ 166.9 (C, I_A and C, I_B), 137.5 (C, I_A), 136.9 (C, I_B), 132.9 (CH, I_A), 132.7 (CH, I_B), 129.0 (CH, I_A), 128.9 (CH, I_B), 128.7 (CH_2, I_A and CH_2, I_B), 128.4 (CH, I_A and CH, I_B), 127.8 (2CH, I_A and 2CH, I_B), 127.5 (CH, I_A and CH, I_B), 126.5

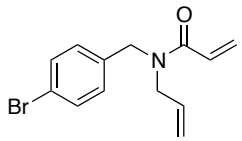
(CH, I_A and CH, I_B), 117.9 (CH_2, I_A), 117.1 (CH_2, I_B), 50.2 (CH_2, I_A), 49.2 (CH_2, I_B), 48.9 (CH_2, I_B), 48.7 (CH_2, I_A). GC-MS (EI): *m/z* 201, 186, 172, 160, 146, 130, 106, 91, 77, 65, 55, 41, 27. I_A and I_B refer to the major and minor rotamer, respectively. The spectral data for this compound correspond to previously reported data.[32]

*5.1.8.3. Synthesis of N-allyl-N-(4-nitrobenzyl)acrylamide (**83c**)*



Substrate **83c** was synthesized from compound **82c** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 4:6, 60% yield) as an orange oil. IR (neat): ν 3080, 2928, 1651, 1520, 1346, 1221, 979, 802 cm^{-1}. ^{1}H NMR: δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.64 – 6.34 (m, 2H), 5.81 – 5.69 (m, 2H), δ 5.25 (d, *J* = 10.3 Hz, 1H), 5.17 (d, *J* = 17.0 Hz, 1H), 4.69 (s, 2H), 4.18 – 3.84 (m, 2H). ^{13}C NMR: δ 167.1 (C), 147.4 (C), 145.2 (C), 132.3 (CH), 129.5 (CH_2), 128.9 (2CH), 127.1 (CH), 123.9 (2CH), 117.7 (CH_2), 49.9 (CH_2), 48.8 (CH_2). GC-MS (EI): *m/z* 246, 205, 151, 137, 110, 89, 78, 55, 41, 27.

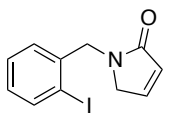
*5.1.8.4. Synthesis of N-allyl-N-(4-bromobenzyl)acrylamide (**83d**)*



Substrate **83d** was synthesized from compound **82d** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 50% yield) as a colorless oil. IR (neat): ν 3474, 3082, 2982, 2926, 1651, 1439, 1220, 1011, 798 cm^{-1}. ^{1}H NMR: δ 7.53 – 7.32 (m, 2H), 7.19 – 7.03 (m, 2H), 6.59 – 6.36 (m, 2H), 5.89 – 5.65 (m, 2H), 5.29 – 5.07 (m, 2H), 4.55 (s, 2H), 4.16 – 3.78 (m, 2H). ^{13}C NMR: δ 165.3 (C), 135.4 (C), 132.4 (CH), 131.7 (2CH), 130.0 (2CH), 128.9 (CH_2), 127.4 (CH), 121.4 (C), 117.7 (CH_2), 49.2 (CH_2), 48.3 (CH_2). GC-MS (EI): *m/z* 279.6, 237.9, 185.8, 170.9, 109.9, 90.0, 54.9, 41.0, 27.0.

5.1.9. Synthesis of benzylic lactams

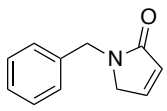
*5.1.9.1. <u>Representative procedure (**RP7**).</u> Synthesis of 1-(2-iodobenzyl)-1H-pyrrol-2(5H)-one (**84a**)*



Compound **83a** (0.09 g, 0.3 mmol) was dissolved in toluene (6 mL) at room temperature, under nitrogen atmosphere. After bubbling N_2 into the solution for 10 min, catalyst **9** (0.006 g, 0.01 mmol) was added. The solution was warmed at 70 °C and stirred for 3 h. At the end of the reaction, the solvent was removed under reduced pressure and reaction residue was purified by filtration through a short pad of silica gel, affording the desired product as a yellow oil (95% yield). Mp: 98 °C. IR (neat): ν 3456, 3058, 2902, 1676, 1450, 1243, 1013, 738 cm^{-1}. ^{1}H NMR: δ 7.83 (dd, *J* = 7.9, 1.1 Hz,

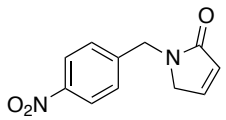
1H), 7.36 – 7.23 (m, 1H), 7.15 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.08 (dt, *J* = 6.0, 1.7 Hz, 1H), 6.96 (td, *J* = 7.7, 1.6 Hz, 1H), 6.22 (dt, *J* = 6.0, 1.9 Hz, 1H), 4.70 (s, 2H), 3.93 (t, *J* = 1.7 Hz, 2H). ^{13}C NMR: δ 171.6 (C), 143.2 (CH), 139.7 (CH), 139.5 (C), 129.4 (CH), 129.1 (CH), 128.9 (CH), 127.9 (CH), 98.8 (C), 52.8 (CH_2), 50.7 (CH_2). GC-MS (EI): *m/z* 299, 217, 172, 144, 127, 115, 104, 90, 68, 63, 51, 39, 27.

*5.1.9.2. Synthesis of 1-benzyl-1H-pyrrol-2(5H)-one (**84b**)*



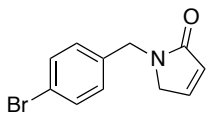
Substrate **84b** was synthesized, following the *RP7*, from compound **83b** and was isolated (filtration through a short pad of silica gel, quantitative yield) as brown oil. IR (neat): ν 3085, 3028, 2918, 1700, 1451, 1244, 732, 698 cm^{-1}. ^{1}H NMR: δ 7.41 – 7.14 (m, 5H), 7.03 (dt, *J* = 6.0, 1.7 Hz, 1H), 6.20 (dt, *J* = 6.0, 1.8 Hz, 1H), 4.62 (s, 2H), 3.85 (t, *J* = 1.7 Hz, 2H). ^{13}C NMR: δ 171.4 (C), 142.9 (CH), 137.3 (C) 128.8 (2CH), 127.9 (3CH), 127.6 (CH), 52.3 (CH_2), 45.9 (CH_2). GC-MS (EI): *m/z* 174, 144, 115, 106, 91, 68, 51, 39, 28. The spectral data for this compound correspond to previously reported data.[32]

*5.1.9.3. Synthesis of 1-(4-nitrobenzyl)-1H-pyrrol-2(5H)-one (**84c**)*



Substrate **84c** was synthesized, following the *RP7*, from compound **83c** and was isolated (filtration through a short pad of silica gel, quantitative yield) as brown solid. Mp: 108 °C. IR (neat): ν 3446, 3088, 2850, 1666, 1515, 1398, 1253, 1151, 987, 813, 721 cm^{-1}. ^{1}H NMR: δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 1H), 6.21 (d, *J* = 5.9 Hz, 1H), 4.70 (s, 2H), 3.92 (s, 2H). ^{13}C NMR: δ 171.5 (C), 147.4 (C), 144.9 (C), 143.4 (CH), 128.5 (2CH), 127.7 (CH), 123.9 (2CH), 52.5 (CH_2), 45.4 (CH_2). GC-MS (EI): *m/z* 218, 201, 171, 143, 136, 115, 106, 89, 82, 68, 41, 30.

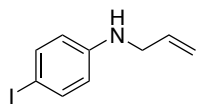
*5.1.9.4. Synthesis of 1-(4-bromobenzyl)-1H-pyrrol-2(5H)-one (**84d**)*



Substrate **84d** was synthesized, following the *RP7*, from compound **83d** and was isolated (filtration through a short pad of silica gel, quantitative yield) as brown solid. Mp: 79 °C. IR (neat): ν 3461, 2916, 2872, 1670, 1488, 1454, 1403, 1246, 1101, 1010, 801 cm^{-1}. ^{1}H NMR: δ 7.42 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 6.0 Hz, 1H), 6.18 (d, *J* = 6.0 Hz, 1H), 4.55 (s, 2H), 3.85 (s, 2H). ^{13}C NMR: δ 171.4 (C), 143.1 (CH), 136.4 (C), 131.9 (2CH), 129.7 (2CH), 127.9 (CH), 121.6 (C), 52.3 (CH_2), 45.4 (CH_2). GC-MS (EI): *m/z* 251, 222, 186, 171, 157, 143, 115, 95, 89, 68, 63, 39, 28.

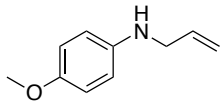
5.1.10. Synthesis of N-allylanilines and N-but-3-enyl-anilines.

*5.1.11.1. Representative procedure (**RP8**). Synthesis of N-allyl-4-iodoaniline (**85b**)*



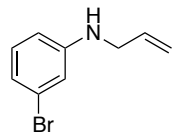
4-iodoaniline (2 g, 9.1 mmol) was dissolved in DMF (15 mL) at room temperature and K_2CO_3 (2.6 g, 19.0 mmol) was added. The mixture was stirred for 15 min then allyl bromide (1.1 g, 0.8 mL, 9.1 mmol) was added. The solution was warmed at 70 °C and stirred for an additional 24 h. At the end of the reaction, the mixture was washed with water (60 mL) and the aqueous phase was extracted with ether (3 x 40 mL). The combined organic layers were treated with brine (2 x 40 mL), dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane, 1:9) affording the desired product as a yellow oil (46% yield). IR: ν 3417, 3079, 3011, 2980, 2848, 1591, 1496, 1317, 1262, 810 cm^{-1}. ^1H NMR: δ 7.50 – 7.36 (m, 2H), 6.48 – 6.32 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.19 (dq, *J* = 10.4, 1.7 Hz, 1H), 3.85 (br, s, 1H), 3.74 (dt, *J* = 5.3, 1.7 Hz, 2H). ^{13}C NMR: δ 147.6 (C), 137.78 (2CH), 134. (CH), 116.6 (CH_2), 115.2 (2CH), 78.1 (C), 46.3 (CH_2). GC-MS (EI): *m/z* 259, 232, 218, 203, 191, 165, 130, 117, 105, 91, 76, 63, 41, 28.The spectral data for this compound correspond to previously reported data.[34]

*5.1.11.2. Synthesis of N-allyl-4-methoxyaniline (**85c**)*



Compound **85c** was synthesized from 4-iodoaniline and allyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 50% yield) as a yellow oil. IR: ν 3417, 3079, 3011, 2980, 2848, 1591, 1496, 1317, 1262, 810 cm^{-1}. ^1H NMR: δ 7.50 – 7.36 (m, 2H), 6.48 – 6.32 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.19 (dq, *J* = 10.4, 1.7 Hz, 1H), 3.85 (br, s, 1H), 3.74 (dt, *J* = 5.3, 1.7 Hz, 2H). ^{13}C NMR: δ 147.6 (C), 137.78 (2CH), 134. (CH), 116.6 (CH_2), 115.2 (2CH), 78.1 (C), 46.3 (CH_2). GC-MS (EI): *m/z* 259, 232, 218, 203, 191, 165, 130, 117, 105, 91, 76, 63, 41, 28. The spectral data for this compound correspond to previously reported data.[35]

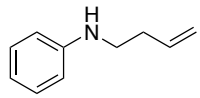
*5.1.11.3. Synthesis of N-allyl-3-bromoaniline (**85d**)*



Compound **85d** was synthesized from 4-iodoaniline and allyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 56% yield) as a yellow oil. IR: ν 3412, 3021, 2919, 2905, 1515, 1115, 750 cm^{-1}. ^1H NMR: δ 7.01 (t, *J* = 8.0 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.75 (t, *J* = 2.1 Hz, 1H), 6.54 – 6.50 (m, 1H),

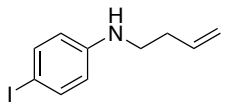
6.02 – 5.84 (m, 1H), 5.35 – 5.22 (m, 1H), 5.19 (dd, *J* = 10.3, 1.4 Hz, 1H), 3.86 (br, s, 1H), 3.75 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR: δ 148.8 (C), 136.7 (CH), 130.6 (CH), 123.9 (CH), 120.3 (CH), 117.6 (CH_2), 112.4 (CH), 111.9 (CH), 34.9 (CH_2). The spectral data for this compound correspond to previously reported data. [34]

*5.1.11.4. Synthesis of N-(but-3-enyl)aniline (**86a**)*



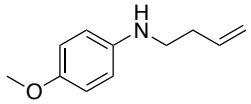
Compound **86a** was synthesized from aniline and 4-bromobut-1-ene, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 49% yield) as a yellow oil. IR: ν 3408, 3053, 2922, 2923, 1603, 1506, 750 cm^{-1}. ^{1}H NMR: δ 7.31 – 7.19 (m, 2H), 6.84 – 6.71 (m, 1H), 6.67 (dd, *J* = 8.5, 0.9 Hz, 2H), 5.88 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.29 – 5.10 (m, 2H), 3.69 (br, s, 1H), 3.23 (t, *J* = 6.7 Hz, 2H), 2.43 (qt, *J* = 6.8, 1.2 Hz, 2H). ^{13}C NMR: δ 148.3(C), 135.9 (CH), 129.3 (2CH), 117.4 (CH), 117.1 (CH_2), 112.9 (CH), 42.9 (CH_2), 33.7(CH_2). GC-MS (EI): *m/z* 147, 130, 106, 91, 77, 65, 51, 39, 27. The spectral data for this compound correspond to previously reported data.[36]

*5.1.11.5. Synthesis of N-(but-3-enyl)-4-iodoaniline (**86b**)*



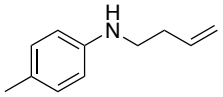
Compound **86b** was synthesized from 4-iodoaniline and 4-bromobut-1-ene, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 51% yield) as a yellow oil. IR: ν 3408, 3075, 2919, 1591, 1496, 1318, 810 cm^{-1}. ^{1}H NMR: δ 7.47 – 7.34 (m, 2H), 6.45 – 6.29 (m, 2H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.24 – 5.06 (m, 2H), 3.74 (br, s, 1H), 3.15 (t, *J* = 6.7 Hz, 2H), 2.38 (qt, *J* = 6.8, 1.2 Hz, 2H). ^{13}C NMR: δ 147.8 (C), 137.8 (2CH), 135.6 (CH), 117.4 (CH_2), 115.2 (2CH), 77.9 (C), 42.7 (CH_2), 33.5 (CH_2). GC-MS (EI): *m/z* 273, 232, 203, 146, 116, 105, 91, 76, 63, 50, 39, 27. The spectral data for this compound correspond to previously reported data. [36]

*5.1.11.6. Synthesis of N-(but-3-enyl)-4-methoxyaniline (**86c**)*



Compound **86c** was synthesized from 4-methoxyaniline and 4-bromobut-1-ene, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 48% yield) as a yellow oil. IR: ν 3889, 2995, 2934, 2831, 1513, 1239, 1038, 820 cm^{-1}. ^{1}H NMR: δ 6.80 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 5.84 (dd, *J* = 17.1, 10.2 Hz, 1H), 5.18 – 5.12 (m, 2H), 3.76 (s, 3H), 3.31 (s, 1H), 3.15 (t, *J* = 6.7 Hz, 2H), 2.38 (dt, *J* = 7.8, 6.7 Hz, 2H).^{13}C NMR: δ 152.3 (C), 142.6 (C), 135.9 (CH), 117.1 (CH_2), 115.0 (2CH), 114.4 (2CH), 55.9 (CH_3), 43.9 (CH_2), 33.8 (CH_2). GC-MS (EI): *m/z* 177, 136, 121, 108, 93, 77, 65, 52, 39. The spectral data for this compound correspond to previously reported data. [37]

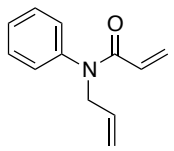
*5.1.11.7. Synthesis of N-(but-3-enyl)-4-methylaniline (**86d**)*



Compound **86d** was synthesized from 4-methylaniline and 4-bromobut-1-ene, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 45% yield) as a yellow oil. IR: ν 3404, 3075, 3016, 2919, 1618, 152, 1301, 915, 808 cm^{-1}. ^{1}H NMR: δ 7.04 (dd, *J* = 7.9, 0.6 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 2H), 5.97 – 5.81 (m, 1H), 5.28 – 5.06 (m, 2H), 3.59 – 3.41 (m, 2H), 3.21 (t, *J* = 6.7 Hz, 2H), 2.48 – 2.35 (m, 2H), 2.29 (s, 3H). ^{13}C NMR: δ 146.1 (C), 135.9 (CH), 129.8 (2CH), 126.7 (C), 117.2 (CH_2), 113.2 (2CH), 43.3 (CH_2), 33.7 (CH_2), 20.5 (CH_3). The spectral data for this compound correspond to previously reported data.[38]

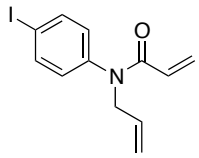
5.1.11. Synthesis of *N*-allyl-*N*-arylacrylamides

*5.1.11.1. Synthesis of N-allyl-N-phenylacrylamide (**87a**)*



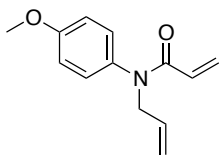
Substrate **87a** was synthesized from *N*-allylaniline (**85a**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 4:6, 76% yield) as a yellow oil. IR (neat): ν 3064, 2983, 2923, 1659, 1594, 1408, 1258, 983, 701 cm^{-1}. ^{1}H NMR: δ 7.45 – 7.28 (m, 3H), 7.22 – 7.07 (m, 2H), 6.37 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.03 (dd, *J* = 16.5, 10.4 Hz, 1H), 5.89 (ddt, *J* = 16.5, 10.3, 6.2 Hz, 1H), 5.51 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.18 – 5.02 (m, 2H), 4.38 (dt, *J* = 6.2, 1.3 Hz, 2H). ^{13}C NMR: δ 165.4 (C), 142.1 (C), 133.1 (CH), 129.6 (CH), 128.8 (3CH), 128.3 (CH), 127.9(CH), 127.8 (CH_2), 117.9 (CH_2), 52.5 (CH_2). GC-MS (EI): *m/z* 187, 172, 159, 144, 132, 119, 106, 93 77, 56 55, 41, 27. The spectral data for this compound correspond to previously reported data.[33]

*5.1.11.2. Synthesis of N-allyl-N-(4-iodophenyl)acrylamide (**87b**)*



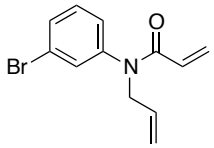
Substrate **87b** was synthesized from *N*-allyl-4-iodoaniline (**85b**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 74% yield) as a yellow solid. Mp: 99 °C. IR (neat): ν 3072, 3053, 2987, 2926, 1647, 1406, 1220, 1100, 1003, 981, 790, 654 cm^{-1}. ^{1}H NMR: δ 7.77 – 7.61 (m, 2H), 6.98 – 6.80 (m, 2H), 6.36 (dd, *J* = 16.8, 1.9 Hz, 1H), 6.01 (dd, *J* = 16.4, 10.4 Hz, 1H), 5.84 (ddt, *J* = 16.5, 10.2, 6.2 Hz, 1H), 5.53 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.21 – 5.00 (m, 2H), 4.33 (dt, *J* = 6.2, 1.2 Hz, 2H). ^{13}C NMR: δ 165.1 (C), 141.8 (C), 138.7 (2CH), 132.7 (CH), 130.1 (CH), 128.5 (2CH), 128.4 (CH_2), 118.3 (CH_2), 93.0 (C), 52.3 (CH_2). GC-MS (EI): *m/z* 313, 298, 285, 259, 232, 219, 203, 185, 158, 145, 130, 103, 94, 76, 63, 55, 41.

*5.1.11.3. Synthesis of N-allyl-N-(4-methoxyphenyl)acrylamide (**87c**)*



Substrate **87c** was synthesized from *N*-allyl-4-methoxyaniline (**85c**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 79% yield) as a yellow solid. Mp: 64 °C. IR (neat): ν 3255, 3063, 2963, 2842, 2543, 1648, 1511, 1407, 1245, 1030, 843, 792 cm^{-1}. ^{1}H NMR: δ 7.08 – 6.99 (m, 2H), 6.96 – 6.82 (m, 2H), 6.34 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.02 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.87 (ddt, *J* = 16.5, 10.2, 6.3 Hz, 1H), 5.49 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.17 – 4.99 (m, 2H), 4.32 (dt, *J* = 6.3, 1.3 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR: δ 165.6 (C), 159.0 (C), 134.7 (C), 133.1 (CH), 129.5 (CH), 128.8 (2CH), 127.6 (CH_2), 118.0 (CH_2), 114.7 (2CH), 55.6 (CH_3), 52.6 (CH_2). GC-MS (EI): *m/z* 217, 202, 189, 174, 163, 148, 134, 123, 122, 94, 92, 77, 64, 55, 41, 27. The spectral data for this compound correspond to previously reported data.[33]

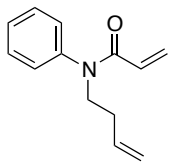
*5.1.11.4. Synthesis of N-allyl-N-(3-bromophenyl)acrylamide (**87d**)*



Substrate **87d** was synthesized from *N*-allyl-3-bromoaniline (**85d**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 2:8, 65% yield) as a yellow oil. IR (neat): ν 3072, 2925, 2360, 1661, 1585, 1407, 1247, 983, 789 cm^{-1}. ^{1}H NMR: δ 7.46 (ddd, *J* = 8.0, 1.7, 0.9 Hz, 1H), 7.33 (t, *J* = 1.9 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.14 – 7.03 (m, 1H), 6.39 (dd, *J* = 16.8, 1.9 Hz, 1H), 6.12 – 5.95 (m, 1H), 5.89 – 5.79 (m, 1H), 5.57 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.20 – 5.03 (m, 2H), 4.35 (dt, *J* = 6.2, 1.3 Hz, 2H). ^{13}C NMR: δ 165.2 (C), 143.4 (C), 132.7 (CH), 131.3 (CH), 131.1 (CH), 130.8 (CH), 128.6 (CH_2), 128.4 (CH), 127.1 (CH), 122.9 (C), 118.4 (CH_2), 52.5 (CH_2). GC-MS (EI): *m/z* 265, 252, 273, 212, 210, 197, 186, 184, 157, 143, 130, 115, 94, 76, 67, 55, 41, 27.

5.1.12. Synthesis of *N*-(but-3-enyl)-*N*-arylacrylamides

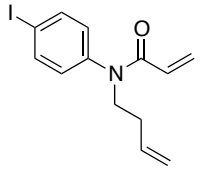
*5.1.12.1. Synthesis of N-(but-3-enyl)-N-phenylacrylamide (**88a**)*



Substrate **88a** was synthesized from *N*-(but-3-enyl)aniline (**86a**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 61% yield) as a brown oil. IR (neat): ν 3064, 2979, 2932, 1659, 1411, 1261, 983, 701 cm^{-1}. ^{1}H NMR: δ 7.45 – 7.37 (m, 2H), 7.37 – 7.30 (m, 1H), 7.19 – 7.11 (m, 2H), 6.34 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.97 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.76 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.48 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.14 – 4.95 (m, 2H), 3.92 – 3.79 (m, 2H), 2.41 – 2.22 (m, 2H). ^{13}C NMR: δ 165.5 (C), 142.0 (C), 135.3 (CH), 129.7

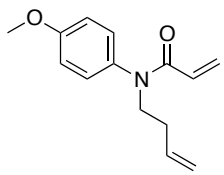
(2CH), 128.9 (CH), 128.5 (2CH), 127.9 (CH), 127.6 (CH_2), 116.8 (CH_2), 48.8 (CH_2), 32.2 (CH_2). GC-MS (EI): *m/z* 201, 160, 147, 106, 93, 77, 55, 51, 39, 27.

*5.1.12.2. Synthesis of N-(but-3-enyl)-N-(4-iodophenyl)acrylamide (**88b**)*



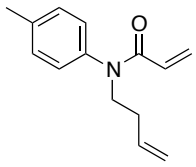
Substrate **88b** was synthesized from *N*-(but-3-enyl)-4-iodoaniline (**86b**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 94% yield) as a yellow oil. IR (neat): ν 3077, 2979, 2932, 1737, 1660, 1484, 1412, 1243, 1047, 1007, 782 cm^{-1}. ^1H NMR: δ 7.80 – 7.67 (m, 2H), 6.98 – 6.85 (m, 2H), 6.36 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.98 (dd, *J* = 16.7, 10.5 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.53 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.12 – 4.94 (m, 2H), 3.88 – 3.73 (m, 2H), 2.38 – 2.21 (m, 2H). ^{13}C NMR: δ 165.3 (C), 141.8 (C), 138.9 (2CH), 135.1 (CH), 130.4 (2CH), 128.6 (CH), 128.1 (CH_2), 117.1 (CH_2), 93.0 (C), 48.7 (CH_2), 32.2 (CH_2). GC-MS (EI): *m/z* 327, 273, 232, 219, 203, 159, 132, 105, 76, 55, 27.

*5.1.12.3. Synthesis of N-(but-3-enyl)-N-(4-methoxyphenyl)-acrylamide (**88c**)*



Substrate **88c** was synthesized from *N*-(but-3-enyl)-4-methoxyaniline (**86c**) and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 6:4, 67% yield) as a yellow oil. IR (neat): ν 3486, 3075, 2977, 2934, 2838, 1657, 1511, 1411, 1249, 1032, 838, 794 cm^{-1}. ^1H NMR: δ 7.12 – 6.99 (m, 2H), 6.96 – 6.83 (m, 2H), 6.31 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.97 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.46 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.03 (dd, *J* = 22.8, 5.7 Hz, 2H), 3.88 – 3.73 (m, 5H), 2.29 (dd, *J* = 14.7, 7.0 Hz, 2H). ^{13}C NMR: δ 165.8 (C), 159.0 (C), 135.4 (CH), 134.6 (C), 129.6 (2CH), 128.9 (CH), 127.3 (CH_2), 116.7 (CH_2), 114.7 (2CH), 55.6 (CH_3), 48.8 (CH_2), 32.2 (CH_2). GC-MS (EI): *m/z* 232, 190, 177, 160, 136, 120, 108, 92, 77, 65, 55, 39, 27. The spectral data for this compound correspond to previously reported data.[34]

*5.1.12.4. Synthesis of N-(but-3-enyl)-N-p-tolylacrylamide (**88f**)*

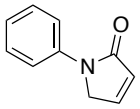


Substrate **88f** was synthesized from *N*-(but-3-enyl)-4-methylaniline (**86f**) and acryloyl chloride, following *RP6* and was isolated (AcOEt/*n*-hexane 4:6, 77% yield) as a yellow oil. IR (neat): ν 3074, 3031, 2978, 2926, 2866, 1656, 1412, 1261, 985, 916, 826 cm^{-1}. ^1H NMR: δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 – 6.96 (m, 2H), 6.33 (dd, *J* = 16.8, 2.1 Hz, 1H), 5.99 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.76 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.47 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.04 (dq, *J* = 10.3, 1.4 Hz, 2H), 3.93 – 3.72 (m, 2H), 2.38 (s, 3H), 2.30 (td, *J* = 7.0, 1.2 Hz, 2H). ^{13}C NMR: δ 165.6 (C), 139.3 (C), 137.9 (C), 135.4 (CH), 130.3 (2CH), 129.0 (CH), 128.3 (2CH), 127.3

(CH_2), 116.8 (CH_2), 48.8 (CH_2), 32.2 (CH_2), 21.2 (CH_3). GC-MS (EI): *m/z* 215, 174, 161, 121, 118, 107, 91, 77, 65, 55, 39, 27.

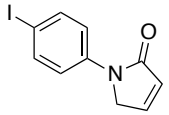
5.1.13. Synthesis of five- and six-membered *N*-aryl-lactams

*5.1.13.1 Synthesis of 1-phenyl-1H-pyrrol-2(5H)-one (**89a**)*



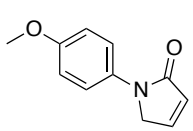
Substrate **89a** was synthesized, following the *RP7*, from compound **87a** and was isolated (AcOEt/*n*-hexane 1:1, 73% yield) as white solid. Mp: 81 °C. IR (neat): ν 3355, 3079, 2940, 1685, 1500, 1384, 1296, 1211, 1066, 801, 756 cm^{-1}. ^1H NMR: δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.31 (m, 2H), 7.21 – 7.08 (m, 2H), 6.26 (dt, *J* = 6.0, 1.8 Hz, 1H), 4.43 (t, *J* = 1.9 Hz, 2H). ^{13}C NMR: δ 170.2 (C), 142.3 (CH), 139.2 (C), 129.3 (2CH), 129.2 (2CH), 124.3 (CH), 119.0 (CH), 53.3 (CH_2). GC-MS (EI): *m/z* 159, 130, 104, 77, 51, 39. The spectral data for this compound correspond to previously reported data.[33]

*5.1.13.2. Synthesis of 1-(4-iodophenyl)-1H-pyrrol-2(5H)-one (**89b**)*



Substrate **89b** was synthesized, following the *RP7*, from compound **87b** and was isolated (AcOEt/*n*-hexane 1:1, 91% yield) as brown solid. Mp: 105 °C. IR (neat): ν 3099, 2918, 1686, 1492, 1374, 1210, 1144, 991, 811 cm^{-1}. ^1H NMR: δ 7.61 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 5.3 Hz, 1H), 6.20 (d, *J* = 4.9 Hz, 1H), 4.35 (s, 2H). ^{13}C NMR: δ 142.5 (CH), 138.9 (C), 137.9 (CH), 129.1 (2CH), 120.4 (2CH), 110.0 (C), 87.4 (C), 52.9 (CH_2). GC-MS (EI): *m/z* 286, 256, 230, 203, 158, 130, 90, 76, 63, 50, 39, 27.

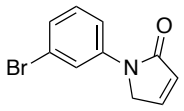
*5.1.13.3. Synthesis of 1-(4-methoxyphenyl)-1H-pyrrol-2(5H)-one (**89c**)*



Substrate **89c** was synthesized, following the *RP7*, from compound **87c** and was isolated (AcOEt/*n*-hexane 1:1, 56% yield) as grey solid. Mp: 104 °C. IR (neat): ν 2952, 2935, 1682, 1515, 1252, 1147, 1034, 828 cm^{-1}. ^1H NMR: δ 7.66 – 7.42 (m, 2H), 7.12 (dt, *J* = 6.0, 1.8 Hz, 1H), 7.00 – 6.80 (m, 2H), 6.35 – 6.09 (m, 1H), 4.38 (t, *J* = 1.8 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR: δ 170.0 (C), 156.5 (C), 142.1 (CH), 132.4 (C), 129.1 (CH), 121.1 (2CH), 114.3 (2CH), 55.5 (CH_3), 53.8 (CH_2). GC-MS (EI): *m/z* 189, 174, 160, 146, 134, 118, 107, 92, 77, 64, 55, 39. The spectral data for this compound correspond to previously reported data.[39]

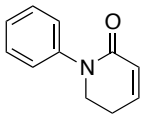
*5.1.13.4. Synthesis of 1-(3-bromophenyl)-1H-pyrrol-2(5H)-one (**89d**)*

Substrate **89d** was synthesized, following the *RP7*, from compound **87d** and was isolated (AcOEt/*n*-hexane 1:1, 80% yield) as white solid. Mp: 97 °C. IR (neat): ν 3366, 3113, 3062,



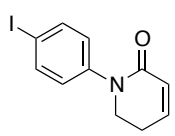
2907, 2848, 1988, 1484, 1201, 985, 774, 651 cm^{-1}. ^{1}H NMR: δ 7.90 (d, *J* = 1.8 Hz, 1H), 7.61 (dt, *J* = 7.1, 2.0 Hz, 1H), 7.26 – 7.09 (m, 3H), 6.21 (d, *J* = 6.1 Hz, 1H), 4.37 (t, *J* = 1.8 Hz, 2H). ^{13}C NMR: δ 170.2 (C), 142.8 (CH), 140.5 (C), 130.5 (CH), 129.1 (CH), 127.0 (CH), 122.9 (C), 121.5 (CH), 116.9 (CH), 53.1 (CH_2). GC-MS (EI): *m/z* 240, 236, 208, 182, 155, 130, 104, 90, 79, 68, 40, 39, 27.

*5.1.13.5. Synthesis of 1-phenyl-5,6-dihydropyridin-2(1H)-one (**90a**)*



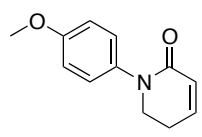
Substrate **90a** was synthesized, following the *RP7*, from compound **88a** and was isolated (AcOEt/*n*-hexane 7:3, 94% yield) as brown solid. Mp: 111 °C. IR (neat): ν 3047, 2962, 2910, 1660, 1592, 1421, 1313, 1137, 819, 694 cm^{-1}. ^{1}H NMR: δ 7.42 – 7.35 (m, 2H), 7.31 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.25 – 7.19 (m, 1H), 6.70 (dt, *J* = 9.7, 4.2 Hz, 1H), 6.08 (dt, *J* = 9.8, 1.8 Hz, 1H), 3.85 (t, *J* = 6.9 Hz, 2H), 2.59 – 2.44 (m, 2H). ^{13}C NMR: δ 164.1 (C), 142.9 (C), 140.3 (CH), 129.0 (2CH), 126.3 (CH), 126.2 (CH), 125.2 (2CH), 48.8 (CH_2), 24.8 (CH_2). GC-MS (EI): *m/z* 173, 144, 105, 77, 68, 51, 39, 27.

*5.1.13.6. Synthesis of 1-(4-iodophenyl)-5,6-dihydropyridin-2(1H)-one (**90b**)*



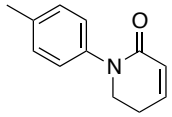
Substrate **90b** was synthesized, following the *RP7*, from compound **88b** and was isolated (AcOEt/*n*-hexane 3:7, quantitative yield) as white solid. Mp: 97 °C. IR (neat): ν 3048, 2955, 1660, 1610, 1485, 1318, 1241, 1137, 1006, 819 cm^{-1}. ^{1}H NMR: δ 7.76 – 7.62 (m, 2H), 7.14 – 7.03 (m, 2H), 6.81 – 6.61 (m, 1H), 6.06 (dt, *J* = 9.8, 1.8 Hz, 1H), 3.82 (t, *J* = 6.9 Hz, 2H), 2.63 – 2.42 (m, 2H). ^{13}C NMR: δ 164.1 (C), 142.5 (C), 140.7 (CH), 137.9 (2CH), 126.9 (2CH), 126.1 (CH), 90.4 (C), 48.5 (CH_2), 24.8 (CH_2). GC-MS (EI): *m/z* 299, 270, 231, 203, 172, 143, 115, 104, 76, 68, 51, 39, 27. The spectral data for this compound correspond to previously reported data.[39]

*5.1.13.7. Synthesis of 1-(4-methoxyphenyl)-5,6-dihydropyridin-2(1H)-one (**90c**)*



Substrate **90c** was synthesized, following the RP7, from compound **88c** and was isolated (filtration through a short pad of silica gel, 90% yield) as grey solid. Mp: 93 °C. IR (neat): ν 3461, 3046, 2936, 2836, 1667, 1511, 1242, 1032, 834 cm^{-1}. ^{1}H NMR: δ 7.26 (q, *J* = 2.1 Hz, 2H), 6.96 – 6.91 (m, 2H), 6.69 (dt, *J* = 9.5, 4.2 Hz, 1H), 6.09 (dt, *J* = 9.8, 1.7 Hz, 1H), 3.88 – 3.76 (m, 5H), 2.58 – 2.46 (m, 2H). ^{13}C NMR: δ 164.4 (C), 157.8 (C), 140.1 (CH), 135.8 (C), 126.6 (2CH), 126.2 (CH), 114.3 (2CH), 55.5 (CH_3), 49.1 (CH_2), 24.8 (CH_2). GC-MS (EI): *m/z* 203, 160, 135, 120, 107, 92, 65, 53, 39, 27. The spectral data for this compound correspond to previously reported data.[39]

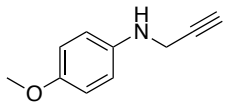
*5.1.13.8. Synthesis of 1-p-tolyl-5,6-dihydropyridin-2(1H)-one (**90f**)*



Substrate **90f** was synthesized, following the *RP7*, from compound **88f** and was isolated (filtration through a short pad of silica gel, 93% yield) as brown solid. Mp: 83 °C. IR (neat): ν 3474, 3032, 2923, 1668, 1607, 1420, 1242, 1139, 1020, 818, 727 cm^{-1}. ^{1}H NMR: δ 7.31 – 7.28 (m, 2H), 7.23 – 7.21 (m, 2H), 6.78 – 6.65 (m, 1H), 6.12 (dt, *J* = 9.8, 1.7 Hz, 1H), 3.84 (t, *J* = 6.9 Hz, 2H), 2.59 – 2.51 (m, 2H), 2.40 (s, 3H). ^{13}C NMR: δ 164.3 (C), 140.3 (C), 140.1 (CH), 135.9 (C), 129.6 (2CH), 126.3 (CH), 125.1 (2CH), 48.8 (CH_2), 24.8 (CH_2), 21.4 (CH_3). GC-MS (EI): *m/z* 187, 15, 144, 119, 104, 91, 77, 65, 51, 39, 27.

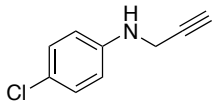
5.1.14. Synthesis of *N*-aryl-*N*-(prop-2-ynyl)acrylamides

*5.1.14.1. Synthesis of 4-methoxy-N-(prop-2-yn-1-yl)aniline (**91a**)*



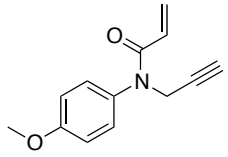
Compound **91a** was synthesized from 4-methoxyaniline and propargyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 55% yield) as a yellow oil. IR: ν 3378, 3288, 2996, 2936, 2249, 1514, 1244, 1037, 822 cm^{-1}. ^{1}H NMR: δ 6.84 – 6.80 (m, 2H), 6.70 – 6.67 (m, 2H), 3.90 (d, *J* = 2.4 Hz, 2H), 3.76 (s, 3H), 3.64 (br, s, 1H), 2.06 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 153.0 (C), 140.9 (C), 115.1 (2CH), 114.8 (2CH), 81.4 (C), 71.2 (CH), 55.7(CH_3), 34.6 (CH_2). GC-MS: *m/z* 161, 146, 122, 117, 108, 95, 91, 65, 52, 39, 28. The spectral data for this compound correspond to previously reported data.[40]

*5.1.14.2. Synthesis of 4-chloro-N-(prop-2-yn-1-yl)aniline (**91b**)*



Compound **91b** was synthesized from 4-chloroaniline and propargyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 57% yield) as a yellow oil. IR: ν 3379, 3285, 2984, 2925, 1601, 1504, 1241, 1035, 822 cm^{-1}. ^{1}H NMR: δ 7.28 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 7.9 Hz, 2H), 3.84 (d, *J* = 2.1 Hz, 2H), 3.71 (br, s, 1H), 2.12 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR: δ 149.1 (C), 129.7 (2CH), 125.4 (C), 114.9 (2CH), 79.9 (C), 71.5 (CH), 32.5 (CH_2). The spectral data for this compound correspond to previously reported data.[41]

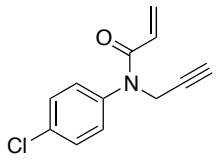
*5.1.14.3. Synthesis of N-(4-methoxyphenyl)-N-(prop-2-ynyl)acrylamide (**92a**)*



Substrate **92a** was synthesized from 4-methoxy-*N*-(prop-2-ynyl)aniline and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 4:6, 73% yield) as a yellow oil. IR (neat): ν 3292, 2962, 2935, 2838, 1657, 1511, 1409, 1251, 1023, 839, 652 cm^{-1}. ^{1}H NMR: δ 7.19 (m,

2H), 6.93 (m, 2H), 6.39 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.04 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.54 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.53 (d, *J* = 2.5 Hz, 2H), 3.84 (s, 3H), 2.20 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: δ 165.5 (C), 159.3 (C), 133.8 (C), 129.5 (2CH), 128.3 (CH_2), 128.1 (CH), 114.7 (2CH), 79.0 (C), 72.1 (CH), 55.5 (CH_3), 38.7 (CH_2). δ GC-MS (EI): *m/z* 216, 200, 186, 172, 161, 146, 134, 122, 117, 108, 91, 77, 55, 39, 27.

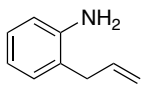
*5.1.14.4. Synthesis of N-(4-chlorophenyl)-N-(prop-2-ynyl)acrylamide (**92b**)*



Substrate **92b** was synthesized from 4-chloro-*N*-(prop-2-ynyl)aniline and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 4:6, 61% yield) as a yellow oil. IR (neat): ν 3292, 3248, 3085, 2920,1733, 1652, 1487, 1410, 1255, 1123, 1017, 793, 634 cm^{-1}. ^{1}H NMR: δ 7.33 (m, 2H), 7.25 (m, 2H), 6.44 (dd, *J* = 16.8, 1.9 Hz, 1H), 5.85 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.57 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.53 (d, *J* = 2.5 Hz, 2H), 2.21 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: δ 163.5 (C), 137.9 (C), 135.0 (C), 131.1 (CH), 130.7 (2CH), 129.5 (CH_2), 127.5 (2CH), 78.4 (C), 72.9 (CH), 31.3 (CH_2). δ GC-MS (EI): *m/z* 220, 206, 162, 147, 132, 121, 117, 92, 77, 65, 39, 27.

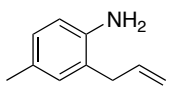
5.1.15. Synthesis of 2-allylanilines

*5.1.15.1 Representative procedure (**RP9**). Synthesis of 2-allylaniline (**93a**)*



N-allylaniline (2 g, 15 mol) was dissolved in *p*-xylene (15 mL) at 0 °C, under nitrogen atmosphere. $BF_3{\cdot}Et_2O$ (2.34 g, 16.5 mmol) was added and the solution was heated at 140 °C for 24 h. After dilution with ether (30 mL), the mixture was washed with a saturated $NaHCO_3$ solution (3 x 50 mL) and the aqueous phase was further extracted with ether (3 x 40 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane, 2:8) affording the desired product as a yellow oil (64% yield). ^{1}H NMR: δ 7.06 −7.03 (m, 2H) 6.74 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.01 − 5.88 (m, 1H), 5.13 − 5.06 (m, 2H), 3.64 (br, s, 2H), 3.30 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR: δ 145.1 (C), 136.3 (CH), 130.5 (CH), 127.8 (CH), 124.3 (C), 119.2 (CH), 116.4 (CH_2), 116.1 (CH), 36.8 (CH_2). The spectral data for this compound correspond to previously reported data.[35]

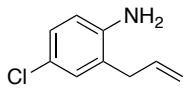
*5.1.15.2 Synthesis of 2-allyl-4-methylaniline (**93b**)*



Compound **93b** was synthesized, following the *RP9*, from *N*-allyl-4-methylaniline and was isolated (AcOEt/*n*-hexane 2:8, 68% yield) as a yellow oil. ^{1}H NMR: δ 6.86 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 5.98 − 5.85

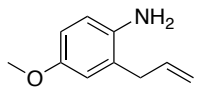
(m, 1H), 5.11 − 5.03 (m, 2H), 3.48 (br, s, 2H), 3.24 (d, *J* = 6.1 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR: δ 142.5 (C), 136.3 (CH), 130.9 (CH), 128.1 (C), 127.9 (CH), 124.3 (C), 116.2 (CH), 116.1 (CH_2), 36.6 (CH_2), 20.6 (CH_3). The spectral data for this compound correspond to previously reported data.[35]

*5.1.15.3. Synthesis of 2-allyl-4-chloroaniline (**93c**)*



Compound **93c** was synthesized, following the *RP9*, from *N*-allyl-4-chloroaniline and was isolated (AcOEt/*n*-hexane 3:7, 44% yield) as a yellow oil. ^{1}H NMR: δ 7.01 (s, 1H), 6.99 (d, *J* = 6.9 Hz, 1H), 6.56 (d, *J* = 6.6 Hz, 1H), 5.94 − 5.84 (m, 1H), 5.15 − 5.06 (m, 2H), 3.63 (s, 2H), 3.22 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR: δ 143.7 (C), 135.2 (CH), 130.0 (CH), 127.5 (C), 125.9 (CH), 123.4 (C), 117.1 (CH), 117.0 (CH_2), 36.3 (CH_2). The spectral data for this compound correspond to previously reported data.[35]

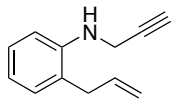
*5.1.15.4. Synthesis of 2-allyl-4-methoxyaniline (**93d**)*



Compound **93d** was synthesized, following the *RP9*, from *N*-allyl-4-methoxyaniline and was isolated (AcOEt/*n*-hexane 2:8, 65% yield) as a yellow oil. ^{1}H NMR: δ 6.65 − 6.54 (m, 3H), 5.99 − 5.85 (m, 1H), 5.12 − 5.04 (m, 2H), 3.71 (s, 3H), 3.35 (br, s, 2H), 3.26 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR: δ 153.7 (C), 138.6 (C), 135.9 (CH), 125.9 (C), 117.1 (CH), 116.9 (CH), 116.1 (CH_2), 112.8 (CH), 55.9 (CH_3), 36.7 (CH_2). The spectral data for this compound correspond to previously reported data.[35]

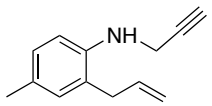
5.1.16. Synthesis of 2-allyl-*N*-(prop-2-ynyl)anilines

*5.1.16.1. Synthesis of 2-allyl-N-(prop-2-ynyl)aniline (**94a**)*



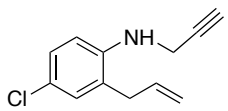
Compound **94a** was synthesized from substrate **93a** and propargyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 44% yield) as a yellow oil. IR (neat): ν 3412, 3291, 3074, 2976, 2910, 2839, 2115, 1601, 1509, 1453, 1257, 1062, 915, 749 cm^{-1}. ^{1}H NMR: δ 7.24 (dd, *J* = 13.0, 5.4 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.80 (dd, *J* = 20.3, 7.7 Hz, 2H), 6.07 – 5.89 (m, 1H), 5.24 – 5.01 (m, 2H), 3.98 (s, 3H), 3.34 (d, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 1.6 Hz, 1H). ^{13}C NMR: δ 145.2 (C), 135.9 (CH), 130.1 (CH), 127.7 (CH), 124.5 (C), 118.6 (CH), 116.5 (CH_2), 111.4 (CH), 81.2 (C), 71.3 (CH), 36.5 (CH_2), 33.6 (CH_2). GC-MS (EI): *m/z* 171, 156, 132, 117, 115, 103, 77, 65, 51, 39, 27.

*5.1.16.2. Synthesis of 2-allyl-4-methyl-N-(prop-2-ynyl)aniline (**94b**)*



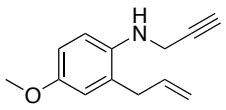
Compound **94b** was synthesized from substrate **93b** and propargyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 5:95, 47% yield) as a yellow oil. IR (neat): ν 3397, 3292, 3076, 3004, 2917, 1515, 1437, 1260, 913, 806, 650 cm^{-1}. ^{1}H NMR: δ 7.09 – 6.97 (m, 1H), 6.92 (d, *J* = 1.7 Hz, 1H), 6.73 – 6.61 (m, 1H), 5.97 (ddt, *J* = 16.3, 10.2, 6.1 Hz, 1H), 5.22 – 5.05 (m, 2H), 3.95 (t, *J* = 3.0 Hz, 2H), 3.85 (br, s, 1H), 3.30 (d, *J* = 6.1 Hz, 2H), 2.28 (s, 3H), 2.22 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 142.9 (C), 136.1 (CH), 130.9 (CH), 128.1 (CH), 127.9 (C), 124.8 (C), 116.4 (CH_2), 111.6 (CH), 81.4 (C), 71.2 (CH), 36.5 (CH_2), 33.9 (CH_2), 20.5 (CH_3). GC-MS (EI): *m/z* 185, 170, 144, 131, 115, 103, 91, 77, 65, 51, 39, 27.

*5.1.16.3. Synthesis of 2-allyl-4-chloro-N-(prop-2-ynyl)aniline (**94c**)*



Compound **94c** was synthesized from substrate **93c** and propargyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 51% yield) as a yellow oil IR (neat): ν 3296, 3078, 2909, 2843, 1505, 1435, 1410, 1312, 1260, 1138, 921, 805 cm^{-1}. ^{1}H NMR: δ 7.15 (dd, J = 8.6, 2.5 Hz, 1H), 7.06 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 8.6 Hz, 1H), 5.92 (ddt, J = 17.0, 10.2, 6.1 Hz, 1H), 5.17 (dq, J = 10.1, 1.5 Hz, 1H), 5.11 (dq, J = 17.1, 1.7 Hz, 1H), 4.10 (br, s, 1H), 3.93 (d, J = 2.4 Hz, 2H), 3.27 (d, J = 6.1 Hz, 2H), 2.22 (t, J = 2.4 Hz, 1H). ^{13}C NMR: δ 143.6 (C), 135.0 (CH), 129.8 (CH), 127.4 (CH), 126.4 (C), 123.5 (C), 117.2 (CH_2), 112.7 (CH), 80.6 (C), 71.7 (CH), 36.1 (CH_2), 33.8 (CH_2). GC-MS (EI): *m/z* 206, 190, 164, 152, 151, 130, 115, 89, 77, 63, 39, 27.

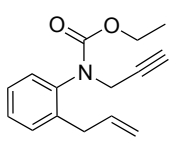
*5.1.16.4. Synthesis of 2-allyl-4-methoxy-N-(prop-2-ynyl)aniline (**94d**)*



Compound **94d** was synthesized from substrate **93d** and propargyl bromide, following the *RP8*, and was isolated (AcOEt/*n*-hexane 1:9, 50% yield) as a yellow oil. IR (neat): ν 3389, 3287, 3074, 2998, 2936, 2833, 1634, 1510, 1232, 1043, 915, 804. cm^{-1}. ^{1}H NMR: δ 6.86 – 6.69 (m, 3H), 6.10 – 5.89 (m, 1H), 5.17 – 5.09 (m, 2H), 3.95 (d, *J* = 2.3 Hz, 2H), 3.80 (s, 3H), 3.68 (br, s, 1H), 3.41 – 3.26 (m, 2H), 2.25 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 152.9 (C), 139.2 (C), 135.7 (CH), 126.8 (C), 116.7 (CH), 116.6 (CH_2), 113.0 (CH), 112.1 (CH), 81.5 (C), 71.3 (CH), 55.7 (CH_3), 36.4 (CH_2), 34.4 (CH_2). GC-MS (EI): *m/z* 201, 186, 162, 147, 130, 118, 103, 78, 65, 51, 39, 27.

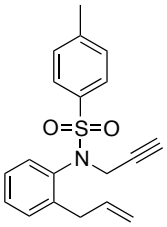
5.1.17. Synthesis of *N*-functionalized 1,8 enynes

*5.1.17.1. Synthesis of ethyl 2-allylphenyl(prop-2-ynyl)carbamate (**95a**)*



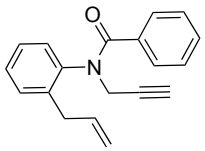
2-allyl-N-(prop-2-ynyl)aniline **94a** (0.3 g, 1.8 mmol) was dissolved in THF (15 mL) at room temperature, under nitrogen atmosphere. Pyridine (0.15 g, 0.15 mL, 1.9 mmol) and ethyl chloroformate (0.29 g, 0.25 mL, 2.6 mmol) were added and the solution was stirred overnight. At the end of the reaction, the mixture was washed with 1M HCl (20 mL) and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic layers were treated with a saturated $NaHCO_3$ solution (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane, 2:8) affording the desired product as a yellow oil (74% yield). IR (neat): ν 3290, 3076, 2980, 2931, 1701, 1404, 1297, 1233, 1142, 1055, 919, 770, 636 cm^{-1}. ^1H NMR: δ 7.37 – 7.15 (m, 4H), 6.06 – 5.74 (br, m, 1H), 5.13 – 5.01 (br, m, 2H), 4.24 – 3.99 (m, 4H), 3.34 (d, *J* = 5.4 Hz, 2H), 2.23 (br, s, 1H), 1.12 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR: δ 155.6 (C), 139.5 (C), 138.2 (C), 136.5 (CH), 130.2 (CH), 128.6 (CH), 128.3 (CH), 127.2 (CH), 116.5 (CH_2), 79.3 (C), 72.4 (CH), 62.1 (CH_2), 40.1 (CH_2), 35.5 (CH_2), 14.7 (CH_3). GC-MS (EI): *m/z* 234, 214, 204, 190, 170, 154, 143, 130, 115, 103, 77, 65, 51, 39, 29.

*5.1.17.2. Synthesis of N-(2-allylphenyl)-4-methyl-N-(prop-2-ynyl)benzenesulfonamide (**96a**)*



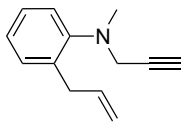
2-allyl-N-(prop-2-ynyl)aniline **94a** (0.3 g, 1.8 mmol) was dissolved in pyridine (10 mL) at room temperature, under nitrogen atmosphere. Tosyl chloride (0.67 g, 3.9 mmol) was added and the solution was stirred overnight. At the end of the reaction, the mixture was washed with 1M HCl (40 mL) and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic layers were treated with a saturated $NaHCO_3$ solution (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane, 2:8) affording the desired product as a colorless oil (41% yield). IR (neat): ν 3287, 3072, 2977, 2922, 1643, 1598, 1489, 1348, 1163, 1093, 918, 813, 661 cm^{-1}. ^1H NMR: δ 7.73 – 7.56 (m, 2H), 7.41 – 7.20 (m, 4H), 7.16 – 7.01 (m, 1H), 6.90 – 6.72 (m, 1H), 5.95 (ddt, *J* = 15.5, 10.4, 6.7 Hz, 1H), 5.22 – 5.02 (m, 2H), 4.54 (br, d, *J* = 17.4 Hz, 1H), 4.30 – 4.10 (br, m, 1H), 3.67 (br, s, 1H), 3.49 (br, s, 1H), 2.45 (s, 3H), 2.13 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: δ 143.9 (C), 141.7 (C), 137.5 (C), 137.1 (CH), 136.3 (C), 130.8 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.4 (CH), 126.7 (CH), 116.6 (CH_2), 77.9 (C), 73.9 (CH), 41.7 (CH_2), 35.6 (CH_2), 21.7 (CH_3). GC-MS (EI): *m/z* 325, 260, 170, 154, 130, 115, 103, 91, 77, 65, 39.

*5.1.17.3. Synthesis of N-(2-allylphenyl)-N-(prop-2-ynyl)benzamide (**97a**)*



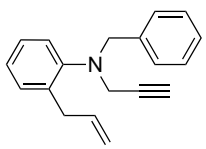
2-allyl-N-(prop-2-ynyl)aniline **94a** (0.3 g, 1.8 mmol) was dissolved in THF (15 mL) at room temperature, under nitrogen atmosphere. Pyridine (0.15 g, 0.15 mL, 1.9 mmol) and benzoyl chloride (0.37 g, 0.30 mL, 2.6 mmol) were added and the solution was stirred overnight. At the end of the reaction, the mixture was washed with 1M HCl (20 mL) and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic layers were treated with a saturated $NaHCO_3$ solution (3 x 30 mL) and brine (2 x 30 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane 3:7) affording the desired product as a colorless oil (69% yield). IR (neat): ν 3294, 3063, 2976, 2925, 2119, 1649, 1450, 1377, 1301, 1154, 921, 623 cm^{-1}. ^1H NMR: δ 7.36 – 7.07 (m, 9H), 5.72 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.05 (t, *J* = 12.8 Hz, 2H), 4.80 (dd, *J* = 17.0, 2.2 Hz, 1H), 4.38 (dd, *J* = 17.0, 2.2 Hz, 1H), 3.39 (dd, *J* = 15.9, 6.7 Hz, 1H), 3.16 (dd, *J* = 15.9, 6.3 Hz, 1H), 2.23 (s, 1H). ^{13}C NMR: δ 170.1 (C), 140.9 (C), 137.2 (C), 135.9 (CH), 135.0 (C), 130.5 (CH), 130.0 (CH), 129.6 (CH), 128.6 (CH), 128.3 (2CH), 127.6 (CH), 127.2 (2CH), 117.1 (CH_2), 78.7 (C), 72.4 (CH), 39.7 (CH_2), 35.0 (CH_2). GC-MS (EI): *m/z* 275, 243, 218, 195, 170, 155, 130, 115, 105, 77, 65, 51, 39, 27.

*5.1.17.4. Synthesis of 2-allyl-N-methyl-N-(prop-2-ynyl)aniline (**98a**)*



Substrate **98a** was synthesized from compound **94a** and iodomethane, following *RP9* and was isolated (AcOEt/*n*-hexane 1:9, 63% yield) as a pale yellow oil. IR (neat): ν 3295, 3074, 3004, 2977, 2935, 2847, 2795, 1600, 1491, 1451, 1258, 1223, 1124, 995, 914, 752, 643 cm^{-1}. ^1H NMR: δ 7.27 – 7.23 (m, 3H), 7.13 – 7.10 (m, 1H), 5.72 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.15 – 5.11 (m, 2H), 3.74 (d, *J* = 2.3 Hz, 2H), 3.53 (d, *J* = 6.4 Hz, 2H), 2.84 (s, 3H), 2.28 (t, *J* = 2.3 Hz, 1H). ^{13}C NMR: δ 147.3 (C), 137.7 (CH), 135.0 (C), 130.3 (CH), 126.7 (CH), 124.2 (CH), 121.2 (CH), 115.8 (CH_2), 79.9 (C), 72.8 (CH), 46.3 (CH_2), 41.0 (CH_3), 34.9 (CH_2). GC-MS (EI): *m/z* 185, 170, 156, 146, 130, 115, 103, 91, 77, 65, 51, 39, 27.

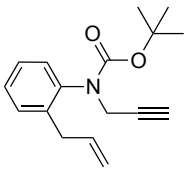
*5.1.17.5. Synthesis of 2-allyl-N-benzyl-N-(prop-2-ynyl)aniline (**99a**)*



Substrate **99a** was synthesized from compound **94a** and benzyl bromide, following the *RP9* and was isolated (CH_2Cl_2/*n*-hexane 2:8, 79% yield) as a colorless oil. IR (neat): ν 3294, 3064, 3028, 2916, 2841, 1491, 1449, 1207, 911, 733, 631 cm^{-1}. ^1H NMR: δ 7.42 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.30 – 7.19 (m, 3H), 7.12 (td, *J* = 7.4, 1.3 Hz, 1H), 6.09 – 5.91 (m, 1H), 5.18 – 4.97 (m, 2H), 4.24 (s, 2H), 3.60 (dd, *J* = 15.9, 4.4 Hz, 4H), 2.25 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR: δ 149.5 (C),

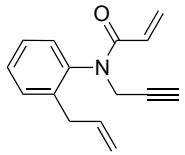
138.4 (C), 137.8 (CH), 135.9 (C), 130.3 (CH), 129.1 (2CH), 128.5 (2CH), 127.4 (CH), 126.8 (CH), 124.8 (CH), 123.5 (CH), 115.9 (CH_2), 79.4 (C), 73.4 (CH), 56.7 (CH_2), 42.7 (CH_2), 35.0 (CH_2). GC-MS (EI): *m/z* 260, 246, 232, 222, 206, 170, 154, 144, 130, 115, 103, 91, 77, 65, 51, 39, 27.

*5.1.17.6. Synthesis of tert-butyl 2-allylphenyl(prop-2-ynyl)carbamate (**100a**)*



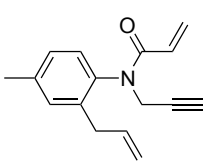
2-allyl-N-(prop-2-ynyl)aniline **94a** (0.6 g, 3.5 mmol) and di-tert-butyl dicarbonate (0.84 g, 3.9 mmol) were heated at 130 °C and stirred overnight. At the end of the reaction, the residue was purified by silica gel chromatography (AcOEt/*n*-hexane 1:9), affording the desired product as a yellow oil (75% yield). IR (neat): ν 3299, 3076, 2979, 2932, 1701, 1384, 1169, 1071, 859, 759 cm^{-1}. ^1H NMR: δ 7.40 – 7.12 (m, 4H), 5.96 – 5.89 (br, m, 1H), 5.09 (dp, *J* = 5.1, 1.8 Hz, 2H), 4.52 – 4.40 (br, m, 1H), 4.23 – 3.97 (br m, 1H), 3.45 – 3.22 (m, 2H), 2.22 (br s, 1H), 1.54 (s, 9H). ^{13}C NMR: δ 154.6 (C), 146.9 (C), 138.0 (C), 136.8 (CH), 129.9 (CH), 128.6 (CH), 127.9 (CH), 127.0 (CH), 116.4 (CH_2), 85.3 (C), 80.7 (C), 72.1 (CH), 39.5 (CH_2), 35.4 (CH_2), 28.3 ($3CH_3$). MS (CI): 272 [M+1].

*5.1.17.7. Synthesis of N-(2-allylphenyl)-N-(prop-2-ynyl)acrylamide (**101a**)*



Substrate **101a** was synthesized from compound **94a** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 15:85, 44% yield) as a yellow oil. IR (neat): ν 3293, 3243, 3074, 2977, 2923, 1655, 1488, 1408, 1258, 1221, 980, 921, 636 cm^{-1}. ^1H NMR: δ 7.44 – 7.19 (m, 4H), 6.42 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.97 – 5.78 (m, 2H), 5.53 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.11 – 5.04 (m, 2H), 4.79 (dd, *J* = 17.1, 2.5 Hz, 1H), 4.17 (dd, *J* = 17.1, 2.5 Hz, 1H), 3.31 (qd, *J* = 15.8, 6.7 Hz, 2H), 2.20 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: δ 165.6 (C), 139.5 (C), 138.4 (C), 135.0 (CH), 130.8 (CH), 129.8 (CH), 129.2 (CH), 128.9 (CH_2), 127.8 (CH), 127.7 (CH), 117.2 (CH_2), 78.8 (C), 72.4 (CH), 38.4 (CH_2), 35.4 (CH_2). GC-MS (EI): *m/z* 225, 196, 184, 170, 154, 143, 130, 115, 103, 77, 65, 55, 39, 27.

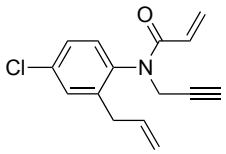
*5.1.17.8. Synthesis of N-(2-allyl-4-methylphenyl)-N-(prop-2-ynyl)acrylamide (**101b**)*



Substrate **101b** was synthesized from compound **94b** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane, 3:7, 55% yield) as a yellow oil. IR (neat): ν 3295, 3243, 3026, 2976, 2921, 1661, 1408, 1260, 1271, 1015, 919, 642 cm^{-1}. ^1H NMR: δ 7.19 – 7.05 (m, 3H), 6.44 – 6.34 (m, 1H), 5.97 – 5.76 (m, 2H), 5.58 – 5.46 (m, 1H), 5.19 – 5.00 (m, 2H), 4.82 – 4.70 (m, 1H), 4.22 – 4.11 (m, 1H), 3.26 (qd, *J* = 15.7, 6.8 Hz, 2H), 2.37 (s, 3H), 2.19 (dd, *J* =

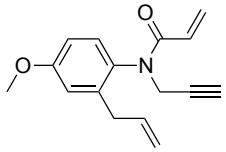
2.9, 2.0 Hz, 1H). ^{13}C NMR: δ 165.6 (C), 139.0 (C), 137.8 (C), 136.7 (C), 135.9 (CH), 131.2 (CH), 129.3 (CH), 128.6 (CH_2), 128.3 (CH), 127.8 (CH), 116.9 (CH_2), 78.7 (C), 72.2 (CH), 38.3 (CH_2), 35.2 (CH_2), 21.2 (CH_3). GC-MS (EI): *m/z* 239, 210, 198, 184, 168, 158, 144, 131, 115, 103, 92, 77, 65, 55, 39.

*5.1.17.9. Synthesis of N-(2-allyl-4-chlorophenyl)-N-(prop-2-ynyl)acrylamide (**101c**)*



Substrate **101c** was synthesized from compound **94c** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 43% yield) as a yellow oil. IR (neat): ν 3299, 3246, 3079, 2921, 1737, 1655, 1488, 1408, 1258, 1124, 1015, 922, 793, 634 cm^{-1}. ^{1}H NMR: δ 7.33 (d, *J* = 2.4 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 16.8, 1.9 Hz, 1H), 5.96 – 5.73 (m, 2H), 5.57 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.21 – 5.01 (m, 2H), 4.77 (dd, *J* = 17.2, 2.5 Hz, 1H), 4.17 (dd, *J* = 17.2, 2.5 Hz, 1H), 3.28 (qd, *J* = 15.8, 6.7 Hz, 2H), 2.21 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: δ 165.4 (C), 140.5 (C), 137.9 (C), 135.0 (C), 134.9 (CH), 131.1 (CH), 130.7 (CH), 129.5 (CH_2), 127.9 (CH), 127.5 (CH), 118.1 (CH_2), 78.4 (C), 72.9 (CH), 38.3 (CH_2), 35.3 (CH_2). GC-MS (EI): *m/z* 260.1, 242.1, 218.1, 204.1, 190.1, 178.1, 164.1, 154.1, 141.1, 130.1, 115.1, 102.1, 92.1, 77.1, 54.9, 38.9, 27.0.

*5.1.17.10. Synthesis of N-(2-allyl-4-methoxyphenyl)-N-(prop-2-ynyl)acrylamide (**101d**)*

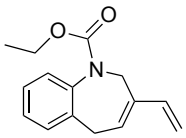


Substrate **101d** was synthesized from compound **94d** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 2:8, 42% yield) as a yellow oil. IR (neat): ν 3293, 3078, 3004, 2936, 2839, 1660, 1409, 1218, 1048, 922, 795 cm^{-1}. ^{1}H NMR: δ 7.16 (d, *J* = 8.6 Hz, 1H), 6.88 – 6.74 (m, 2H), 6.39 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.97 – 5.75 (m, 2H), 5.51 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.13 – 5.01 (m, 2H), 4.76 (dd, *J* = 17.1, 2.5 Hz, 1H), 4.14 (dd, *J* = 17.1, 2.5 Hz, 1H)., 3.82 (s, 3H), 3.25 (qd, *J* = 15.7, 6.7 Hz, 2H), 2.19 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR: δ 166.1 (C), 159.9 (C), 139.8 (C), 135.8 (CH), 132.3 (C), 130.8 (CH), 128.8 (CH_2), 127.9 (CH), 117.4 (CH_2), 115.8 (CH), 112.8 (CH), 78.9 (C), 72.5 (CH), 55.6 (CH_3), 38.6 (CH_2), 35.7 (CH_2). GC-MS (EI): *m/z* 255, 254, 283, 214, 200, 186, 160, 146, 130, 117, 115, 92, 77, 65, 55, 39, 27.

5.1.18. Synthesis of 1-benzazepines

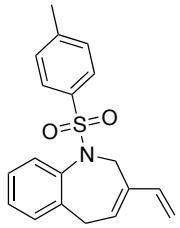
*5.1.18.1. <u>Representative procedure (**RP10**).</u> Synthesis of ethyl 3-vinyl-2,5-dihydro-1H-benzo[b]azepine-1-carboxylate (**102a**)*

Compound **95a** (0.08 g, 0.3 mmol) was dissolved in toluene (15 mL) at room temperature, under nitrogen atmosphere. After bubbling N_2 into the solution for 10 min, catalyst **9** (0.006



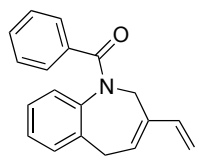
g, 0.01 mmol) was added. The solution was warmed at 70 °C and stirred for 3 h. At the end of the reaction, the solvent was removed under reduced pressure and reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane 1:9) affording the desired product as a yellow oil (45% yield). IR (neat): ν 3396, 2979, 2932, 1701, 1495, 1406, 1306, 1239, 1172, 1050, 887, 766 cm^{-1}. ^{1}H NMR (373K): δ 7.40 – 7.16 (m, 4H), 6.31 (dd, *J* = 18.0, 11.2 Hz, 1H), 5.93 (dd, *J* = 6.0, 5.3 Hz, 1H), 5.12 (d, *J* = 17.8 Hz, 1H), 5.00 (d, *J* = 11.1 Hz, 1H), 4.52 (br, s, 2H), 4.22 (dd, *J* = 14.0, 7.1 Hz, 2H), 3.51 (d, *J* = 5.3 Hz, 2H), 1.30 – 1.18 (m, 3H). ^{13}C NMR: δ 155.9 (C), 141.2 (C), 139.1 (C), 138.8 (CH), 135.8 (C), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 111.3 (CH_2), 61.9 (CH_2), 47.1 (CH_2), 31.9 (CH_2), 14.8 (CH_3). GC-MS (EI): *m/z* 243, 214, 170, 154, 130, 115, 103, 77, 65.

*5.1.18.2. Synthesis of 1-tosyl-3-vinyl-2,5-dihydro-1H-benzo[b]azepine (**103a**)*



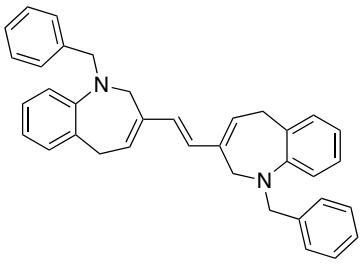
Substrate **103a** was synthesized, following the *RP10*, from compound **96a** and was isolated (AcOEt/*n*-hexane 2:8, 39% yield) as a yellow oil. IR (neat): ν 3029, 2923, 1598, 1492, 1345, 1161, 1106, 898, 658 cm^{-1}. ^{1}H NMR: δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.17 (m, 6H), 6.22 (dd, *J* = 17.9, 11.2 Hz, 1H), 5.72 (t, *J* = 5.8 Hz, 1H), 5.05 (d, *J* = 17.8 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.53 (s, 2H), 3.04 (d, *J* = 5.7 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR: δ 143.4 (C), 140.7 (C), 138.9 (C), 138.8 (C), 138.6 (CH), 129.9 (C), 129.7 (CH), 129.1 (2CH), 128.7 (CH), 127.8 (CH), 127.7 (CH),127.1 (2CH), 127.2 (CH_2), 111.3 (CH), 48.7 (CH_2), 32.2 (CH_2), 21.7 (CH_3). GC-MS (EI): *m/z* 325, 271, 246, 170, 168, 154, 142, 128, 115, 95, 77, 65.

*5.1.18.3. Synthesis of phenyl(3-vinyl-2,5-dihydro-1H-benzo[b]azepin-1-yl)methanone (**104a**)*



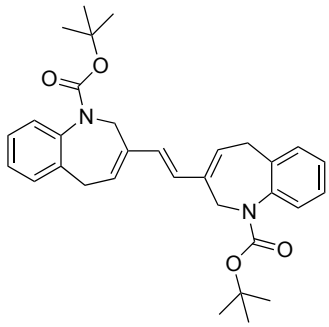
Substrate **104a** was synthesized, following the *RP10*, from compound **97a** and was isolated (AcOEt/*n*-hexane 1:9, 57% yield) as a brown oil. IR (neat): ν 3474, 3059, 2973, 1651, 1493, 1381, 1302 1240, 905, 701 cm^{-1}. ^{1}H NMR: δ 7.32 – 7.11 (m, 7H), 6.99 (br, s, 1H), 6.79 (d, *J* = 7.1 Hz, 1H), 6.61 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.98 (br, s, 1H), 5.87 (br, s, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.01 (d, *J* = 10.8, 1H), 4.13 (br, 1H), 3.71 (br, 1H), 3.27 (br, 1H). ^{13}C NMR: δ 170.0 (C), 142.8 (C), 138.6 (CH), 138.4 (C), 135.6 (C), 135.4 (C), 129.8 (CH), 128.5 (CH), 124.4 (CH), 128.0 (CH), 127.7 (4CH), 127.6 (CH), 126.9 (CH), 111.5 (CH_2), 45.7 (CH_2), 32.3 (CH_2). GC-MS (EI): *m/z* 275, 256, 220, 170, 155, 143, 115, 105, 89, 77, 65, 51, 39, 27.

5.1.18.4. Synthesis of (E)-1,2-bis((Z)-1-benzyl-2,5-dihydro-1H-benzo[b]azepin-3-yl)ethane ***(105a)***



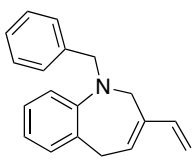
Substrate **105a** was synthesized, following the *RP10*, from compound **99a** and was isolated (AcOEt/*n*-hexane 1:9, 43% yield) as yellow oil. IR (neat): ν 3430, 3060, 3027, 2925, 1496, 1450, 1261, 1136, 739 cm^{-1}. ^{1}H NMR: δ 7.42 (d, *J* = 7.5 Hz, 4H), 7.35 – 7.27 (m, 4H), 7.25 – 7.16 (m, 4H), 7.08 – 7.05 (m, 4H), 6.93 (t, *J* = 7.3 Hz, 2H), 5.86 (t, *J* = 6.2 Hz, 2H), 5.69 (s, 2H), 4.28 (s, 4H), 3.59 (d, *J* = 6.1 Hz, 4H), 3.51 (s, 4H). ^{13}C NMR: δ 143.2 (2C), 139.2 (2C), 137.5 (2C), 135.4 (2C), 128.4 (6CH), 128.0 (4CH), 127.5 (2CH), 127.2 (2CH), 127.1 (2CH), 126.9 (2CH), 122.9 (2CH), 119.3 (2CH) 58.9 ($2CH_2$), 54.0 ($2CH_2$), 32.5 ($2CH_2$). MS (CI): *m/z* 495 (M+1).

5.1.18.5. Synthesis of (3Z,3'Z)-tert-butyl 3,3'-((E)-ethene-1,2-diyl)bis(2,5-dihydro-1H-benzo[b]azepine-1-carboxylate) ***(106a)***



Substrate **106a** was synthesized, following the *RP10*, from compound **100a** and was isolated (AcOEt/*n*-hexane 1:9, 51% yield) as yellow oil. IR (neat): ν 3009, 2975, 2931, 1696, 1388, 1248, 1164, 1039, 870, 756 cm^{-1}. ^{1}H NMR: δ 7.29 – 7.11 (m, 8H), 6.01 (br, s, 2H), 5.82 (br, s, 2H), 4.32 (br, s, 4H), 3.41 (br, s, 4H), 1.35 (s, 18H). ^{13}C NMR: δ 154.72 (2C), 141.7 (2C), 138.7 (2C), 135.4 (2C), 128.5 (2CH), 128.0 (2CH), 127.7 (4CH), 127.2 (2CH), 126.9 (2CH), 80.1 (2C), 46.5 ($2CH_2$), 32.0 ($2CH_2$), 28.3 ($6CH_3$). MS (CI): *m/z* 515 (M+1), 517.

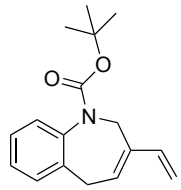
5.1.18.6. Synthesis of 1-benzyl-3-vinyl-2,5-dihydro-1H-benzo[b]azepine ***(107a)***



Compound **99a** (0.12 g, 0.5 mmol) was dissolved in toluene (10 mL) at room temperature, under nitrogen atmosphere. After bubbling ethylene into the solution for 15 min, catalyst **9** (0.009 g, 0.014 mmol) was added. The mixture was warmed at 70 °C and stirred for 8 h. At the end of the reaction, the solvent was removed under reduced pressure and reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane, 1:9) affording the desired product as a yellow oil (49% yield). IR (neat): ν 3425, 3084, 3061, 3027, 2926, 2872, 1597, 1494, 1452, 1368, 1239, 1141, 895, 751 cm^{-1}. ^{1}H NMR: δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 – 7.21 (m, 2H), 7.16 – 7.03 (m, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.19 (dd, *J* = 17.9, 11.2 Hz,

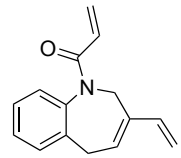
1H), 5.92 (t, *J* = 5.8 Hz, 1H), 4.87 – 4.78 (m, 2H), 4.36 (s, 2H), 3.68 (d, *J* = 6.1 Hz, 2H), 3.64 (s, 2H). ^{13}C NMR: δ 151.3 (C), 139.2 (CH), 137.5 (C), 135.4 (C), 128.4 (CH), 128.2 (2CH), 127.6 (2CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 123.0 (CH), 119.4 (CH), 115.5 (C), 109.8 (CH_2), 59.0 (CH_2), 53.8 (CH_2), 32.5 (CH_2). GC-MS (EI): *m/z* 262, 246, 220, 208, 170, 154, 142, 128, 115, 103, 91, 65, 51, 39, 27.

5.1.18.7. Synthesis of tert-butyl 3-vinyl-2,5-dihydro-1H-benzo[b]azepine-1-carboxylate ***(108a)***



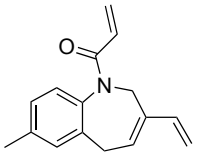
Compound **100a** (0.09g, 0.3mmol) was dissolved in toluene (7mL) at room temperature, under nitrogen atmosphere. After bubbling ethylene into the solution for 15 min, catalyst **9** (0.006g, 0.01mmol) was added. The mixture was warmed at 70 °C and stirred for 8 h. At the end of the reaction, the solvent was removed under reduced pressure and reaction residue was purified by silica gel chromatography (AcOEt/*n*-hexane, 1:9) affording the desired product as a yellow oil (51% yield). IR (neat): ν 3009, 2975, 2931, 1696, 1388, 1248, 1164, 1039, 870, 756 cm^{-1}. ^{1}H NMR: δ 7.40 – 7.16 (m, 4H), 6.25 (dd, *J* = 17.9, 10.8 Hz, 1H), 6.13 (dd, *J* = 6.0, 5.3 Hz, 1H), 5.09 (br, 1H), 5.00 (br, 1H), 4.52 (br, s, 2H), 3.51 (d, *J* = 5.3 Hz, 2H), 1.38 (s, 9H). ^{13}C NMR: δ 155.1 (C), 140.2 (C), 138.9 (CH), 136.1 (C), 129.9 (C), 127.6 (CH), 127.3 (CH), 126.4 (CH), 125.8 (CH), 124.7 (CH), 113.1 (CH_2), 80.1 (C), 52.3 (CH_2), 35.3 (CH_2), 28.4 ($3CH_3$). MS (CI): *m/z* 272 (M+1).

5.1.18.8. Synthesis of 1-(3-vinyl-2,5-dihydro-1H-benzo[b]azepin-1-yl)prop-2-en-1-one ***(109a)***.



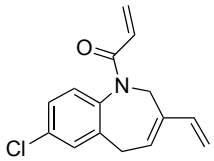
Substrate **109a** was synthesized, following the *RP10*, from compound **101a** and was isolated (AcOEt/*n*-hexane 4:6 46% yield) as yellow oil. IR (neat): ν 3419, 3032, 2927, 1661, 1409, 1227, 983, 752 cm^{-1}. ^{1}H NMR: δ 7.41 – 7.03 (m, 4H), 6.39 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.22 (dd, *J* = 17.8, 11.1 Hz, 1H), 6.00 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.83 (d, *J* = 9.5 Hz, 1H), 5.67 (d, *J* = 17.2 Hz, 1H), 5.51 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.10 (d, *J* = 17.8 Hz, 1H), 4.94 (d, *J* = 11.0 Hz, 1H), 3.76 (d, *J* = 12.3 Hz, 1H), 3.55 (d, *J* = 17.1 Hz, 1H), 3.05 (dd, *J* = 16.6, 8.8 Hz, 1H). ^{13}C NMR: δ 165.3 (C), 141.3 (C), 139.7 (C), 138.8 (CH), 135.5 (C), 128.8 (CH), 128.6 (CH), 128.5 (CH_2), 128.1 (CH), 128.0 (CH), 127.9 (CH), 126.9 (CH), 111.6 (CH_2), 44.8 (CH_2), 31.7 (CH_2). GC-MS (EI): *m/z* 225, 196, 182, 170, 155, 143, 128, 118, 91, 77, 65, 55, 39, 27.

*5.1.18.9. Synthesis of 1-(7-methyl-3-vinyl-2,5-dihydro-1H-benzo[b]azepin-1-yl)prop-2-en-1-one (**109b**)*



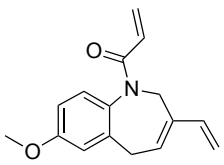
Substrate **109b** was synthesized, following the *RP10*, from compound **101b** and was isolated (AcOEt/*n*-hexane 3:7, 39% yield) as yellow oil. IR (neat): ν 3269, 2922, 2853, 1660, 1503, 1409, 1223, 983, 795 cm^{-1}. ^{1}H NMR: δ 7.16 – 7.01 (m, 3H), 6.40 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.24 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.05 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.85 (d, *J* = 9.8 Hz, 1H), 5.67 (d, *J* = 17.0 Hz, 1H), 5.53 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.11 (d, *J* = 17.8 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 3.74 (d, *J* = 14.8 Hz, 1H), 3.56 (d, *J* = 16.6 Hz, 1H), 3.01 (dd, *J* = 16.6, 8.9 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR: δ 165.6 (C), 139.3 (C), 138.8 (CH), 138.6 (C), 138.4 (C), 135.6 (C), 129.5 (CH), 128.6 (CH), 128.3 (CH_2), 128.0 (CH), 127.8 (CH), 127.0 (CH), 111.6 (CH_2), 44.9 (CH_2), 31.7 (CH_2), 21.2 (CH_3). GC-MS (EI): *m/z* 240, 121, 198, 184, 170, 158, 144, 131, 115, 91, 77, 55, 41.

*5.1.18.10. Synthesis of 1-(7-chloro-3-vinyl-2,5-dihydro-1H-benzo[b]azepin-1-yl)prop-2-en-1-one (**109c**)*



Substrate **109c** was synthesized, following the *RP10*, from compound **101c** and was isolated (AcOEt/*n*-hexane 3:7, 53% yield) as brown oil. IR (neat): ν 2963, 1664, 1489, 1407, 1227, 982 cm^{-1}. ^{1}H NMR: δ 7.33 – 7.21 (m, 2H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.42 (dd, *J* = 16.8, 1.9 Hz, 1H), 6.24 (dd, *J* = 17.9, 11.1 Hz, 1H), 6.01 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.82 (d, *J* = 11.0 Hz, 1H), 5.68 (d, *J* = 18.6 Hz, 1H), 5.57 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.13 (d, *J* = 17.8 Hz, 1H), 4.99 (d, *J* = 11.1 Hz, 1H), 3.75 (d, *J* = 16.1 Hz, 1H), 3.55 (d, *J* = 17.4 Hz, 1H), 3.03 (dd, *J* = 16.5, 8.9 Hz, 1H). ^{13}C NMR: δ 165.4 (C), 141.5 (C), 139.7 (C), 138.5 (CH), 135.7 (C), 134.3 (C), 129.4 (CH), 129.1 (CH_2), 128.9 (CH), 127.6 (CH), 127.4 (CH), 125.9 (CH), 112.1 (CH_2), 44.8 (CH_2), 31.5 (CH_2). GC-MS (EI): *m/z* 259, 244, 230, 204, 189, 168, 154, 151, 127, 115, 89, 75, 63, 55, 39, 27.

*5.1.18.11. Synthesis of 1-(7-methoxy-3-vinyl-2,5-dihydro-1H-benzo[b]azepin-1-yl)prop-2-en-1-one (**109d**)*

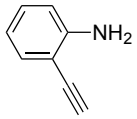


Substrate **109d** was synthesized, the following *RP10*, from compound **101d** and was isolated (AcOEt/*n*-hexane 3:7, 27% yield) as yellow oil. IR (neat): ν 3354, 2960, 2925, 1658, 1503, 1411, 1271, 1037, 796 cm^{-1}. ^{1}H NMR: δ 7.10 (d, *J* = 8.5 Hz, 1H), 6.86 – 6.69 (m, 2H), 6.39 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.24 (dd, *J* = 17.9, 11.0 Hz, 1H), 6.06 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.84 (d, *J* = 7.4 Hz, 1H), 5.66 (d, *J* = 17.2 Hz, 1H), 5.53 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.12 (d, *J* = 17.7

Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 3.92 – 3.67 (m, 4H), 3.56 (d, *J* = 17.9 Hz, 1H), 3.00 (dd, *J* = 16.6, 8.9 Hz, 1H). ^{13}C NMR: δ 165.9 (C), 159.5 (C), 140.0 (C), 138.8 (CH), 135.7 (C), 134.1 (C), 129.0 (CH), 128.4 (CH_2), 128.0 (CH), 126.8 (CH), 114.3 (CH), 112.7 (CH), 111.7 (CH_2), 55.6 (CH_3), 45.1 (CH_2), 32.0 (CH_2). GC-MS (EI): *m/z* 255, 240, 226, 200, 184, 169, 157, 141, 128, 115, 104, 91, 77, 65, 55, 51, 27.

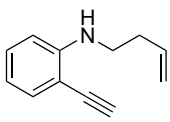
5.1.19. Synthesis of and reactivity of a 5-aza-1,8-enyne framework

*5.1.19.1. Synthesis of 2-ethynylaniline (**110**)*



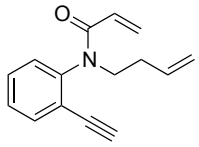
To a solution of 2-iodoaniline (5.0 g, 22.8 mmol) in THF (40 mL) and Et_3N (40 mL), $PdCl_2(PPh_3)_2$ (1.28 g, 1.8 mmol), CuI (0.35 g, 1.8 mmol) and trimethylsilylacetylene (2.6 g, 3.9 mL, 27.4 mmol) were added sequentially, under nitrogen atmosphere. The mixture was stirred at room temperature for 24 h, then concentrated under reduced pressure and taken up with AcOEt (40 mL). The solution was washed with water (40 mL) and the aqueous phase was extracted with AcOEt (3 x 20 mL). The combined organic layers were treated with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The resulting brown oil was dissolved in THF (40 mL), treated with TBAF (0.72 g, 2.28 mmol) and stirred at room temperature for 2 h. The mixture was then rotary evaporated and the reaction residue purified by silica gel chromatography (AcOEt/*n*-hexane 3:7) affording the desired product as a brown oil (quantitative yield). IR (neat): ν 3470, 3377, 3280, 3030, 2096, 1616, 1490, 1453, 1314, 1258, 1158, 752 cm^{-1}. ^{1}H NMR: δ 7.35 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.22 – 7.11 (m, 1H), 6.78 – 6.62 (m, 2H), 4.18 (br, s, 2H), 3.40 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR: δ 148.6 (C), 132.7 (CH), 130.2 (CH), 117.9 (CH), 114.4 (CH), 106.7 (C), 82.6 (CH), 80.7 (C). GC-MS (EI): *m/z* 117, 89, 74, 63, 58, 50, 39, 38, 37. The spectral data for this compound correspond to previously reported data.[42]

*5.1.19.2. Synthesis of N-(but-3-enyl)-2-ethynylaniline (**111**)*



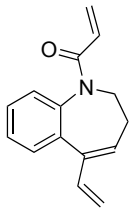
Substrate **111** was synthesized, following the *RP9*, from 2-ethynylaniline and 4-bromobut-1-ene and was isolated (AcOEt/*n*-hexane 1:9, 34% yield) as a pale yellow oil. IR (neat): ν 3401, 3297, 3076, 2977, 2914, 2851, 2094, 1511, 1322, 918, 746 cm^{-1}. ^{1}H NMR: δ 7.33 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29 – 7.17 (m, 1H), 6.66 – 6.55 (m, 2H), 5.86 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.23 – 5.08 (m, 2H), 4.70 (br, s, 1H), 3.39 (s, 1H), 3.25 (t, *J* = 6.8 Hz, 2H), 2.43 (qt, *J* = 6.8, 1.2 Hz, 2H). ^{13}C NMR: δ 149.6 (C), 135.6 (CH), 132.8 (CH), 130.5 (CH), 117.4 (CH_2), 116.2 (CH), 109.7 (CH), 106.3 (C), 82.9 (CH), 80.9 (C), 42.5 (CH_2), 33.7 (CH_2). GC-MS (EI): *m/z* 171, 130, 115, 103, 89, 77, 63, 51, 39, 27. The spectral data for this compound correspond to previously reported data.[42]

*5.1.19.3. Synthesis of N-(but-3-enyl)-N-(2-ethynylphenyl)-acrylamide (**112**)*



Substrate **112** was synthesized from compound **111** and acryloyl chloride, following the *RP6* and was isolated (AcOEt/*n*-hexane 3:7, 48% yield) as a yellow oil. IR (neat): ν 3290, 3223, 3074, 2978, 2105, 1658, 1411, 1257, 979, 757 cm^{-1}. ^{1}H NMR: δ 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.40 (td, *J* = 7.6, 1.6 Hz, 1H), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H), 7.18 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.35 (dd, *J* = 16.7, 2.0 Hz, 1H), 5.88 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.77 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.48 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.11 – 4.91 (m, 2H), 4.13 – 4.06 (m, 1H), 3.65 – 3.58 (m, 1H), 3.22 (s, 1H), 2.40 – 2.24 (m, 2H). ^{13}C NMR: δ 165.6 (C), 143.8 (C), 135.5 (CH), 134.1 (CH), 130.0 (CH), 129.8 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH_2), 122.5 (C), 116.7 (CH_2), 83.1 (CH), 79.7 (C), 48.4 (CH_2), 32.2 (CH_2). GC-MS (EI): *m/z* 225, 184, 171, 156, 143, 130, 103, 101, 89, 75, 55, 39, 27.

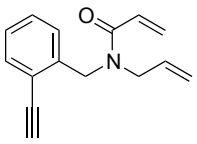
*5.1.19.4. Synthesis of 1-(5-vinyl-2,3-dihydro-1H-benzo[b]azepin-1-yl)prop-2-en-1-one (**113**)*



Substrate **113** was synthesized, following the *RP10*, from compound **112** and was isolated (AcOEt/*n*-hexane 4:6, 83% yield) as a brown solid. Mp: 57 °C. IR (neat): ν 3088, 3027, 2927, 2878, 1652, 1408, 1216, 1073, 979, 904, 774 cm^{-1}. ^{1}H NMR: δ 7.45 – 7.31 (m, 3H), 7.19 – 7.09 (m, 1H), 6.47 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.26 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.14 (t, *J* = 7.1 Hz, 1H), 5.83 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.42 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.09 (d, J = 10.9 Hz, 1H), 4.73 (td, J = 13.1, 5.4 Hz, 1H), 3.53 (ddd, *J* = 12.8, 6.2, 2.1 Hz, 1H), 2.32 – 2.27 (m, 1H), 2.19 – 2.08 (m, 1H). ^{13}C NMR: δ 166.2 (C), 140.4 (C), 139.7 (C), 137.4 (CH), 136.3 (C), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.2 (CH), 128.4 (CH), 127.9 (CH), 127.1 (CH_2), 115.1 (CH_2), 53.3 (CH_2), 25.4 (CH_2). GC-MS (EI): *m/z* 225, 196, 182, 170, 143, 128, 115, 102, 89, 77, 63, 55, 39, 27.

5.1.20. Synthesis of a 2-benzazepine framework

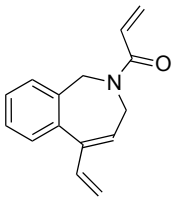
*5.1.20.1. N-allyl-N-(2-ethynylbenzyl)acrylamide (**114**)*



To a solution of compound **83a** (1.0 g, 3.1 mmol) in Et_3N (30 mL), $PdCl_2(PPh_3)_2$ (0.05 g, 0.8 mmol), CuI (0.02 g, 0.8 mmol) and trimethylsilylacetylene (0.4 g, 0.5 mL, 3.7 mmol) were added sequentially, under nitrogen atmosphere. The mixture was stirred at room temperature for 24 h, then concentrated under reduced pressure and taken up with AcOEt (40 mL). The solution was washed with water (40 mL) and the aqueous phase was extracted with AcOEt (3 x 20 mL). The combined organic layers were treated with brine (2 x 30 mL), dried over anhydrous

Na_2SO_4, then concentrated *in vacuo*. The resulting brown oil was dissolved in THF (40 mL), treated with TBAF (0.08 g, 0.31 mmol) and stirred at room temperature for 2 h. The mixture was then rotary evaporated and reaction residue purified by silica gel chromatography (AcOEt/*n*-hexane 3:7) affording the desired product as a yellow oil (49% yield). IR (neat): ν 3292, 3220, 3068, 2983, 2925, 1650, 1434, 1221, 978, 761 cm^{-1}. ^1H NMR: δ 7.50 (dd, *J* = 17.3, 7.6 Hz, 1H), 7.42 – 7.11 (m, 3H), 6.65 – 6.35 (m, 2H), 5.93 – 5.58 (m, 2H), 5.25 – 5.09 (m, 2H), 4.87 (s, 1H), 4.73 (s, 1H), 4.08 (d, *J* = 5.9 Hz, 1H), 3.94 (d, *J* = 4.7 Hz, 1H), 3.33 (d, *J* = 37.8 Hz, 1H). ^{13}C NMR: δ 167.1 (C, I_A), 166.9 (C, I_B), 139.9 (C, I_A), 139.3 (C, I_B), 133.3 (CH, I_A), 132.9 (CH, I_B), 132.8 (CH, I_A and CH, I_B), 129.5 (CH, I_A), 129.4 (CH, I_B), 129.1 (CH_2, I_A), 128.8 (CH_2, I_B), 128.3 (CH, I_A), 127.7 (CH, I_A and CH, I_B), 127.4 (CH, I_A), 127.3 (CH, I_B), 125.8 (CH, I_B), 121.6 (C, I_A), 120.5 (C, I_B), 118.0 (CH_2, I_A), 117.1 (CH_2, I_B), 83.4 (CH, I_A), 81.9 (CH, I_B), 81.7 (C, I_A), 80.8 (C, I_B), 49.7 (CH_2, I_A), 49.0 (CH_2, I_B), 47.1 (CH_2, I_A and CH_2, I_B). GC-MS (EI): *m/z* 224, 196, 184, 170, 156, 142, 130, 115, 103, 89, 75, 63, 55, 41, 27. I_A and I_B refer to the major and minor rotamer, respectively.

*5.1.20.2. Synthesis of 1-(5-vinyl-1H-benzo[c]azepin-2(3H)-yl)prop-2-en-1-one (**115**)*

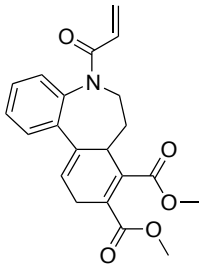


Substrate **115** was synthesized, following the *RP10*, from compound **114** and was isolated (AcOEt/*n*-hexane 1:1, 74% yield) as yellow oil. IR (neat): ν 3473, 3026, 2919, 2861, 1645, 1610, 1431, 1215, 979, 774 cm^{-1}. ^1H NMR: δ 7.50 – 7.29 (m, 4H), 6.73 – 6.49 (m, 2H), 6.32 – 6.29 (m, 1H), 6.12 (dt, *J* = 18.1, 7.0 Hz, 1H), 5.75 – 5.66 (m, 1H), 5.38 – 5.24 (m, 2H), 4.51 (s, 1H), 4.41 (s, 1H), 3.97 (d, *J* = 6.9 Hz, 1H), 3.81 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR: δ 165.2 (C, I_A), 165.0 (C, I_B), 144.9 (C, I_A), 143.8 (C, I_B), 137.3 (CH, I_A), 137.2 (C, I_A), 137.0 (C, I_B), 136.9 (CH, I_B), 135.9 (C, I_A), 135.5 (C, I_B), 130.5 (CH, I_A), 129.3 (CH, I_A), 128.9 (CH, I_B), 128.5 (CH, I_B), 128.3 (2CH, I_A and CH, I_B), 128.0 (CH, I_A), 127.9 (CH, I_B), 127.8 (CH_2, I_A), 127.7 (CH_2, I_B), 127.6 (CH, I_B), 125.1 (CH, I_A), 123.6 (CH, I_B), 118.2 (CH_2, I_A), 117.5 (CH_2, I_B), 50.1 (CH_2, I_A), 47.2 (CH_2, I_B), 43.6 (CH_2, I_A), 41.3 (CH_2, I_B). GC-MS (EI): *m/z* 225, 196, 170, 155, 141, 128, 115, 102, 89, 63, 55, 39, 27. I_A and I_B refer to the major and minor rotamer, respectively.

5.1.21. Orthogonal functionalizations of the benzazepine scaffold

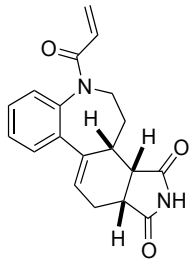
*5.1.21.1 Synthesis of dimethyl 5-acryloyl-6,7,7a,10-tetrahydro-5H-dibenzo[b,d]azepine-8,9-dicarboxylate (**116**)*

Compound **113** (0.03 g, 0.13 mmol) was dissolved in toluene (5 mL) under nitrogen atmosphere. DMAD (0.04 g, 0.26 mmol) was added and the solution was stirred at reflux for



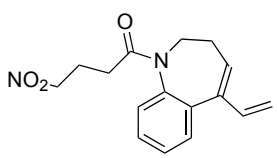
4 h. At the end of the reaction, the solvent was removed *in vacuo*. The resulting residue was purified by silica gel chromatography (AcOEt/*n*-hexane 1:1) affording the desired product as a yellow oil (66% yield). IR (neat): ν 3432, 2951, 1724, 1652, 1270, 1079, 763, 623 cm^{-1}. ^{1}H NMR: δ 7.47 – 6.95 (m, 4H), 6.32 (d, *J* = 16.8 Hz, 1H), 5.93 (br, s, 1H), 5.70 (br, s, 1H), 5.49 (d, *J* = 9.1 Hz, 1H), 4.90 (br, s, 1H), 3.78 (d, *J* = 6.2 Hz, 6H), 3.20 – 3.03 (br, m, 3H), 2.98 – 2.82 (br, m, 1H), 2.07 (br, s, 1H), 1.91 – 1.79 (br, m, 1H). ^{13}C NMR: δ 171.3 (C), 168.2 (C), 164.9 (C), 140.1 (C), 140.7 (C), 139.1 (C), 137.6 (C), 132.2 (C), 129.6 (CH), 128.6 (CH), 128.5 (2CH), 128.0 (CH), 127.8 (CH_2), 122.8 (CH), 52.5 ($2CH_3$), 46.7 (CH_2), 40.7 (CH), 29.8 (CH_2), 28.3 (CH_2). GC-MS (EI): *m/z* 367, 335, 296, 280, 248, 238, 220, 193, 180, 165, 152, 139, 115, 77, 58.

5.1.21.2. Synthesis of (3aR,3bS*,12aS*)-6-acryloyl-3b,4,5,6,12,12a-hexahydrobenzo [6,7]azepino [4,5-e]isoindole-1,3(2H,3aH)-dione (**117**)*



Compound **113** (0.037 g, 0.16 mmol) was dissolved in toluene (5 mL) under nitrogen atmosphere. Maleimide (0.031 g, 0.32 mmol) was added and the solution was stirred at reflux for 4 h. At the end of the reaction, the solvent was removed *in vacuo*. The resulting residue was purified by silica gel chromatography (AcOEt) affording the desired product as a white solid (58% yield). Mp: 253 °C. IR (neat): ν 3406, 2924, 2853, 1715, 1649, 1420, 1167, 1022, 732 cm^{-1}. ^{1}H NMR: δ 8.26 (s, 1H), 7.43 – 7.30 (m, 2H), 7.25 – 7.16 (m, 1H), 7.09 – 6.95 (m, 1H), 6.29 (dd, *J* = 16.8, 1.7 Hz, 1H), 6.11 – 6.00 (m, 1H), 5.73 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.44 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.64 (td, *J* = 12.8, 6.0 Hz, 1H), 3.32 – 3.18 (m, 3H), 2.84 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.55 (d, *J* = 8.8 Hz, 1H), 2.34 – 2.18 (m, 1H), 2.18 – 2.05 (m, 2H). ^{13}C NMR: δ 179.7 (C), 177.5 (C), 166.7 (C), 144.0 (C), 138.6 (C), 136.4 (C), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.7 (CH_2), 125.8 (CH), 46.2 (CH), 45.7 (CH_2), 41.7 (CH), 36.3 (CH), 26.7 (CH_2), 24.9 (CH_2). GC-MS (EI): *m/z* 322, 294, 267, 250, 224, 207, 196, 180, 170, 130, 115, 98, 77, 55.

*5.1.21.3. Synthesis of 4-nitro-1-(5-vinyl-2,3-dihydro-1H-benzo[b]azepin-1-yl)butan-1-one (**118**)*

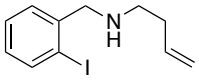


Nitromethane (0.04 g, 0.035 mL, 0.65 mmol) was dissolved in DMF (2 mL), at 0 °C under nitrogen atmosphere. NaH (60% dispersion in mineral oil) (0.003 g, 0.65 mmol) was added slowly and the mixture stirred for 10 minutes. Compound **113** (0.03 g, 0.13 mmol) was added; the solution was warmed at room temperature and stirred for an additional 2 h. At the

end of the reaction, the solvent was removed *in vacuo*. The resulting residue was purified by silica gel chromatography (AcOEt/*n*-hexane 3:7) affording the desired product as a brown oil (43% yield). IR (neat): ν 3384, 2923, 2853, 1649, 1552, 1489, 1412, 1261, 1075, 911 cm^{-1}. ^{1}H NMR: δ 7.48 – 7.34 (m, 3H), 7.21 (d, *J* = 7.6 Hz, 1H), 6.51 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.13 (t, *J* = 7.1 Hz, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 4.81 (td, *J* = 13.0, 5.6 Hz, 1H), 4.38 (dt, *J* = 10.4, 6.7 Hz, 1H), 4.29 (dt, *J* = 13.3, 6.4 Hz, 1H), 3.43 (dd, *J* = 12.9, 6.7 Hz, 1H), 2.27 – 2.10 (m, 4H), 2.10 – 2.00 (m, 1H), 1.94 – 1.84 (m, 1H). ^{13}C NMR: δ 171.5 (C), 140.4 (C), 139.8 (C), 137.2 (CH), 136.7 (C), 130.2 (CH), 130.1 (CH), 128.9 (2CH), 128.6 (2CH), 115.2 (CH_2), 74.8 (CH_2), 52.8 (CH_2), 30.8 (CH_2), 25.4 (CH_2), 22.8 (CH_2). GC-MS (EI): *m/z* 286, 238, 210, 182, 168, 156, 143, 128, 115, 89, 77, 41.

5.1.22. Synthesis of a benzazocine derivative

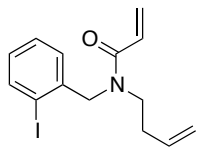
*5.1.22.1. Synthesis of N-(2-iodobenzyl)but-3-en-1-amine (**119**)*



2-iodo-benzaldehyde (2,7 g, 11.0 mmol) was dissolved in $CHCl_3$ (40 mL) at room temperature. Na_2SO_4 (4.4 g, 33.0 mmol), Et_3N (1.66 g, 2.5 mL,16.0 mmol) and but-3-en-1-amine hydrochloride (1,5 g, 13.0 mmol) were added and the solution was stirred at room temperature for 2 h. At the end of the reaction, the mixture was filtered over a Buchner funnel and the solvent was removed under reduced pressure. The resulting white sloid was dissolved in MeOH (40 mL) at 0 °C, $NaBH_3CN$ (0.7 g, 12.0 mmol) was added and the reaction was stirred at room temperature overnight. The solution was then diluted with AcOEt (30 mL), washed with water (50 mL) and the aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic layers were treated with brine (2 x 40 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The required product was obtained as a yellow oil and was used without further purification (quantitative yield). IR (neat): ν 3316, 3061, 2913, 2830, 1458, 1435, 1108, 1011, 914, 749 cm^{-1}. ^{1}H NMR: δ 7.78 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.37 – 7.23 (m, 2H), 6.91 (td, *J* = 7.6, 1.8 Hz, 1H), 5.78 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.14 – 4.98 (m, 2H), 3.78 (s, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.33 – 2.21 (m, 2H), 1.81 (br, s, 1H). ^{13}C NMR: δ 142.2 (C), 139.4 (CH), 136.4 (CH), 129.6 (CH), 128.7 (CH), 128.3 (CH), 116.4 (CH_2), 99.7 (C), 58.1 (CH_2), 48.1 (CH_2), 34.3 (CH_2). GC-MS (EI): *m/z* 288, 245, 216, 118, 104, 90, 63, 39, 28.

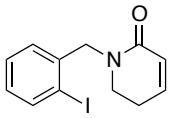
*5.1.22.2. Synthesis of N-(but-3-en-1-yl)-N-(2-iodobenzyl)-acrylamide (**120**)*

Substrate **120** was synthesized from compound **119** and acryloyl chloride, following the *RP3* and was isolated (AcOEt/hexane 4:6, 87% yield) as a yellow oil. IR (neat): ν 3073, 978, 2930, 1736, 1651, 1433, 1217, 1013, 749 cm^{-1}. ^{1}H NMR: δ 7.87 – 7.73 (m, 1H), 7.28 (dt, *J* = 15.4,



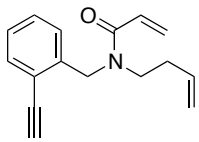
7.3 Hz, 1H), 7.18 – 6.85 (m, 2H), 6.71 – 6.19 (m, 2H), 5.90 – 5.55 (m, 2H), 5.16 – 4.99 (m, 2H), 4.69 (s, 1H), 4.48 (s, 1H), 3.54 – 3.41 (m, 1H), 3.41 – 3.31 (m, 1H), 2.46 – 2.24 (m, 2H). ^{13}C NMR: δ 166.9 (C, I_A), 166.5 (C, I_B), 139.7 (CH, I_A), 139.4 (CH, I_B), 138.5 (2C, I_A and I_B), 131.4 (CH, I_A), 130.6 (CH, I_B), 129.4 (CH, I_A), 129.0 (CH, I_B), 128.9 (CH_2, I_A), 128.9 (CH_2, I_B), 128.7 (CH, I_A), 128.6 (CH, I_B), 128.4 (CH, I_A), 127.4 (CH, I_A), 127.2 (CH, I_B), 126.9 (CH, I_B), 117.8 (CH_2, I_A), 116.9 (CH_2, I_B), 98.9 (C, I_A), 97.4 (C, I_B), 56.9 (CH_2, I_A), 53.7 (CH_2, I_B), 46.9 (CH_2, I_A), 46.5 (CH_2, I_B), 33.5 (CH_2, I_A), 32.1 (CH_2, I_B). GC-MS (EI): *m/z* 342, 300, 246, 216, 160, 144, 117, 90, 63, 54.I_A and I_B refer to the major and minor rotamer, respectively.

*5.1.22.3. Synthesis of 1-(2-iodobenzyl)-5,6-dihydropyridin-2(1H)-one (**121**)*



Substrate **121** was synthesized, following the *RP4*, from compound **120** and was isolated (filtration through a short pad of silica gel, 76% yield yield) as brown solid. Mp: 82 °C. IR (neat): ν 3463, 3053, 2938, 2893, 1665, 1608, 1483, 1436, 1292, 1013, 819, 748 cm^{-1}. ^{1}H NMR: δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 6.94 (dd, *J* = 10.7, 4.3 Hz, 1H), 6.63 – 6.55 (m, 1H), 6.00 (d, *J* = 9.8 Hz, 1H), 4.66 (s, 2H), 3.35 (t, *J* = 7.1 Hz, 2H), 2.44 – 2.29 (m, 2H).^{13}C NMR: δ 164.7 (C), 139.9 (CH), 139.6 (CH), 139.2 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 125.3 (CH), 98.9 (C), 54.6 (CH_2), 45.1 (CH_2), 24.3 (CH_2). GC-MS (EI): *m/z* 314, 217, 186, 157, 118, 107, 91, 63, 53.

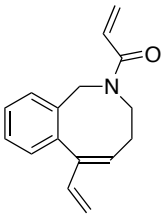
*5.1.22.4. Synthesis of N-(but-3-en-1-yl)-N-(2-ethynylbenzyl)-acrylamide (**122**)*



To a solution of compound **120** (1.4 g, 4.0 mmol) in Et_3N (40 mL), $PdCl_2(PPh_3)_2$ (0.071 g, 0.1 mmol), CuI (0.02 g, 0.1 mmol) and trimethylsilylacetylene (0.5 g, 0.7 mL, 5.0 mmol) were added sequentially, under nitrogen atmosphere. The mixture was stirred at room temperature overnight, then concentrated under reduced pressure and taken up with Et_2O (40 mL). The solution was washed with water (50 mL) and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic layers were treated with brine (2 x 40 mL), dried over anhydrous Na_2SO_4, then concentrated *in vacuo*. The resulting brown oil was dissolved in THF (40 mL), treated with TBAF (0.55 g, 2.0 mmol) and stirred at room temperature for 2 h. The mixture was then rotary evaporated and reaction residue purified by silica gel chromatography (AcOEt/hexane 2:8) affording the desired product as a yellow oil (53% yield yield). IR (neat): ν 3291, 3217, 3074, 2978, 2929, 1651, 1612, 1431, 1217, 920, 762 cm^{-1}. ^{1}H NMR: δ 7.38 – 7.11 (m, 4H), 6.69 – 6.37 (m, 2H), 5.79 – 5.71 (m, 2H), 5.15 – 4.99 (m, 2H), 4.89 (s, 1H), 4.76 (s, 1H), 4.57 (s, 1H), 3.37 (dd, *J* = 14.6, 6.9 Hz, 2H), 2.35 (td, *J* = 14.8, 7.2

Hz, 2H). ^{13}C NMR: δ 164.1 (C, I_A), 163.9 (C, I_B), 140.1 (2C, I_A and I_B), 133.3 (CH, I_A), 132.9 (CH, I_B), 129.5 (2CH, I_A and I_B), 128.7 (2CH_2, I_A and I_B), 128.4 (CH, I_A), 128.2 (CH, I_B), 127.8 (CH, I_A), 127.5 (CH, I_B), 127.3 (CH, I_A), 125.8 (CH, I_B), 125.6 (CH, I_A), 123.9 (CH, I_B), 120.7 (C, I_A), 120.5 (C, I_B), 117.7 (CH_2, I_A), 116.9 (CH_2, I_B), 84.9 (2C, I_A and I_B), 83.4 (CH, I_A), 81.8 (CH, I_B), 50.8 (CH_2, I_A), 50.1 (CH_2, I_B), 46.9 (CH_2, I_A), 46.5 (CH_2, I_B), 32.2 (CH_2, I_A), 31.8 (CH_2, I_B). GC-MS (EI): *m/z* 238, 198, 170, 144, 115, 89, 63, 55.

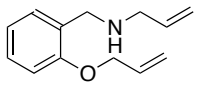
*5.1.22.5. Synthesis of 1-(6-vinyl-3,4-dihydrobenzo[c]azocin-2(1H)-yl)prop-2-en-1-one (**123**).*



Substrate **123** was synthesized, following the *RP4*, from compound **122** and was isolated (AcOEt/hexane 1:1, 69% yield) as yellow oil. IR (neat): ν 3454, 2933, 2852, 1664, 1610, 1483, 1293, 1141, 908, 820, 769 cm^{-1}. ^{1}H NMR: δ 7.36 – 7.18 (m, 3H), 7.16 – 7.05 (m, 1H), 6.63 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.57 – 6.49 (m, 1H), 6.00 (dt, *J* = 9.8, 1.7 Hz, 1H), 5.48 – 5.37 (m, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 5.09 (s, 1H), 4.72 (d, *J* = 17.3 Hz, 1H), 4.56 (s, 2H), 3.21 (t, *J* = 7.2 Hz, 2H), 2.34 – 2.22 (m, 2H). ^{13}C NMR: δ 164.9 (C), 147.4 (C), 139.51 (CH), 139.2 (CH), 135.2 (C), 129.9 (CH), 127.9 (CH), 127.5 (C), 127.1 (CH), 126.4 (CH), 125.5 (CH), 119.2 (CH_2), 117.7 (CH_2), 46.8 (CH_2), 44.5 (CH_2), 24.3 (CH_2). GC-MS (EI): *m/z* 238, 170, 142, 128, 115, 98, 53, 42.

5.1.23. Synthesis of large-sized ring heterocycles

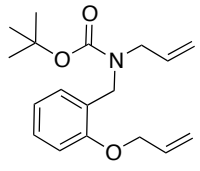
*5.1.23.1. Synthesis of allyl-(2-allyloxy-benzyl)-amine (**124**)*



Substrate **124** was synthesized, following the *RP5*, from 2-allyloxybenzaldehyde and was isolated (AcOEt/*n*-hexane 4:6, 64% yield) as yellow oil. IR (neat): ν 3329, 3060, 3029, 2910, 2809, 1455, 1110, 925, 741, 699 cm^{-1}. ^{1}H NMR: δ 7.27 – 7.23 (m, 2H), 6.95 (td, *J* = 7.4, 0.9 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.11 – 5.98 (m, 1H), 5.97 – 5.93 (m, 1H), 5.43 (dq, *J* = 17.3,1.6 Hz, 1H), 5.30 (dq, *J* = 10.6, 1.5 Hz, 1H), 5.22 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.6 Hz, 1H), 4.63 – 4.55 (m, 2H), 3.89 – 3.83 (s, 2H), 3.29 – 3.25 (m, 2H), 2.06 (br, 1H). ^{13}C NMR: δ 157.1 (C), 136.5 (CH), 133.5 (CH), 129.1 (CH), 128.0 (CH), 122.1 (C), 120.9 (CH), 118.5 (CH_2), 118.1 (CH_2), 115.3 (CH), 70.5 (CH_2), 52.3 (CH_2), 48.7 (CH_2). MS (CI): *m/z* 204 (M+1).

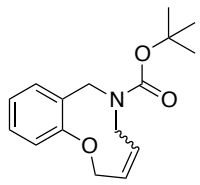
*5.1.23.2. Synthesis of allyl-(2-allyloxy-benzyl)-N-Boc-amine (**125**)*

Compound **124** (0.3090 g, 1.5 mmol) was placed in a one-necked 50 mL round bottomed flask and was dissolved in AcOEt (10 mL). Boc_2O (0.365 g, 1.7 mmol) was added and the mixture was stirred at room temperature for 72 hours. The product formation was controlled



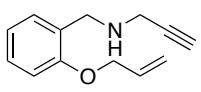
with TLC analysis, using *n*-hexane/AcOEt (6:4) as eluent. At the end of the reaction, the mixture was washed with a 0.5M HCl solution (3 x 10 mL). The organic phase was collected and dried on Na_2SO_4. The solvent was removed *in vacuo* to give the required product as a yellow oil that can be used without further purification (quantitative yield). IR (neat): ν 3295, 3070, 2970, 2934, 1703, 1385, 1161, 1070, 860, 755 cm^{-1}. ^1H NMR: δ 7.25 – 7.23 (m, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.10 – 5.97 (m, 1H), 5.80 (br, 1H), 5.42 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 5.11 (br, 2H), 4.55 (d, *J* = 4.8 Hz, 2H), 4.49 (br, 2H), 3.85 (br, 2H), 1.54 (s, 9H). ^{13}C NMR: δ 160.1 (C), 157.5 (C), 133.5 (CH), 131.2 (CH), 128.9 (CH), 128.6 (CH), 122.3 (C), 120.9 (CH), 118.5 (CH_2), 117.8 (CH_2), 115.3 (CH), 80.1 (C), 70.9 (CH_2), 52.3 (CH_2), 48.9 (CH_2), 27.0 ($3CH_3$). MS (CI): *m/z* 304 (M+1).

*5.1.23.3. Synthesis of tert-butyl 5,7-dihydrobenzo[b][1,5]oxazonine-6(2H)-carboxylate (**126**)*



Compound **125** (0.2063 g, 0.68 mmol) was placed in a two-necked 50 mL round bottomed flask, under nitrogen atmosphere, then dissolved in toluene (15 mL). Grubbs' catalyst **8** (0.018 g, 0.022 mmol) was added and the mixture stirred at 70 °C for 24 hours. The product formation was controlled with TLC analysis, using PE/AcOEt (8:2) as eluent. At the end of the reaction, the mixture was concentrated *in vacuo*. The oil residue was purified by column chromatography using CH_2Cl_2 as eluent to give the pure product as a yellow oil (40% yield). IR (neat): ν 3297, 3069, 2971, 2931, 1711, 1389, 1160, 1072, 863, 750 cm^{-1}. ^1H NMR: δ 6.68 – 7.28 (m, 8H, I_A and I_B), 6.04 – 6.00 (m, 1H, I_A), 5.91 – 5.87 (m, 1H, I_B), 5.48 (m, 2H, I_A and I_B), 4.87 (d, *J* = 4.8 Hz, 4H, I_A and I_B), 4.46 (s, 2H, I_A), 4.42 (s, 2H, I_B), 4.09 – 4.05 (m, 4H, I_A and I_B), 1.51 (s, 9H, I_A), δ 1.46 (s, 9H, I_B). GC-MS (EI): *m/z* 275, 232, 219, 216, 202, 176, 175, 160, 145, 138, 105, 91, 69, 57. I_A and I_B refer to the *Z* and the *E* isomer, respectively.

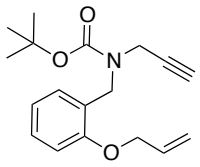
*5.1.23.4. Synthesis of propargyl-(2-allyloxy-benzyl)-amine (**127**)*



Substrate **127** was synthesized, following the *RP5*, from 2-allyloxybenzaldehyde and propargylamine, and was isolated (AcOEt/*n*-hexane 4:6, 49% yield) as yellow oil. IR (neat): ν 3330, 3064, 3029, 2810, 2118, 1456, 1108, 920, 743, 695 cm^{-1}. ^1H NMR: δ 7.29 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.24 (td, *J* = 8.0, 1.6 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.09 – 6.03 (m, 1H), δ 5.47 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.31 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.61 – 4.57 (m, 2H), 3.92 (s, 2H), 3.44 (d, *J* = 2.4 Hz, 2H), 2.25 (t, *J* = 2.4 Hz, 1H), 1.94 (br, 1H). ^{13}C NMR: δ 157.1 (C), 136.5 (CH), 129.1

(CH), 128.0 (CH), 122.1 (C), 120.9 (CH), 118.1 (CH_2), 115.3 (CH), 80.1 (C), 79.3 (CH), 70.5 (CH_2), 42.3 (CH_2), 40.7 (CH_2). GC-MS (EI): *m/z* 201, 162, 160, 145, 131, 107, 94, 91, 66, 54.

*5.1.23.5. Synthesis of propargyl-(2-allyloxy-benzyl)-amine (**128**)*



Compound **128** (0.4056 g, 2.0 mmol) was placed in a one-necked 50 mL round bottomed flask and was dissolved in AcOEt (10 mL). Boc_2O (0.4998 g, 2.2 mmol) was added and the mixture was stirred at room temperature for 14 hours. The product formation was controlled with TLC analysis, using *n*-hexane/AcOEt (6:4) as eluent. At the end of the reaction, the mixture was washed with a 0.5M HCl solution (3 x 10 mL). The organic phase was collected and dried on Na_2SO_4. The solvent was removed *in vacuo* to give the required product as a yellow oil that can be used without further purification (quantitative yield). IR (neat): ν 3290, 3071, 2973, 2933, 2118, 1705, 1388, 1162, 1050, 863, 757 cm^{-1}. ^1H NMR: δ 7.29 – 7.21 (m, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.11 – 6.07 (m, 1H), 5.44 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.61 – 4.57 (m, 4H), 4.14 – 4.10 (m, 2H), 2.18 (br, 1H), 1.54 (s, 9H). ^{13}C NMR: δ 160.1 (C), 157.5 (C), 133.5 (CH), 128.9 (CH), 128.6 (CH), 122.3 (C), 120.9 (CH), 117.8 (CH_2), 115.3 (CH), 81.3 (C), 80.1 (C), 79.3 (CH), 70.9 (CH_2), 52.3 (CH_2), 48.9 (CH_2), 26.9 ($3CH_3$). GC-MS (EI): *m/z* 301, 245, 201, 184, 162, 160, 145, 131, 107, 92, 91, 77, 54.

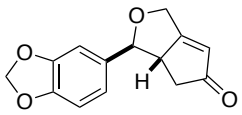
5.2. PAUSON-KHAND REACTIONS

5.2.1 General Remarks

All Pauson-Khand reactions were carried out under an ambient pressure of carbon monoxyde in oven-dried glassware. Distilled toluene was used for all reactions. Thin-layer chromatography (TLC) was performed on Macherey-Nagel polygram silica gel with fluorescent indicator UV_{254}. Carlo Erba reagents silica gel 60A (70-200 μm) was employed for column chromatography. NMR spectra were recorded at 298K in $CDCl_3$ solutions (unless otherwise stated) on a Bruker Avance 400 MHz spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C NMR. Chemical shifts are given in parts per million, referenced to the residual proton resonance of the solvents (δ = 7.26 ppm for $CDCl_3$) or to the residual carbon resonance of the solvent (δ = 77.16 ppm for $CDCl_3$). When possible, ^1H and ^{13}C signals were assigned mostly on the basis of DEPT and 2D NMR (COSY, HMBC) experiments. The terms m, s, d, t, q represent multiplet, singlet, doublet, triplet, quadruplet, respectively, the term br means a broad signal, the terms d1 and d2 mean diastereomer 1 and diastereomer 2 respectively. GC–MS analyses were run on Shimadzu GC-MS-QP5000. IR spectra were obtained using the Nicolet Magna-IR Spectrometer 550.

5.2.2. Synthesis of racemic PKR adducts

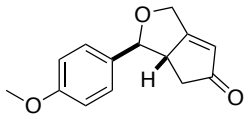
*5.2.2.1. Representative procedure (**RP11**). Synthesis of (3R*,3aR*)-3-(benzo[d][1,3]dioxol-5-yl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**168a**)*



Compound **60a** (0.1142 g, 0.5 mmol) was placed in a two-necked 50 mL round bottomed flask, under CO (1 atm), and was dissolved in toluene (10 mL). $Co_2(CO)_8$ (0.018 g, 0.05 mmol) was added, then the mixture was heated to reflux and stirred for 7 hour. The product formation was controlled with TLC analysis, using *n*-hexane/AcOEt (8:2 and 1:1) as eluent. At the end of the reaction, the solution was concentrated *in vacuo*. The oil residue was purified by column chromatography using *n*-hexane/AcOEt (1:1) as eluent to yield the required pure product as a yellow oil (51% yield). IR (neat): ν 3409, 3058, 2908, 2782, 1709, 1646, 1503, 1445, 1250, 1037, 1007, 934, 809, 736 cm^{-1}. ^1H NMR: δ 6.93 (s, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.11 (s, 1H), 4.98 (s, 2H), 4.92 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 10.4 Hz, 1H), 3.21 – 3.15 (m, 1H), 2.60 (dd, *J* = 17.7, 6.4 Hz, 1H), 2.25 (dd, *J* = 17.7, 3.5 Hz, 1H). ^{13}C NMR: δ 208.4 (C), 184.0 (C), 148.1 (C), 147.8 (C), 132.7 (C), 124.9

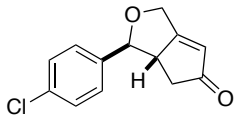
(CH), 119.7 (CH), 108.3 (CH), 106.4 (CH), 101.5 (CH_2), 84.6 (CH), 66.3 (CH_2), 52.9 (CH), 38.4 (CH_2). GC-MS (EI): *m/z* 244, 216, 149, 121, 103, 94, 77, 66, 51, 39, 27.

5.2.2.2. Synthesis of (3R,3aR*)-3-(4-methoxyphenyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**168b**)*



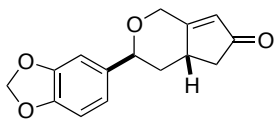
Substrate **168b** was synthesized, following the *RP11*, from compound **60b** and was isolated (AcOEt/*n*-hexane 1:1, 55% yield) as yellow oil. IR (neat): ν 3424, 3056, 2929, 2848, 1740, 1611, 1513, 1251, 1175, 1030, 735 cm^{-1}. ^1H NMR: δ 7.35 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.16 – 6.11 (m, 1H), 4.94 (d, *J* = 16.0 Hz, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 4.40 (d, *J* = 10.5 Hz, 1H), 3.83 (s, 3H), 3.45 – 3.40 (m, 1H), 2.60 (dd, *J* = 17.8, 6.4 Hz, 1H), 2.26 (dd, *J* = 17.8, 3.7 Hz, 1H). ^{13}C NMR: δ 208.9 (C), 184.7 (C), 160.2 (C), 131.2 (C), 128.1 (2CH), 125.3 (CH), 114.5 (2CH), 84.9 (CH), 66.7 (CH_2), 55.7 (CH_3), 53.2 (CH), 39.1 (CH_2). GC-MS (EI): *m/z* 230, 202, 187, 171, 158, 135, 128, 115, 94, 78, 66, 55.

5.2.2.3. Synthesis of (3R,3aR*)-3-(4-chlorophenyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**168d**)*



Substrate **168d** was synthesized, following the *RP11*, from compound **60d** and was isolated (AcOEt/*n*-hexane 1:1, 49% yield) as yellow oil. IR (neat): ν 3407, 3057, 2926, 2857, 1712, 1593, 1407, 1266, 1090, 736 cm^{-1}. ^1H NMR: δ 7.36 – 7.32 (m, 4H), 6.15 (s, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 4.74 (d, *J* = 16.0 Hz, 1H), 4.43 (d, *J* = 10.4 Hz, 1H), 3.37 – 3.33 (m, 1H), 2.62 (dd, *J* = 17.7, 6.4 Hz, 1H), 2.29 (dd, *J* = 17.7, 3.7 Hz, 1H). ^{13}C NMR: δ 208.2 (C), 183.6 (C), 137.6 (C), 134.2 (C), 128.9 (2CH), 127.2 (2CH), 125.2 (CH), 84.3 (CH), 66.4 (CH_2), 53.1 (CH), 36.7 (CH_2). GC-MS (EI): *m/z* 234, 139, 94, 75, 66, 55, 39, 27.

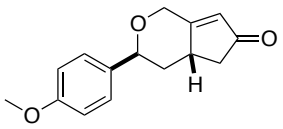
5.2.2.4. Synthesis of (3R,4aR*)-3-(benzo[d][1,3]dioxol-5-yl)-3,4,4a,5-tetrahydrocyclopenta-[c]pyran-6(1H)-one (**169a**)*



Substrate **169a** was synthesized, following the *RP11*, from compound **61a** and was isolated (AcOEt/*n*-hexane, 1:1, 31% yield) as yellow oil. IR (neat): ν 3406, 3058, 2961, 2919, 2850, 1708, 1441, 1259, 1037, 803, 737 cm^{-1}. ^1H NMR: δ 6.87 (s, 1H), 6.78 – 6.84 (m, 2H), 6.03 (s, 1H), 5.96 (s, 2H), 4.85 (d, *J* = 13.5 Hz, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 13.5 Hz, 1H), 3.13 – 3.07 (m, 1H), 2.69 (dd, *J* = 18.7, 6.9 Hz, 1H), 2.34 (dd, *J* = 12.7, 5.4 Hz, 1H), 2.12 (dd, *J* = 18.7, 2.8 Hz, 1H), 1.64 (dd, *J* = 24.2, 12.2 Hz, 1H). ^{13}C NMR: δ 208.0 (C), 175.1 (C), 148.2 (C), 147.6 (C), 135.3 (C), 127.9 (CH), 119.8 (CH), 108.6 (CH), 106.9 (CH), 101.5

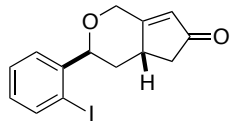
(CH_2), 79.4 (CH), 67.6 (CH_2), 42.6 (CH_2), 42.2 (CH_2), 39.9 (CH). GC-MS (EI): *m/z* 258, 207, 199, 187, 164, 149, 135, 121, 108, 93, 80, 67, 51.

5.2.2.5. Synthesis of (3R,4aR*)-3-(4-methoxyphenyl)-3,4,4a,5-tetrahydrocyclopenta [c]pyran-6(1H)-one (**169b**)*



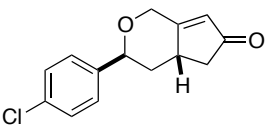
Substrate **169b** was synthesized, following the *RP11*, from compound **61b** and was isolated (AcOEt/*n*-hexane 1:1, 36% yield) as yellow oil. IR (neat): ν 3398, 2924, 2851, 1711, 1602, 1513, 1252, 1029, 829 cm^{-1}. ^1H NMR: δ 7.29 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.03 (s, 1H), 4.86 (d, *J* = 13.5 Hz, 1H), 4.60 (d, *J* = 10.6 Hz, 1H), 4.43 (d, *J* = 13. 5 Hz, 1H), 3.82 (s, 3H), 3.15 – 3.11 (m, 1H), 2.69 (dd, *J* = 18.7, 6.5 Hz, 1H), 2.35 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.12 (dd, *J* = 18.7, 2.6 Hz, 1H), 1.67 (dd, *J* = 24.0, 12.2 Hz, 1H). ^{13}C NMR: δ 208.1 (C), 175.4 (C), 159.7 (C), 133.5 (C), 127.9 (2CH), 127.6 (CH), 114.3 (2CH), 79.2 (CH), 67.7 (CH_2), 55.7 (CH_3), 42.4 (CH_2), 42.3 (CH_2), 39.9 (CH). GC-MS (EI): *m/z* 244, 226, 213, 196, 185, 171, 150, 135, 121, 108, 92, 80, 77, 51.

5.2.2.6. Synthesis of (3R,4aR*)-3-(2-iodophenyl)-3,4,4a,5-tetrahydrocyclopenta[c]pyran-6(1H)-one (**162c**)*



Substrate **162c** was synthesized, following the *RP11*, from compound **61c** and was isolated (AcOEt/*n*-hexane 1:1, 39% yield) as yellow oil. IR (neat): ν 3407, 3056, 2923, 1709, 1633, 1434, 1266, 1077, 1011, 737 cm^{-1}. ^1H NMR: δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.06 (s, 1H), 4.90 (d, *J* = 13.5 Hz, 1H), 4.81 (d, *J* = 10.6 Hz, 1H), 4.49 (d, *J* = 13.5 Hz, 1H), 3.21 – 3.15 (m, 1H), 2.71 (dd, *J* = 18.7, 6.5 Hz, 1H), 2.54 (dd, *J* = 12.9, 5.5 Hz, 1H), 2.10 (dd, *J*= 18.7, 2.7 Hz, 1H), 1.49 (dd, *J* = 23.7, 12.0 Hz, 1H). ^{13}C NMR: δ 208,0 (C), 174.9 (C), 143.5 (C), 139.7 (CH), 129.9 (CH), 129.6 (CH), 129.1 (CH), 128.9 (CH), 97.6 (C), 82.9 (CH), 67.7 (CH_2), 42.2 (CH_2), 41.2 (CH_2), 39.8 (CH). GC-MS (EI): *m/z* 340, 322, 295, 284, 267, 257, 230, 213, 202, 185, 153, 129, 108, 79, 67, 51, 38, 27.

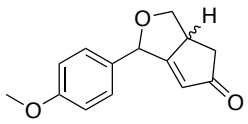
5.2.2.7. Synthesis of (3R,4aR*)-3-(4-chlorophenyl)-3,4,4a,5-tetrahydrocyclopenta[c]pyran-6(1H)-one (**169d**)*



Substrate **169d** was synthesized, following the *RP11*, from compound **61d** and was isolated (AcOEt/*n*-hexane 1:1, 36% yield) as yellow oil. IR (neat): ν 3409, 2924, 2855, 1710, 1490, 1265, 1086, 823, 734 cm^{-1}. ^1H NMR: δ 7.35 – 7.29 (m, 4H), 6.04 (s, 1H), 4.87 (d, *J* = 13.4 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 13.5 Hz, 1H), 3.15 – 3.09 (m, 1H), 2.69 (dd, *J* = 18.6,

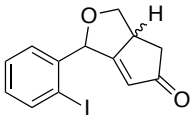
5.9 Hz, 1H), 2.37 – 2.33 (m, 1H), 2.14 – 2.09 (m, 1H), 1.67 (dd, *J* = 24.0, 11.9 Hz, 1H). ^{13}C NMR: δ 208.1 (C), 174.8 (C), 139.8 (C), 134.0 (C), 129.1 (CH), 128.1 (2CH), 127.6 (2CH), 78.8 (CH), 67.6 (CH_2), 42.6 (CH_2), 39.8 (CH), 30.1 (CH_2). GC-MS (EI): *m/z* 248, 213, 204, 192, 165, 141, 139, 125, 108, 94, 78, 67, 39, 27.

*5.2.2.8. Synthesis of 1-(4-methoxyphenyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**170b**)*



Substrate **170b** was synthesized, following the *RP11*, from compound **62b** and was isolated (AcOEt/*n*-hexane 1:1, 31% yield) as yellow oil. IR (neat): ν 3410, 2934, 2858, 1715, 1491, 1266, 1076, 735 cm^{-1}. ^{1}H NMR: δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 4H), 6.11 (s, 1H), 5.76 (s, 1H), 5.64 – 5.58 (m, 2H), 4.49 – 4.46 (m, 2H), 3,80 (s, 6H), 3.59 – 3.44 (m, 4H), 2.67 – 2.63 (m, 2H), 2.27 – 2.17 (m, 2H). ^{13}C NMR: δ 208.9 (C, d1), 208.6 (C, d2), 186.9 (C, d1), 185.8 (C, d2), 159.7 (C, d1), 159.6 (C, d2), 131.6 (C, d1), 130.5 (C, d2), 127.6 (2CH, d1), 127.4 (2CH, d2), 126.4 (CH d1), 124.7 (CH d2), 114.2 (4CH, d1 and d2), 77.5 (2CH, d1 and d2), 71.7 ($2CH_2$, d1 and d2), 55.3 ($2CH_3$, d1 and d2), 45.3 (CH, d1), 44.9 (CH, d2), 40.2 (CH_2, d1), 39.6 (CH_2, d2). GC-MS (EI): *m/z* 230, 216, 202, 147, 126, 115, 105, 90, 78, 63, 40, 27.

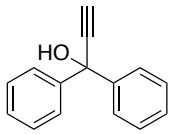
*5.2.2.9. Synthesis of 1-(2-iodophenyl)-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**170c**)*



Substrate **170c** was synthesized, following the *RP11*, from compound **62c** and was isolated (AcOEt/*n*-hexane 1:1, 44% yield) as yellow oil. IR (neat): ν 3412, 2936, 2849, 1711, 1491, 1260, 1080, 737 cm^{-1}. ^{1}H NMR: δ 7.87 (m, 2H), 7.28 – 7.49 (m, 4H), 7.06 – 7.02 (m, 2H), 6.59 (s, 1H), 5.96 (s, 1H), 5.92 – 5.88 (m, 2H), 4.63 – 4.59 (m, 2H), 3.72 – 3.67 (m, 1H), 3.61 – 6.57 (m, 1H), 3.55 – 3.51 (m, 1H), 3.48 – 3.44 (m, 1H), 2.70 – 2.66 (m, 2H), 2.24 – 2.20 (m, 2H). ^{13}C NMR: δ 208.7 (C, d1), 208.5 (C, d2), 186.9 (C, d1), 185.7 (C, d2), 164.2 (C, d1), 164.1 (C, d2), 137.3 (C, d1), 137.1 (C, d2), 129.2 (2CH d1 and d2), 128.0 (2CH d1 and d2), 127.0 (2CH d1 and d2), 126.4 (CH d1), 126.2 (2CH, d1 and d2),124.7 (CH d2), 77.5 (2CH, d1 and d2), 71.7 ($2CH_2$, d1 and d2), 45.3 (CH, d1), 44.9 (CH, d2), 40.2 (CH_2, d1), 39.6 (CH_2, d2). GC-MS (EI): *m/z* 326, 273, 244, 230, 216, 202, 147, 126, 115, 105, 90, 78, 63, 40, 27.

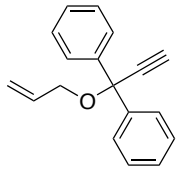
5.2.3. Synthesis of 1,1-Diphenyl-1-allyloxy-2-propyne

*5.2.3.1. Synthesis of 1,1-Diphenyl-prop-2-yn-1-ol (**171**)*



Substrate **171** was synthesized from benzophenone and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a white solid. Mp: 78 °C. ^{1}H NMR: δ 7.69 – 7.67 (m, 2H), 7.66- 7.64 (m, 2H), 7.39 – 7.35 (m, 4H), 7.33 – 7.29 (m, 2H), 3.01 (br, 1H), 2.07 (s, 1H). GC-MS (EI): *m/z* 208, 191, 179, 165, 155, 139, 130, 113, 102, 77, 53. The spectral data for this compound correspond to previously reported data.[43]

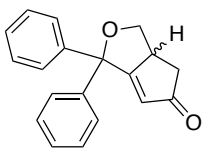
*5.2.3.2. Synthesis of 1,1-Diphenyl-1-allyloxy-2-propyne (**172**)*



Substrate **172** was synthesized from **171** and allylbromide, following the *RP2* and was isolated (*n*-hexane/AcOEt 9:1, 51% yield) as a colorless oil. IR (neat): ν 3292, 3067, 2859, 2114, 1711, 1431, 1304, 1063, 930, 755, 645 cm^{-1}. ^{1}H NMR: δ 7.57 (d, *J* = 7.3 Hz, 4H), 7.29 – 2.25 (m, 6H), 5.99 – 5.55 (m, 1H), 5.17 - 5.40 (m, 2H), 4.36 (s, 1H), 4.12 (d, *J* = 5.8 Hz, 1H), 4.06 (d, *J* = 6.9 Hz, 1H) ^{13}C NMR: δ 143.2 (2C), 134.8 (CH), 128.2 (4CH), 127.7 (2CH), 126.6 (4CH), 116.1 (CH_2), 83.3 (C), 80.1 (C), 77.6 (CH), 66.0 (CH_2). GC-MS (EI): *m/z* 248, 207, 191, 189, 165, 152, 143, 128, 115, 105, 82, 77, 53. The spectral data for this compound correspond to previously reported data.[44]

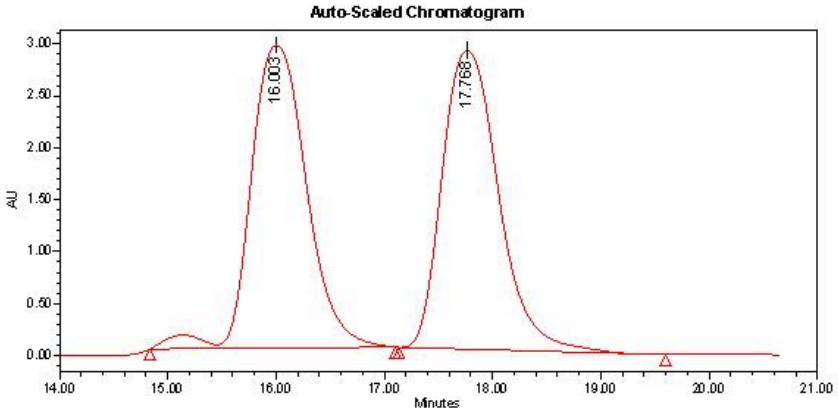
5.2.4. Toward asymmetric PKR

*5.2.4.1. Racemic synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one (**173**)*



Substrate **173** was synthesized, following the *RP11*, from compound **172** and was isolated (AcOEt/*n*-hexane 1:1, 36% yield) as yellow solid. Mp: 118 °C. IR (neat): ν 3420, 1712, 1636, 1112, 1020, 731, 698 cm^{-1}. ^{1}H NMR: δ 7.39 – 7.27 (m, 10H), 6.08 (d, *J* = 2.4 Hz, 1H), 4.56 (t, *J* = 8.1 Hz, 1H), 3.73 (dd, *J* = 10.7, 8.0 Hz, 1H), 3.68 – 3.41 (m, 1H), 2.70 (dd, *J* = 17.8, 6.4 Hz, 1H), 2.29 (dd, *J* = 17.8, 3.6 Hz, 1H). ^{13}C NMR: δ 208.5 (C), 187.4 (C), 143.4 (C), 142.4 (C), 128.6 (2CH), 128.5 (2CH), 128.0 (CH), 127.7 (CH), 127.2 (CH), 126.4 (2CH), 126.1 (2CH), 86.1 (C), 71.6 (CH_2), 45.2 (CH), 40.3 (CH_2). GC-MS (EI): *m/z* 277, 249, 234, 199, 181, 165, 128, 105, 77, 51.

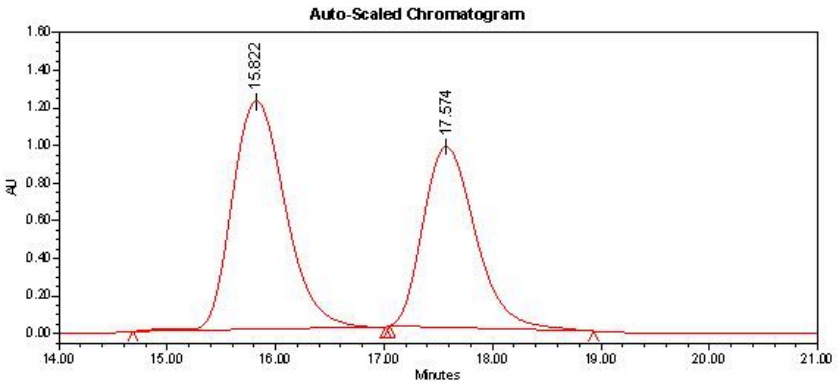
HPLC analysis was performed using a daicel chiralpack® AD-H column, *n*-hexane/isopropanol 9/1 as eluent and a 0.4 mL/min flow rate.



Enantiomer	T_R	% Area
1	16.003	50.40
2	17.768	49.60

*5.2.4.2. Representative procedure (**RP12**). Cobalt-catalyzed asymmetric synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one with BINAP (**173**)*

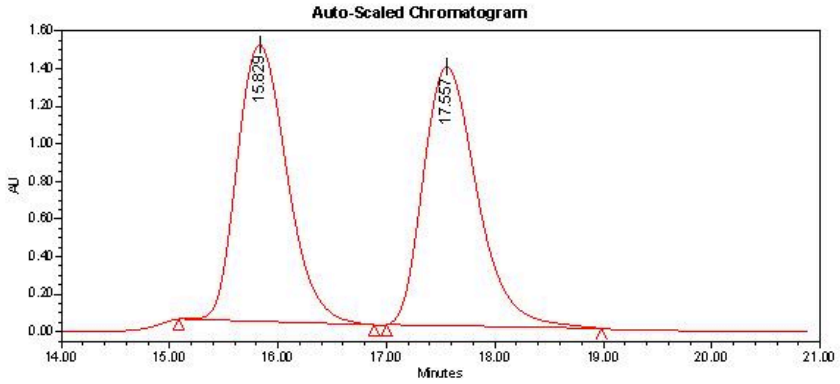
$Co_2(CO)_8$ (0.007 g, 0.021 mmol) and BINAP (0.12 g, 0.021 mmol) were placed in a two-necked 50 mL round bottomed flask, under a nitrogen atmosphere and were dissolved in toluene (2 mL). The solution was stirred at 80 °C for 1 h. After this time, the flask was saturated with gaseous CO (1 atm) and compound **172** (0.050 g, 0.21 mmol) in toluene (2 mL) was added. The mixture was stirred at reflux for an additional 7 hour. The product formation was controlled with TLC analysis, using *n*-hexane/AcOEt (8:2 and 1:1) as eluent. At the end of the reaction, the solution was concentrated *in vacuo*. The oil residue was purified by column chromatography using *n*-hexane/AcOEt (4:6) as eluent to yield the desired pure product as a yellow oil (29% yield). HPLC analysis was performed using a daicel chiralpack® AD-H column, *n*-hexane/isopropanol 9:1 as eluent and a 0.4 mL/min flow rate. 12% *ee*.



Enantiomer	T_R	% Area
1	15.822	56.11
2	17.574	43.89

*5.2.4.3. Cobalt-catalyzed asymmetric synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one with tetraMe-BITIOP (**173**)*

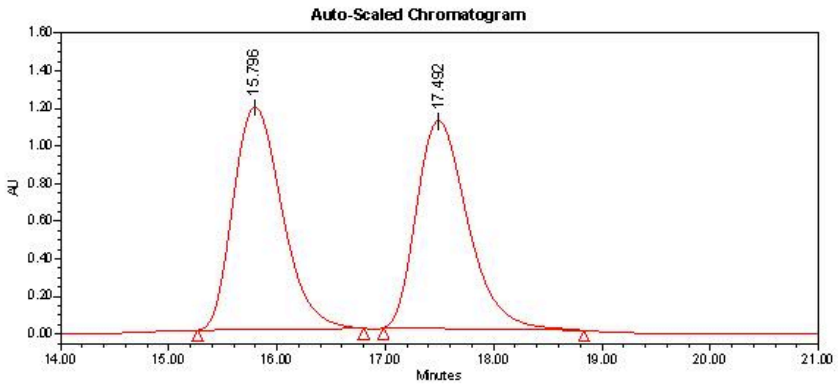
The reaction was carried out following *RP12* and using tetraMe-BITIOP as chiral, non-racemic ligand. Compound **173** was isolated in 26% yield as a racemic product.



Enantiomer	T_R	% Area
1	15.829	49.66
2	17.577	50.34

*5.2.4.4. Cobalt-catalyzed asymmetric synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one with BITIANP (**173**)*

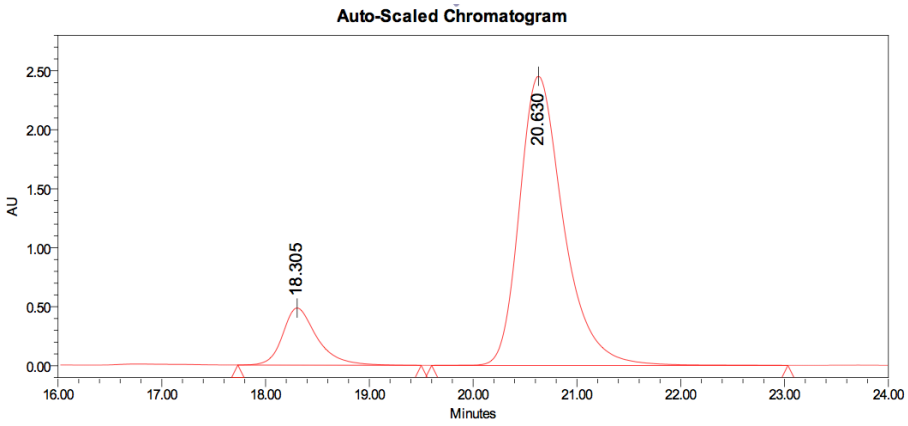
The reaction was carried out following *RP12* and using BITIANP as chiral, non-racemic ligand. Compound **173** was isolated in 26% yield as a racemic product.



Enantiomer	T_R	% Area
1	15.796	50.50
2	17.492	49.50

*5.2.4.5. Representative procedure (**RP13**). Rhodium-catalyzed asymmetric synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one with BINAP (**173**).*

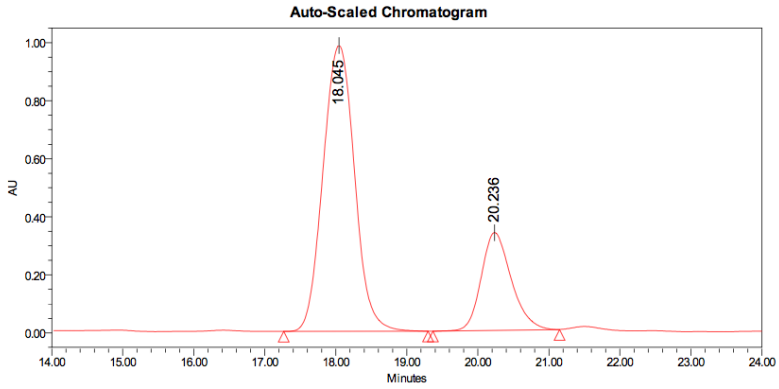
$[Rh(COD)Cl]_2$ (0.012 g, 0.024 mmol), BINAP (0.27 g, 0.048 mmol) and cynnamaldehyde (159 mg, 1.2 mmol) were charged in a schlenk tube at room temperature. Enyne (**172**) (200 mg, 0.8 mmol) was then added. After three vacuum-nitrogen cycles, unpurified *tert*-amyl alcohol (0.5 mL, degassed) was added. The reaction mixtures were stirred at 100 °C for 5 days. After cooling to room temperature, ethyl acetate (5 mL) was added. The crude reaction mixture was purified by silica gel chromatography (AcOEt/*n*-hexane, 2:8) to yield the desired pure product as a yellow oil (37% yield). HPLC analysis was performed using a daicel chiralpack® AD-H column, *n*-hexane/isopropanol 9:1 as eluent and a 0.4 mL/min flow rate. 74% *ee*.



Enantiomer	T_R	% Area
1	18.305	13.40
2	20.630	86.60

*5.2.4.6. Rhodium-catalyzed asymmetric synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one with tetraMe-BITIOP (**173**)*

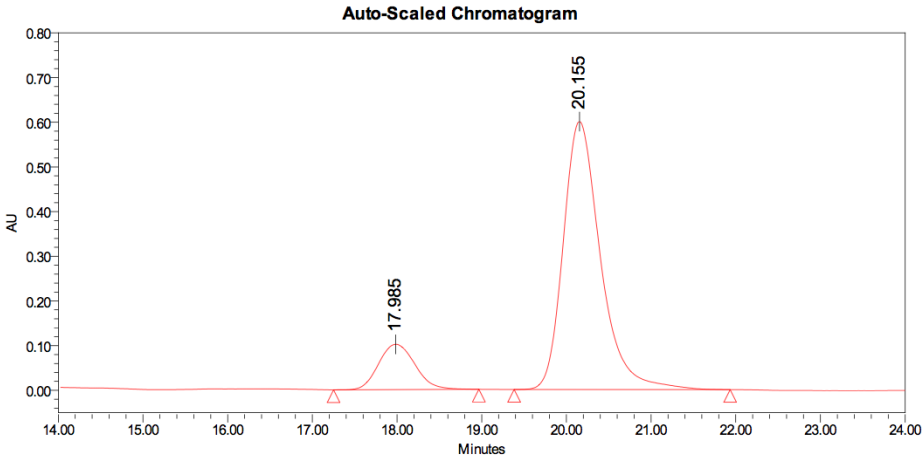
The reaction was carried out following *RP13* and using tetraMe-BITIOP as chiral, non-racemic ligand. Compound **173** was isolated in 35% yield, 51% *ee*.



Enantiomer	T_R	% Area
1	18.045	75.50
2	20.236	24.50

*5.2.4.7. Rhodium-catalyzed asymmetric synthesis of 1,1-diphenyl-3a,4-dihydro-1H-cyclopenta[c]furan-5(3H)-one with BITIANP (**173**)*

The reaction was carried out following *RP13* and using BITIANP as chiral, non-racemic ligand. Compound **173** was isolated in 36% yield, 72% *ee*.



Enantiomer	T_R	% Area
1	17.985	14.20
2	20.155	85.80

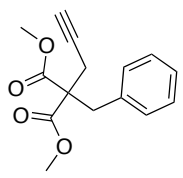
5.3. TRANSITION METAL-CATALYZED ELECTROPHILIC ACTIVATION OF ALKYNES

5.3.1.General Remarks

Reactions were carried out under argon in oven-dried glassware. THF was distilled over sodium/benzophenone. Toluene, CH_2Cl_2 and DCE were distilled from CaH_2. Different commercial sources of $[IrCp^*Cl_2]_2$ were purchased from Sigma-Aldrich and Strem Chemicals. Homemade $[IrCp^*Cl_2]_2$ was also used to promote cycloisomerizations.[45] Thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel. Merck Gerudan SI 60 P silica gel (35–70 mm) was used for column chromatography. The melting point reported was measured with a Reichert hot stage apparatus and is uncorrected. IR spectra were recorded with a Bruker Tensor 27 ATR diamant PIKE spectrometer. NMR spectra (^1H, ^{13}C, DEPT, [^1H,^1H] and [^1H,^{13}C] correlations) were recorded at room temperature on Bruker AV 300 and 400 AVANCE spectrometers. Chemical shifts are given in parts per million, referenced to the residual proton resonance of the solvent (δ = 7.26 ppm for $CDCl_3$) or to the residual carbon resonance of the solvent (δ = 77.16 ppm for $CDCl_3$) When possible, ^1H and ^{13}C signals were assigned mostly on the basis of DEPT and 2D NMR (COSY, HMBC) experiments. Stereochemistry of products was deduced from NOE measurements. The terms m, s, d, t, q represent multiplet, singlet, doublet, triplet, quadruplet, respectively and the term br means a broad signal. High resolution mass spectroscopy (ESI-HRMS) were performed by the Plateforme technique d'analyse et de spectroscopie (UMR 7201), Université Pierre et Marie Curie, Paris 6.

5.3.2 Preparation of dialkyl malonates

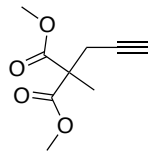
*5.3.2.1. Representative procedure (**RP14**). Synthesis of dimethyl 2-benzyl-2-(prop-2-ynyl)malonate (**264a**)*



Dimethyl 2-(prop-2-ynyl)malonate (0.45 mL, 2.9 mmol) was added to a suspension of NaH (0.14 g, 3.1 mmol) in THF (40 mL) at 0 °C, under an argon atmosphere and the solution was stirred for 15 minutes at room temperature. Benzyl bromide (0.6 g, 3.5 mmol) was added and stirring was kept on for an additional 3 h. After dilution with ether (30 mL), the mixture was washed with a saturated NH_4Cl solution (3 x 50 mL) and the aqueous phase was further extracted with ether (3 x 40 mL). The combined organic layers were dried over anhydrous $MgSO_4$, then

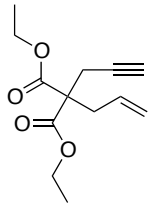
concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/pentane 5:95) affording the desired product as a white solid (89% yield). Mp: 55 °C. IR (neat): ν 3290, 3087,3031, 2852, 1745, 1332, 1118, 961 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.09 (m, 5H), 3.76 (s, 6H), 3.42 (s, 2H), 2.69 (d, *J* = 2.7 Hz, 2H), 2.16 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (2C), 135.6 (C), 129.9 (2CH), 128.6 (2CH), 127.4 (CH), 79.4 (C), 72.3 (CH), 58.4 (C), 52.9 ($2CH_3$), 37.6 (CH_2), 22.3 (CH_2). The spectral data for this compound correspond to previously reported data.[46]

*5.3.2.2. Synthesis of dimethyl 2-methyl-2-(prop-2-ynyl)malonate (**264b**)*



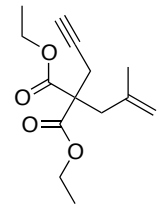
Compound **264b** was synthesized using *RP14* and was isolated (pentane/AcOEt 95:5, 95% yield) as a colorless oil. IR (neat): ν 3002, 2925, 1715, 1454, 1319, 1112 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H), 2.78 (d, *J* = 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (2C), 79.2 (C), 71.4 (CH), 53.3 (C), 52.9 ($2CH_3$), 26.0 (CH_2), 19.9 (CH_3). The spectral data for this compound correspond to previously reported data.[47]

*5.3.2.3. Synthesis of diethyl 2-allyl-2-(prop-2-ynyl)malonate (**264c**)*



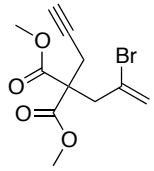
Compound **264c** was synthesized using *RP14* and was isolated (pentane/AcOEt 95:5, 97% yield) as a colorless oil. IR (neat): ν 2982, 2936, 2587, 1734, 1214, 1192, 926 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66 – 5.57 (m, 1H), 5.33 – 4.98 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 4H), 2.89 – 2.79 (m, 4H), 2.01 (t, *J* = 2.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (2C), 131.9 (CH), 119.9 (CH_2), 79.0 (C), 71.5 (CH), 61.7 ($2CH_2$), 56.7 (C), 36.5 (CH_2), 22.7 (CH_2), 14.2 ($2CH_3$). The spectral data for this compound correspond to previously reported data.[48]

*5.3.2.4. Synthesis of diethyl 2-(2-methylallyl)-2-(prop-2-ynyl)malonate (**264d**)*



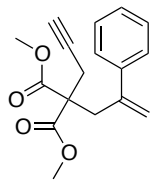
Compound **264d** was synthesized using *RP14* and was isolated (pentane/AcOEt 95:5, 86% yield) as a colorless oil. IR (neat): ν 3295, 3079, 3031, 2982, 2939, 1739, 1205, 1075, 646 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 – 4.72 (m, 2H), 4.36 – 4.06 (m, 4H), 3.02 – 2.72 (m, 4H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.65 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (2C), 140.1 (C), 116.4 (CH_2), 79.4 (C), 71.7 (CH), 61.8 ($2CH_2$), 56.4 (C), 39.5 (CH_2), 23.4 (CH_3), 22.7 (CH_2), 14.1 ($2CH_3$). The spectral data for this compound correspond to previously reported data.[49]

*5.3.2.5. Synthesis of dimethyl 2-(2-bromoallyl)-2-(prop-2-ynyl)malonate (**264e**)*



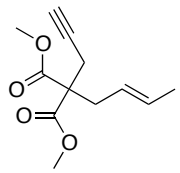
Compound **264e** was synthesized using *RP14* and was isolated (pentane/AcOEt 95:5, 53% yield) as a colorless oil. IR (neat): ν 3291, 2954, 1751, 1626, 1435, 1218, 903, 654 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 – 5.81 (m, 1H), 5.62 (d, *J* = 1.6 Hz, 1H), 3.76 (s, 6H), 3.30 (br s, 2H), 2.92 (d, *J* = 2.7 Hz, 2H), 2.04 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (2C), 126.2 (C), 123.0 (CH_2), 78.8 (C), 72.2 (CH), 56.1 (C), 53.2 ($2CH_3$), 43.0 (CH_2), 22.4 (CH_2). The spectral data for this compound correspond to previously reported data.[50]

*5.3.2.6. Synthesis of dimethyl 2-(2-phenylallyl)-2-(prop-2-ynyl)malonate (**264f**)*



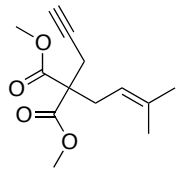
Compound **264f** was synthesized using *RP14* and was isolated (pentane/AcOEt 96:4, 70% yield) as a colorless oil. IR (neat): ν 3289, 2953, 1737, 1436, 1332, 1211, 912, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.13 (m, 5H), 5.28 – 5.26 (m, 2H), 3.40 (s, 6H), 3.31 (s, 2H), 2.74 (d, *J* = 2.7 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.07 (2C), 144.0 (C), 141.0 (C), 128.2 (2CH), 127.7 (CH), 127.1 (2CH), 119.1 (CH_2), 79.4 (C), 71.9 (CH), 56.6 (C), 52.57 ($2CH_3$), 37.0 (CH_2), 22.48 (CH_2). The spectral data for this compound correspond to previously reported data.[51]

*5.3.2.7. Synthesis of (E)-dimethyl 2-(but-2-enyl)-2-(prop-2-ynyl)malonate (**264g**)*



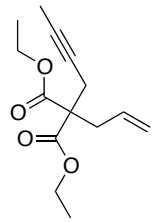
Compound **264g** was synthesized using *RP14* and was isolated (pentane/AcOEt 96:4, 88% yield) as a colorless oil. IR (neat): ν 3288, 2955, 1736, 1437, 1205, 972, 652 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 – 5.47 (m, 1H), 5.24 – 5.16 (m, 1H), 3.73 (s, 6H), 2.89 – 2.65 (m, 4H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.70 – 1.58 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5 (2C), 130.9 (CH), 124.0 (CH), 79.4 (C), 71.4 (CH), 57.1 (C), 52.8 ($2CH_3$), 35.5 (CH_2), 22.7 (CH_2), 18.2 (CH_3). The spectral data for this compound correspond to previously reported data.[52]

*5.3.2.8. Synthesis of dimethyl 2-(3-methylbut-2-enyl)-2-(prop-2-ynyl)malonate (**264h**)*



Compound **264h** was synthesized using *RP14* and was isolated (pentane/AcOEt 95:5, 90% yield) as a colorless oil. IR (neat): ν 3290, 2949, 1732, 1445, 1201, 900, 678 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.98 – 4.78 (m, 1H), 3.72 (s, 6H), 2.86 – 2.66 (m, 4H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.69 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (2C), 137.1 (C), 117.1 (CH), 79.4 (C), 71.3 (CH), 57.3 (C), 52.8 (CH_3), 30.9 (CH_2), 26.2 ($2CH_3$), 22.6 (CH_2), 18.0 (CH_3). The spectral data for this compound correspond to previously reported data.[53]

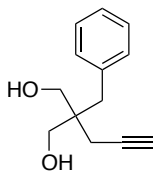
*5.3.2.9. Synthesis of diethyl 2-allyl-2-(but-2-ynyl)malonate (**264i**)*



Compound **264i** was synthesized using *RP14* and was isolated (pentane/AcOEt 95:5, 89% yield) as a colorless oil. IR (neat): ν 3646, 3472, 3083, 2982, 2929, 2233, 1739, 1639, 1465, 1441, 1325, 1292, 1218, 1136, 1096, 1036, 912, 855, 661, 574 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.63 (m, 1H), 5.15 (d, *J* = 17.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 4H), 2.78 (d, *J* = 7.5 Hz, 2H), 2.72 (q, *J* = 2.5 Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.9 (2C), 131.8 (CH), 119.3 (CH_2), 78.6 (C), 73.2 (C), 61.3 ($2CH_2$), 56.8 (C), 36.3 (CH_2), 22.7 (CH_2), 13.9 ($2CH_3$), 3.3 (CH_3). The spectral data for this compound correspond to previously reported data.[54]

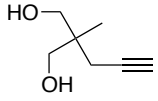
5.3.3. Preparation of bis-homopropargilic alcohols

*5.3.3.1. Representative procedure (**RP15**). Synthesis of 2-benzyl-2-(prop-2-ynyl)propane-1,3-diol (**265a**)*



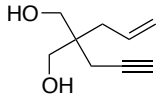
$LiAlH_4$ (1M in CH_2CL_2, 6 mL, 5.3 mmol) was added to compound **264a** (1.2 g, 2.7 mmol) in dry CH_2Cl_2 (15 mL), at 0 °C, under an argon atmosphere. The mixture was stirred for 1 h at room temperature and then poured into a saturated NH_4Cl solution (100 mL). The aqueous phase was extracted with ether (3 x 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, then concentrated under reduced pressure. The resulting crude product was purified by silica gel chromatography (AcOEt/pentane 4:6) affording the desired product as colorless oil (91% yield). IR (neat): ν 3307, 3085, 3028, 2115, 1428, 1337, 1120 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.16 (m, 5H), 3.62 (br, q, *J* = 10.9 Hz, 4H), 2.72 (s, 2H), 2.33 (br, s, 2H), 2.20 – 2.05 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0 (C), 130.6 (2CH), 128.4 (2CH), 126.6 (CH), 81.3 (C), 71.7 (CH), 67.2 ($2CH_2$), 43.1 (C), 37.0 (CH_2), 21.2 (CH_2). The spectral data for this compound correspond to previously reported data.[55]

*5.3.3.2. Synthesis of 2-methyl-2-(prop-2-ynyl)propane-1,3-diol, (**265b**)*



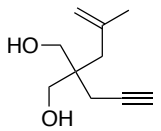
Compound **265b** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, quantitative yield) as a colorless oil. IR (neat): ν 3307, 2961, 1427, 1043, 716 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (br, 4H), 2.53 – 2.20 (m, 4H), 2.02 (t, *J* = 2.7 Hz, 1H), 0.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.4 (C), 70.8 (CH), 69.5 ($2CH_2$), 39.4 (C), 24.0 (CH_2), 18.9 (CH_3). The spectral data for this compound correspond to previously reported data.[56]

*5.3.3.3. Synthesis of 2-allyl-2-(prop-2-ynyl)propane-1,3-diol (**265c**)*



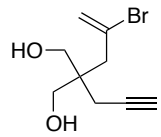
Compound **265c** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, quantitative yield) as a colorless oil. IR (neat): ν 3412, 3065, 3001, 2971, 1458, 1023, 973 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 – 5.67 (m, 1H), 5.26 – 5.02 (m, 2H), 3.61 (br, 4H), 2.93 (br, s, 2H), 2.25 (dd, *J* = 8.3, 2.7 Hz, 2H), 2.22 – 2.09 (m, 2H), 2.02 (dd, *J* = 3.5, 1.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.3 (CH), 118.8 (CH_2), 81.0 (C), 71.0 (CH), 67.2 ($2CH_2$), 42.1 (C), 36.1 (CH_2), 21.5 (CH_2). The spectral data for this compound correspond to previously reported data.[57]

*5.3.3.4. Synthesis of 2-(2-methylallyl)-2-(prop-2-ynyl)propane-1,3-diol (**265d**)*



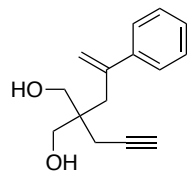
Compound **265d** was synthesized using *RP15* and was isolated (pentane/AcOEt 7:3, quantitative yield) as a colorless oil. IR (neat): ν 3302, 3025, 2966, 1429, 1041, 645 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.02 – 4.75 (m, 2H), 3.68 (s, 4H), 2.32 (d, *J* = 2.7 Hz, 2H), 2.26 (br, s, 2H), 2.15 (d, *J* = 0.6 Hz, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.83 (dd, *J* = 1.4, 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0 (C), 115.7 (CH_2), 81.3 (C), 71.3 (CH), 67.9 ($2CH_2$), 42.8 (C), 39.3 (CH_2), 25.2 (CH_3), 22.1 (CH_2). The spectral data for this compound correspond to previously reported data.[58]

*5.3.3.5. Synthesis of 2-(2-bromoallyl)-2-(prop-2-ynyl)propane-1,3-diol (**265e**)*



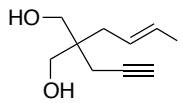
Compound **265e** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, 95% yield) as a colorless oil. IR (neat): ν 3310, 2972, 2116, 2056, 1623, 1416, 1049, 913, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (d, *J* = 0.6 Hz, 1H), 5.64 (d, *J* = 1.5 Hz, 1H), 3.87 – 3.59 (m, 4H), 2.71 (s, 2H), 2.33 (d, *J* = 2.7 Hz, 2H), 2.18 (t, *J* = 5.7 Hz, 2H), 2.07 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.7 (C), 122.2 (CH_2), 80.6 (C), 71.7 (CH), 66.5 ($2CH_2$), 43.3 (C), 42.1 (CH_2), 21.7 (CH_2). HRMS calcd. for $C_9H_{14}O_2{}^{79}Br$ ([M + H]$^+$): 233.0172, found 233.0173.

*5.3.3.6. Synthesis of (E)-2-(2-phenylallyl)-2-(prop-2-ynyl)propane-1,3-diol (**265f**)*



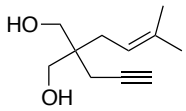
Compound **265f** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, quantitative yield) as a colorless oil. IR (neat): ν 3309, 3058, 3028, 2972, 2116, 2056, 1623, 1428, 1047, 712 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 – 7.09 (m, 5H), 5.32 (d, *J* = 21.0 Hz, 2H), 3.53 (br, s, 4H), 2.71 (s, 2H), 2.22 (d, *J* = 2.0 Hz, 2H), 2.17 – 2.05 (br, m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.30 (C), 142.8 (C), 128.7 (2CH), 127.9 (CH), 126.4 (2CH), 118.2 (CH_2), 81.3 (C), 71.3 (CH), 67.3 ($2CH_2$), 43.2 (C), 36.7 (CH_2), 22.0 (CH_2). The spectral data for this compound correspond to previously reported data.[59]

*5.3.3.7. Synthesis of 2-(but-2-enyl)-2-(prop-2-ynyl)propane-1,3-diol (**265g**)*



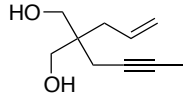
Compound **265g** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, 89% yield) as a colorless oil. IR (neat): ν 3312, 3024, 2883, 1438, 1039, 658 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 – 5.50 (m, 1H), 5.53 – 5.35 (m, 1H), 3.73 – 3.56 (br, m, 4H), 2.36 – 2.23 (br m, 4H), 2.10 – 2.03 (m, 2H), 2.04 – 1.99 (m, 1H), 1.71 – 1.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.4 (CH), 125.6 (CH), 81.3 (C), 70.9 (CH), 67.8 ($2CH_2$), 42.3 (C), 35.0 (CH_2), 21.6 (CH_2), 18.2 (CH_3). The spectral data for this compound correspond to previously reported. [60]

*5.3.3.8. Synthesis of 2-(3-methylbut-2-enyl)-2-(prop-2-ynyl)propane-1,3-diol (**265h**).*



Compound **265h** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, 87% yield) as a colorless oil. IR (neat): ν 3321, 2967, 1441, 1329, 1021, 623 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (br, t, J = 1.3 Hz, 1H), 3.73 – 3.58 (br, m, 4H), 2.39 (br, s, 2H), 2.26 (d, J = 2.7 Hz, 2H), 2.14 – 1.96 (m, 4H), 1.72 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4 (C), 118.6 (CH), 81.5 (C), 70.8 (CH), 67.9 ($2CH_2$), 42.9 (C), 30.3 (CH_2), 26.2 (CH_3), 21.6 (CH_2), 18.0 (CH_3). The spectral data for this compound correspond to previously reported.[55]

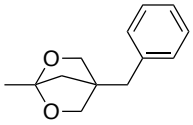
*5.3.3.9. Synthesis of 2-allyl-2-(but-2-ynyl)propane-1,3-diol (**265i**)*



Compound **265i** was synthesized using *RP15* and was isolated (pentane/AcOEt 6:4, 91% yield) as a colorless oil. IR (neat): ν 3401, 3076, 3004, 2969, 1461, 1041, 952 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 – 5.75 (m, 1H), 5.19 – 5.05 (m, 2H), 3.63 (br, qd, J = 11.0, 3.9 Hz, 4H), 2.26 (br, s, 2H), 2.21 – 2.16 (m, 2H), 2.16 – 2.11 (m, 2H), 1.79 (t, J = 2.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.8 (CH), 118.5 (CH_2), 78.4 (C), 75.4 (C), 67.8 ($2CH_2$), 42.4 (C), 36.6 (CH_2), 22.2 (CH_2), 3.6 (CH_3). The spectral data for this compound correspond to previously reported data.[61]

5.3.4. $[IrCp^*Cl_2]_2$-catalyzed cycloisomerization of bis-homopropargylic alcohols

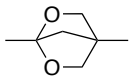
*5.3.4.1. <u>Representative procedure (**RP16**).</u> Synthesis of 4-benzyl-1-methyl-2,6-dioxabicyclo[2.2.1]heptane (**266a**)*



$[IrCp^*Cl_2]_2$ (0.002 mmol) was dissolved in dry DCE (1 mL) under an argon atmosphere. A solution of bis-homopropargylic alcohol **265a** (0.2 mmol) in dry DCE (1 mL) was added. The mixture was stirred at room temperature for 30 minutes then filtered through a short pad of celite. Removal of the solvent under reduced pressure afforded the product as colorless oil (quantitative yield). IR (neat): ν 3062, 1603, 1443, 1363, 1213, 1111, 796 cm^{-1}. ^{1}H NMR (300

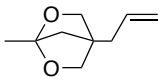
MHz, $CDCl_3$): δ 7.42 – 7.16 (m, 3H), 7.13 – 6.99 (m, 2H), 3.72 (br, m, 4H), 2.86 (s, 2H), 1.68 (s, 2H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ137.5 (C), 129.3 (2CH), 128.6 (2CH), 126.8 (CH), 108.5 (C), 76.4 ($2CH_2$), 50.0 (C), 44.7 (CH_2), 35.3 (CH_2), 18.1 (CH_3). The spectral data for this compound correspond to previously reported.[55]

*5.3.4.2. Synthesis of 1,4-dimethyl-2,6-dioxabicyclo[2.2.1]heptane (**266b**)*



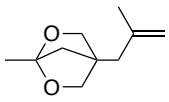
Compound **266b** was synthesized using *RP16* and was isolated (82% yield) as a colorless oil. IR (neat): ν 2925, 2852, 951, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 – 3.65 (m, 4H), 1.70 (s, 2H), 1.55 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.1 (C), 78.0 ($2CH_2$), 46.5 (CH_2), 45.3 (C), 18.1 (CH_3), 12.9 (CH_3). $C_7H_{12}O_2Na$ ([M + Na]$^+$): 151.0729, found 151.0727.

*5.3.4.3. Synthesis of 4-allyl-1-methyl-2,6-dioxabicyclo[2.2.1]heptane (**266c**)*



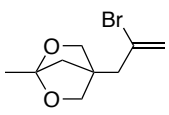
Compound **266c** was synthesized using *RP16* and was isolated (quantitative yield) as a colorless oil. IR (neat): ν 2923, 2856, 2361, 2338, 1017, 829 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 – 5.67 (m, 1H), 5.10 – 2.04 (m, 2H), 3.81 – 3.71 (m, 4H), 2.33 (d, J = 7.4 Hz, 2H), 1.69 (s, 2H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5 (CH), 118.0 (CH_2), 108.6 (C), 76.4 ($2CH_2$), 48.9 (C), 44.3 (CH_2), 33.0 (CH_2), 18.1 (CH_3). The spectral data for this compound correspond to previously reported.[55]

*5.3.4.4. Synthesis of 1-methyl-4-(2-methylallyl)-2,6-dioxabicyclo[2.2.1]heptane (**266d**)*



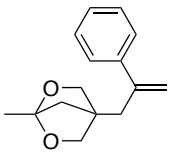
Compound **266d** was synthesized using *RP16* and was isolated (94% yield) as a colorless oil. IR (neat): ν 2925, 2872, 1649, 1446, 1396, 1320, 1159, 1013, 827 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.89 – 4.79 (m, 1H), 4.68 (d, J = 0.9 Hz, 1H), 3.77 (dt, J = 8.7 Hz, 5.7 Hz, 4H), 2.31 (s, 2H), 1.73 (s, 3H),), 1.73 (s, 2H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7 (C), 114.2 (CH_2), 108.5 (C), 76.7 ($2CH_2$), 48.7 (C), 45.5 (CH_2), 37.1 (CH_2), 24.1 (CH_3), 18.1 (CH_3). HRMS calcd. for $C_{10}H_{16}O_2Na$ ([M + Na]$^+$): 191.1043, found 191.1045.

*5.3.4.5. Synthesis of 4-(2-bromoallyl)-1-methyl-2,6-dioxabicyclo[2.2.1]heptane (**266e**)*



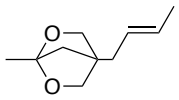
Compound **266e** was synthesized using *RP16* and was isolated (quantitative yield) as a colorless oil. IR (neat): ν 2925, 2872, 1649, 1446, 1396, 1320, 1159, 1013, 827 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.66 – 5.56 (m, 1H), 5.51 (d, J = 1.7 Hz, 1H), 3.90 (t, J = 4.5 Hz, 2H), 3.83 (t, J = 4.5 Hz, 2H), 2.83 (s, 2H), 1.84 (s, 2H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.1 (C), 120.3 (CH_2), 108.6 (C), 76.2 ($2CH_2$), 48.3 (C), 45.3 (CH_2), 41.3 (CH_2), 18.0 (CH_3). HRMS calcd. for $C_9H_{13}O_2{}^{79}BrNa$ ([M + Na]$^+$): 254.9991, found 254.9992.

*5.3.4.6. Synthesis of 1-methyl-4-(2-phenylallyl)-2,6-dioxabicyclo[2.2.1]heptane (**266f**)*



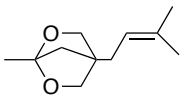
Compound **266f** was synthesized using *RP16* and was isolated (quantitative yield) as a colorless oil. IR (neat): ν 3061, 3015, 2371, 2329, 1469, 1382, 1319, 1206, 1010, 623 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37 – 7.29 (br m, 6H), 5.28 (s, 1H), 5.07 (s, 1H), 3.67 - 3.54 (br m, 4H), 2.83 (s, 2H), 1.59 (s, *2*H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5 (C), 141.5 (C), 128.6 (2CH), 128.0 (CH), 126.3 (2CH), 115.9 (CH_2), 108.5 (C), 76.6 ($2CH_2$), 49.0 (C), 45.2 (CH_2), 35.0 (CH_2), 18.0 (CH_3). The spectral data for this compound correspond to previously reported.[59]

5.3.4.7. Synthesis of **(***E)-4-(but-2-enyl)-1-methyl-2,6-dioxabicyclo[2.2.1]heptanes (**266g**)*



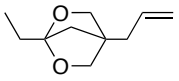
Compound **266g** was synthesized using *RP16* and was isolated (92% yield) as colorless oil. IR (neat): ν 3081, 2975, 1465, 1389, 1321, 1145, 1000, 944, 878 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 – 5.41 (m, 1H), 5.42 – 5.25 (m, 1H), 3.75 (m, 4H), 2.24 (d, *J*=7.2 Hz, 2H), 1.75 – 1.55 (m, 5H), 1.59 – 1.47 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5 (CH), 125.9 (CH), 108.6 (C), 76.5 ($2CH_2$), 49.3 (C), 44.3 (CH_2), 31.6 (CH_2), 18.1 (CH_3), 17.9 (CH_3). The spectral data for this compound correspond to previously reported.[59]

*5.3.4.8. Synthesis of 1-methyl-4-(3-methylbut-2-enyl)-2,6-dioxabicyclo[2.2.1]heptane (**266h**)*



Compound **266h** was synthesized using *RP16* and was isolated (86% yield) as colorless oil. IR (neat): ν 3083, 2969, 1453, 1374, 1311, 1125, 1023, 956, 883 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.06 – 5.12 (m, 1H), 3.70 – 3.76 (m, 4H), 2.23 (d, *J* = 7.6 Hz, 2H), 1.69 (s, 3H), 1.67 (s, 2H), 1.58 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.4 (C), 118.9 (CH), 108.4 (C), 76.3 ($2CH_2$), 49.6 (C), 44.2 (CH_2), 26.5 (CH_2), 25.7 (CH_3), 17.9 (CH_3), 17.6 (CH_3). The spectral data for this compound correspond to previously reported.[59]

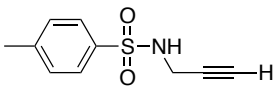
*5.3.4.9. Synthesis of 4-allyl-1-ethyl-2,6-dioxabicyclo[2.2.1]heptane (**266i**)*



Compound **266i** was synthesized using *RP16* and was isolated (67% yield) as a colorless oil. IR (neat): ν 3078, 2979, 1467, 1390, 1326, 1159, 1008, 939, 850 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 – 5.70 (m, 1H), 5.11 – 5.04 (m, 2H), 3.81 – 3.71 (m, 4H), 2.33 (d, *J* = 7.4 Hz, 2H), 1.85 (q, *J* = 7.6 Hz, 2H), 1.64 (d, *J* = 5.1 Hz, 2H), 1.01 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.5 (CH), 118.0 (CH_2), 111.7 (C), 76.3 ($2CH_2$), 48.5 (C), 42.1 (CH_2), 33.0 (CH_2), 25.2 (CH_2), 9.2 (CH_3). HRMS calcd. for $C_{10}H_{17}O_2$ ([M + H]$^+$): 169.1223, found 169.1221.

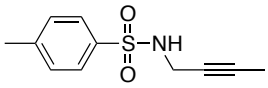
5.3.5. Preparation of *N*-(alk-2-ynyl)-*p*-toluenesulfonamides

*5.3.5.1. Representative procedure (**RP17**). Synthesis of N-(prop-2-ynyl)-4-methyl benzenesulfonamide (**267**)*



N-Boc *p*-toluenesulfonamide[62] (2.5 g, 9.2 mmol) was added to a suspension of potassium carbonate (2.07 g, 15 mmol) in DMF (10 mL) and the solution was stirred for 1 h at room temperature. Propargyl bromide (0.9 mL, 9.2 mmol) was added and stirring was kept on for an additional 2h. After dilution with ether (60 mL), the solution was washed with water (3 x 30 mL) and the aqueous phase was further extracted with ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, then concentrated *in vacuo*. The resulting crude product was taken up with CH_2Cl_2 (2 mL) and trifluoroacetic acid (3 mL) and the mixture was stirred overnight. After removal of the solvent under reduced pressure, the reaction residue was purified by silica gel chromatography (AcOEt/pentane 3:7). Compound **267** was isolated as a white solid in 61% yield. IR (neat): ν 3281, 3242, 2862, 1597, 1429, 1349, 1148, 1068, 809, 663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 16.1 Hz, 2H), 7.30 (d, *J* = 16.1 Hz, 2H), 4.78 (br, s, 1H), 3.82 (d, *J* = 2.5 Hz, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0 (C), 136.7 (C), 129.8 (2CH), 127.5 (2CH), 78.1 (C), 73.1 (CH), 33.0 (CH_2), 21.7 (CH_3). The spectral data for this compound correspond to previously reported.[63]

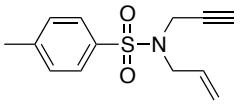
*5.3.5.2. Synthesis of N-(but-2-ynyl)-4-methylbenzenesulfonamide (**268**).*



Compound **268** was synthesized using *RP17* and isolated (pentane/AcOEt 7:3, 97% yield) as a white solid. IR (neat): ν 3273, 2920, 2855, 2329, 1494, 1379, 1163, 1010, 811, 654 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.93 (s, 1H), 3.73 (s, 2H), 2.40 (s, 3H), 1.56 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (100: MHz, $CDCl_3$): δ 143.6 (C), 136.9 (C), 129.6 (2CH), 127.5 (2CH), 81.1 (C), 73.3 (CH), 33.4 (CH_2), 21.5 (CH_3), 3.3 (CH_3). The spectral data for this compound correspond to previously reported.[64]

5.3.6. Preparation of nitrogen-tethered 1,6-enynes

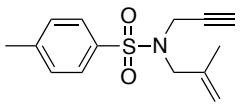
*5.3.6.1. Representative procedure (**RP18**). Synthesis of N-allyl-N-(prop-2-ynyl)-4-methylbenzenesulfonamide (**269a**)*



DIAD (diisopropyl azodicarboxylate) (1.06 g, 5.3 mmol) was added to a solution of allylic alcohol (0.36 mL, 5.3 mmol), compound **267** (1.1 g, 5.3 mmol), and PPh_3 (1.38 g, 5.3 mmol) in THF (50 mL), under an argon atmosphere. The mixture was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the crude product was purified by silica gel

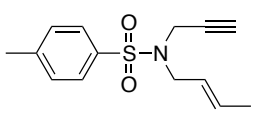
chromatography (AcOEt/pentane 1:9). Compound **269a** was isolated as a white solid in 75% yield. IR (neat): ν 3275, 2982, 2922, 1644, 1329, 1150, 1092, 930, 757, 661 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.15 (m, 2H), 5.73 – 5.60 (m, 1H), 5.31 – 5.20 (m, 2H), 4.09 (d, *J* = 2.5 Hz, 2H), 3.83 (d, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.00 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (C), 136.2 (C), 132.0 (CH), 129.6 (2CH), 127.9 (2CH), 120.1 (CH_2), 76.6 (C), 73.8 (CH), 49.1 (CH_2), 35.9 (CH_2), 21.7 (CH_3). The spectral data for this compound correspond to previously reported.[65]

*5.3.6.2. Synthesis of N-(2-methylallyl)-N-(prop-2-ynyl)-4-methylbenzenesulfonamide (**269b**).*



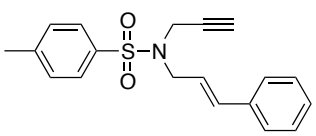
Compound **269b** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 81% yield) as a white solid. IR (neat): ν 3075, 2919, 1656, 1442, 1369, 1168, 899, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.65 (m, 2H), 7.28 (dd, *J* = 11.8, 3.7 Hz, 2H), 4.97 (s, 2H), 4.05 (d, *J* = 2.4 Hz, 2H), 3.73 (s, 2H), 2.42 (s, 3H), 1.96 (t, *J* = 2.4 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6 (C), 139.3 (C), 136.2 (C), 129.6 (2CH), 127.9 (2CH), 115.7 (CH_2), 76.5(C), 73.9 (CH), 52.5 (CH_2), 35.58 (CH_2), 21.7 (CH_3), 19.8 (CH_3). The spectral data for this compound correspond to previously reported.[66]

*5.3.6.3. Synthesis of N-(but-2-enyl)-N-(prop-2-ynyl) -4-methylbenzenesulfonamide (**269c**)*



Compound **269c** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 74% yield) as a white solid. IR (neat): ν 3075, 2919, 1672, 1413, 1159, 1091, 890, 658 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.76 – 5.61 (m, 1H), 5.43 – 5.27 (m, 1H), 4.06 (d, *J* = 2.2 Hz, 2H), 3.74 (d, *J* = 6.8 Hz, 2H), 2.41 (s, 3H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.68 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5 (C), 136.9 (C), 131.7 (CH), 129.5 (2CH), 127.9 (2CH), 124.6 (CH), 76.5(C), 73.6 (CH), 48.4 (CH_2), 35.6 (CH_2), 21.6 (CH_3), 17.8 (CH_3). The spectral data for this compound correspond to previously reported.[67]

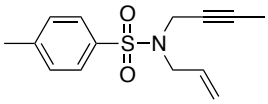
*5.3.6.4. Synthesis of (E)-N-cinnamyl-N-(prop-2-ynyl)-4-methylbenzenesulfonamide (**269d**)*



Compound **269d** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 88% yield) as a white solid. IR (neat): ν 3075, 2919, 1672, 1413, 1159, 1091, 890, 658 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.17 (m, 7H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.08 (dt, *J* = 15.8, 6.8Hz, 1H), 4.13 (d, *J* = 2.4 Hz, 2H), 4.00 (dd, *J* = 6.8, 1.0 Hz, 2H), 2.44 (s, 3H), 2.05 (t, *J* = 2.4, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 136.3 (C), 135.1 (C and CH), 129.7 (2CH), 128.8 (2CH), 128.2 (CH), 127.9 (2CH), 126.7 (2CH), 123.1 (CH), 76.7

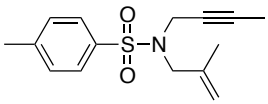
(C), 73.9 (CH), 48.7 (CH_2), 36.0 (CH_2), 21.7 (CH_3). The spectral data for this compound correspond to previously reported.[68]

*5.3.6.5. Synthesis of N-allyl-N-(but-2-ynyl)-4-methylbenzenesulfonamide (**269e**)*



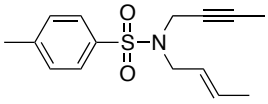
Compound **269e** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 79% yield) as a white solid. IR (neat): ν 3071, 2917, 1672, 1410, 1165, 1111, 883, 650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.82 – 5.61 (m, 1H), 5.34 – 5.15 (m, 2H), 4.01 (d, *J* = 2.4 Hz, 2H), 3.79 (d, *J* = 6.4 Hz, 2H), 2.42 (s, 3H), 1.54 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (C), 136.4 (C), 132.4 (CH), 129.4 (2CH), 128.0 (2CH), 119.6 (CH_2), 81.6 (C), 71.8 (C), 49.1 (CH_2), 36.5 (CH_2), 21.6 (CH_3), 3.3 (CH_3). The spectral data for this compound correspond to previously reported.[65]

*5.3.6.6. Synthesis of N-(but-2-ynyl)-N-(2-methylallyl)-4-methylbenzenesulfonamide (**269f**)*



Compound **269f** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 60% yield) as a white solid. IR (neat): ν 2919, 1598, 1439, 1351, 1159, 1096, 904, 708, 655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84 – 7.62 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.94 (s, 2H), 3.97 (d, *J* = 2.2 Hz, 2H), 3.69 (s, 2H), 2.42 (s, 3H), 1.75 (d, *J* = 0.9 Hz, 3H), 1.50 (t, *J* = 2.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3 (C), 139.6 (C), 136.4 (C), 129.3 (2CH), 128.1 (2CH), 115.2 (CH_2), 81.6 (C), 71.7 (C), 52.5 (CH_2), 36.2 (CH_2), 21.6 (CH_3), 19.8 (CH_3), 3.3 (CH_3). The spectral data for this compound correspond to previously reported.[69]

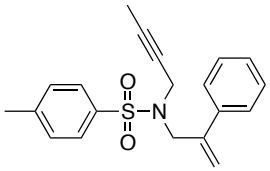
*5.3.6.7. Synthesis of (E)-N-(but-2-enyl)-N-(but-2-ynyl)-4-methylbenzenesulfonamide (**269g**)*



Compound **269g** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 73% yield) as a white solid. IR (neat): ν 2919, 2856, 1672, 1440, 1364, 1171, 1091, 908, 731, 651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.68 (m, 2H), 7.35 – 7.25 (m, 2H), 5.92 – 5.49 (m, 1H), 5.43 – 5.25 (m, 1H), 4.08 – 3.94 (m, 2H), 3.73 (dd, *J* = 3.5, 2.1 Hz, 2H), 2.43 (d, *J* = 3.9 Hz, 3H), 1.75 – 1.61 (m, 3H), 1.55 (dt, *J* = 4.6, 2.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2 (C), 136.5 (C), 131.1 (CH), 129.3 (2CH), 128.0 (2CH), 124.98 (CH), 81.5 (C), 71.9 (C), 48.4 (CH_2), 36.1 (CH_2), 21.6 (CH_3), 17.8 (CH_3), 3.3 (CH_3). The spectral data for this compound correspond to previously reported.[70]

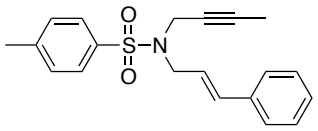
*5.3.6.8. Synthesis of N-(but-2-ynyl)-N-(2-phenylallyl)-4-methylbenzenesulfonamide (**269h**)*

Compound **269h** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 65% yield) as a white solid. IR (neat): ν 3057, 2919, 1629, 1465, 1367, 1306, 1175, 1092, 899, 708, 659



cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 – 7.67 (m, 2H), 7.62 – 7.46 (m, 2H), 7.44 – 7.21 (m, 5H), 5.56 (s, 1H), 5.33 (d, *J* = 1.1 Hz, 1H), 4.23 (s, 2H), 3.93 (q, *J* = 2.3 Hz, 2H), 2.44 (s, 3H), 1.51 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (C), 141.8 (C), 138.1 (C), 136.0 (C), 129.3 (2CH), 128.5 (2CH), 128.2 (2CH), 128.1 (CH), 126.6 (2CH), 117.0 (CH_2), 82.0 (C), 71.5 (C), 50.4 (CH_2), 36.2 (CH_2), 21.6 (CH_3), 3.3 (CH_3). The spectral data for this compound correspond to previously reported.[71]

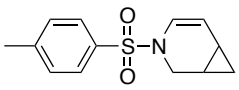
*5.3.6.9. Synthesis of N-(but-2-ynyl)-(E)-N-cinnamyl-4-methylbenzenesulfonamide (**269i**)*



Compound **269i** was synthesized using *RP18* and isolated (pentane/AcOEt 9:1, 82% yield) as a white solid. IR (neat): ν 3027, 2919, 2854, 1597, 1494, 1356, 1141, 901, 752, 649 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.17 (m, 7H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.09 (dt, *J* = 15.8 Hz, 6.8 Hz, 1H), 4.22 – 3.83 (m, 4H), 2.43 (s, 3H), 1.57 (t, *J* = 2.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4 (C), 136.4 (C), 134.5 (CH), 129.4 (2CH), 128.7 (2CH), 128.0 (CH), 127.9 (2CH), 126.6 (2CH), 123.5 (CH), 81.7 (C), 71.9 (C), 48.7 (CH_2), 36.8 (CH_2), 21.9 (CH_3), 3.4 (CH_3). The spectral data for this compound correspond to previously reported.[68]

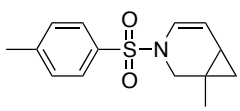
5.3.7. [IrCp*Cl$_2$]$_2$-catalyzed cycloisomerization of nitrogen-tethered 1,6-enynes

*5.3.7.1. Representative procedure (**RP19**). Synthesis of 3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270a**).*



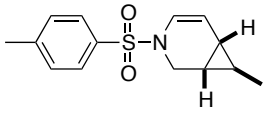
[IrCp*Cl_2]$_2$ (0.01 mmol) was dissolved in dry DCE (1 mL) at room temperature under an argon atmosphere. A solution of compound **269a** (0.2 mmol) in dry DCE (1 mL) was added. The mixture was stirred at reflux for 3 hours. After cooling to room temperature, the solution was filtered through a short pad of silica gel. The solvent was removed *in vacuo* and the residue was purified by flash chromatography over silica gel (AcOEt/pentane 5:95) affording product **270a** as a white solid (55% yield). IR (neat): ν 2924, 2855, 1642, 1598, 1348, 1151, 958, 708, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.33 (d, *J* = 8.1, Hz 1H), 5.40 (dd, *J* = 8.0, 5.4 Hz, 1H), 3.87 (d, *J* = 11.5 Hz, 1H), 3.05 (dd, *J* = 11.6, 2.9, 1H), 2.42 (s, 3H), 1.57 – 1.45 (m, 2H), 1.12 (td, *J* = 8.4, 4.3 Hz, 1H), 0.79 (ddd, *J* = 8.3, 7.6, 4.6 Hz, 1H), 0.34 (dd, *J* = 9.8, 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 135.1 (C), 129.8 (2CH), 127.2 (2CH), 121.3 (CH), 112.2 (CH), 41.0 (CH_2), 21.7 (CH_3), 18.6 (CH), 13.6 (CH_2), 7.2 (CH). The spectral data for this compound correspond to previously reported.[72]

*5.3.7.2. Synthesis of 1-methyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270b**)*



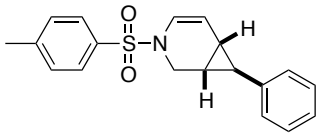
Compound **270b** was synthesized using *RP19* and isolated (pentane/AcOEt 97:3, 82% yield) as white solid. IR (neat): ν 2922, 2868, 1642, 1597, 1332, 1161, 1018, 734, 646 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.28 (d, *J* = 7.9 Hz, 1H), 5.39 (dd, *J* = 7.9, 5.6 Hz, 1H), 3.83 (d, *J* = 11.4 Hz, 1H), 2.72 (d, *J* = 11.3 Hz, 1H), 2.42 (s, 3H), 1.11 (s, 3H), 0.97 – 0.85 (m, 1H), 0.66 – 0.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 135.2 (C), 129.9 (2CH), 127.1 (2CH), 120.4 (CH), 112.8 (CH), 46.10 (CH_2), 25.9 (C), 22.1 (CH), 21.7 (CH_3), 20.4 (CH_2), 16.0 (CH_3). The spectral data for this compound correspond to previously reported.[72]

5.3.7.3. Synthesis of (1R,6S*,7S*)-7-methyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270c**)*



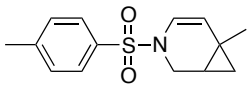
Compound **270c** was synthesized using *RP19* and isolated (pentane/AcOEt 98:2, 61% yield) as white solid. IR (neat): ν 2952, 2925, 2897, 1642, 1596, 1364, 1118, 969, 716, 686 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.28 (d, *J* = 8.1 Hz, 1H), 5.40 (dd, *J* = 8.1, 5.4 Hz, 1H), 3.88 (d, *J* = 11.5 Hz, 1H), 2.95 (dd, *J* = 11.5, 3.1 Hz, 1H), 2.42 (s, 3H), 1.33 – 1.13 (m, 1H), 0.96 (d, *J* = 6.1 Hz, 3H), 0.91 – 0.77 (m, 1H), 0.79 – 0.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 135.0 (C), 129.7 (2CH), 127.2 (2CH), 120.8 (CH), 112.0 (CH), 40.8 (CH_2), 26.5 (CH), 21.7 (CH), 21.6 (CH), 17.5 (CH_3), 15.6 (CH_3). The spectral data for this compound correspond to previously reported.[73]

5.3.7.4. Synthesis of (1R,6R*,7R*)-7-phenyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270d**)*



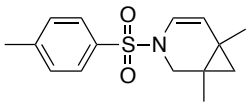
Compound **270d** using *RP19* and isolated (pentane/AcOEt 96:4, 60% yield) as white solid. IR (neat): ν 3030, 2923, 1638, 1600, 1348, 1166, 916, 685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.22 (dd, *J* = 10.2 Hz, 4.6 Hz, 2H), 7.18 – 7.11 (m, 1H), 6.88 – 6.74 (m, 2H), 6.43 (d, *J* = 8.0 Hz, 1H), 5.51 (dd, *J* = 8.0, 5.4 Hz, 1H), 4.03 (d, *J* = 12.0 Hz, 1H), 3.16 (dd, *J* = 12.1, 2.9 Hz, 1H), 2.47 (s, 3H), 1.90 (dd, *J* = 7.3 Hz, 3.6 Hz, 1H), 1.65 – 1.60 (m, 1H), 1.47 (dd, *J* = 6.8 Hz, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9 (C), 140.6 (C), 135.0 (C), 130.0 (2CH), 128.5 (2CH), 127.3 (2CH), 126.1 (CH), 125.4 (2CH), 121.6 (CH), 111.3 (CH), 40.3 (CH_2), 31.3 (CH), 29.1 (CH), 21.7 (CH_3), 19.5 (CH). The spectral data for this compound correspond to previously reported.[74]

*5.3.7.5. Synthesis of 6-methyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270e**)*



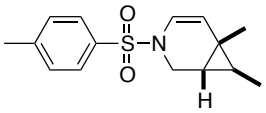
Compound **270e** was synthesized using *RP19* and isolated (pentane/AcOEt 97:3, 35% yield) as white solid. IR (neat): ν 2925, 2871, 1645, 1597, 1378, 1166, 778, 710 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.29 (d, *J* = 8.1 Hz, 1H), 5.22 (d, *J* = 8.1 Hz, 1H), 3.83 (d, *J* = 11.4 Hz, 1H), 3.04 (dd, *J* = 11.5, 2.7 Hz, 1H), 2.42 (s, 3H), 1.25 (br 1H), 1.09 (s, 3H), 0.57 (dd, *J* = 8.3, 4.4 Hz, 1H), 0.45 (t, *J* = 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 135.1 (C), 129.8 (2CH), 127.2 (2CH), 120.4 (CH), 116.7 (CH), 41.1 (CH_2), 25.8 (CH_3), 23.3 (CH), 21.7 (CH_3), 21.0 (CH_2), 12.8 (C). The spectral data for this compound correspond to previously reported.[72]

*5.3.7.6. Synthesis of 1,6-dimethyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270f**)*

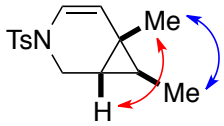


Compound **270f** was synthesized using *RP19* and isolated (pentane/AcOEt 98:2, 84% yield) as white solid. IR (neat): ν 2987, 2924, 2873, 1645, 1598, 1348, 1169, 1090, 988, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.25 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.17 (d, *J* = 8.0 Hz, 1H), 3.77 (d, *J* = 11.3 Hz, 1H), 2.67 (d, *J* = 11.3 Hz, 1H), 2.42 (s, 3H), 1.11 (d, *J* = 1.0 Hz, 6H), 0.72 (d, *J* = 4.3 Hz, 1H), 0.32 (dd, *J* = 4.3, 0.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 135.2 (C), 129.7 (2CH), 127.2 (2CH), 120.2 (CH), 118.3 (CH), 46.7 (CH_2), 29.5 (C), 26.4 (CH_2), 21.7 (CH_3), 18.3 (CH_3), 17.7 (C), 17.6 (CH_3). The spectral data for this compound correspond to previously reported.[72]

5.3.7.7. Synthesis of (1R,6S*,7R*)-6,7-dimethyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270g**)*

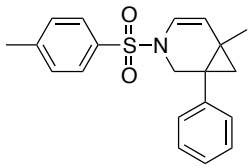


Compound **270g** was synthesized using *RP19* and isolated (pentane/AcOEt 97:3, 64% yield) as white solid. Mp 68-69 °C. IR (neat): ν 2924, 2870, 1644, 1597, 1345, 1354, 1089, 928, 710, 656 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.26 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.17 (d, *J* = 8.0 Hz, 1H), 3.87 (d, *J* = 11.3 Hz, 1H), 2.92 (dd, *J* = 11.3, 2.7 Hz, 1H), 2.41 (s, 3H), 1.04, (s, 3H), 0.93 (d, *J* = 1.2 Hz, 3H), 0.88 (br m, 1H), 0.68 – 0.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7 (C), 135.1 (C), 129.9 (2CH), 127.1 (2CH), 119.8 (CH), 118.3 (CH), 40.5 (CH_2), 32.5 (CH), 25.2 (CH), 21.7 (CH_3), 17.3 (CH_3), 16.4 (C), 13.1 (CH_3). HRMS calcd. for $C_{15}H_{19}O_2NNaS$ ([M + Na]$^+$): 300.1029, found 300.1026.



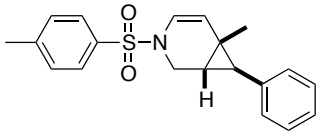
*NOE Correlations for compound **270g***

*5.3.7.8. Synthesis of 6-methyl-1-phenyl-3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270h**)*



Compound **270h** was synthesized using *RP19* and isolated (pentane/AcOEt 95:4, 80% yield) as white solid. IR (neat): ν 3059, 2924, 2869, 1644, 1597, 1350, 981, 671 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.19 (m, 7H), 6.38 (dd, *J* = 8.0, 0.6 Hz, 1H), 5.36 (d, *J* = 8.0 Hz, 1H), 3.96 (d, *J* = 11.5 Hz, 1H), 2.99 (d, *J* = 11.5 Hz, 1H), 2.43 (s, 3H), 1.21 (d, *J* = 4.6 Hz, 1H), 0.97 (dd, *J* = 4.6, 0.9 Hz, 1H), 0.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C), 139.1 (C), 135.1 (C), 129.9 (4 CH), 128.63 (2CH), 127.3 (CH), 127.2 (2CH), 121.0 (CH), 118.2 (CH), 48.2 (CH_2), 39.8 (C), 24.3 (CH_2), 21.7 (CH_3), 21.0 (CH_3), 18.9 (C). The spectral data for this compound correspond to previously reported.[75]

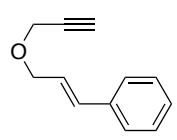
5.3.7.9. Synthesis of (1S,6R*,7R*)-6-methyl-7-phenyl- 3-(p-tosyl)-3-azabicyclo[4.1.0]hept-4-ene (**270i**)*



Compound **270i** was synthesized using *RP19* and isolated (pentane/AcOEt 95:4, 58% yield) as white solid. IR (neat): ν 2924, 2869, 1641, 1599, 1346, 1166, 1109, 709, 672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 – 7.62 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.20 (m, 2H), 7.21 – 7.13 (m, 1H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.42 (d, *J* = 8.1 Hz, 1H), 5.31 (d, *J* = 8.1 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.15 (dd, *J* = 11.6, 2.8 Hz, 1H), 2.40 (s, 3H), 1.91 (d, *J* = 5.9 Hz, 1H), 1.85 – 1.76 (m, 1H), 0.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C), 137.4 (C), 134.9 (2CH), 129.9 (2CH), 128.7 (2CH), 128.1 (2CH), 127.2 (CH), 126.2 (CH), 120.8 (CH), 117.5 (CH), 40.5 (CH_2), 35.9 (CH), 29.5 (CH), 21.6 (CH_3), 20.5 (C), 17.7 (CH_3). The spectral data for this compound correspond to previously reported.[72]

5.3.8. Synthesis and cycloisomerization of an oxygen-tethered 1,6-enyne

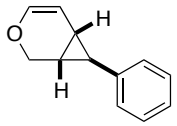
*5.3.8.1. Synthesis of (E)-(3-(but-2-ynyloxy)prop-1-enyl)benzene (**271**)*



(*E*)-3-phenylprop-2-en-1-ol (2g, 15 mmol) was added to a suspension of NaH (0.5 g, 15 mmol) in DMF (20 mL) at 0 °C, under an argon atmosphere and the solution was stirred for 1h at room temperature. Allyl bromide (1.3 mL, 16.5 mmol) was added and stirring was kept on for an additional 3 h. After dilution with ether (60mL), the solution was washed with water (3 x 70 mL) and the aqueous phase was further extracted with ether (3 x 40 mL). The combined organic layers were treated with brine (2 x 70 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (Et_2O/pentane 3:97) affording the desired product

as a colorless oil (quantitative yield). IR (neat): ν 3350, 3082, 3059, 3026, 2850, 1354, 1101, 965, 742, 636 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.39 (m, 2H), 7.32 – 7.27 (m, 3H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, *J* = 14.1, 8.0 Hz, 1H), 4.27 (dd, *J* = 6.2, 1.3 Hz, 2H), 4.23 (d, *J* = 2.4 Hz, 2H), 2.48 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6 (C), 133.5 (CH), 128.7 (2CH), 127.9 (CH), 126.6 (2CH), 125.2 (CH), 79.8 (C), 74.6 (CH), 70.3 (CH_2), 57.1 (CH_2). The spectral data for this compound correspond to previously reported.[68]

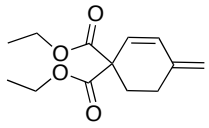
5.3.8.2. Synthesis of (1R,6S*,7R*)-7-phenyl-3-oxabicyclo[4.1.0]hept-4-ene (**272**)*



Compound **272** was synthesized using *RP19* and isolated (pentane/Et_2O 97:3, 15% yield) as colorless oil. IR (neat): ν 3350, 3082, 3059, 3026, 2850, 1354, 1160, 1108, 712, 658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.22 (m, 3H), 7.20 – 7.10 (m, 1H), 7.12 – 6.95 (m, 1H), 6.23 (d, *J* = 5.9 Hz, 1H), 5.33 (t, *J* = 5.5 Hz, 1H), 4.21 (dd, *J* = 10.7, 1.4 Hz, 1H), 3.91 (dd, *J* = 10.7, 2.6 Hz, 1H), 2.33 – 2.20 (m, 1H), 1.86 (br, 1H), 1.53 – 1.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1 (CH), 141.5 (C), 128.6 (2CH), 125.9 (CH), 125.6 (2CH), 105.3 (C), 62.0 (CH_2), 31.1 (CH), 27.6 (CH), 18.4 (CH). The spectral data for this compound correspond to previously reported.[76]

5.3.9. $[IrCp^*Cl_2]_2$-catalyzed cycloisomerization of dialkyl malonates

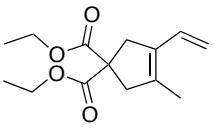
*5.3.9.1. Synthesis of diethyl 4-methylenecyclohex-2-ene-1,1-dicarboxylate (**273**)*



Compound **264c** (0.05 g, 0.21 mmol) in DCE (1 mL) was added to a solution of $[IrCp^*Cl_2]_2$ (0.016 g, 0.021 mmol) in DCE (1 mL) at room temperature, under an argon atmosphere. The solution was then stirred at 100 °C in a sealed tube for 2 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (Et_2O/pentane 3:97), affording the pure product as colorless oil (36% yield). IR (neat): ν 2981, 2973, 1732, 1297, 1236, 1116 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.32 (d, *J* = 9.6 Hz, 1H), 5.96 (d, *J* = 9.6 Hz, 1H), 4.92 (t, *J* = 1.8 Hz, 2H), 4.19 (dq, *J* = 7.2, 1.8 Hz, 4H), 2.51 – 2.43 (m, 2H), 2.22 – 2.14 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (2C), 140.7 (C), 132.0 (CH), 125.6 (CH), 113.9 (CH_2), 61.8 ($2CH_2$), 54.9 (C), 29.1 (CH_2), 27.0 (CH_2), 14.2 ($2CH_3$). HRMS calcd. for $C_{13}H_{18}O_4Na$ ($[M + Na]^+$): 261.1097, found 261.1094.

*5.3.9.2. Synthesis of diethyl 3-methyl-4-vinylcyclopent-3-ene-1,1-dicarboxylate (**274**)*

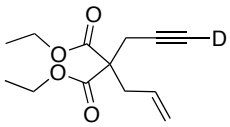
Compound **264d** (0.05 g, 0.19 mmol) in DCE (1 mL) was added to a solution of $[IrCp^*Cl_2]_2$ (0.008 g, 0.009 mmol) in DCE (1 mL) at room temperature, under an argon atmosphere. The solution was then stirred for 2 h. At the end of the reaction, the solvent was removed under



reduced pressure and the crude product was purified by silica gel chromatography (Et_2O/pentane 5:95), affording the pure product as colorless oil (79% yield). IR (neat): ν 3088, 2980, 2935, 1656, 1181, 1069 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.55 (dd, *J* = 17.1, 11.4 Hz, 1H), 5.07 – 5.02 (m, 2H), 4.19 (q, *J* = 7.2 Hz, 4H), 3.12 (s, 2H), 3.04 (s, 2H), 1.75 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (2C), 134.9 (C), 131.4 (C), 130.2 (CH), 113.7 (CH_2), 61.6 ($2CH_2$), 57.1 (C), 46.5 (CH_2), 40.5 (CH_2), 14.1 ($2CH_3$), 13.6 (CH_3). The spectral data for this compound correspond to previously reported.[74]

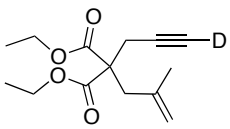
5.3.10. Synthesis and cycloisomerization of deuterated dialkyl malonates

*5.3.10.1. Synthesis of deuterated compound **275***



Compound **264c** (0.1 g, 0.42 mmol) was placed in a one-necked round-bottomed flask under argon atmosphere and was dissolved in THF (10 mL). The temperature was cooled to -78 °C and *n*-BuLi (2M in THF, 0.21 mL) was added. The solution was stirred at -78 °C for 15 min then D_2O (0.1 mL) was added. The mixture was warmed to r.t. and stirring was kept on for an additional 4 h. After dilution with ether (10 mL), the solution was washed with brine (3 x 30 mL) and the aqueous phase was further extracted with ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/pentane 5:95) affording the desired product as a colorless oil (quantitative yield). IR (neat): ν 2982, 2936, 2587, 1734, 1214, 1192 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.68 – 5.58 (m, 1H), 5.02 – 5.11 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 4H), 2.81 – 2.79 (m, 4H), (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (2C), 131.9 (CH), 119.9 (CH_2), 61.8 ($2CH_2$), 80.1 (C), 56.8 (C), 39.2 (t, *J* = 20.0 Hz, CD), 36.4 (CH_2), 22.7 (CH_2), 14.2 ($2CH_3$).

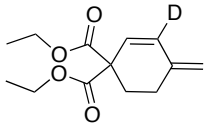
*5.3.10.2. Synthesis of deuterated compound **276***



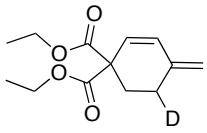
Compound **264d** (0.1 g, 0.39 mmol) was placed in a one-necked round-bottomed flask under argon atmosphere and was dissolved in THF (10 mL). The temperature was cooled to -78 °C and *n*-BuLi (2M in THF, 0.19 mL) was added. The solution was stirred at -78 °C for 15 min then D_2O (0.1 mL) was added. The mixture was warmed to r.t. and stirring was kept on for an additional 4 h. After dilution with ether (10 mL), the solution was washed with brine (3 x 30 mL) and the aqueous phase was further extracted with ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The reaction residue was purified by silica gel chromatography (AcOEt/pentane 5:95) affording the desired product as

a colorless oil (quantitative yield). IR (neat): ν 2980, 2586, 1732, 1185, 862Cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 – 4.85 (m, 2H), 4.24 – 4.15 (m, 4H), 2.84 (t, *J* = 0.8 Hz, 4H) 1.67 – 1.66 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1 (2C), 139.9 (C), 116.2 (CH_2), 61.6 ($2CH_2$), 81.1 (C), 56.3 (C), 39.4 (CD), 39.3 (CH_2), 23.2 (CH_3), 22.6 (CH_2), 14.1 ($2CH_3$).

*5.3.10.3. Synthesis of deuterated compounds **277** and **277'***

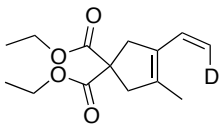


and



Compound **275** (0.05 g, 0.21 mmol) in DCE (1 mL) was added to a solution of $[IrCp^*Cl_2]_2$ (0.016 g, 0.021 mmol) in DCE (1 mL) at room temperature, under an argon atmosphere. The solution was then stirred at 100 °C in a sealed tube for 2 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (Et_2O/pentane 3:97), affording the pure product as colorless oil (15% yield). IR (neat): ν 2980, 1751, 1199, 1171 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (d, *J* = 9.9 Hz, 1H, I_B), 5.96 (t, *J* = 4.8 Hz, 2H, I_A and I_B), 4.96 (t, *J* = 1.8 Hz, 4H, I_A and I_B), 4.24 – 4.16 (m, 8H, I_A and I_B), 2.49 – 2.45 (m, 2H I_A and 1H I_B), 2.21 – 2.17 (m, 4H, I_A and I_B), 1.25 (t, *J* = 7.2 Hz, 12H, I_A and I_B). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (4C, I_A and I_B), 134.6 (2C, I_A and I_B), 132.1 (2CH, I_A and I_B), 129.9 (2C I_A and I_B), 125.1 (m, CH I_B and CD I_A), 114.15 (m, CH_2 I_A and CHD I_B), 61.6 ($4CH_2$, I_A and I_B), 29.1 ($2CH_2$, I_A and I_B), 26.9 ($2CH_2$, I_A and I_B), 14.1 ($4CH_3$, I_A and I_B). I_A and I_B refer to products **277** and **277'**, respectively.

*5.3.10.4. Synthesis of deuterated compound **278***



Compound **276** (0.05 g, 0.19 mmol) in DCE (1 mL) was added to a solution of $[IrCp^*Cl_2]_2$ (0.008g, 0.009 mmol) in DCE (1 mL) at room temperature, under an argon atmosphere. The solution was then stirred for 2 h. At the end of the reaction, the solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography (Et_2O/pentane 5:95), affording the pure product as a colorless oil (quantitative yield). IR (neat): ν 2980, 2933, 1751, 1214, 1180, 1018 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (d, *J* = 10.8 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 4.20 (q, *J* = 6.9 Hz, 4H), 3.10 (d, *J* = 1.5 Hz, 2H), 3.02 (s, 2H), 1.73, (s, 3H), 1.22 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (2C), 134.8 (C), 131.3 (C), 130.1 (CH), 113.4 (t, *J* = 110.8 Hz, CHD), 61.6 ($2CH_2$), 57.1 (C), 46.4 (CH_2), 39.1 (CH_2), 14.1 ($2CH_3$), 13.4 (CH_3).

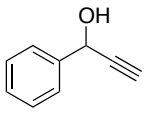
5.4. GOLD-CATALYZED CYCLOISOMERIZATIONS OF ALLENES

5.4.1. General Remarks

Reactions were carried out under argon in oven-dried glassware. THF was distilled over sodium/benzophenone. Toluene, CH_2Cl_2 and DCE were distilled from CaH_2. Microwave reactions were carried out in a Biotage microwave synthesizer. Thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel. Merck Gerudan SI 60 P silica gel (35–70 mm) was used for column chromatography. The melting points reported were measured with a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded with a Bruker Tensor 27 ATR diamant PIKE spectrometer. NMR spectra (^{1}H, ^{13}C, DEPT, [^{1}H,^{1}H] and [^{1}H,^{13}C] COSY) were recorded at room temperature on a Bruker 400 AVANCE spectrometer fitted with a BBFO probehead. Chemical shifts are given in parts per million, referenced to the residual proton resonance of the solvents (δ = 7.26 ppm for $CDCl_3$, δ = 5.30 ppm for CD_2Cl_2, δ = 2.05 ppm for acetone) or to the residual carbon resonance of the solvent (δ = 77.16 ppm for $CDCl_3$, δ = 53.00 ppm for CD_2Cl_2, δ = 206.06 ppm for acetone) When possible, ^{1}H and ^{13}C signals were assigned mostly on the basis of DEPT and 2D NMR (COSY, HMBC) experiments. Regiochemistry of products was deduced from NOE measurements. The terms m, s, d, t, q represent multiplet, singlet, doublet, triplet, quadruplet, respectively, the term br means a broad signal, the terms d1 and d2 correspond to diastereomer 1 and diastereomer 2 respectively. High resolution mass spectroscopy (HRMS) and X-ray diffraction were performed by the Plate-forme technique d'analyse et de spectroscopie (UMR 7201), Université Pierre et Marie Curie, Paris 6.

5.4.2. Synthesis of propargylic alcohols

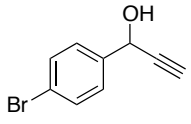
*5.4.2.1. Synthesis of 1-phenylprop-2-yn-1-ol (**370c**)*



Substrate **370c** was synthesized from benzaldehyde and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 – 7.54 (m, 5H), 5.55 (s, 1H), 2.69 (s, 1H), 2.59 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9 (C), 128.9 (2CH), 128.3 (2CH), 126.2 (CH), 83.4 (C), 74.7 (CH), 64.1 (CH). The spectral data for this compound correspond to previously reported data.[77]

*5.4.2.2. Synthesis of 1-(4-bromophenyl)prop-2-yn-1-ol (**370d**).*

Substrate **370d** was synthesized from 4-bromo-benzaldehyde and ethynylmagnesium bromide, following the *RP1* and was isolated (quantitative yield) as a yellow oil. ^{1}H NMR



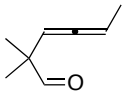
(400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.66 (s, 1H) 2.64 (s, 1H), 2.43 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7 (C), 133.4 (2CH), 129.2 (2CH), 122.1 (C), 83.2 (C), 74.5 (CH), 64.5 (CH). The spectral data for this compound correspond to previously reported data.[78]

5.4.3. Synthesis of β-allenyl aldehydes

*5.4.3.1. General for the synthesis of β-allenyl aldehydes (**GP1**)*

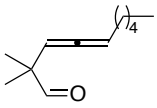
A solution of propargyl alcohol (0.02 mol), aldehyde (0.1 mol) and *p*-toluenesulfonic acid (0.2 mmol) under argon atmosphere, in 35 mL of toluene was heated at reflux and stirred for 24 hours in a 100 mL round bottomed flask equipped with a Dean-Stark water separator. After cooling to room temperature, the mixture concentrated *in vacuo* and the reaction residue was purified by flash chromatography over silica gel. Aldehydes are unstable compounds and were used directly in the next synthetic step.

*5.4.3.2. Synthesis of 2,2-dimethylhexa-3,4-dienal (**371a**)*



Substrate **371a** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 71% yield) as a colorless oil. IR (neat): ν 2963, 2875, 1946, 1728, 1470, 1100, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 5.25 – 5.29 (m, 1H), 5.00 – 5.03 (m, 1H), 1.68 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.16 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1 (C), 202.7 (CH), 94.00 (CH), 88.1 (CH), 46.6 (C), 21.9 ($2CH_3$), 14.5 (CH_3). The spectral data for this compound was in accordance with that previously published.[79]

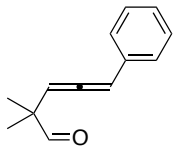
*5.4.3.3. Synthesis of 2,2-dimethyldeca-3,4-dienal (**371b**)*



Substrate **371b** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 80% yield) as a colorless oil. IR (neat): ν 2961, 2874, 2355, 1978, 1728, 1260, 1091, 1020, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 5.30 (q, *J* = 6.6 Hz, 1H), 5.04 (dt, *J* = 6.2, 3.0 Hz, 1H), 2.10 – 1.91 (m, 2H), 1.47 – 1.35 (m, 2H), 1.36 – 1.22 (m, 4H), 1.16 (s, 6H), 0.93 – 0.83 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (C), 202.7 (CH), 94.6 (CH), 94.5 (CH), 46.5 (C), 31.5 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 22.6 (CH_2), 21.9 (CH_3), 21.8 (CH_3), 14.2 (CH_3).

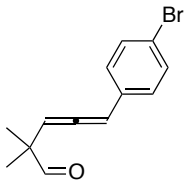
*5.4.3.4. Synthesis of 2,2-dimethyl-5-phenylpenta-3,4-dienal (**371c**)*

Substrate **371c** was synthesized using *GP1* and isolated (pentane/diethyl ether 99:1, 56% yield) as a pale yellow oil. IR (neat): ν 2960, 2926, 2856, 2357, 1973, 1729, 1466, 1266, 1074, 1021 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.38 – 7.17 (m, 5H), 6.35 (d, *J* = 6.4 Hz, 1H), 5.57 (d, *J* = 6.4 Hz, 1H), 1.27 (d, *J* = 3.7 Hz, 6H). ^{13}C NMR (100 MHz,



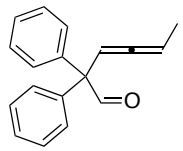
$CDCl_3$): δ 205.2 (C), 202.3 (CH), 133.8 (C), 128.9 (2CH), 127.3 (CH), 126.8 (2CH), 98.6 (CH), 97.8 (CH), 47.5 (C), 22.1 (CH_3), 22.0 (CH_3).

*5.4.3.5. Synthesis of 5-(4-bromophenyl)-2,2-dimethylpenta-3,4-dienal (**371d**)*



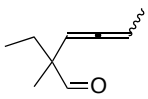
Substrate **371d** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 64% yield) as a pale yellow oil. IR (neat): ν 2970, 2929, 2805, 2705, 1947, 1724, 1588, 1068, 1009, 878, 832 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.28 (d, *J* = 6.4 Hz, 1H), 5.58 (d, *J* = 6.4 Hz, 1H), 1.25 (d, *J* = 3.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.2 (C), 202.0 (CH), 132.9 (C), 132.0 (2CH), 128.3 (2CH), 121.2 (C), 99.1 (CH), 96.9 (CH), 47.5 (C), 22.1 (CH_3), 22.0 (CH_3).

*5.4.3.6. Synthesis of 2,2-diphenylhexa-3,4-dienal (**371e**)*



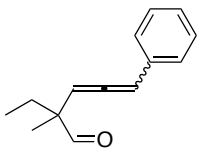
Substrate **371e** was synthesized using *GP1* and isolated (pentane/diethyl ether 95:5, 41% yield) as a yellow oil. IR (neat): ν 2960, 2877, 1951, 1726, 1472, 1103, 1027, 873, 842 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.46 – 7.13 (m, 10H), 5.86 (dd, *J* = 6.3, 3.2 Hz, 1H), 5.18 – 5.06 (m, 1H), 1.55 (dd, *J* = 6.8, 3.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1 (C), 197.5 (CH), 140.1 (C), 139.8 (C), 129.5 (2CH), 129.4 (2CH), 128.6 (2CH), 128.5 (2CH), 127.6 (CH), 127.5 (CH), 93.3 (CH), 89.6 (CH), 65.0 (C), 13.8 (CH_3).

*5.4.3.7. Synthesis of 2-ethyl-2-methylhexa-3,4-dienal (**371f**)*



Substrate **371f** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 67% yield) as a colorless oil. IR (neat): ν 2968, 2937, 2879, 2359, 1962, 1729, 1461, 1183, 1044 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 2H, d1 and d2), 5.26 – 5.22 (m, 2H, d1 and d2), 4.96 – 5.01 (m, 2H, d1 and d2), 1.68 – 1.59 (m, 10H, d1 and d2), 1.10 (s, 6H, d1 and d2), 0.88 – 0.84 (m, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6 (C, d1), 205.5 (C, d2), 203.0 (2CH, d1 and d2), 92.7 (2CH, d1 and d2), 88.8 (CH, d1), 88.7 (CH, d2), 50.4 (2C, d1 and d2), 29.2 ($2CH_2$, d1 and d2), 20.6 ($2CH_3$, d1 and d2), 11.5 ($2CH_3$, d1 and d2), 8.5 (CH_3, d1), 8.4 (CH_3, d2).

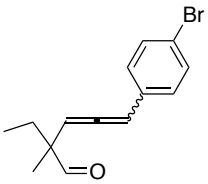
*5.4.3.8. Synthesis of 2-ethyl-2-methyl-5-phenylpenta-3,4-dienal (**371g**)*



Substrate **371g** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 39% yield) as a pale yellow oil. IR (neat): ν 2962, 2928, 2873, 1956, 1723, 1479, 1132, 1001, 846 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H, d1), 9.49 (s, 1H, d2), 7.44 – 7.20 (m, 10H, d1 and d2), 6.34 – 6.38 (m, 2H, d1 and d2), 5.49 – 5.61 (m, 2H, d1 and d2), 1.80 – 1.68 (m, 4H, d1 and d2), 1.23

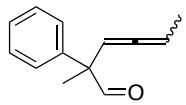
(d, J = 1.2 Hz, 6H, d1 and d2), 0.94 – 0.86 (m, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6 (C, d1), 205.5 (C, d2), 202.5 (CH, d1), 202.4 (CH, d2), 133.9 (2C, d1 and d2), 128.8 (4CH, d1 and d2), 127.4 (2CH, d1 and d2), 126.8 (4CH, d1 and d2), 97.5 (2CH, d1 and d2), 97.3 (2CH, d1 and d2), 51.4 (C, d1), 51.3 (C, d2), 29.2 (CH_2, d1), 28.9 (CH_2, d2), 18.5 (CH_3, d1), 18.4 (CH_3, d2), 8.6 ($2CH_3$, d1 and d2).

*5.4.3.9. Synthesis of 5-(4-bromophenyl)-2-ethyl-2-methylpenta-3,4-dienal (**371h**)*



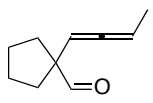
Substrate **371h** was synthesized using *GP1* and isolated (pentane/diethyl ether 95:5, 31% yield) as a yellow oil. IR (neat): ν 3294, 2967, 2929, 2868, 1956, 1728, 1478, 1266, 1143, 1001, 829 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 1H, d1), 9.45 (s, 1H, d2), 7.44 – 7.40 (m, 4H, d1 and d2), 7.10 – 7.17 (m, 4H, d1 and d2), 6.24 – 6.29 (m, 2H, d1 and d2), 5.53 – 5.61 (m, 2H, d1 and d2), 1.65 – 1.74 (m, 4H, d1 and d2), 1.19 (s, 3H, d1), 1.18 (s, 3H, d2), 0.87 – 0.99 (m, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6 (C, d1), 205.5 (C, d2), 202.6 (CH, d1), 202.5 (CH, d2), 132.9 (2C, d1 and d2), 132.0 (2CH, d1 and d2), 128.3 (4 CH, d1 and d2), 121.1 (2C, d1 and d2), 97. (4CH, d1 and d2), 96.7 (CH, d1), 96.6 (CH, d2), 51.5 (C, d1), 51.4 (C, d2), 28.8 (CH_2, d1), 28.7 (CH_2, d2), 18.6 (CH_3, d1), 18.4 (CH_3, d2), 8.7 ($2CH_3$, d1 and d2).

*5.4.3.10. Synthesis of 2-methyl-2-phenylhexa-3,4-dienal (**371i**)*



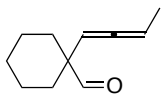
Substrate **371i** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 55% yield) as a pale yellow oil. IR (neat): ν 2967, 2935, 2871, 1943, 1726, 1476, 1172, 1035, 1004, 834 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H, d1), 9.53 (s, 1H, d2), 7.38 – 7.26 (m, 10H, d1 and d2), 5.51 – 5.43 (m, 2H, d1 and d2), 5.36 – 5.27 (m, 2H, d1 and d2), 1.76 – 1.65 (m, 6H, d1 and d2), 1.51 (s, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4 (2C, d1 and d2), 199.0 (2CH, d1 and d2), 140.7 (2C, d1 and d2), 129.0 (4CH, d1 and d2), 127.5 (2CH, d1 and d2), 127.4 (4CH, d1 and d2), 93.0 (CH, d1), 92.9 (CH, d2), 89.7 (CH, d1), 89.6 (CH, d2), 55.1 (C, d1), 55.0 (C, d2), 21.4 ($2CH_3$, d1 and d2), 14.3 ($2CH_3$, d1 and d2).

*5.4.3.11. Synthesis of 1-(buta-1,2-dienyl)cyclopentanecarbaldehyde (**371j**)*



Substrate **371j** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 55% yield) as a colorless oil. IR (neat): ν 2933, 2867, 1955, 1723, 1441, 822 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 5.27 – 5.19 (m, 1H), 5.13 (dq, J = 6.4, 3.2 Hz, 1H), 1.89 – 1.99 (m, 2H), 1.87 – 1.35 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8 (C), 202.0 (CH), 92.9 (CH), 88.8 (CH), 58.4 (C), 33.2 (CH_2), 33.1 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 14.4 (CH_3).

*5.4.3.12. Synthesis of 1-(buta-1,2-dienyl)cyclohexanecarbaldehyde (**371k**)*



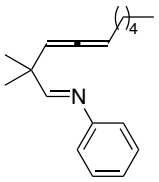
Substrate **371k** was synthesized using *GP1* and isolated (pentane/diethyl ether 98:2, 40% yield) as a pale yellow oil. IR (neat): ν 2927, 2853, 1960, 1722, 1448, 829 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.26 (s, 1H), 5.22 (dt, *J* = 13.4, 6.7 Hz, 1H), 4.82 (dt, *J* = 6.4, 3.2 Hz, 1H), 1.79 – 1.70 (m, 2H), 1.65 (dd, *J* = 7.1, 3.2 Hz, 3H), 1.58 – 1.46 (m, 5H), 1.45 – 1.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0 (C), 202.5 (CH), 92.3 (CH), 88.7 (CH), 50.6 (C), 30.8 (CH_2), 30.8 (CH_2), 25.8 (CH_2), 22.3 (CH_2), 22.3 (CH_2), 14.3 (CH_3). The spectral data for this compound was in accordance with that previously published.[80]

5.4.4 Synthesis of β-allenyl imines and β-allenyl hydrazones

*5.4.4.1. General procedure for the synthesis of β-allenyl imines (**GP2**)*

Aniline (3 mmol) was added to a solution of β-allenic aldehyde (2 mmol) and $MgSO_4$ (5 mmol) in dry CH_2Cl_2 (25 mL) under argon atmosphere. The solution was stirred at room temperature for 5 hours. The solvent was removed in vacuo and the reaction residue was purified by filtration through a short pad of alumina.

*5.4.4.2. Synthesis of (E)-N-(2,2-dimethyldeca-3,4-dienylidene)aniline (**372**)*

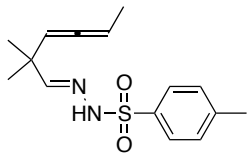


Substrate **372** was synthesized using *GP2* and isolated (rapid filtration over a short pad of alumine, quantitative yield) as a colorless oil. IR (neat): ν 3308, 2966, 2926, 2866, 1960, 1645, 1594, 1462, 839, 724 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 7.76 (s, 1H), 7.40 – 7.27 (m, 2H), 7.23 – 7.11 (m, 1H), 7.06 – 6.91 (m, 2H), 5.28 – 5.36 (m, 2H), 2.12 – 1.92 (m, 2H), 1.49 – 1.39 (m, 2H), 1.39 – 1.22 (m, 10H), 0.88 (dt, *J* = 2.4, 5.7, 3H). ^{13}C NMR (100 MHz, acetone): δ 203.5 (C), 170.8 (CH), 153.4 (C), 129.8 (2CH), 126.0 (CH), 121.3 (2CH), 98.9 (CH), 94.5 (CH), 41.3 (C), 32.1 ($2CH_2$), 29.6 (CH_2), 25.6 (CH_3), 25.5 (CH_3), 23.2 (CH_2), 14.3 (CH_3). HRMS calcd. for $C_{18}H_{26}N$ ([M + H]$^{+}$): 256.2060, found 256.2061.

*5.4.4.3. General procedure for the synthesis of β-allenyl hydrazones (**GP3**)*

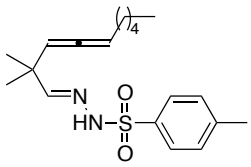
Hydrazine (3 mmol) was added to a solution of β-allenic aldehyde (2 mmol) and $MgSO_4$ (5 mmol) in EtOH (30 mL) under argon atmosphere. The solution was heated at reflux and stirred for 3 hours. After cooling at r.t., the solvent was removed *in vacuo* and the reaction residue was purified by column chromatography over silica gel.

*5.4.4.4. Synthesis of (E)-N'-(2,2-dimethylhexa-3,4-dienylidene)-4-methyl-benzenesulfono hydrazide (**373a**)*



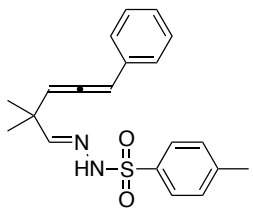
Substrate **373a** was synthesized using *GP3* and isolated (CH_2Cl_2/pentane 9:2, 72% yield) as a yellow solid. Mp 69 °C. IR (neat): ν 3196, 2968, 2926, 1960, 1597, 1400, 1185, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.71 (m, 2H), 7.59 (s, 1H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.04 (s, 1H), 5.14 – 5.08 (m, 1H), 4.95 (dq, *J* = 6.3, 3.2 Hz, 1H), 2.42 (s, 3H), 1.58 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3 (C), 158.0 (CH), 144.2 (C), 135.3 (C), 129.6 (2CH), 128.2 (2CH), 97.6 (CH), 88.8 (CH), 38.9 (C), 25.5 (CH_3), 25.5 (CH_3), 21.7 (CH_3), 14.5 (CH_3). HRMS calcd. for $C_{15}H_{20}O_2N_2NaS$ ([M + Na]$^+$): 315.1137, found 315.1137.

*5.4.4.5. Synthesis of (E)-N'-(2,2-dimethyldeca-3,4-dienylidene)-4-methyl-benzenesulfono hydrazide (**373b**)*



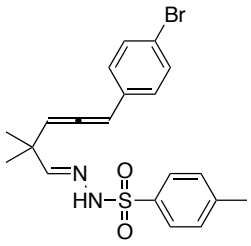
Substrate **373b** was synthesized using *GP3* and isolated (CH_2Cl_2, 71% yield) as yellow oil. IR (neat): ν 3200, 2961, 2927, 2858, 1960, 1598, 1357, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.04 (s, 1H), 5.16 (q, *J* = 6.6 Hz, 1H), 4.98 (dt, *J* = 6.1, 2.9 Hz, 1H), 2.43 (s, 3H), 1.92 (dd, *J* = 7.3, 2.6 Hz, 2H), 1.40 – 1.22 (m, 6H), 1.11 (s, 6H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4 (C), 158.1 (CH), 144.2 (C), 135.3 (C), 129.6 (2CH), 128.2 (2CH), 98.1 (CH), 94.5 (CH), 38.9 (C), 31.5 (CH_2), 28.9 ($2CH_2$), 25.6 (CH_3), 25.5 (CH_3), 22.6 (CH_2), 21.7 (CH_3), 14.2 (CH_3). HRMS calcd. for $C_{19}H_{28}O_2N_2NaS$ ([M + Na]$^+$): 371.1764, found 371.1767.

*5.4.4.6. Synthesis of (E)-N'-(2,2-dimethyl-5-phenylpenta-3,4-dienylidene)-4-methyl-benzene sulfonohydrazide (**373c**)*



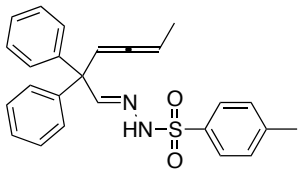
Substrate **373c** was synthesized using *GP3* and isolated (pentane/ethyl acetate 8:2, 55% yield) as a yellow oil. IR (neat): ν 3198, 2963, 2924, 1951, 1596, 1323, 1165, 880, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.80 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.33 – 7.16 (m, 7H), 7.14 (s, 1H), 6.18 (d, *J* = 6.4 Hz, 1H), 5.51 (d, *J* = 6.4 Hz, 1H), 2.41 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7 (C), 157.17 (CH), 144.1 (C), 135.2 (C), 134.2 (C), 129.6 (2CH), 128.8 (2CH), 128.1 (2CH), 127.2 (CH), 126.7 (2CH), 102.1 (CH), 97.5 (CH), 39.7 (C), 25.7 (CH_3), 25.7 (CH_3), 21.7 (CH_3). HRMS calcd. for $C_{20}H_{22}O_2N_2NaS$ ([M + Na]$^+$): 377.1294, found 377.1295.

*5.4.4.7. Synthesis of (E)-N'-(5-(4-bromophenyl)-2,2-dimethylpenta-3,4-dienylidene)-4-methyl-benzenesulfonohydrazide (**373d**)*



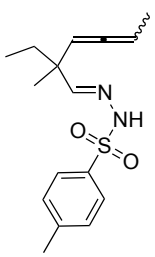
Substrate **373d** was synthesized using *GP3* and isolated (pentane/ethyl acetate 8:2, 72% yield) as white solid. Mp 123 °C. IR (neat): ν 3197, 2968, 2927, 1949, 1597, 1354, 1163, 1037, 880, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.65 (s, 1H), 7.41 – 7.34 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.13 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.13 (d, *J* = 6.4 Hz, 1H), 5.52 (d, *J* = 6.4 Hz, 1H), 2.43 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8 (C), 156.9 (CH), 144.3 (C), 135.3 (C), 133.3 (C), 131.9 (2CH), 129.6 (2CH), 128.2 (2CH), 128.1 (2CH), 120.9 (C), 102.6 (CH), 96.7 (CH), 39.8 (C), 25.8 (CH_3), 25.7 (CH_3), 21.8 (CH_3). HRMS calcd. for $C_{20}H_{21}O_2N_2BrNaS$ ([M + Na]$^+$): 457.0380, found 457.0381.

*5.4.4.8. Synthesis of (E)-N'-(2,2-diphenylhexa-3,4-dienylidene)-4-methylbenzenesulfono hydrazide (**373e**)*



Substrate **373e** was synthesized using *GP3* and isolated (CH_2Cl_2, 59% yield) as pale yellow oil. IR (neat): ν 3195, 3059, 3029, 2923, 1965, 1597, 1357, 1185, 1049, 907, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.68 (s, 1H), 7.31 – 7.19 (m, 8H), 7.12 – 6.99 (m, 4H), 5.83 – 5.89 (m, 1H), 5.05 – 4.98 (m, 1H), 2.47 (s, 3H), 1.47 (dd, *J* = 3.2, 7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7 (C), 155.6 (CH), 144.0 (C), 143.0 (C), 142.8 (C), 135.0 (C), 129.5 (2CH), 129.0 (2CH), 128.9 (2CH), 128.2 (2CH), 128.0 (2CH), 127.9 (2CH), 126.9 (CH), 126.8 (CH), 96.4 (CH), 89.3 (CH), 56.4 (C), 21.7 (CH_3), 13.8 (CH_3). HRMS calcd. for $C_{25}H_{24}O_2N_2BrNaS$ ([M + Na]$^+$): 439.1450, found 439.1451.

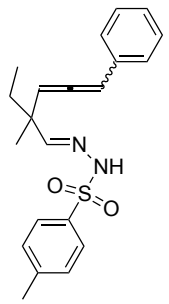
*5.4.4.9. Synthesis of (E)-N'-(2-ethyl-2-methylhexa-3,4-dienylidene)-4-methylbenzenesulfono hydrazide (**373f**)*



Substrate **373f** was synthesized using *GP3* and isolated (CH_2Cl_2, 64% yield) as yellow oil. IR (neat): ν 3196, 2967, 2924, 1961, 1597, 1355, 1185, 1019, 812, 666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 2H, d1 and d2), 7.81 (d, *J* = 8.3 Hz, 4H, d1 and d2), 7.30 (d, *J* = 8.0 Hz, 4H, d1 and d2), 7.05 (s, 2H, d1 and d2), 5.12 – 5.08 (m, 2H, d1 and d2), 4.95 (dt, *J* = 6.1, 3.0 Hz, 2H, d1 and d2), 2.43 (s, 6H, d1 and d2), 1.56 – 1.61 (m, 6H, d1 and d2), 1.47 (q, *J* = 7.5 Hz, 4H, d1 and d2), 1.06 (s, 3H, d1), 1.05 (s, 3H, d2), 0.65 – 0.74 (m, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8 (C, d1), 203.7 (C, d2), 157.7 (CH, d1), 157.6 (CH, d2), 144.1 (2C, d1 and d2), 135.2 (2C, d1 and d2), 129.53 (4CH, d1 and

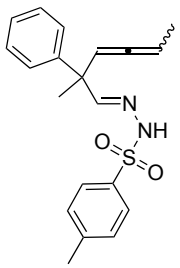
d2), 128.07 (4CH, d1 and d2), 96.2 (CH, d1), 96.1 (CH, d2), 88.5 (CH, d1), 88.4 (CH, d2), 42.36 (2C, d1 and d2), 31.8 (CH_2, d1), 31.4 (CH_2, d2), 22.0 ($2CH_3$, d1 and d2), 21.6 ($2CH_3$, d1 and d2), 14.5 (CH_3, d1), 14.4 (CH_3, d2), 8.50 ($2CH_3$, d1 and d2). HRMS calcd. for $C_{16}H_{22}O_2N_2BrNaS$ ([M + Na]$^+$): 329.1294, found 329.1293.

*5.4.4.10. Synthesis of (E)-N'-(2-ethyl-2-methyl-5-phenylpenta-3,4-dienylidene)-4-methyl-benzenesulfonohydrazide (**373g**)*



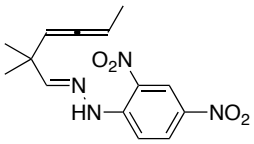
Substrate **373g** was synthesized using *GP3* and isolated (pentane/diethyl ether 1:1, 79% yield) as a yellow oil. IR (neat): ν 3197, 2981, 2929, 1963, 1597, 1358, 1185, 1023, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 – 7.81 (m, 4H, d1 and d2), 7.36 (s, 2H, d1 and d2), 7.32 – 7.25 (m, 10H, d1 and d2), 7.18 – 7.23 (m, 4H, d1 and d2), 7.08 (s, 2H, d1 and d2), 6.15 – 6.21 (m, 2H, d1 and d2), 5.46 – 5.52 (m, 2H, d1 and d2), 2.42 (s, 3H, d1), 2.41 (s, 3H, d2), 1.52 – 1.59 (m, 4H, d1 and d2), 1.16 (s, 3H, d1), 1.15 (s, 3H, d2), 0.83 – 0.73 (m, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (C, d1), 204.1 (C, d2), 156.9 (CH, d1), 156.8 (CH, d2), 144.2 (2C, d1 and d2), 135.3 (2C, d1 and d2), 134.3 (2C, d1 and d2), 129.6 (4CH, d1 and d2), 128.8 (4CH, d1 and d2), 128.2 (4CH, d1 and d2), 127.3 (2CH, d1 and d2), 126.7 (4CH, d1 and d2), 100.9 (2CH, d1 and d2), 97.4 (CH, d1), 97.3 (CH, d2), 43.5 (C, d1), 43.4 (C, d2), 32.2 (CH_2, d1), 32.1 (CH_2, d2), 22.5 (CH_3, d1), 22.3 (CH_3, d2), 21.8 ($2CH_3$, d1 and d2), 8.8 ($2CH_3$, d1 and d2). HRMS calcd. for $C_{21}H_{24}O_2N_2BrNaS$ ([M + Na]$^+$): 391.1450, found 391.1454.

*5.4.4.11. Synthesis of (E)-4-methyl-N'-(2-methyl-2-phenylhexa-3,4-dienylidene)-benzene sulfonohydrazide (**373i**)*



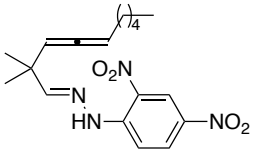
Substrate **373i** was synthesized using *GP3* and isolated (CH_2Cl_2, 41% yield) as a yellow oil. IR (neat): ν 3199, 2979, 2927, 1964, 1598, 1356, 1186, 1027, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, J = 8.0, 6.2 Hz, 4H, d1 and d2), 7.54 (s, 2H, d1 and d2), 7.31 (t, J = 7.0 Hz, 4H, d1 and d2), 7.25 – 7.15 (m, 8H, d1 and d2), 7.16 – 7.04 (m, 4H, d1 and d2), 5.31 – 5.41 (m, 2H, d1 and d2), 5.26 – 5.12 (m, 2H, d1 and d2), 2.46 (s, 6H, d1 and d2), 1.59 (dd, J = 7.0, 3.4 Hz, 6H, d1 and d2), 1.47 (s, 3H, d1), 1.46 (s, 3H, d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1 (2C, d1 and d2), 155.9 (CH, d1), 155.8 (CH, d2), 144.3 (2C, d1 and d2), 144.0 (2C, d1 and d2), 135.3 (C, d1), 135.2 (C, d2), 129.7 (4CH), 128.5 (4CH), 128.3 (4CH), 127.0 (2CH), 126.9 (4CH), 96.2 (CH, d1), 96.0 (CH, d2), 89.5 (CH, d1), 89.4 (CH, d2), 47.0 (2C, d1 and d2), 24.8 (CH_3, d1), 24.7 (CH_3, d2), 21.75 ($2CH_3$, d1 and d2), 14.3 ($2CH_3$, d1 and d2). HRMS calcd. for $C_{20}H_{22}O_2N_2BrNaS$ ([M + Na]$^+$): 377.1294, found 377.1296.

*5.4.4.12. Synthesis of (E)-1-(2,2-dimethylhexa-3,4-dienylidene)-2-(2,4-dinitrophenyl) hydrazine (**374a**)*



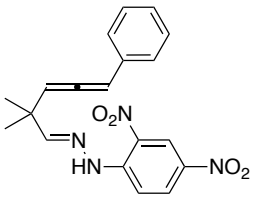
Substrate **374a** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 60% yield) as a orange solid. Mp 117 °C. IR (neat): ν 3282, 3110, 2964, 2974, 1975, 1727, 1517, 1335, 1307, 1070 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (s, 1H), 9.12 (d, *J* = 2.6 Hz, 1H), 8.30 (dd, 9.6, 2.6 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.42 (s, 1H), 5.31 – 5.24 (m, 1H), 5.14 (dq, *J* = 6.3, 3.2 Hz, 1H), 1.70 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.31 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5 (C), 157.7 (CH), 145.4 (C), 130.1 (CH), 129.0 (C), 127.1 (C), 123.6 (CH), 116.8 (CH), 97.4 (CH), 89.3 (CH), 39.3 (C), 25.8 (CH_3), 25.7 (CH_3), 14.7 (CH_3). HRMS calcd. for $C_{14}H_{16}N_4O_4Na$ ([M + Na]$^+$): 327.1064, found 327.1065.

*5.4.4.13. Synthesis of (E)-1-(2,2-dimethyldeca-3,4-dienylidene)-2-(2,4-dinitrophenyl) hydrazine (**374b**)*



Substrate **374b** was synthesized using *GP3* and isolated (pentane/diethyl ether 8:2, 88% yield) as a orange solid. Mp 61 °C. IR (neat): ν 3280, 3108, 2967, 2929, 1973, 1731, 1522, 1329, 1300, 1065 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (s, 1H), 9.11 (d, *J* = 2.6 Hz, 1H), 8.30 (dd, 9.6, 2.6 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.42 (s, 1H), 5.30 (q, *J* = 6.6 Hz, 1H), 5.17 (dt, *J* = 6.2, 3.0 Hz, 1H), 2.09 – 1.94 (m, 2H), 1.40 – 1.31 (m, 12H), 0.87 (dd, *J* = 9.8, 4.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7 (C), 157.8 (CH), 145.4 (C), 137.9 (C), 130.1 (CH), 127.0 (C), 123.6 (CH), 116.8 (CH), 98.0 (CH), 94.8 (CH), 39.3 (C), 31.4 (CH_2), 28.9 (CH_2), 25.8 (CH_2), 25.7 (CH_3), 22.6 (CH_2), 14.2 ($2CH_3$). HRMS calcd. for $C_{18}H_{24}N_4O_4Na$ ([M + Na]$^+$): 383.1690, found 383.1686.

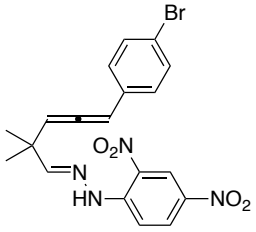
*5.4.4.14. Synthesis of (E)-1-(2,2-dimethyl-5-phenylpenta-3,4-dienylidene)-2-(2,4-dinitrophenyl)hydrazine (**374c**)*



Substrate **374c** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 44% yield) as a orange solid. Mp 115 °C. IR (neat): ν 3298, 3110, 2969, 2927, 1948, 1617, 1517, 1329, 1073 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.00 (s, 1H), 9.11 (d, *J* = 2.6 Hz, 1H), 8.30 (dd, 9.6, 2.6 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 7.51 (d, *J* = 0.4 Hz, 1H), 7.38 – 7.15 (m, 5H), 6.34 (d, *J* = 6.4 Hz, 1H), 5.70 (d, *J* = 6.4 Hz, 1H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0 (C), 157.0 (CH), 145.4 (C), 138.1 (C), 134.1 (C), 130.1 (CH), 129.2 (C), 128.9 (CH), 127.5 (2CH), 126.8 (CH), 123.6 (2CH),

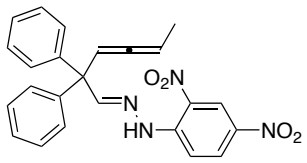
116.8 (CH), 102.0 (CH), 97.9 (CH), 40.2 (C), 26.1 (CH_3), 26.0 (CH_3). HRMS calcd. for $C_{19}H_{18}N_4O_4Na$ ([M + Na]$^+$): 389.1220, found 389.1221.

*5.4.4.15. Synthesis of (E)-1-(5-(4-bromophenyl)-2,2-dimethylpenta-3,4-dienylidene)-2-(2,4-dinitrophenyl)hydrazine (**374d**)*



Substrate **374d** was synthesized using *GP3* and isolated (pentane/diethyl ether 95:5, 67% yield) as a orange solid. Mp 67 °C. IR (neat): ν 3297, 3110, 2970, 2359, 1950, 1617, 1517, 1330, 1071 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.00 (s, 1H), 9.10 (d, *J* = 2.5 Hz, 1H), 8.29 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.50 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 6.4 Hz, 1H), 5.71 (d, *J* = 6.4 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0 (C), 156.7 (CH), 145.3 (C), 138.1 (C), 133.1 (C), 132.0 (2CH), 130.1 (CH), 129.2 (C), 128.5 (2CH), 123.6 (CH), 121.1 (C), 116.7 (CH), 102.5 (CH), 97.1 (CH), 40.2 (C), 26.1 (CH_3), 26.0 (CH_3). HRMS calcd. for $C_{19}H_{17}O_4N_4BrNa$ ([M + Na]$^+$): 467.0325, found 467.0327.

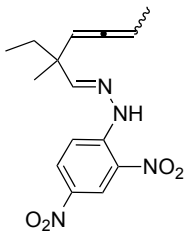
*5.4.4.16. Synthesis of (E)-1-(2,4-dinitrophenyl)-2-(2,2-diphenylhexa-3,4-dienylidene) hydrazine (**374e**)*



Substrate **374e** was synthesized using *GP3* and isolated (pentane/diethyl ether 8:2, 51% yield) as a yellow solid. Mp 112 °C. IR (neat): ν 3296, 3105, 3027, 2923, 2855, 1964, 1618, 1517, 1341, 1056, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.19 (s, 1H), 9.09 (d, *J* = 2.6 Hz, 1H), 8.25 (dd, *J* = 9.6, 2.5 Hz, 1H), 8.04 (s, 1H), 7.78 (d, *J* = 9.6 Hz, 1H), 7.61 – 7.17 (m, 10H), 6.04 (dq, *J* = 6.3, 3.1 Hz, 1H), 5.17 (dd, *J* = 7.0, 6.5 Hz, 1H), 1.58 (dd, *J* = 7.1, 3.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0 (C), 155.0 (CH), 145.3 (C), 143.1 (C), 143.0 (C), 138.1 (C), 130.1 (CH), 129.2 (C), 129.0 (2CH), 128.9 (2CH), 128.3 (2CH), 128.2 (2CH), 127.3 (CH), 127.2 (CH), 123.4 (CH), 116.9 (CH), 96.3 (CH), 89.7 (CH), 56.8 (C), 14.0 (CH_3). HRMS calcd. for $C_{24}H_{20}O_4N_4Na$ ([M + Na]$^+$): 451.1377, found 451.1372.

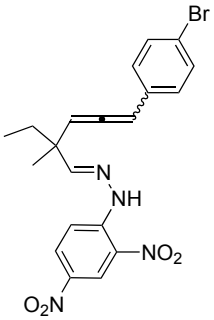
*5.4.4.17. Synthesis of (E)-1-(2,4-dinitrophenyl)-2-(2-ethyl-2-methylhexa-3,4-dienylidene) hydrazine (**374f**)*

Substrate **374f** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 72% yield) as a yellow solid. Mp 108 °C. IR (neat): ν 3284, 3110, 2971, 2925, 1965, 1616, 1515, 1335, 1307, 1266, 1072, 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (s, 2H, d1 and d2), 9.12 (d, *J* = 2.6 Hz, 2H, d1 and d2), 8.30 (dd, *J* = 9.6, 2.5 Hz, 2H, d1 and d2), 7.93 (d, *J* = 9.6 Hz, 2H,



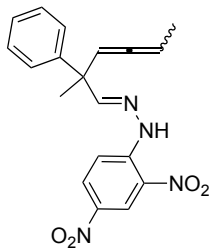
d1 and d2), 7.40 (s, 2H, d1 and d2), 5.40 – 5.17 (m, 2H, d1 and d2), 5.12 (dt, J = 6.4, 3.3 Hz, 2H, d1 and d2), 1.71 – 1.65 (m, 10H, d1 and d2), 1.26 (d, J = 2.2 Hz, 6H, d1 and d2), 0.96 – 0.91 (m, 6H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1 (2C, d1 and d2), 157.5 (2CH, d1 and d2), 145.4 (2C, d1 and d2), 137.9 (2C, d1 and d2), 130.0 (2CH, d1 and d2), 129.0 (2C, d1 and d2), 123. 6 (2CH, d1 and d2), 116.7 (2CH, d1 and d2), 96.1 (CH, d1), 96.0 (CH, d2), 89.0 (2CH, d1 and d2), 42.8 (2C d1 and d2), 32.1 (CH_2, d1), 32.0 (CH_2, d2), 22.4 (CH_3, d1), 22.3 (CH_3, d2), 14.6 (CH_3, d1), 14.5 (CH_3, d2), 8.9 (CH_3, d1), 8.8 (CH_3, d2). HRMS calcd. for $C_{15}H_{18}O_4N_4Na$ ([M + Na]$^+$): 341.1220, found 341.1222.

*5.4.4.18. Synthesis of (E)-1-(5-(4-bromophenyl)-2-ethyl-2-methylpenta-3,4-dienylidene)-2-(2,4-dinitrophenyl)hydrazine (**374h**)*



Substrate **374h** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 64% yield) as a orange solid. Mp 120 °C. IR (neat): ν 3297, 3109, 2967, 2931, 1949, 1615, 1487, 1327, 1308, 1072, 881 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.01 (s, 1H, d1), 11.00 (s, 1H, d2), 9.09 (t, J = 2.5 Hz, 2H, d1 and d2), 8.28 (d, J = 9.6 Hz, 2H, d1 and d2), 7.91 (dd, J = 9.6, 3.7 Hz, 2H, d1 and d2), 7.48 (d, J = 4.6 Hz, 2H, d1 and d2), 7.46 – 7.34 (m, 4H, d1 and d2), 7.15 (d, J = 8.4 Hz, 4H, d1 and d2), 6.27 (d, J = 6.4 Hz, 2H, d1 and d2), 5.69 (dd, J = 6.3, 4.8 Hz, 2H, d1 and d2), 1.77 (d, J = 6.9 Hz, 4H, d1 and d2), 1.35 (s, 3H, d1), 1.34 (s, 3H, d2), 1.03 – 0.97 (m, 6H, d1 and d2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.5 (C, d1), 204.4 (C, d2), 156.5 (CH, d1), 156.4 (CH, d2), 145.3 (2C, d1 and d2), 138.1 (C, d1), 138.0 (C, d2), 133.2 (2C, d1 and d2), 131.9 (4CH, d1 and d2), 130.0 (CH, d1), 129.9 (CH, d2), 130.1 (C, d1), 130.0 (C, d2), 128.2 (4CH, d1 and d2), 123.5 (2CH, d1 and d2), 121.0 (2C, d1 and d2), 116.7 (2CH, d1 and d2), 101.20 (2CH, d1 and d2), 96.9 (CH, d1), 96.8 (CH, d2), 43.8 (2C, d1 and d2), 32.5 (CH_2, d1), 32.4 (CH_2, d2), 22.7 (CH_3, d1), 22.5 (CH_3, d2), 9.1 (CH_3, d1), 9.0 (CH_3, d2). HRMS calcd. for $C_{20}H_{19}BrO_4N_4Na$ ([M + Na]$^+$): 481.0482, found 481.0475.

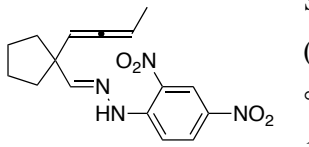
*5.4.4.19. Synthesis of (E)-1-(2,4-dinitrophenyl)-2-(2-methyl-2-phenylhexa-3,4-dienylidene) hydrazine (**374i**)*



Substrate **374i** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 45% yield) as a yellow solid. Mp 105 °C. IR (neat): ν 3299, 3109, 2980, 1963, 1617, 1517, 1329, 1137 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.05 (s, 2H, d1 and d2), 9.13 (d, J = 2.5 Hz, 2H, d1 and d2), 8.37 – 8.30 (m, 2H, d1 and d2), 7.96 (dd, J = 9.6, 2.1 Hz, 2H, d1 and d2), 7.61 (s, 2H, d1 and d2), 7.40 – 7.18 (m, 10H, d1 and d2), 5.54 (dt, J = 9.9, 3.3 Hz, 2H, d1 and

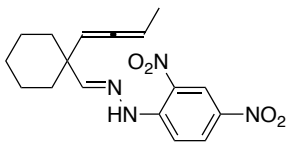
d2), 5.38 – 5.29 (m, 2H, d1 and d2), 1.74 – 1.54 (m, 12H, d1 and d2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2 (2C, d1 and d2), 155.7 (CH, d1), 155.6 (CH, d2), 145.5 (2C, d1 and d2), 143.9 (2C, d1 and d2), 138.2 (2C, d1 and d2), 130.2 (2CH, d1 and d2), 129.3 (2C, d1 and d2), 128.8 (4CH, d1 and d2), 127.3 (2CH, d1 and d2), 127.0 (4CH, d1 and d2), 123.6 (2CH, d1 and d2), 116.9 (2CH, d1 and d2), 96.3 (2CH, d1 and d2), 89.9 (2CH, d1 and d2), 47.3 (2C, d1 and d2), 24.9 ($2CH_3$, d1 and d2), 14.5 ($2CH_3$, d1 and d2). HRMS calcd. for $C_{19}H_{19}O_4N_4$ ([M + H]$^+$): 367.1401, found 367.1401.

*5.4.4.20. Synthesis of (E)-1-((1-(buta-1,2-dienyl)cyclopentyl)methylene)-2-(2,4-dinitrophenyl) hydrazine (**374j**)*



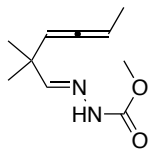
Substrate **374j** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 73% yield) as a orange solid. Mp 108 °C. IR (neat): ν 3287, 3107, 2944, 2870, 1960, 1614, 1518, 1330, 1304, 1069, 666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 9.08 (d, *J* = 2.5 Hz, 1H), 8.27 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.91 (d, *J* = 9.6 Hz, 1H), 7.49 (s, 1H), 5.28 – 5.19 (m, 2H), 2.00 – 1.80 (m, 2H), 1.79 – 1.08 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8 (C), 156.9 (CH), 145.4 (C), 137.8 (C), 130.1 (CH), 130.0 (CH), 127.1 (C), 123.6 (CH) , 116.7 (CH), 95.7 (CH), 89.0 (CH_2), 50.8 (C), 36.5 (CH_2), 36.2 (CH_2), 24.1 (CH_2), 14.5 (CH_3). HRMS calcd. for $C_{16}H_{18}O_4N_4Na$ ([M + Na]$^+$): 353.1220, found 353.1222.

*5.4.4.21. Synthesis of (E)-1-((1-(buta-1,2-dienyl)cyclohexyl)methylene)-2-(2,4-dinitrophenyl) hydrazine (**374k**)*



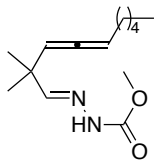
Substrate **374k** was synthesized using *GP3* and isolated (pentane/diethyl ether 9:1, 73% yield) as a yellow solid. Mp 134 °C. IR (neat): ν 3284, 3086, 2928, 2855, 1962, 1618, 1503, 1333, 1306, 1085 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.97 (s, 1H), 9.11 (d, *J* = 2.5 Hz, 1H), 8.29 (dd, *J* = 9.6, 2.3 Hz, 1H), 7.91 (d, *J* = 9.6 Hz, 1H), 7.31 (s, 1H), 5.25 – 5.20 (m, 1H), 5.01 (dq, *J* = 6.3, 3.1 Hz, 1H), 1.82 – 1.75 (m, 2H), 1.75 – 1.64 (m, 4H), 1.62 – 1.53 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8 (C), 157.6 (CH), 145.5 (C), 137.9 (C), 130.1 (CH), 129.0 (C), 123.6 (CH), 116.8 (CH), 96.0 (CH), 89.0 (CH), 43.0 (C), 34.2 (CH_2), 34.1 (CH_2), 26.0 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 14.5 (CH_3). HRMS calcd. for $C_{17}H_{20}O_4N_4Na$ ([M + Na]$^+$): 367.1377, found 367.1376.

*5.4.4.22. Synthesis of (E)-methyl 2-(2,2-dimethylhexa-3,4-dienylidene)hydrazinecarboxylate (**375a**)*



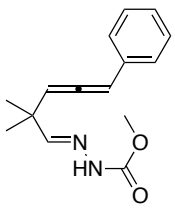
Substrate **375a** was synthesized using *GP3* and isolated pentane/diethyl ether 7:3, 65% yield) as a white solid. Mp 78 °C. IR (neat): ν 3238, 2967, 1961, 1717, 1547, 1257, 1046 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 7.33 (s, 1H), 5.24 – 5.13 (m, 2H), 3.66 (s, 3H), 1.63 (dd, *J* = 6.9, 3.3 Hz, 3H), 1.17 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, acetone): δ 203.5 (C), 154.5 (CH), 153.2 (C), 98.6 (CH), 88.6 (CH), 51.9 (C), 38.7 (CH_3), 25.8 (CH_3), 25.7 (CH_3), 14.4 (CH_3). HRMS calcd. for $C_{10}H_{16}O_2N_2Na$ ([M + Na]$^+$): 219.1104, found 219.1100.

*5.4.4.23. Synthesis of (E)-methyl 2-(2,2-dimethyldeca-3,4-dienylidene)hydrazinecarboxylate (**375b**)*



Substrate **375b** was synthesized using *GP3* and isolated (pentane/diethyl ether 1:1, 61% yield) as a yellow oil. IR (neat): ν 3245, 2958, 2926, 2856, 2372, 1959, 1721, 1491, 1301, 1040 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 7.35 (s, 1H), 5.27 – 5.17 (m, 2H), 3.65 (br, 3H), 2.05 – 1.90 (m, 2H), 1.47 – 1.35 (m, 2H), 1.32 (br, 4H), 1.18 (s, 6H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, acetone): δ 203.0 (C), 153.5 (CH), 153.4 (C), 99.5 (CH), 94.5 (CH), 52.2 (C), 39.0 (CH_3), 32.1 (CH_2), 29.6 ($2CH_2$), 26.2 (CH_2), 26.1 (CH_3), 23.2 (CH_3), 14.3 (CH_3). HRMS calcd. for $C_{14}H_{24}O_2N_2Na$ ([M + Na]$^+$): 275.1730, found 275.1726.

*5.4.4.24. Synthesis of (E)-methyl 2-(2,2-dimethyl-5-phenylpenta-3,4-dienylidene)hydrazine carboxylate (**375c**).*



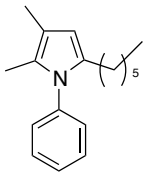
Substrate **375c** was synthesized using *GP3* and isolated (pentane/diethyl ether 6:4, 63% yield) as a yellow oil. IR (neat): ν 3239, 3061, 2964, 2373, 1948, 1739, 1454, 1293, 1044 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 7.44 – 7.18 (m, 6H), 6.37 (d, *J* = 6.4 Hz, 1H), 5.74 (d, *J* = 6.4 Hz, 1H), 3.67 (br, 3H), 1.29 (3H), 1.28 (3H). ^{13}C NMR (100 MHz, acetone): δ 204.0 (C), 154.7 (CH), 152.8 (C), 135.4 (C), 129.5 (2CH), 127.8 (CH), 127.4 (2CH), 103.3 (CH), 97.6 (CH), 54.9 (C), 39.8 (CH_3), 26.2 (CH_3), 26.1 (CH_3). HRMS calcd. for $C_{15}H_{18}O_2N_2Na$ ([M + Na]$^+$): 281.1261, found 281.1254.

5.4.5. Synthesis of pyrroles derivatives

5.4.5.1. General procedure for gold-catalyzed cycloisomerization reactions (**GP4**)

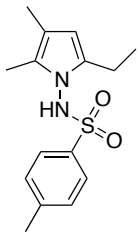
The gold catalyst (0.01 mmol) was added to a solution of β-allenylimines or hydrazones (0.2 mmol) in dry DCE (3.5 mL) under argon atmosphere, and the solution was heated at 100 °C, under microwave conditions, for 20 minutes. After cooling to room temperature, the mixture was filtered through a short pad of silica gel. The solvent was removed *in vacuo* and the reaction residue was purified by flash chromatography over silica gel.

5.4.5.2. Synthesis of 2,3-dimethyl-5-pentyl-1-phenyl-1H-pyrrole (**376**)



Substrate **376** was synthesized using *GP4* and isolated (pentane/diethyl ether 98:2, 15% yield) as a pale yellow oil. IR (neat): ν 3105, 3035, 2968, 2923, 1610, 1535, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.38 (m, 3H), 7.20 (dd, *J* = 8.2, 1.2 Hz, 2H), 5.82 (s, 1H), 2.34 – 2.25 (m, 2H), 2.07 (s, 3H), 1.92 (s, 3H), 1.39 – 1.48 (m, 2H), 1.13 – 1.27 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.0 (C), 129.1 (2CH), 128.7 (2CH), 127.6 (CH), 126.1 (C), 124.8 (C), 113.9 (C), 106.8 (CH), 31.7 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 27.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 11.4 (CH_3), 10.6 (CH_3). HRMS calcd. for $C_{18}H_{26}N$ ([M + H]$^+$): 256.2060, found 256.2058.

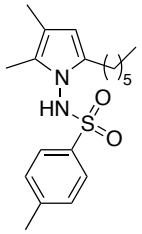
5.4.5.3. Synthesis of N-(5-ethyl-2,3-dimethyl-1H-pyrrol-1-yl)-4-methylbenzenesulfonamide (**377a**)



Substrate **377a** was synthesized using *GP4* and isolated (pentane/ethyl acetate 8:2, 57% yield) as a yellow oil. IR (neat): ν 3251, 2968, 2923, 1599, 1341, 1186, 813, 665 cm^{-1}. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.68 – 7.59 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.10 (s, 1H), 5.56 (s, 1H), 2.42 (s, 3H), 2.26 – 1.98 (m, 2H), 1.86 (s, 3H), 1.67 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 144.8 (C), 135.3 (C), 134.1 (C), 129.6 (2CH), 127.8 (2CH), 124.2 (C), 112.5 (C), 104.8 (CH), 21.1 (CH_3), 18.0 (CH_2), 12.1 (CH_3), 10.9 (CH_3), 8.3 (CH_3). HRMS calcd. for $C_{15}H_{20}O_2N_2NaS$ ([M + Na]$^+$): 315.1138, found 315.1138.

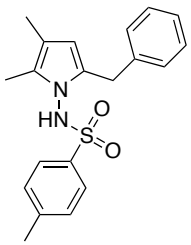
5.4.5.4. Synthesis of N-(5-hexyl-2,3-dimethyl-1H-pyrrol-1-yl)-4-methylbenzenesulfonamide (**377b**)

Substrate **377b** was synthesized using *GP4* and isolated (pentane/ethyl acetate 7:3, 61% yield) as a yellow oil. IR (neat): ν 3245, 2925, 2858, 1597, 1342, 1161, 813, 663 cm^{-1}. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H),



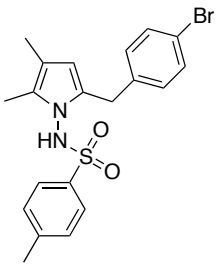
5.54 (s, 1H), 2.42 (s, 3H), 2.15 – 1.98 (m, 1H), 1.77 – 1.97 (m, 4H), 1.76 (s, 3H), 1.42 – 1.10 (m, 8H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 144.7 (C), 135.4 (C), 132.5 (C), 129.6 (2CH), 127.8 (2CH), 124.3 (C), 112.4 (C), 105.3 (CH), 31.3 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 24.8 (CH_2), 22.3 (CH_2), 21.1 (CH_3), 13.6 (CH_3), 10.9 (CH_3), 8.4 (CH_3). HRMS calcd. for $C_{19}H_{28}O_2N_2NaS$ ([M + Na]$^+$): 371.1764, found 371.1766.

*5.4.5.5. Synthesis of N-(5-benzyl-2,3-dimethyl-1H-pyrrol-1-yl)-4-methylbenzenesulfonamide (**377c**)*



Substrate **377c** was synthesized using *GP4* and isolated (pentane/ethyl acetate 9:1, 67% yield) as a yellow oil. IR (neat): ν 3259, 2936, 2891, 1593, 1363, 1178, 813, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.24 (m, 2H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.68 (s, 1H), 5.61 (s, 1H), 3.58 (d, *J* = 16.2 Hz, 1H), 3.39 (d, *J* = 16.2 Hz, 1H), 2.49 (s, 3H), 1.93 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1 (C), 139.0 (C), 135.6 (C), 130.6 (C), 130.0 (2CH), 128.7 (2CH), 128.7 (2CH), 128.5 (2CH), 126.5 (CH), 125.9 (C), 113.0 (C), 108.5 (CH), 32.0 (CH_2), 21.8 (CH_3), 11.6 (CH_3), 9.1 (CH_3). HRMS calcd. for $C_{20}H_{22}O_2N_2NaS$ ([M + Na]$^+$): 377.1294, found 377.1291.

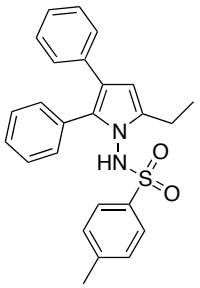
*5.4.5.6. Synthesis of N-(5-(4-bromobenzyl)-2,3-dimethyl-1H-pyrrol-1-yl)-4-methylbenzene-sulfonamide (**377d**)*



Substrate **377d** was synthesized using *GP4* and isolated (pentane/ethyl acetate 9:1, 70% yield) as a white solid. Mp 146 °C. IR (neat): ν 3250, 2921, 1597, 1341, 1160, 813, 664 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.36 (m, 4H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.75 (s, 1H), 5.55 (s, 1H), 3.51 (q, *J* = 16.2 Hz, 2H), 2.46 (s, 3H), 1.88 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2 (C), 138.2 (C), 135.5 (C), 131.7 (2CH), 130.5 (2CH), 130.4 (C), 130.0 (2CH), 128.5 (2CH), 125.8 (C), 120.2 (C), 113.2 (C), 108.5 (CH), 31.5 (CH_2), 21.8 (CH_3), 11.6 (CH_3), 9.0 (CH_3). HRMS calcd. for $C_{20}H_{22}O_2N_2BrNaS$ ([M + Na]$^+$): 455.0399, found 455.0404.

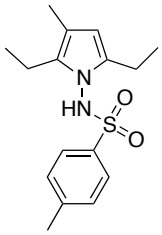
*5.4.5.7. Synthesis of N-(5-ethyl-2,3-diphenyl-1H-pyrrol-1-yl)-4-methylbenzenesulfonamide (**377e**)*

Substrate **377e** was synthesized using *GP4* and isolated (pentane/CH_2Cl_2 = 1:9, 69% yield) as a white solid. Mp 156 °C. IR (neat): ν 3268, 2974, 2935, 1599, 1341, 1162, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.23 – 6.99 (m, 10H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.81



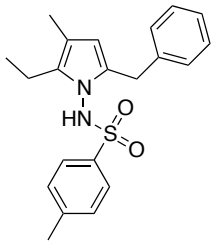
– 6.68 (m, 2H), 6.15 (s, 1H), 3.05 – 2.70 (m, 2H), 2.31 (s, 3H), 1.35 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2 (C), 137.9 (C), 136.0 (C), 134.2 (C), 130.9 (C), 130.0 (2CH), 129.6 (2CH), 128.5 (C), 128.2 (2CH), 128.2 (2CH), 128.1 (2CH), 127.9 (2CH), 126.7 (CH), 125.7 (CH), 121.7 (C), 105.3 (CH), 21.7 (CH_3), 19.3 (CH_2), 12.5 (CH_3). HRMS calcd. for $C_{25}H_{24}O_2N_2NaS$ ([M + Na]$^+$): 439.1451, found 439.1450.

*5.4.5.8. Synthesis of N-(2,5-diethyl-3-methyl-1H-pyrrol-1-yl)-4-methylbenzenesulfonamide (**377f**)*



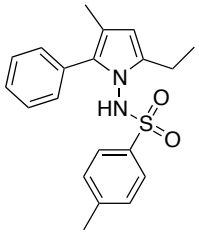
Substrate **377f** was synthesized using *GP4* and isolated (pentane/CH_2Cl_2 1:9, 94% yield) as yellow oil. IR (neat): ν 3250, 2967, 2932, 2873, 1597, 1375, 1159, 813, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.19 (s, 1H), 5.62 (s, 1H), 2.45 (s, 3H), 2.35 – 1.99 (m, 4H), 1.95 (s, 3H), 1.05 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9 (C), 135.6 (C), 134.2 (C), 130.8 (C), 129.9 (2CH), 128.3 (2CH), 112.7 (C), 105.6 (CH), 21.8 (CH_3), 18.5 (CH_2), 16.8 (CH_2), 14.2 (CH_3), 12.4 (CH_3), 11.6 (CH_3). HRMS calcd. for $C_{16}H_{22}O_2N_2NaS$ ([M + Na]$^+$): 329.1294, found 329.1296.

*5.4.5.9. Synthesis of N-(5-benzyl-2-ethyl-3-methyl-1H-pyrrol-1-yl)-4-methylbenzene sulfonamide (**377g**)*



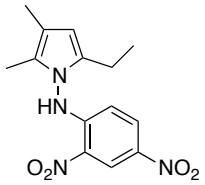
Substrate **377g** was synthesized using *GP4* and isolated (pentane/diethyl ether 7:3, 71% yield) as a yellow oil. IR (neat): ν 3255, 3028, 2965, 2925, 1598, 1344, 1161, 814, 663 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H), 7.40 – 7.12 (m, 5H), 6.98 (d, J = 7.0 Hz, 2H), 6.65 (s, 1H), 5.57 (s, 1H), 3.53 (d, J = 16.5 Hz, 1H), 3.31 (d, J = 16.4 Hz, 1H), 2.47 (s, 3H), 2.41 – 2.35 (m, 1H), 2.31 – 2.14 (m, 1H), 1.94 (s, 3H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1 (C), 139.0 (C), 135.6 (C), 131.9 (C), 130.3 (C), 130.0 (2CH), 128.7 (2CH), 128.6 (2CH), 128.4 (2CH), 126.5 (CH), 112.7 (C), 108.9 (CH), 32.0 (CH_2), 21.8 (CH_3), 16.9 (CH_2), 14.1 (CH_3), 11.6 (CH_3). HRMS calcd. for $C_{21}H_{24}O_2N_2NaS$ ([M + Na]$^+$): 391.1451, found 391.1451.

*5.4.5.10. Synthesis of N-(5-ethyl-3-methyl-2-phenyl-1H-pyrrol-1-yl)-4-methylbenzene sulfonamide (**377i**)*



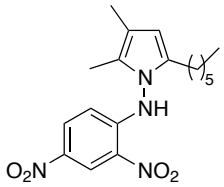
Substrate **377i** was synthesized using *GP4* and isolated (pentane/diethyl ether 8:2, quantitative yield) as a yellow oil. IR (neat): ν 3266, 2969, 2925, 1598, 1341, 1161, 809, 661 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.16 – 7.09 (m, 2H), 7.04 – 7.11 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.75 – 6.70 (m, 2H), 5.84 (s, 1H), 2.90 – 2.71 (m, 2H), 2.35 (s, 3H), 1.94 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (C), 137.5 (C), 134.3 (C), 131.1 (C), 129.4 (2CH), 128.9 (2CH), 128.7 (C), 128.0 (2CH), 127.9 (2CH), 125.9 (CH), 116.5 (C), 106.4 (CH), 21.7 (CH_3), 19.2 (CH_2), 12.6 (CH_3), 12.2 (CH_3). HRMS calcd. for $C_{20}H_{22}O_2N_2NaS$ ([M + Na]$^+$): 377.1294, found 377.1296.

*5.4.5.11. Synthesis of N-(2,4-dinitrophenyl)-5-ethyl-2,3-dimethyl-1H-pyrrol-1-amine (**378a**)*



Substrate **378a** was synthesized using *GP4* and isolated (pentane/diethyl ether 9:1, 93% yield) as a red oil. IR (neat): ν 3354, 3104, 2969, 2921, 1615, 1498, 1334, 1229 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 9.16 (d, *J* = 2.5 Hz, 1H), 8.23 (dd, *J* = 9.4, 2.2 Hz, 1H), 6.20 (d, *J* = 9.4 Hz, 1H), 5.83 (s, 1H), 2.55 – 2.35 (m, 1H), 2.39 – 2.21 (m, 1H), 2.04 (s, 3H), 1.98 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (C), 139.1 (C), 133.0 (C), 131.0 (CH), 130.7 (C), 123.5 (CH), 123.4 (C), 114.9 (CH), 114.2 (C), 106.1 (CH), 18.7 (CH_2), 13.1 (CH_3), 11.5 (CH_3), 8.8 (CH_3). HRMS calcd. for $C_{14}H_{17}O_4N_4Na$ ([M + Na]$^+$): 305.1244, found 305.1246.

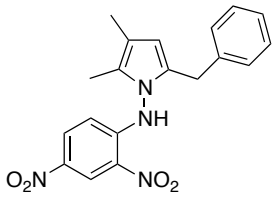
*5.4.5.12. Synthesis of N-(2,4-dinitrophenyl)-5-hexyl-2,3-dimethyl-1H-pyrrol-1-amine (**378b**)*



Substrate **378b** was synthesized using *GP4* and isolated (pentane/diethyl ether 95:5, 92% yield) as a orange oil. IR (neat): ν 3356, 3111, 2966, 2915, 1616, 1496, 1331, 1230 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 9.16 (d, *J* = 2.5 Hz, 1H), 8.23 (dd, *J* = 9.4, 2.5 Hz, 1H), 6.19 (d, *J* = 9.4 Hz, 1H), 5.82 (s, 1H), 2.44 – 2.21 (m, 2H), 2.03 (s, 3H), 1.98 (s, 3H), 1.46 – 1.56 (m, 2H), 1.55 – 1.21 (m, 6H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (C), 139.1 (C), 131.6 (C), 130.9 (CH), 130.6 (C), 123.5 (CH), 123.2 (C), 114.9 (CH), 114.2 (C), 106.8 (CH), 31.6 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 11.6 (CH_3), 8.9 (CH_3). HRMS calcd. for $C_{18}H_{25}O_4N_4$ ([M + H]$^+$): 361.1870, found 361.1870.

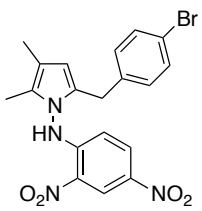
*5.4.5.13. Synthesis of 5-benzyl-N-(2,4-dinitrophenyl)-2,3-dimethyl-1H-pyrrol-1-amine (**378c**)*

Substrate **378c** was synthesized using *GP4* and isolated (pentane/diethyl ether 9:1,



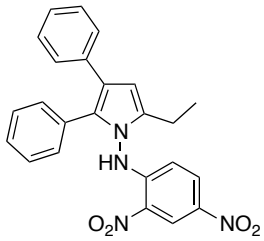
quantitative yield) as a red solid. Mp 153 °C. IR (neat): ν 3355, 3103, 2920, 1617, 1496, 1336, 1230 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 9.06 (d, *J* = 2.5 Hz, 1H), 8.00 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.17 – 6.94 (m, 5H), 6.00 (d, *J* = 9.4 Hz, 1H), 5.93 (s, 1H), 3.73 (q, *J* = 15.9 Hz, 2H), 2.04 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6 (C), 130.4 (CH), 130.1 (C), 130.0 (C), 128.6 (2CH), 128.6 (C), 128.5 (2CH), 126.5 (CH), 124.4 (C), 123.2 (C), 123.2 (CH), 114.9 (C), 114.1 (CH), 108.8 (CH), 32.7 (CH_2), 11.6 (CH_3), 8.9 (CH_3). HRMS calcd. for $C_{19}H_{18}O_4N_4H$ ([M + H]$^+$): 367.1398, found 367.1401.

*5.4.5.14. Synthesis of 5-(4-bromobenzyl)-N-(2,4-dinitrophenyl)-2,3-dimethyl-1H-pyrrol-1-amine (**378d**)*



Substrate **378d** was synthesized using *GP4* and isolated (pentane/diethyl ether 95:5, quantitative yield) as brown crystals. Mp 166 °C. IR (neat): ν 3354, 3102, 2920, 1615, 1497, 1335, 1230 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 9.02 (d, *J* = 2.5 Hz, 1H), 7.98 – 8.02 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.92 (d, *J* = 9.4 Hz, 1H), 5.87 (s, 1H), 3.66 (br s, 2H), 1.99 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4 (C), 138.8 (C), 137.7 (C), 131.4 (2CH), 130.4 (C), 130.3 (3 CH), 129.2 (C), 124.4 (C), 122.9 (CH), 120.0 (C), 114.7 (CH), 113.9 (C), 108.6 (CH), 31.8 (CH_2), 11.2 (CH_3), 8.5 (CH_3). HRMS calcd. for $C_{19}H_{17}O_4N_4BrNa$ ([M + H]$^+$): 467.0325, found 467.0325.

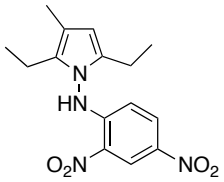
*5.4.5.15. Synthesis of N-(2,4-dinitrophenyl)-5-ethyl-2,3-diphenyl-1H-pyrrol-1-amine (**378e**)*



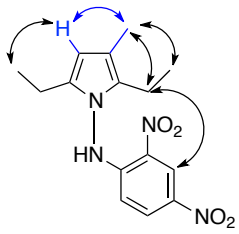
Substrate **378e** was synthesized using *GP4* and isolated (pentane/diethyl ether 9:1, 90% yield) as a brown solid. Mp 170 °C. IR (neat): ν 3359, 3103, 2972, 1616, 1499, 1336, 1230 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 9.00 (d, *J* = 2.5 Hz, 1H), 8.19 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.36 – 7.09 (m, 10H), 6.36 (s, 1H), 6.28 (d, *J* = 9.4 Hz, 1H), 2.72 – 2.38 (m, 2H), 1.31 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6 (C), 139.1 (C), 135.8 (C), 135.3 (C), 130.7 (CH), 130.5 (C), 130.3 (C), 130.2 (2CH), 129.2 (C), 128.7 (2CH), 128.4 (2CH), 128.1 (CH), 127.8 (2CH), 126.2 (CH), 123.3 (CH), 122.2 (C), 115.1 (CH), 105.6 (CH), 19.0 (CH_2), 12.8 (CH_3). HRMS calcd. for $C_{24}H_{20}O_4N_4Na$ ([M + Na]$^+$): 451.1372, found 451.1377.

*5.4.5.16. Synthesis of N-(2,4-dinitrophenyl)-2,5-diethyl-3-methyl-1H-pyrrol-1-amine (**378f**)*

Substrate **378f** was synthesized using *GP4* and isolated (pentane/diethyl ether 8:2, quantitative yield) as a red oil. IR (neat): ν 3356, 3105, 2968, 2931, 1615, 1498, 1334, 1229

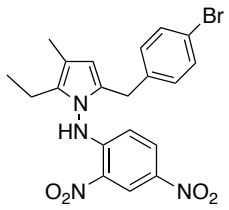


cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 9.16 (d, *J* = 2.5 Hz, 1H), 8.23 (dd, *J* = 9.4, 2.5 Hz, 1H), 6.19 (d, *J* = 9.4 Hz, 1H), 5.83 (s, 1H), 2.51 – 2.38 (m, 2H), 2.37 – 2.22 (m, 2H), 2.06 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (C), 139.1 (C), 132.8 (C), 130.9 (CH), 130.6 (C), 129.4 (C), 123.5 (CH), 115.1 (CH), 113.8 (C), 106.4 (CH), 18.7 (CH_2), 17.2 (CH_2), 15.0 (CH_3), 12.8 (CH_3), 11.5 (CH_3). HRMS calcd. for $C_{15}H_{19}O_4N_4$ ([M + H]$^+$): 319.1401, found 319.1402.



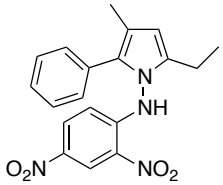
*NOE Correlations for compound **378f***

*5.4.5.17. Synthesis of 5-(4-bromobenzyl)-N-(2,4-dinitrophenyl)-2-ethyl-3-methyl-1H-pyrrol-1-amine (**378h**)*



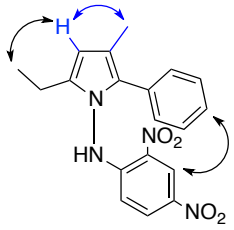
Substrate **378h** was synthesized using *GP4* and isolated (pentane/diethyl ether 9:1, 89% yield) as a red oil. IR (neat): ν 3355, 3103, 2966, 2925, 1615, 1498, 1337, 1228 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 9.08 (d, *J* = 2.5 Hz, 1H), 8.06 – 8.01 (m, 1H), 7.27 – 7.20 (m, 2H), 6.89 – 6.67 (m, 2H), 5.97 (d, *J* = 9.4 Hz, 1H), 5.89 (s, 1H), 3.87 – 3.58 (br s, 2H), 2.53 – 2.33 (m, 1H), 2.27 – 2.02 (m, 1H), 2.06 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (C), 139.0 (C), 137.5 (C), 131.6 (2CH), 130.6 (C), 130.5 (C), 130.4 (2CH), 130.4 (CH), 129.2 (C), 123.1 (CH), 120.5 (C), 115.1 (CH), 113.9 (C), 109.2 (CH), 32.1 (CH_2), 17.1 (CH_2), 14.9 (CH_3), 11.5 (CH_3). HRMS calcd. for $C_{20}H_{19}BrO_4N_4Na$ ([M + H]$^+$): 483.0457, found 483.0461.

*5.4.5.18. Synthesis of N-(2,4-dinitrophenyl)-5-ethyl-3-methyl-2-phenyl-1H-pyrrol-1-amine (**378i**)*



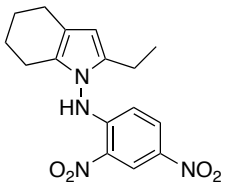
Substrate **378i** was synthesized using *GP4* and isolated (pentane/diethyl ether 9:1, quantitative yield) as a orange solid. Mp 173 °C. IR (neat): ν 3359, 3099, 2968, 2360, 1617, 1500, 1338, 1017, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 9.02 (d, *J* = 2.5 Hz, 1H), 8.18 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.38 – 7.14 (m, 5H), 6.12 (d, *J* = 9.4 Hz, 1H), 6.04 (s, 1H), 2.56 (m, 1H), 2.45 – 2.39 (m, 1H), 2.18 (s, 3H), 1.26 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (C), 138.9 (C), 135.2 (C), 130.6 (CH), 130.5 (C), 130.4 (C), 129.4 (C), 129.3 (CH),

128.6 (CH), 127.4 (CH), 123.3 (CH), 116.9 (C), 115.1 (CH), 107.5 (CH), 18.9 (CH_2), 12.9 (CH_3), 12.2 (CH_3). HRMS calcd. for $C_{19}H_{19}O_4N_4$ ([M + H]$^+$): 367.1401, found 367.1397.



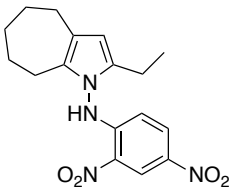
*NOE Correlations for compound **378i***

*5.4.5.19. Synthesis of N-(2,4-dinitrophenyl)-2-ethyl-4,5,6,7-tetrahydro-1H-indol-1-amine (**378j**)*



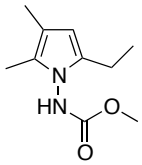
Substrate **378j** was synthesized using *GP4* and isolated (pentane/diethyl ether 95:5, quantitative yield) as an orange solid. Mp 93 °C. IR (neat): ν 3355, 3104, 2929, 2849, 1616, 1499, 1336, 1147 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (s, 1H), 9.15 (d, *J* = 1.9, 1H), 8.25 (dd, *J* = 1.6, 9.3, 1H), 6.28 (d, *J* = 9.4, 1H), 5.83 (s, 1H), 2.62 – 2.26 (m, 5H), 2.14 (br, 1H), 1.74 (br, 4H), 1.17 (t, *J* = 7.5, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (C), 139.0 (C), 133.4 (C), 130.9 (CH), 130.7 (C), 126.7 (C), 123.5 (CH), 117.1 (C), 114.9 (CH), 104.0 (CH), 23.7 (CH_2), 23.0 (CH_2), 22.9 (CH_2), 20.9 (CH_2), 18.7 (CH_2), 13.2 (CH_3). HRMS calcd. for $C_{16}H_{19}O_4N_4$ ([M + H]$^+$): 331.1401, found 331.1402.

*5.4.5.20. Synthesis of N-(2,4-dinitrophenyl)-2-ethyl-5,6,7,8-tetrahydrocyclohepta[b]pyrrol-1(4H)-amine (**378k**)*



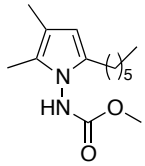
Substrate **378k** was synthesized using *GP4* and isolated (pentane/diethyl ether 9:1, 83% yield) as an orange oil. IR (neat): ν 3358, 3104, 2920, 2848, 1615, 1498, 1335, 1279, 1146 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 9.15 (d, *J* = 2.5, 1H), 8.24 (m, 1H), 6.18 (d, *J* = 9.4, 1H), 5.81 (s, 1H), 2.58 – 2.49 (m, 3H), 2.37 (m, 3H), 1.79 (m, 2H), 1.75 – 1.65 (m, 2H), 1.64 – 1.58 (m, 1H), 1.56 – 1.47 (m, 1H), 1.15 (t, *J* = 7.5, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (C), 139.1 (C), 131.7 (C), 130.9 (CH), 130.6 (C), 129.6 (C), 123.5 (CH), 121.6 (C), 114.9 (CH), 105.9 (CH), 31.9 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 25.5 (CH_2), 18.8 (CH_2), 13.0 (CH_3). HRMS calcd. for $C_{17}H_{21}O_4N_4$ ([M + H]$^+$): 345.1557, found 345.1559.

*5.4.5.21. Synthesis of methyl 5-ethyl-2,3-dimethyl-1H-pyrrol-1-ylcarbamate (**379a**).*



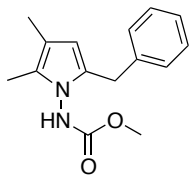
Substrate **379a** was synthesized using *GP4* and isolated (pentane/diethyl ether 7:3, 61% yield) as a yellow oil. IR (neat): ν 3290, 2968, 2921, 2863, 1724, 1453, 1251, 1063 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 5.96 (s, 1H), 4.29 – 4.01 (m, 3H), 2.85 (q, *J* = 7.5, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 1.56 (t, *J* = 7.5, 3H). ^{13}C NMR (100 MHz, acetone): δ 157.1 (C), 133.8 (C), 124.4 (C), 111.6 (C), 104.5 (CH), 52.9 (CH_3), 19.2 (CH_2), 13.4 (CH_3), 11.6 (CH_3), 8.7 (CH_3). HRMS calcd. for $C_{10}H_{16}O_2N_2Na$ ([M + H]$^+$): 219.1104, found 219.1100.

*5.4.5.22. Synthesis of methyl 5-hexyl-2,3-dimethyl-1H-pyrrol-1-ylcarbamate (**379b**)*



Substrate **379b** was synthesized using *GP4* and isolated (pentane/diethyl ether 8:2, 51% yield) as a yellow oil. IR (neat): ν 3288, 2956, 2926, 2860, 1726, 1453, 1250, 1065 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 5.52 (s, 1H), 3.73 (br, 2H), 2.48 – 2.29 (m, 2H), 1.95 (s, 3H), 1.90 (s, 3H), 1.53 (m, 2H), 1.38 – 1.24 (m, 6H), 0.88 (t, *J* = 6.9, 3H). ^{13}C NMR (100 MHz, acetone): δ 156.7 (C), 131.9 (C), 123.9 (C), 111.3 (C), 104.9 (CH), 52.5 (CH_3), 32.1 (CH_2), 29.7 (CH_2), 25.7 (CH_2), 22.9 ($2CH_2$), 14.0 (CH_3), 11.2 (CH_3), 8.4 (CH_3). HRMS calcd. for $C_{14}H_{24}O_2N_2Na$ ([M + H]$^+$): 275.1730, found 275.1726.

*5.4.5.23. Synthesis of methyl 5-benzyl-2,3-dimethyl-1H-pyrrol-1-Cylcarbamate (**379c**)*



Substrate **379c** was synthesized using *GP4* and isolated (pentane/diethyl ether 6:4, 67% yield) as a yellow oil. IR (neat): ν 3286, 3027, 2917, 2862, 2434, 1721, 1453, 1240, 1064, 672 cm^{-1}. ^{1}H NMR (400 MHz, acetone): δ 7.37 – 7.01 (m, 5H), 5.48 (s, 1H), 3.73 (br, 4H), 3.39 (m, *J* = 6.9, 1H), 1.97 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, acetone): δ 156.9 (C), 140.7 (C), 130.9 (C), 129.6 (CH), 128.9 (2CH), 126.7 (2CH), 125.0 (C), 111.9 (C), 106.9 (CH), 52.9 (CH_3), 32.5 (CH_2), 11.6 (CH_3), 8.8 (CH_3). HRMS calcd. for $C_{15}H_{18}O_2N_2Na$ ([M + H]$^+$): 281.1261, found 281.1261.

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General conclusions

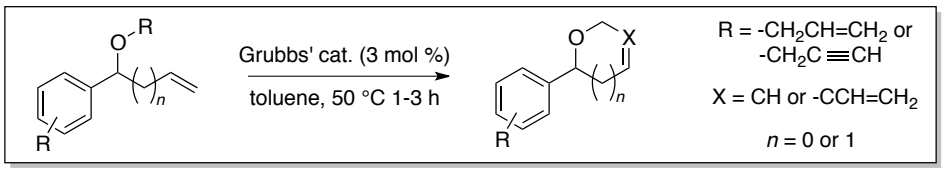
The synthesis of complex organic molecules from simple, readily available starting materials is one of the most investigated issues in organic chemistry. Efficient synthetic methods, required to assemble complex molecular arrays and high valuable compounds, include reactions that are both selective (chemo-, regio-, diastereo-, and enantio-) and atom-economical (maximum number of atoms of reactants appearing in the products). Transition metal-catalyzed procedures that are both selective and economical for the formation of cyclic structures represent an important starting point for this long-term goal.

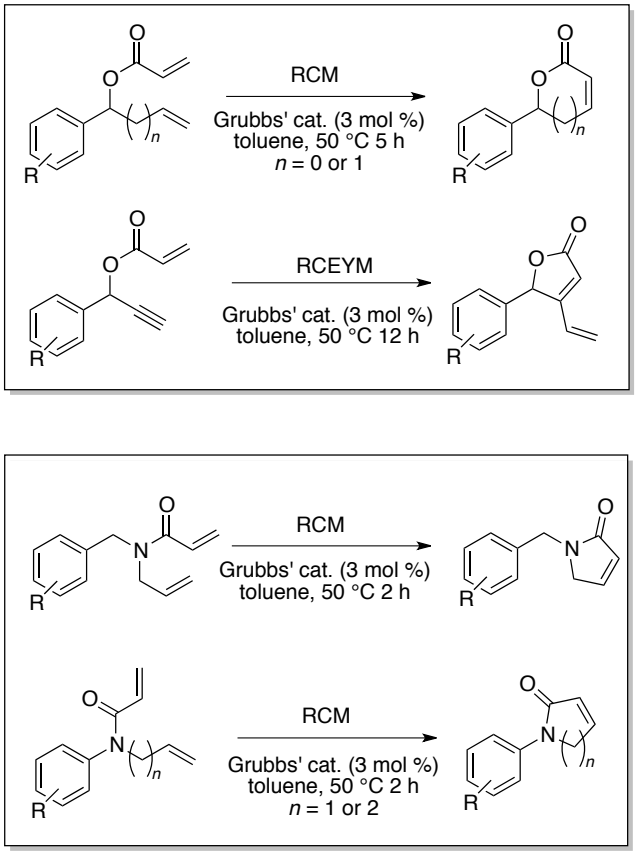
The transition-metal-catalyzed reactions of (poly)unsaturated substrates offer an attractive pathway for the conversion of simple acyclic molecules into cyclic compounds. Moreover, since these processes exhibit excellent chemoselectivity towards C-C π systems, the cyclized products usually retain a range of functional groups that can be used for further synthetic transformations.

In this dissertation we described four different class of transition metal-catalyzed reactions, which provided an atom- and step-economical entry into a range of oxygen- and nitrogen-containing heterocycles: (1) ring-closing diene and enyne metathesis, (2) Pauson-Khand reactions, (3) platinum-, gold-, and iridium-catalyzed activation of alkynes towards nucleophiles and (4) gold-catalyzed cyclizations of allenes.

In the last few years, diene and enyne metathesis have emerged as versatile synthetic techniques. Since the discovery of stable, reactive and functional group tolerant catalysts, these multiple-bond reorganizations have provided organic chemists with a powerful tool to access molecules, which are difficult to achieve by conventional ways. Thus, in the last decade, metatheses have known an explosion of their applications being nicely exploited for the synthesis of complex natural and non-natural products.

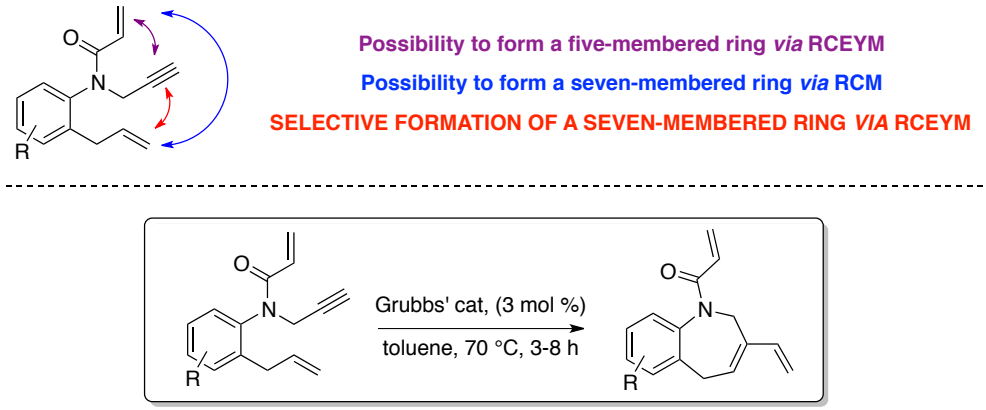
While considering the high tolerance of metathesis catalysts towards heteroatoms, we envisaged to employ RCM and RCEYM for the construction of functionalized building blocks, which could be useful in target-directed syntheses. As illustrated in the first chapter of this manuscript, both processes have been successfully used for the synthesis of five- and six-membered ethers, lactones and lactams (Scheme 6.1).





Scheme 6.1. *RCM and RCEYM for the synthesis of ethers, lactones and lactams*

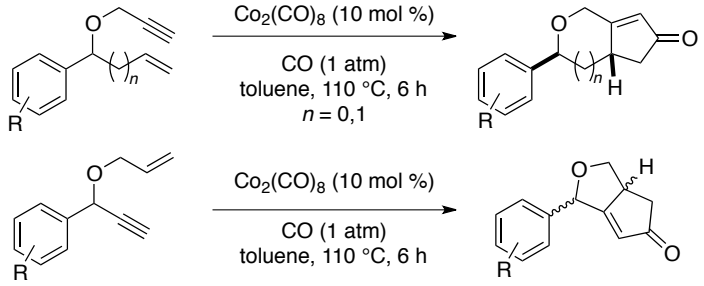
Moreover, a convenient regioselective RCEYM procedure has been developed to achieve variously substituted benzazepine scaffolds (Scheme 6.2).



Scheme 6.2. *Regioselective RCEYM for the synthesis of 1- and 2-benzazepine scaffolds*

Finally, the synthetic utility of ring-closed products was demonstrated by a two-directional funcionalization *via* either Diels–Alder reactions or Michael addition.

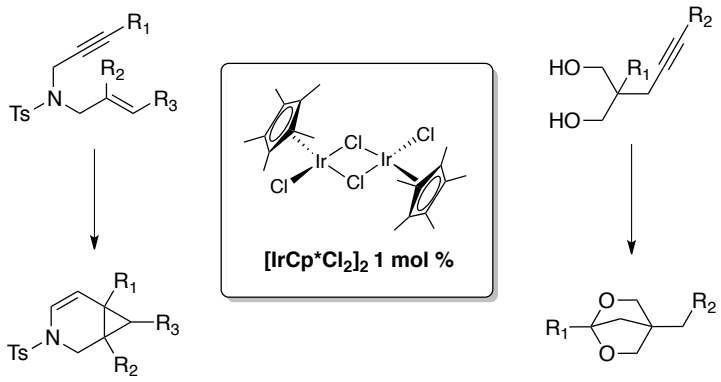
The Pauson-Khand reaction is another transition-metal catalyzed process, which allows for a rapid increase in molecular complexity from relatively simple starting materials, containing alkene and alkyne moieties. In the aim to develop a new asymmetric version of this carbonylation process, some of the acyclic enyne precursors, previously engaged in RCEYM to form cyclic dienes, have also been employed for the construction of oxygen-containing bicyclic skeletons (Scheme 6.3).



Scheme 6.3. *PKR for the synthesis of oxygen-containing bicyclic skeletons*

Furthermore, in the second chapter of this manuscript, preliminary results concerning the low activity of chiral biheteroaromatic diphosphine ligands in the enantioselective Co-catalyzed PKR have been reported.

Platinum-, gold- and iridium-based complexes provide a different atom-economical entry into functionalized cyclic scaffolds. Indeed, these soft Lewis acidic compounds have emerged in the past few years as the most powerful catalysts for electrophilic activation of alkynes toward a variety of nucleophiles. In chapter three, we have presented a general overview of this peculiar reactivity. Particular emphasis has been placed on the synthesis of dioxabicyclo[2.2.1]ketals and azabicyclo[4.1.0]heptenes through new efficient $[IrCp^*Cl_2]_2$-catalyzed cyclizations of homopropargylic diols and nitrogen-tethered 1,6-enynes (Scheme 6.4).

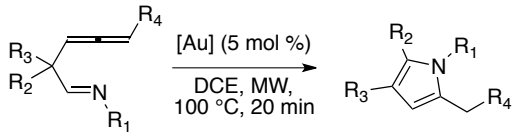


Scheme 6.4. *Ir(III)-catalyzed cyclizations of homopropargylic diols and nitrogen-tethered 1,6-enynes*

Our Ir(III)-based catalyst is effective under mild conditions, in low catalytic loadings and in absence of any other additive. For these reasons, the protocol developed seems to have valuable applicability, especially if compared to previously reported Ir(I)-catalyzed cyclizations. Moreover, the formation of an unprecedented cyclized product was achieved while applying the cycloisomerization to malonate-tethered 1,6-enyne.

As outlined in chapter three, gold complexes are highly reactive catalysts for the acidic activation of C-C multiple bonds toward nucleophilic attack. Despite a number of reports on gold-catalyzed addition of *O*- and *N*-nucleophiles to alkynes, analogous reactions of alkenes or allenes have been studied less frequently. In our opinion, allenes are a class of valuable synthetic precursors in preparative organic chemistry because of their ability to undergo a variety of transformations. Additionally, their axial chirality offers the opportunity to obtain new products in a stereoselective fashion by chirality transfer.

In chapter four, we have shown that the gold-catalyzed cyclizations of allenes allow the rapid construction of highly useful hetero- or carbocycles by formation of new C-O, C-N, C-S, or C-C bonds. In this field, a new cycloisomerization of β-allenylimines or β-allenylhydrazones has been presented, which opens up a versatile access to 2,3,5-trisubstituted pyrroles rings through selective intramolecular 1,2-alkyl or -aryl migrations (Scheme 6.5). This original and easy to handle protocol was effective for a broad range of *N*-substituted precursors and tolerated both alkyl and aryl groups at the terminal allenyl atom.



Scheme 6.5. *Gold-catalysed cyclizations of β-allenylimines or β-allenylhydrazones*

In conclusion, metathesis reactions, as well as Pauson-Khand carbonylations and transition metal-catalyzed nucleophilic attack to C-C multiple bonds, allow for a rapid increase in molecular complexity from relatively simple starting materials. Manuscripts adding to the scope of these reactions are being published at a rapid rate attesting to their interest in the chemical community and it is likely that many other applications will be disclosed in the next decade. The development of new transformations should be facilitated by the mechanistic foundation provided by the previous studies. Finally, with the discovery of new asymmetric methodologies, the transition-metal catalyzed transformations described in this manuscript will continue to occupy, in the next future, a remarkable role in organic synthesis.

Summary in Italian

REAZIONI DI CICLOISOMERIZZAZIONE CATALIZZATE DA COMPLESSI DI METALLI DI TRANSIZIONE. SINTESI DI COMPOSTI ETEROCICLICI CONTENENTI OSSIGENO E AZOTO

INTRODUZIONE GENERALE

Negli ultimi anni, la necessità di mezzi eco-sostenibili per la preparazione della vasta gamma di prodotti chimici richiesti dalla società ha spinto la ricerca verso lo sviluppo di nuovi processi sintetici efficaci ed efficienti.

Al fine di ridurre al minimo l'utilizzo di materie prime e la produzione di rifiuti, una reazione chimica dovrebbe procedere con alti livelli di "economia d'atomo". Più in dettaglio, una sequenza sintetica ideale dovrebbe avvenire in resa quantitativa, con un controllo completo della stereochimica e senza la formazione di sottoprodotti.

Le reazioni di ciclizzazione di sistemi polinsaturi, catalizzate da metalli di transizione, offrono una possibilità concreta di raggiungere tutti gli obiettivi sopra descritti. Inoltre, l'elevata versatilità sintetica dei sistemi polinsaturi rende accessibile una grande varietà di composti, utili come intermedi nella preparazione di molecole più complesse.

In questa tesi sono trattate quattro diverse classi di reazioni di ciclizzazione catalizzate da metalli di transizione: (1) metatesi con chiusura d'anello, (2) carbonilazioni di Pauson-Khand, (3) attivazioni elettrofile di alchini mediate da platino, oro e iridio (4) cicloisomerizzazioni di alleni catalizzate da oro. Queste metodologie, oltre a rientrare tra le reazioni ad elevata "economia d'atomo", permettono di ottenere elevate complessità molecolari in un unico passaggio sintetico.

Le quattro tipologie di reazioni sopra elencate sono state impiegate con successo per la sintesi di composti eterociclici contenenti ossigeno e azoto, strutture base di molte molecole naturali o biologicamente attive.

1. REAZIONI DI METATESI CON CHIUSURA D'ANELLO

Scoperte nel 1950, le reazioni di metatesi delle olefine, che procedono mediante rottura e riformazione di legami multipli carbonio-carbonio, oggi rappresentano uno dei processi più attraenti e utilizzati della sintesi organica.

Negli ultimi dieci anni, grazie allo sviluppo di catalizzatori stabili, altamente attivi e tolleranti nei confronti della maggior parte dei gruppi funzionali (Figura 1), i processi metatetici hanno permesso di isolare una grande varietà di molecole organiche, difficilmente ottenibili utilizzando strategie sintetiche convenzionali.

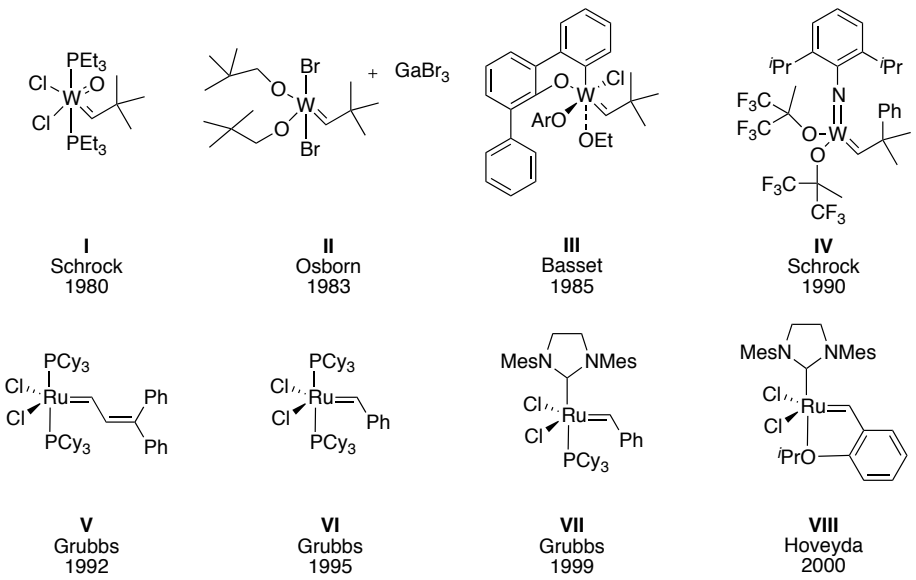
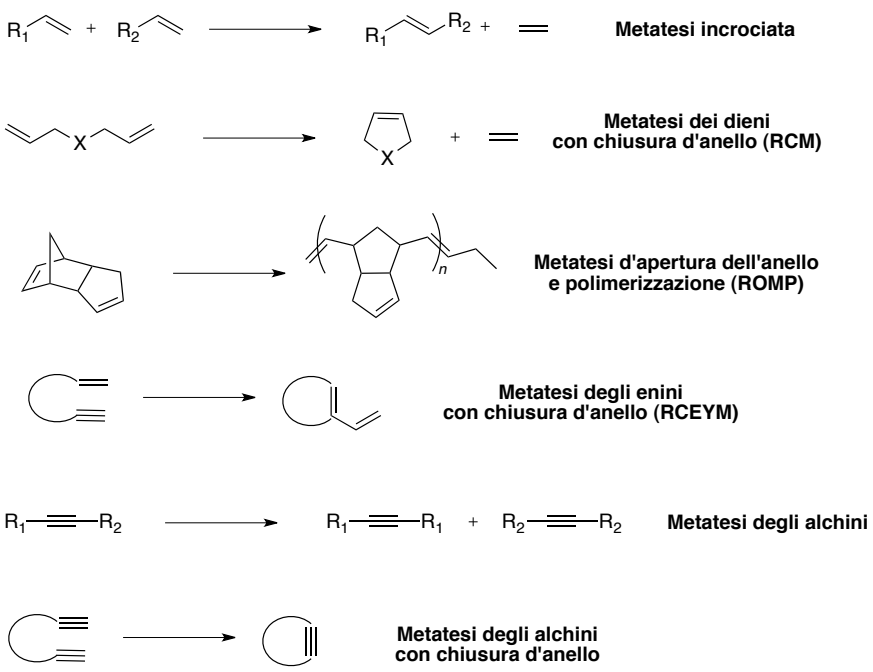


Figura 1. *Esempi di catalizzatori di metatesi*

In base al tipo di legame insaturo coinvolto nel processo, tre categorie principali di reazioni di metatesi possono essere individuate: quelle dei composti dienici, eninici e diinici (Schema 1). Inoltre, il cambiamento strutturale, che avviene durante il processo, può essere ulteriormente suddiviso in chiusura ad anello, apertura d'anello e metatesi incrociata (Schema 1).

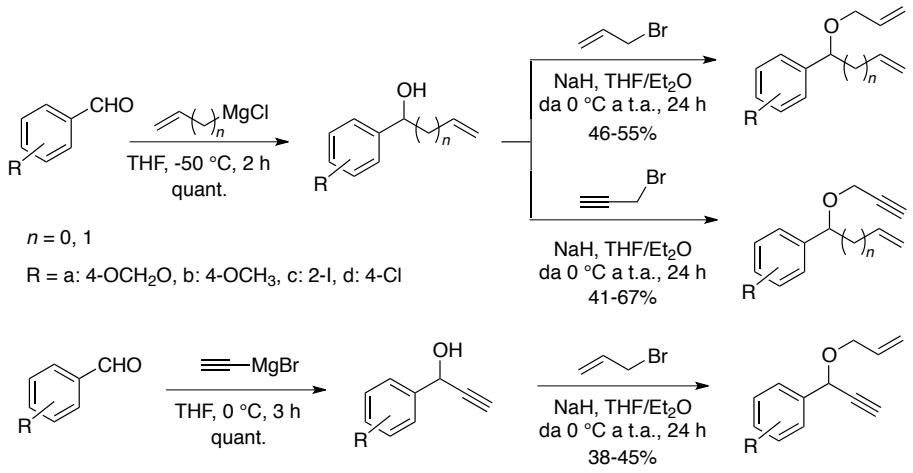


Schema 1. *Diverse classi di reazione di metatesi*

Nel primo capitolo della tesi sono state approfondite le reazioni di metatesi con chiusura d'anello di substrati dienici (RCM) ed eninici (RCEYM). Più in particolare, queste riorganizzazioni di legami multipli C-C sono state utilizzate per ottenere gli scheletri eterociclici più diffusi in prodotti naturali o in composti dotati di interessanti proprietà farmacologiche.

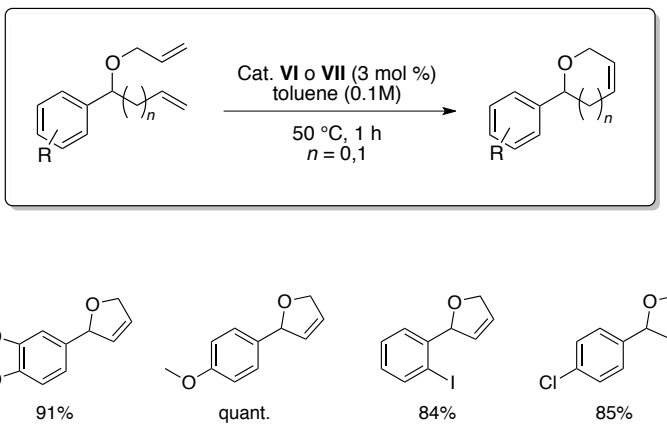
Concentrandoci su composti ossigenati e azotati, abbiamo iniziato le nostre indagini sviluppando una procedura sintetica capace di formare eteri ciclici a cinque o sei termini.

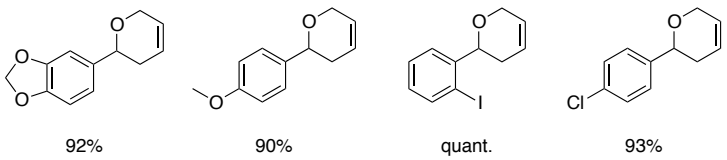
I substrati dienici ed eninici, precursori della ciclizzazione, sono stati ottenuti in buone rese da aldeidi aromatiche commercialmente disponibili, mediante l'addizione di reattivi di Grignard al gruppo carbonilico e la successiva eterificazione dei risultanti alcoli secondari (Schema 2).



Schema 2. *Sintesi di composti 1,6- e 1,7-dienici ed eninici*

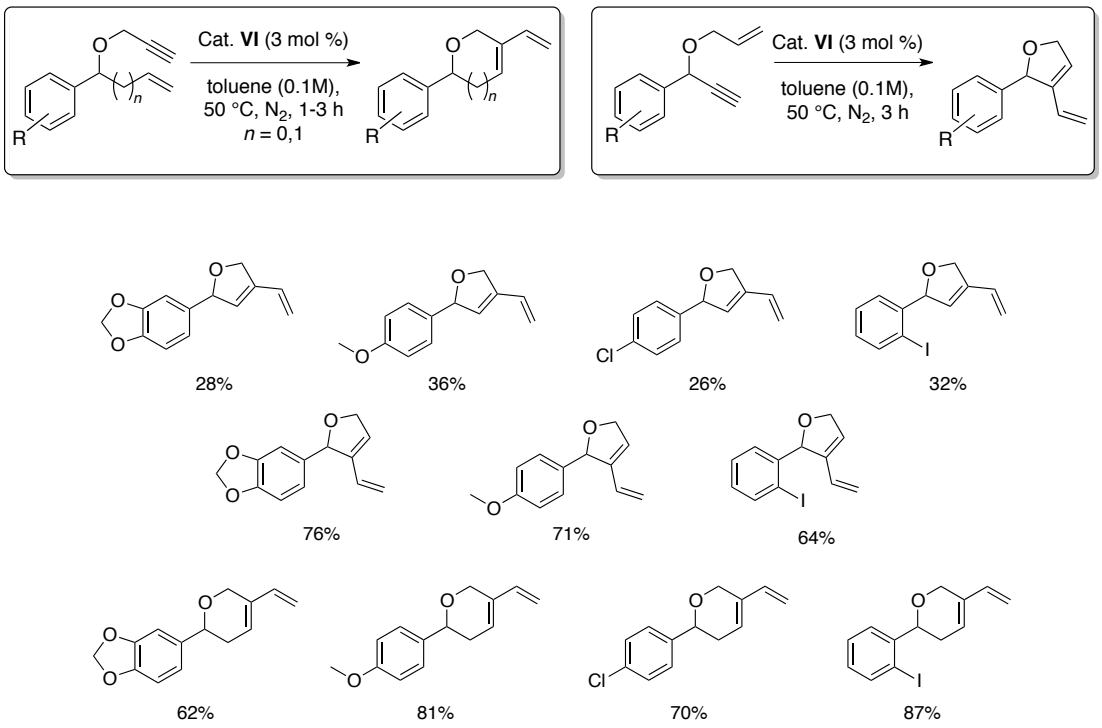
Le reazioni di ciclizzazione dei precursori dienici, eseguite utilizzando i catalizzatori di Grubbs **VI** e **VII** (3 mol%), in toluene, a 50 °C, hanno portato alla rapida formazione dei diidrofurani e diidropirani corrispondenti in ottime rese (Schema 3).





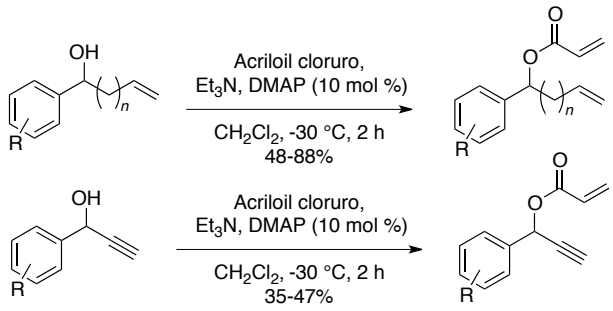
Schema 3. *RCM di sistemi 1,6- e 1,7-dienci*

In maniera analoga, diversi 1,6- e 1,7-enini, sono stati convertiti, in presenza del catalizzatore di metatesi **VI**, negli 1,3-dieni corrispondenti in rese da moderate a buone (Schema 4). Tutte le RCEYM, così come le RCM, tollerano la presenza di gruppi elettron donatori ed elettron attrattori sull'anello aromatico dei substrati di partenza.



Schema 4. *RCEYM di sistemi 1,6- e 1,7-eninici*

I lattoni sono altre unità strutturali comuni a numerosi prodotti biologicamente attivi, molti dei quali presentano proprietà antitumorali. Al fine di ottenere esteri ciclici a cinque e sei termini, una diversa strategia sintetica è stata sviluppata per la preparazione dei substrati da far reagire nelle reazioni di metatesi. In questo caso, gli alcoli allilici, omoallilici e propargilici, isolati in precedenza, sono stati funzionalizzati mediante un'esterificazione classica con acriloil cloruro: Gli acrilati desiderati sono stati così isolati in tempi di reazione brevi e con buone rese (Schema 5).

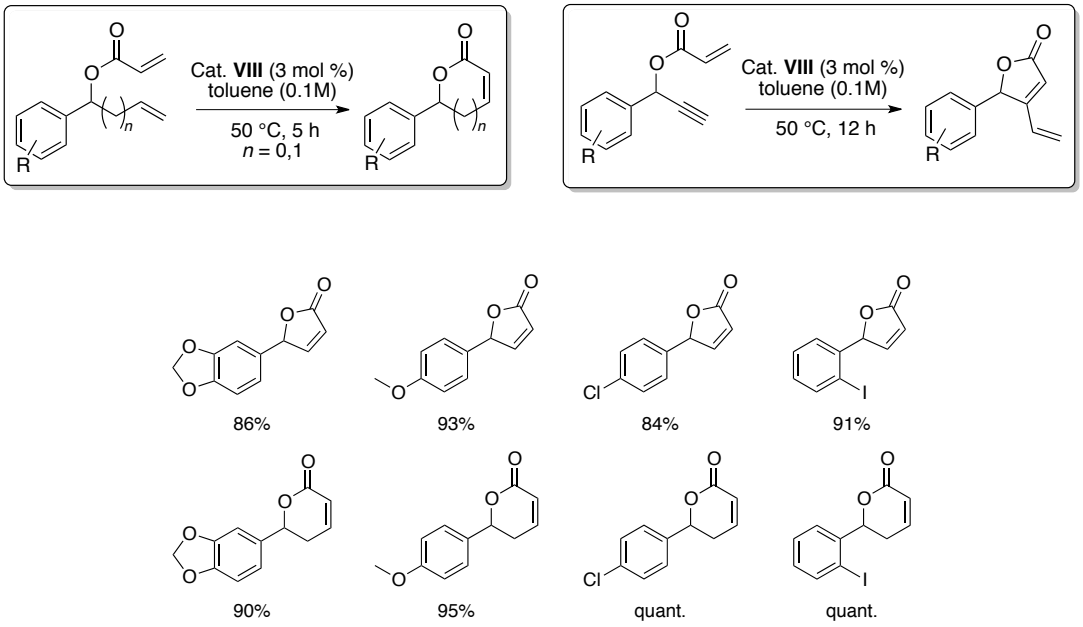


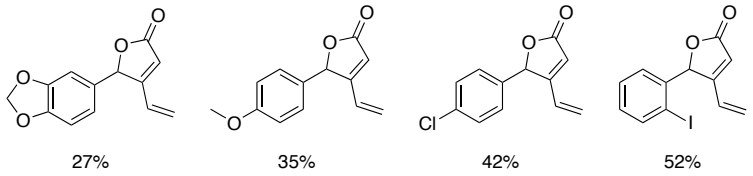
n = 0,1; R = a: 4-OCH_2O, b: 4-OCH_3, c: 2-I, d: 4-Cl

Schema 5. *Sintesi di esteri acrilici*

Risultati preliminari, ottenuti sottoponendo un substrato modello alle condizioni di metatesi, hanno chiaramente dimostrato che il catalizzatore di Grubbs di prima generazione (**VI**) è inefficace nel promuovere la ciclizzazione degli acrilati, poiché solo materiale di partenza è stato recuperato dopo la reazione. Diversi catalizzatori sono, quindi, stati testati, e il complesso **VIII** si è dimostrato il più adatto a promuovere la formazione di lattoni.

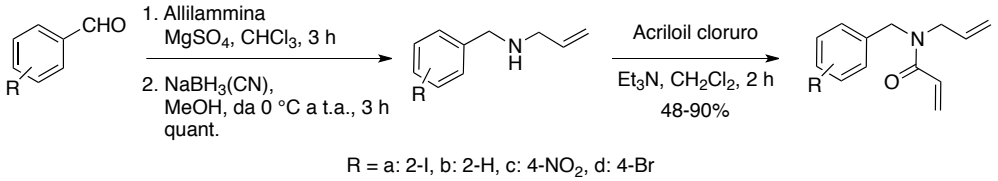
Tutti i prodotti di RCM sono stati isolati in rese eccellenti, mentre la formazione dei prodotti di RCEYM richiede tempi di reazione più lunghi e avviene con rese moderate (Schema 6). In quest'ultimo caso, la rigidità strutturale del gruppo acriloile, così come la coniugazione del doppio legame al gruppo carbonilico, probabilmente risultano in una ridotta affinità di questa catena laterale verso il catalizzatore elettrofilo a base di rutenio.

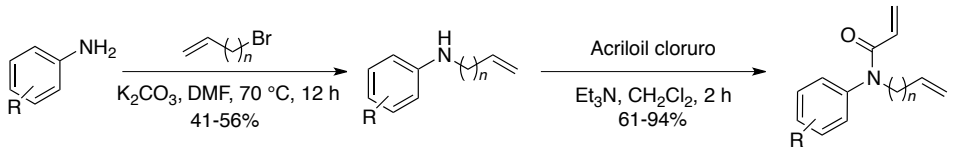




Schema 6. *Sintesi di lattoni a cinque e sei termini*

Lo scheletro lattamico è un altro elemento strutturale ricorrente nei composti naturali. Precursori di RCM, specificamente progettati per generare lattami benzilici, sono stati sintetizzati mediante una reazione di condensazione tra aldeidi benziliche e allilammina, seguita dalla riduzione degli intermedi imminici con $NaBH_3CN$. Le ammine così prodotte sono poi state sottoposte a una reazione di acilazione con acriloil cloruro in modo da formare le ammidi corrispondenti in buone rese (Schema 7). Substrati in cui l'atomo di azoto sia direttamente collegato all'anello aromatico sono stati ugualmente sintetizzati. Utilizzando diverse aniline disponibili in commercio, un comodo processo in due fasi è stato impiegato in questo caso, il quale prevede una classica reazione di alchilazione e una successiva acilazione con acriloil cloruro e trietilammina (Schema 7).

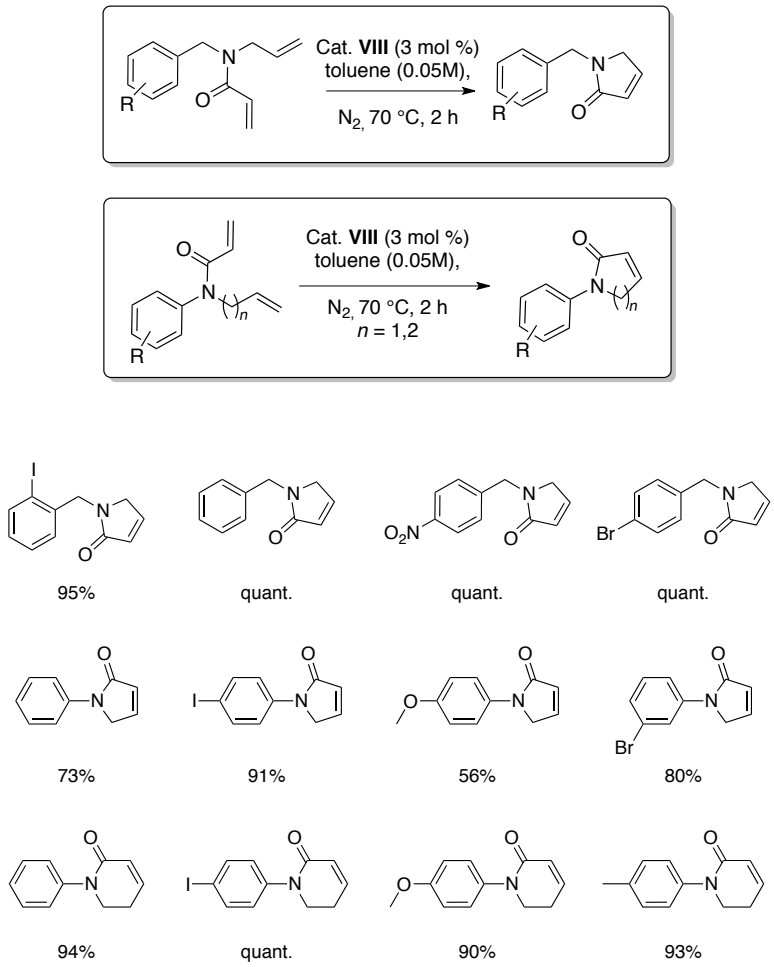




Schema 7. *Sintesi di ammidi acriliche*

La reazione delle ammidi acriliche con il catalizzatore **VIII** (3 mol%), in toluene, a 70 ° C, ha portato alla rapida formazione di lattami a cinque e sei termini, che sono stati isolati in ottima resa dopo purificazione su gel di silice (Schema 8). In questo caso però, soluzioni diluite dei substrati di partenza (0.05M) si sono rese necessarie per minimizzare la formazione di sottoprodotti derivanti da reazioni di metatesi incrociata. Sfortunatamente, ogni tentativo di

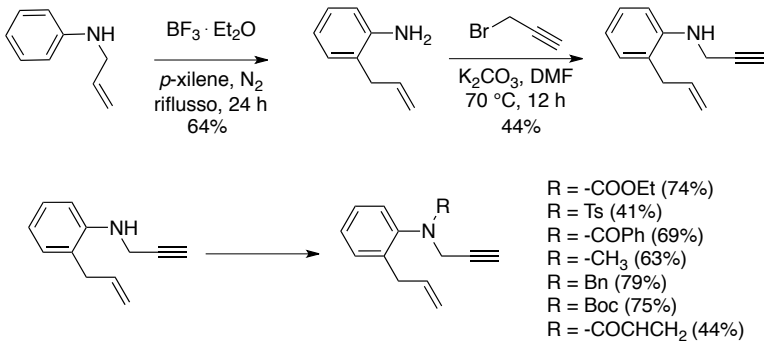
ottenere anelli lattamici attraverso processi di RCEYM ha portato al recupero del substrato di partenza dopo la reazione.



Schema 8. *Sintesi di lattami a cinque e sei termini*

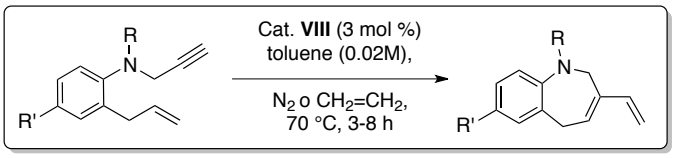
In questi ultimi anni, i composti azotati caratterizzati da anelli a sette termini fusi con cicli aromatici hanno attirato un sempre maggiore interesse a causa delle loro potenziali attività biologiche. Nonostante questo, i sistemi 1- e 2-benzazepinici sono stati solo scarsamente studiati, anche se entrambi questi composti sono considerati elementi farmacoforici cruciali nella scoperta di nuovi farmaci.

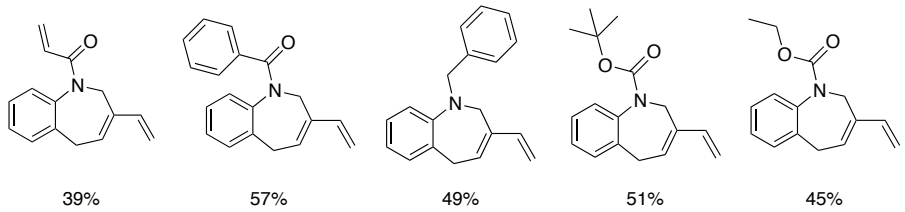
Recentemente, la rilevanza biologica delle benzazepine ci ha incoraggiato a sviluppare nuove reazioni di RCEYM per la loro sintesi. I precursori delle ciclizzazioni sono stati ottenuti a partire dalla *N*-allil anilina mediante un riarrangiamento di aza-Claisen e successiva alchilazione della risultante 2-allil anilina con propargil bromuro. Substrati eninici diversamente funzionalizzati all'atomo di azoto sono infine stati ottenuti mediante reazioni classiche di sostituzione nucleofila (Schema 9).



Schema 9. *Sintesi di1,8 enini diversamente funzionalizzati*

Numerose benzazepine diversamente sostituite sono state sintetizzate con successo attraverso la ciclizzazione dei precursori eninici, effettuata utilizzando il catalizzatore **VIII** (3 mol%) in toluene a 70 °C (Schema 10).





Schema 10. *Sintesi di anelli benzazepinici diversamente N-funzionalizzati*

In qualche caso, tuttavia, un'atmosfera di etilene si è resa necessaria per evitare la formazione di sottoprodotti dovuti a reazioni tandem RCEYM / homo-CM (Figura 2).

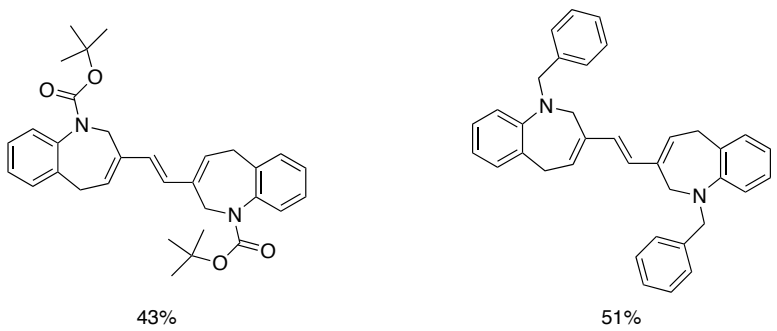


Figura 2. *Sottoprodotti dovuti a reazioni tandem RCEYM / homo-CM*

A scopo di confronto, abbiamo poi analizzato il comportamento di precursori eninici contenenti un gruppo acriloile legato all'atomo di azoto. In questo caso, tre diversi percorsi di reazione possono essere previsti: 1) la formazione di un anello a cinque termini *via* RCEYM (enone-ino), 2) la sintesi di un ciclo a sette termini *via* RCM (enone-ene) e 3) l'ottenimento di un anello a sette termini *via* RCEYM (ene-ino) (Figura 3).

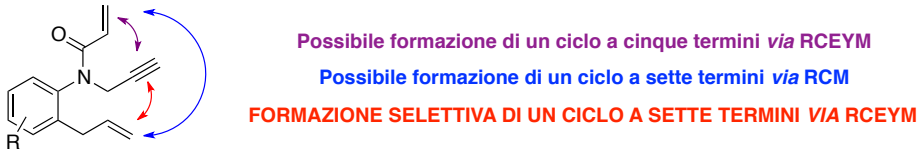
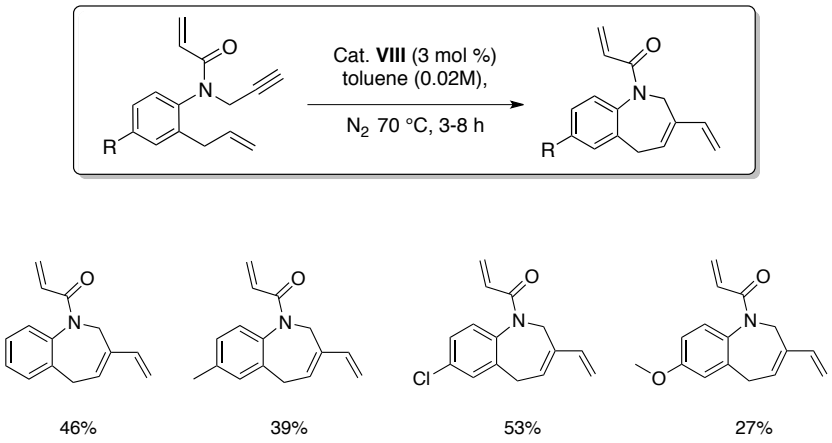


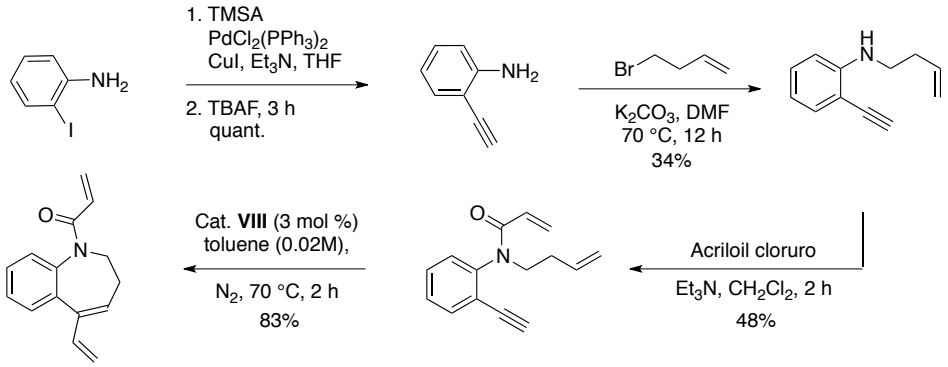
Figura 3. *Diversi percorsi possibili di chiusura metatetica ad anello*

La sola formazione del ciclo benzazepinico *via* metatesi ene-ino è stata osservata, con conseguente ottenimento di prodotti altamente funzionalizzabili (Schema 11). Si pensa che la regioselettività di questa reazione derivi dall'alta reattività dei legami doppi e tripli C-C *vs* una bassa affinità del gruppo acriloile nei confronti del catalizzatore di metatesi impiegato.



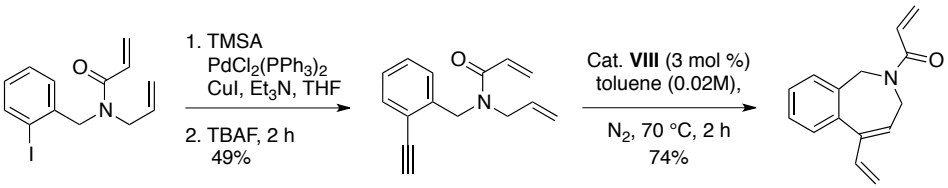
Schema 11. *Sintesi regioselettiva di anelli benzazepinici*

Questi risultati ci hanno spinto a studiare il comportamento di un substrato 5-aza-1,8-eninico, facilmente ottenibile a partire dalla 2-iodo anilina. L'azione del catalizzatore **VIII** (3% mol) su questo composto ha portato alla formazione rapida dell'1,3-diene desiderato con una resa dell'83% (Schema 12).



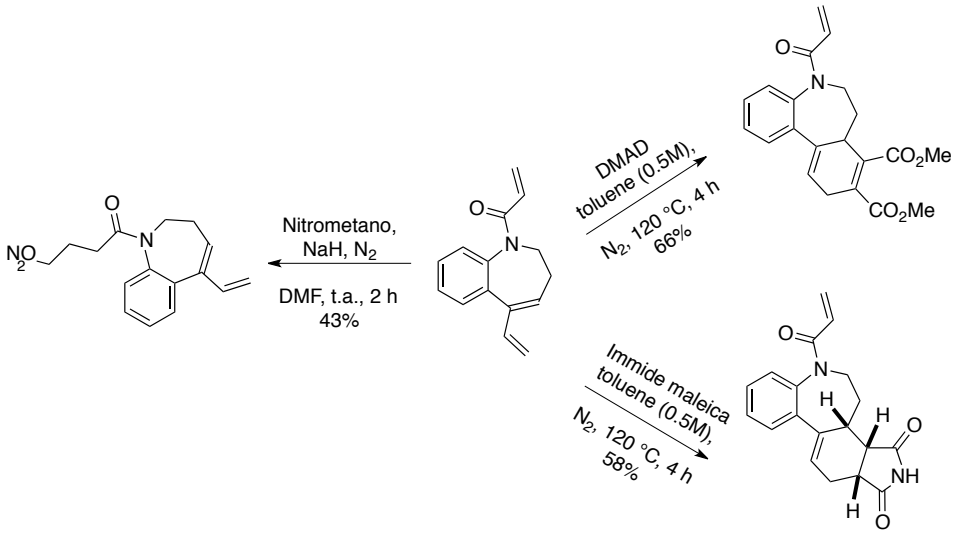
Schema 12. *Reazione di un substrato 5-aza-1,8-eninici*

Operando nelle stesse condizioni di reazione, lo scheletro di una 2-benzazepina è stato ottenuto con una resa del 74%, partendo da un substrato 4-aza-1,8-eninico (Schema 13). Abbiamo così dimostrato che il nostro approccio sintetico è applicabile anche a questa classe di composti.



Schema 13. *Reazione di un substrato 4-aza-1,8-eninici*

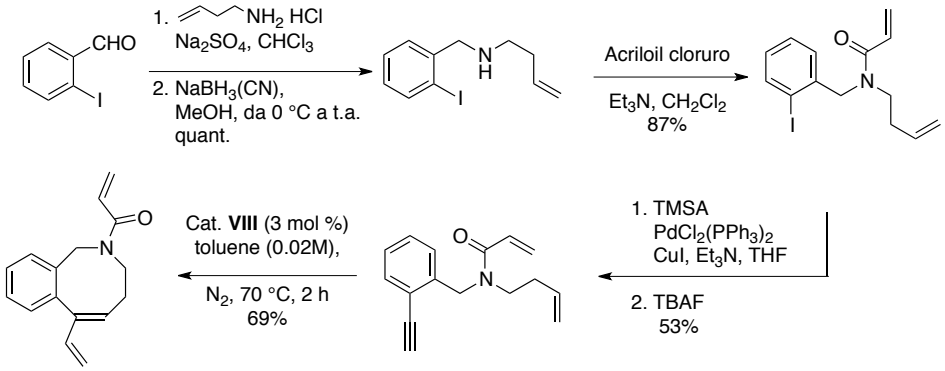
Va sottolineato che i nostri scheletri benzazepinici incorporano almeno due punti di diversità molecolare (la funzione 1,3-diene e in gruppo acril ammide). Tali gruppi funzionali sono stati fatti reagire con successo sia mediante addizioni di Michael, sia attraverso reazioni Diels-Alder (Schema 14). Per questo motivo, i nostri prodotti possono essere considerati utili intermedi sintetici per l'ottenimento di molecole a elevata complessità molecolare.



Schema 14. *Funzionalizzazione degli scheletri benzazepinci ottenuti*

Infine, il complesso **VIII** è stato impiegato nella sintesi regioselettiva di un ciclo benzofuso a otto termini (Schema 15). In questo caso, il substrato da sottoporre alla ciclizzazione è stato ottenuto a partire dalla 2-iodo benzaldeide, mediante una reazione di amminazione riduttiva con butenilammina e $NaBH_3(CN)$. L'ammina secondaria risultante ha poi reagito con acriloil cloruro, generando l'ammide corrispondente con una resa dell'87%. Il substrato 1,9-eninico necessario per la ciclizzazione è stato infine preparato utilizzando una reazione Sonogashira e un successivo sblocco dell'alchino terminale con TBAF.

Come osservato nel caso degli scheletri benzazepinici, la reazione di RCEYM procede in maniera regioselettiva, portando alla formazione della benzazocina desiderata con una resa del 69% (Schema 15).



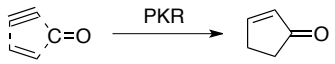
Schema 15. *Sintesi regioselettiva di un anello benzofuso a otto termini*

Quest'ultimo risultato suggerisce che la procedura sintetica da noi sviluppata potrebbe in futuro essere impiegata come protocollo generale per la preparazione regioselettiva di anelli eterociclici azotati a dimensioni medio/grandi.

2. REAZIONI DI PAUSON-KHAND

La reazione di Pauson-Khand (PKR) è formalmente una cicloaddizione [2+2+1] in cui un doppio legame, un triplo legame e monossido di carbonio reagiscono a dare un derivato ciclopentenonico. Questo processo implica la formazione di tre nuovi legami C-C, di un ciclo nella versione intermolecolare della reazione oppure di due cicli nella versione intramolecolare (Schema 16).

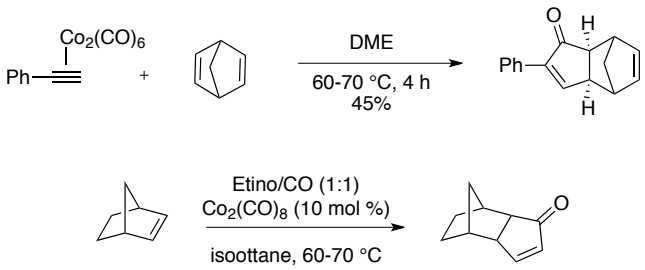
Poche sono le procedure in grado di competere con la PKR nell'incrementare la complessità molecolare in un solo passaggio sintetico.



Schema 16. *Connettività della reazione di PKR*

I primi esempi di questa reazione, che inizialmente era condotta termicamente in condizioni relativamente severe, risalgono agli anni settanta (Schema 17).

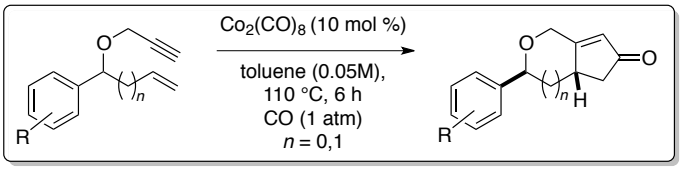
Anche se fino alla metà degli anni novanta il dicobalto ottacarbonile era il solo mediatore utilizzato per promuovere la reazione, numerosi catalizzatori mono- e bi-nucleari sono ora disponibili per la realizzazione di questo processo.

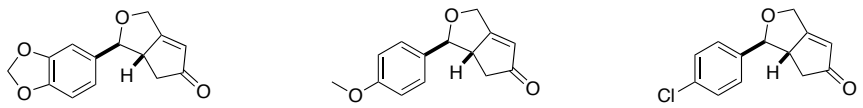


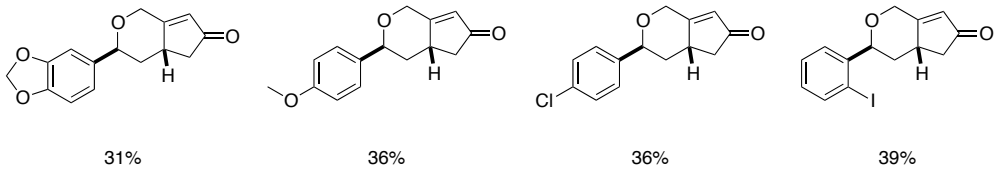
Schema 17. *Primi esempi di reazioni di PKR*

Nel secondo capitolo di questa tesi è descritto come i sistemi eninici, inizialmente impiegati nelle reazioni di metatesi, sono stati sottoposti a reazioni di Pauson-Khand Co-catalizzate, per la costruzione di scheletri biciclici contenenti eteroatomi. Più in dettaglio, mentre le RCEYM degli eteri 1,5- e 1,6-eninici si sono dimostrate un metodo particolarmente efficiente per la sintesi di diidrofurani e diidropirani, le PRK hanno permesso di ottenere di bicicli ossigenati 5,5- e 5,6-fusi.

Le reazioni di carbonilazione sono state condotte in toluene, a 110 ° C per 6 ore, utilizzando 10% mol di $Co_2(CO)_8$ come catalizzatore e 1 atm di monossido di carbonio (Schema 18).





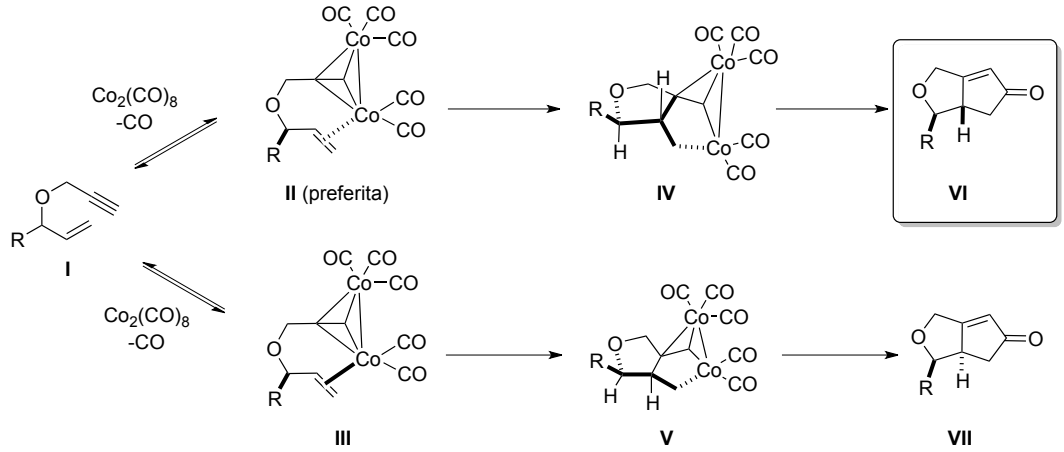


Schema 18. *Sintesi di bicicli ossigenati 5,5- e 5,6-fusi via PKR*

In queste condizioni di reazione, i sistemi biciclici desiderati sono stati isolati in rese accettabili dopo purificazione cromatografia su gel di silice.

La bassa conversione dei prodotti di PKR dipende soprattutto dalla formazione di complessi intermedi stabili tra il catalizzatore a base di cobalto e i substrati di partenza.

Va evidenziato che i composti biciclici riportati nello Schema 18 sono stati ottenuti come singoli diastereoisomeri. La configurazione relativa *cis* di questi prodotti è stata stabilita mediante analisi NMR-NOE. L'origine dello stereocontrollo è stata razionalizzata invocando la tendenza del metallo a legare preferenzialmente una delle due facce del doppio legame del substrato di partenza (Schema 19), a causa dell'ingombro sterico dovuto alla presenza del sostituente R sul centro stereogenico.



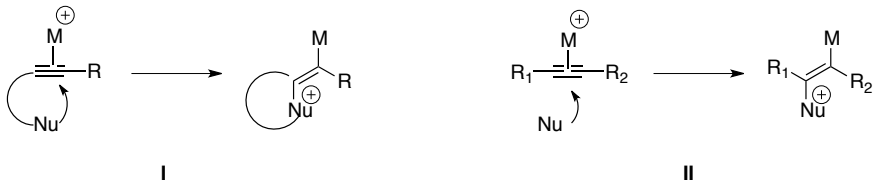
Schema 19. *Origine dello stereocontrollo delle PKR*

In collaborazione con il gruppo di Sannicolò (Università di Milano), abbiamo, poi, esaminato la possibilità di impiegare nuovi leganti chirali bieteroaromatici, contenenti fosforo, per una versione enantioselettiva della PKR Co-catalizzata. Risultati preliminari hanno però evidenziato una scarsa attività dei leganti testati. Nel prossimo futuro si cercherà di applicare gli stessi leganti a PKR catalizzate da complessi di rodio, con lo scopo di valutare ogni eventuale relazione tra enantioselettività e densità elettronica sul legante al fosforo impiegato.

3. ATTIVAZIONE ELETTROFILICA DEGLI ALCHINI CATALIZZATA DA METALLI DI TRANSIZIONE

L'attivazione elettrofila degli alchini, catalizzata da metalli di transizione, è una delle più importanti strategie impiegate per la sintesi di strutture cicliche e acicliche di origine naturale e non. L'importanza di questo processo deriva dal rapido aumento nella complessità molecolare a partire da composti aciclici relativamente semplici, contenenti alchini.

Tra i complessi a base di metalli di transizione in grado di catalizzare l'attivazione elettrofilica degli alchini, quelli derivati da platino e oro hanno dimostrato una capacità eccezionale di promuovere numerose trasformazioni organiche, generando una vasta gamma di prodotti strutturalmente vari in condizioni blande e con elevata efficienza. Questi interessanti processi derivano dalle peculiari proprietà acide (acidità di Lewis) dei complessi di platino e oro, così come dalla loro capacità di formare selettivamente interazioni π con legami insaturi carbonio-carbonio. In questo modo è possibile promuovere l'attacco intramolecolare (**I**) o intermolecolare (**II**) di un nucleofilo (Schema 20).

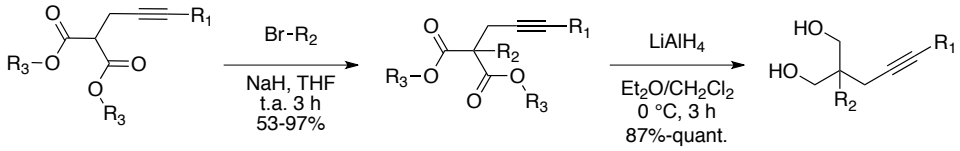


Schema 20. *Attacco nucleofilo intra- e intermolecolare su alchini attivati*

Nonostante l'elevata reattività dei complessi a base di platino e oro, il miglioramento dei sistemi catalitici rimane una sfida continua.

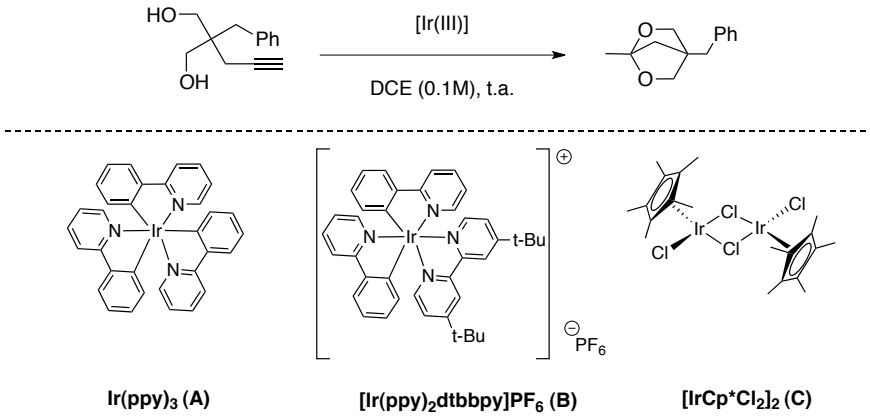
Nel terzo capitolo della tesi, un nuovo catalizzatore a base di Ir(III) è stato descritto, il quale ha permesso la sintesi di composti eterociclici contenenti ossigeno e azoto in ottime rese.

L'elevata efficienza delle reazioni di alcossilazione oro-catalizzate, già descritte in letteratura, ci ha incoraggiato a sintetizzare alcuni dioli omopropargilici e a testarli in ciclizzazioni Ir(III)-catalizzate. Tali alcoli sono stati ottenuti utilizzando una procedura sintetica in due fasi, che comporta un'iniziale alchilazione di esteri malonici e una successiva riduzione dei gruppi esterei con $LiAlH_4$ (Schema 21).



Schema 21. *Sintesi dei dioli omopropargilici*

Partendo da un substrato modello, la ciclizzazione è stata inizialmente condotta con catalizzatori quali $IrCl_3$ e i complessi a **A** e **B** (Tabella 1). Purtroppo, in nessun caso è stato possibile osservare la formazione del prodotto desiderato e solo materiale di partenza è stato isolato dopo la reazione. Data la sua capacità d'interazione con gli alchini in condizioni blande, il complesso $[IrCp^*Cl_2]_2$ (**C**) è stato ugualmente testato, perché considerato adatto a promuovere l'alcossilazione. In effetti, ponendo un substrato modello in presenza del 5% in moli di catalizzatore **C**, in dicloroetano (DCE), a temperatura ambiente, è stato possibile osservare la rapida formazione di un chetale biciclico in resa quantitativa.



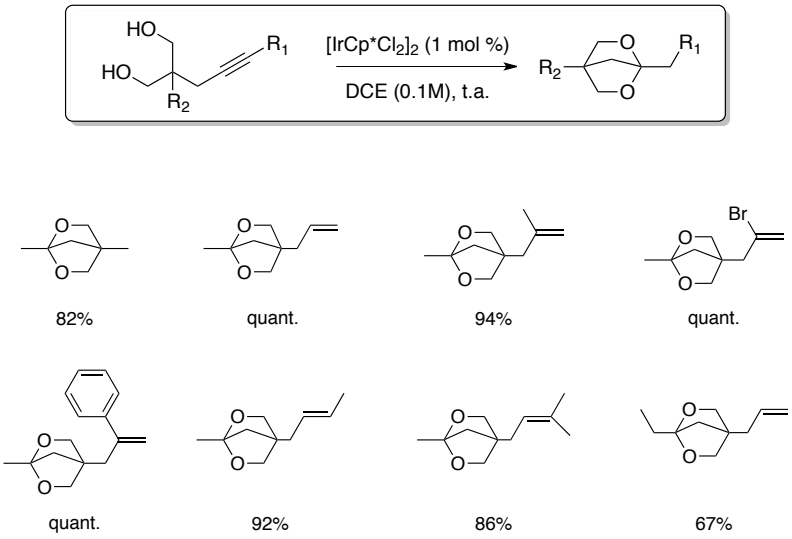
Catalizzatore	Quantità catalitica (mol %)	t (h)	Resa (%)
$IrCl_3 \cdot 3H_2O$	10	1	0
$IrCl_3$	10	1	0
$Ir(ppy)_3$	5	1	0
$[Ir(ppy)_2dtbbpy]PF_6$	5	1	0
$[IrCp^*Cl_2]_2$	5	0.25	quant.
$[IrCp^*Cl_2]_2$	2.5	0.25	quant.
$[IrCp^*Cl_2]_2$	1	0.5	quant.

Tabella 1. *Ottimizzazione delle condizioni di alcossilazione*

La quantità catalitica è poi stata ridotta con successo fino all'1% in moli senza alterazione delle rese, anche se tempi di reazione più lunghi si sono resi necessari per ottenere la conversione completa del substrato di partenza (Tabella 1).

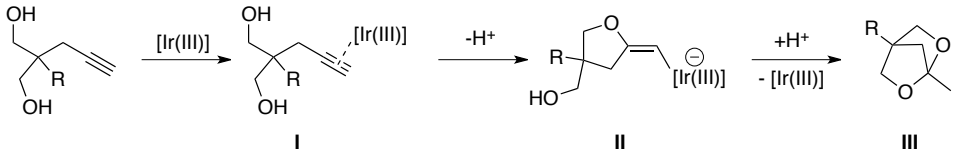
Numerosi dioli omopropargilici sono stati sottoposti con successo alle condizioni di reazione sopra descritte, con formazione degli addotti corrispondenti in ottime rese (Schema 22).

Sorprendentemente, partendo da substrati contenenti gruppi allilici, la ciclizzazione si è rivelata altamente chemoselettiva nei confronti degli alchini, dato che le catene alliliche non hanno dato origine a nessuna reazione collaterale.



Schema 22. *Alcossilazioni catalizzate da Ir(III)*

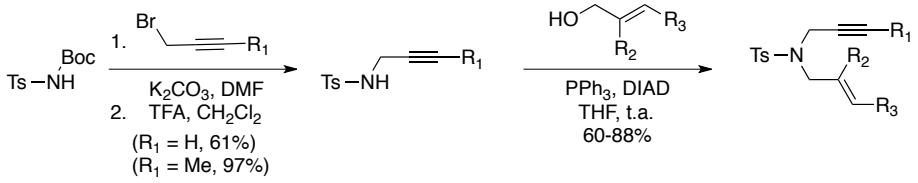
Un meccanismo proposto per le reazioni di alcossilazione catalizzate da Ir(III) è riportato nello Schema 23. Un primo momento, si suppone che la complessazione π del triplo legame, da parte del catalizzatore, generi il complesso metallico **I**. Un'addizione nucleofila intramolecolare del primo gruppo ossidrilico sull'alchino attivato porta quindi alla formazione dell'intermedio **II**. La protodemetallazione di **II** e la successiva somma dell'ossidrile rimanente sul vinil etere risultante genera infine il chetale biciclico **III**.



Schema 23. *Meccanismo delle alcossilazioni catalizzate da Ir(III)*

Le alte rese e le condizioni blande di reazione osservate per le alcossilazioni catalizzate da Ir(III), ci hanno poi spinto a studiare altri tipi di reazione, per la sintesi di prodotti ciclici a diverso scheletro eteroatomico. In quest'ottica, l'applicazione del nostro sistema catalitico a 1,6-enini contenenti azoto, ci è sembrata la più adatta allo sviluppo di cicloisomerizzazioni che coinvolgano contemporaneamente sia il doppio, sia il triplo legame dei substrati di partenza. Diversi enini contenenti azoto sono, quindi, stati sintetizzati e testati in reazioni di ciclizzazione catalizzate da Ir(III).

Due alchinil tosil ammidi sono state ottenute dalla *N*-Boc-*p*-toluensolfonammide, utilizzando una reazione di alchilazione e la successiva deprotezione dell'atomo di azoto. Questi composti hanno, poi, reagito con alcoli allilici diversamente sostituiti, mediante una reazione di Mitsunobu, in modo da generare i substrati eninici desiderati con buone rese (Schema 24).



Schema 24. *Sintesi di 1,6-enini contenenti azoto*

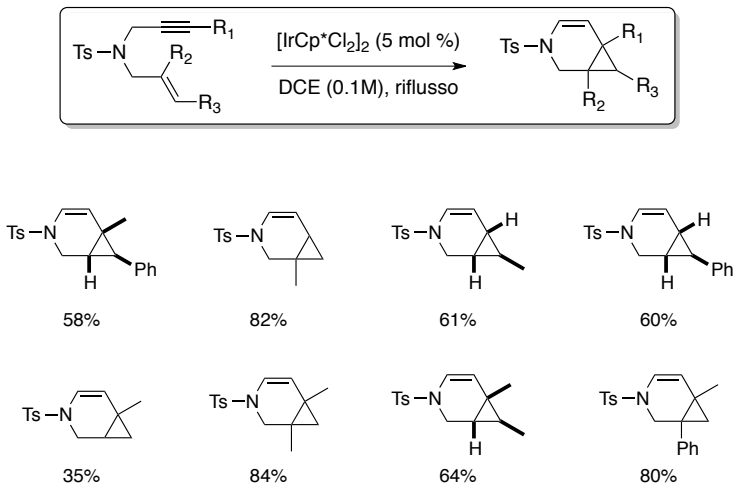
Partendo un derivato 1,6-eninico scelto come modello, le condizioni di reazione sviluppate in precedenza per le alcossilazioni si sono dimostrate inefficaci nel promuovere la ciclizzazione. Condizioni di reazione differenti sono quindi state esaminate (Tabella 2). Con soddisfazione, l'utilizzo del catalizzatore $[IrCp^*Cl_2]_2$ (5% in moli) in DCE a riflusso, ha consentito la formazione di un derivato ciclopropanico con una resa del 55%. Un risultato simile è stato ottenuto impiegando toluene come solvente di reazione.

Quantità catalitica (mol %)	Solvente	T (°C)	t (h)	Resa (%)
1	DCE	r.t.	24	0
2.5	DCE	r.t.	24	0
5	DCE	r.t.	24	30
5	DCE	riflusso	3	55
5	Toluene	riflusso	3	53

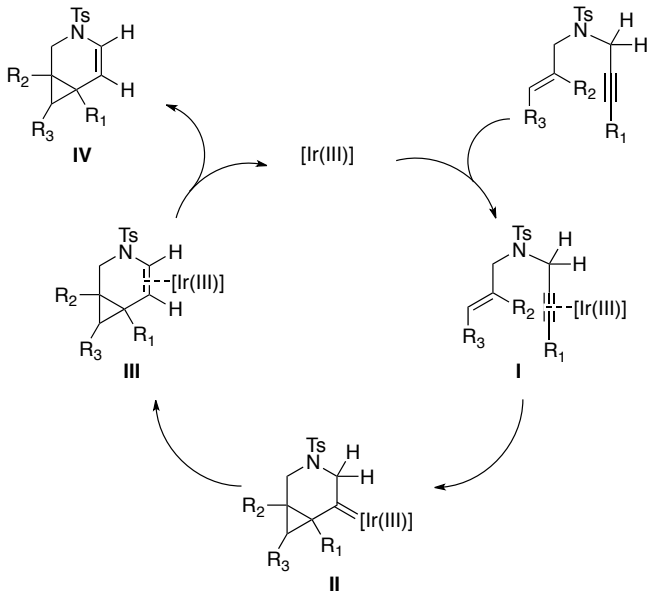
Tabella 2. *Ottimizzazione delle condizioni di ciclopropanazione*

La reazione di ciclopropanazione è stata applicata con successo a una grande varietà composti 1,6-eninici contenenti azoto e ha permesso di isolare numerosi prodotti biciclici sotto forma di singoli diastereoisomeri (Schema 25). Gruppi alchilici e arilici sono stati ugualmente tollerati dalle condizioni di reazione, così come gli alchini interni.

Va evidenziato che il complesso $[IrCp^*Cl_2]_2$ si è dimostrato efficace in basse quantità catalitiche e in assenza di qualsiasi altro additivo. Per questo motivo, il protocollo che abbiamo sviluppato sembra avere un'elevata applicabilità, soprattutto se confrontato con altre procedure catalitiche riportate in letteratura.



Schema 25. *Ciclopropanazioni catalizzate da Ir(III)*



Schema 26. *Meccanismo delle ciclopropanazioni catalizzate da Ir(III)*

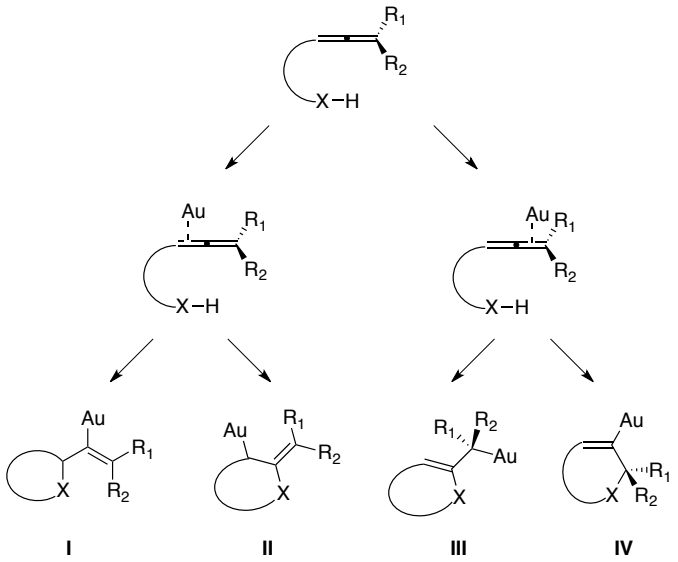
Sulla base dei nostri risultati e considerando studi precedenti, è stato proposto che il meccanismo delle ciclopropanazioni catalizzate da Ir(III) proceda mediante l'attivazione elettrofila della componente alchino dei substrati di partenza, seguita dalla formazione di un complesso Ir-carbene, stabilizzato da eteroatomi donatori. La successiva migrazione 1,2 d'idruro e la decomplessazione del metallo portano infine all'ottenimento del composto biciclico osseravto (Schema 26).

Nel prossimo futuro, l'elevata attività catalitica del complesso $[IrCp^*Cl_2]_2$, così come le blande condizioni di reazione impiegate, potranno risultare in interessanti applicazioni del nostro sistema catalitico nella sintesi di prodotti naturali e di altri eterocicli biologicamente attivi.

4. CICLOISOMERIZZAZIONI DI ALLENI CATALIZZATE DA ORO

Come precedentemente descritto, complessi a base di platino, iridio e oro sono blandi acidi di Lewis capaci di attivare i legami multipli C-C nei confronti dei nucleofili, al fine di formare nuovi legami C-C o C-eteroatomo. Tra vari substrati suscettibili di attivazione, gli alchini giocano un ruolo dominante, mentre le reazioni degli alcheni o degli alleni sono state studiate con minore frequenza.

Negli ultimi anni, i catalizzatori a base d'oro si sono rivelati particolarmente adatti per l'attivazione selettiva degli alleni in presenza di altri gruppi funzionali e numerose reazioni di addizione nucleofila intramolecolare sono state riportate.

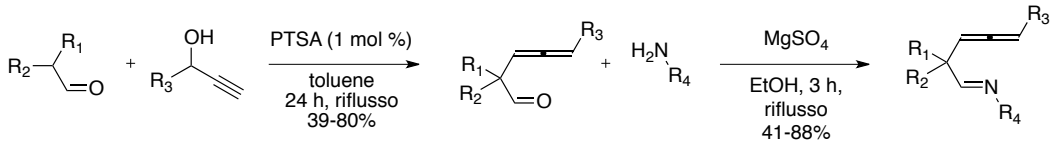


Schema 27. *Regioselettività delle reazioni di ciclizzazione intramolecolare degli alleni*

Più in particolare, il catalizzatore d'oro può coordinare l'uno o l'altro dei doppi legami cumulati che caratterizzano la funzione allene, originando diverse possibilità di ciclizzazione (Schema 27). La regioselettività dell'attacco nucleofilo dipende da diversi fattori quali le proprietà del catalizzatore impiegato, la struttura del substrato di partenza e le caratteristiche del nucleofilo che muove l'attacco.

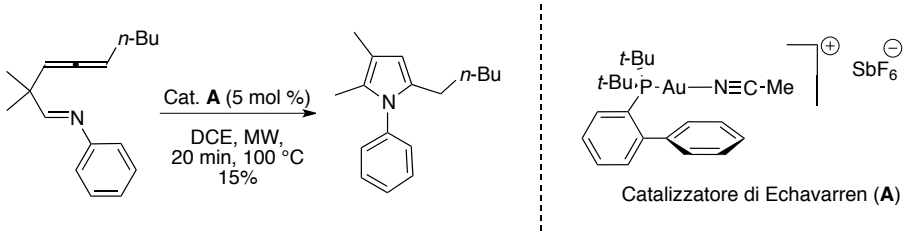
Nel quarto capitolo della tesi è stata presentata una nuova reazione di cicloisomerizzazione di *β*-allenilimmine e *β*-allenilidrazoni, che porta alla formazione di pirroli altamente sostituiti via migrazione 1,2 di gruppi alchilici o arilici.

I precursori della ciclizzazione, in questo caso, sono stati sintetizzati utilizzando la procedura in due fasi descritta nello Schema 28. Inizialmente, una reazione tra aldeidi enolizzabili e alcooli propargilici, catalizzata da acidi, ha permesso di isolare diverse aldeidi β-alleniche in rese da moderate a buone. In un secondo momento, la condensazione di tali aldeidi con anilina ha portato alla formazione delle immine corrispondenti in resa quantitativa. Utilizzando una reazione di condensazione analoga, numerosi idrazoni diversamente sostituiti sono, infine, stati isolati dopo rapida purificazione su gel di silice.



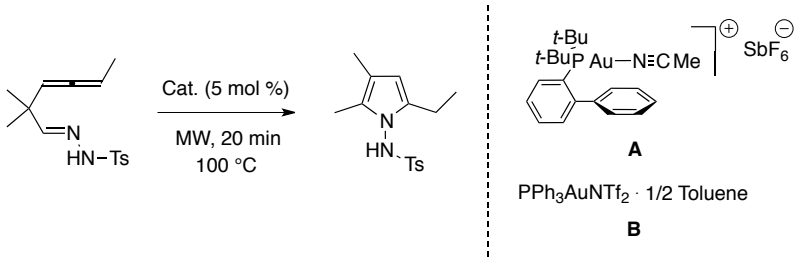
Schema 28. *Sintesi di β-allenilimmine e β-allenilidrazoni*

La reazione di cicloisomerizzazione è stata inizialmente condotta a partire dall'immina modello riportata nello Schema 29. Il precursore scelto è stato trattato con il 5% in moli di AuCl, $AuCl_3$ e del catalizzatore di Echavarren (**A**), in CH_2Cl_2 a temperatura ambiente, senza successo. Nonostante i primi risultati insoddisfacenti, diverse condizioni di reazione sono state studiate e il complesso **A** si è rivelato un possibile catalizzatore della ciclizzazione in DCE, a 100 °C per 20 minuti, sotto irraggiamento microonde. In questo caso, infatti, il pirrolo desiderato è stato isolato in una resa incoraggiante del 15% (Schema 29).



Schema 29. *Cicloisomerizzazione delle β-allenilimmine*

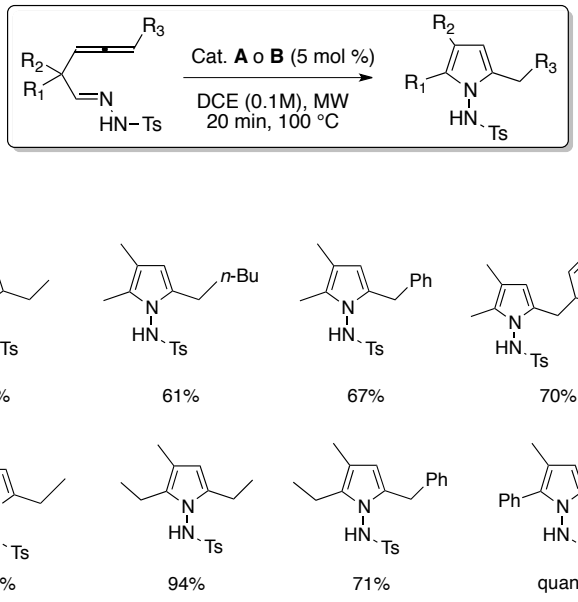
La scarsa stabilità e reattività delle immine ci ha spinto a esaminare il comportamento dei *β*-allenilidrazoni. Anche in questo caso la reazione è stata condotta su un substrato modello sotto irraggiamento microonde, a 100 °C per 20 minuti. Usando DCE come solvente, il pirrolo desiderato è stato ottenuto con una resa del 57% (Tabella 3). Altri composti capaci di originare isomerizzazione sono stati testati nelle stesse condizioni di reazione, ma solo il catalizzatore **A** e il complesso **B** si sono rivelati efficaci nel promuovere il processo (Tabella 3).



Catalizzatore	Solvente	Resa
A	DCE	57%
$AuCl_3$	DCE	n.r.
AuCl	DCE	n.r.
B	DCE	55%
$AgNO_3$	DCE	n.r.
$AgSbF_6$	DCE	tracce
AgOTf	DCE	n.r.
CuI	DCE	n.r.
$Cu(OTf)_2$	DCE	n.r.
$FeCl_3$	DCE	n.r.
TfOH	DCE	n.r.
$HN(OTf)_2$	DCE	n.r.

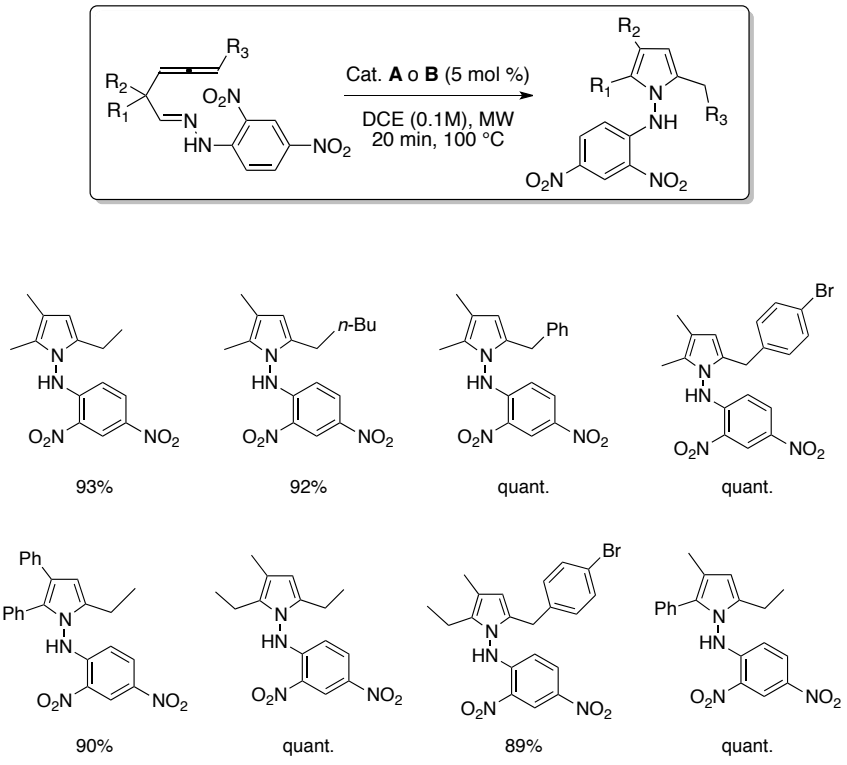
Tabella 3. *Ottimizzazione delle condizioni di reazione*

Numerosi tosilidrazoni sono stati fatti reagire con successo utilizzando le condizioni di reazione sopra descritte, generando i pirroli corrispondenti con buone rese (Schema 30). La ciclizzazione tollera gruppi sia alchilici, sia arilici sulla metà allenica dei substrati di partenza. In tre esempi, inoltre, è stato possibile osservare una migrazione selettiva dei gruppi etile e fenile rispetto al metile.



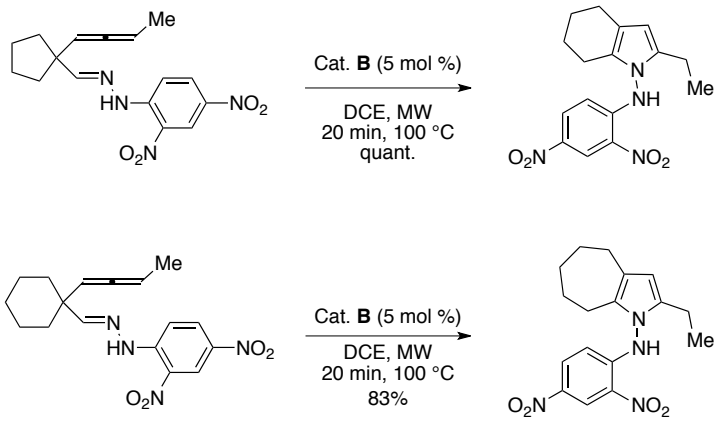
Schema 30. *Cicloisomerizzazione dei tosilidrazoni*

L'influenza dei sostituenti sull'atomo di azoto è stata, poi, studiata ponendo diversi 2,4-dinitrofenil idrazoni nelle stesse condizioni di ciclizzazione (Schema 31). In questo caso, la reazione procede con estrema efficienza, generando i pirroli desiderati con rese eccellenti.



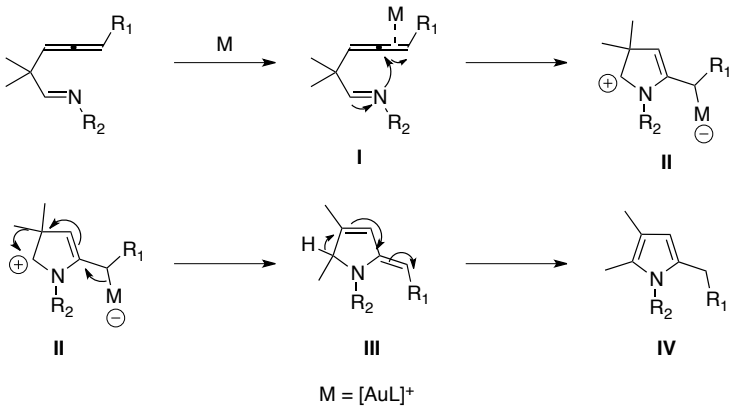
Schema 31. *Cicloisomerizzazione dei 2,4-dinitrofenil idrazoni*

Con soddisfazione, la cicloisomerizzazione di un precursore contenente un ciclopentano ha portato all'espansione dell'anello, con formazione di un pirrolo fuso con un ciclo a sei termini in resa quantitativa (Schema 32). Allo stesso modo, un pirrolo fuso con un ciclo a sette termini è stato isolato con una resa dell'83%, partendo da un substrato contenente un anello cicloesanico.



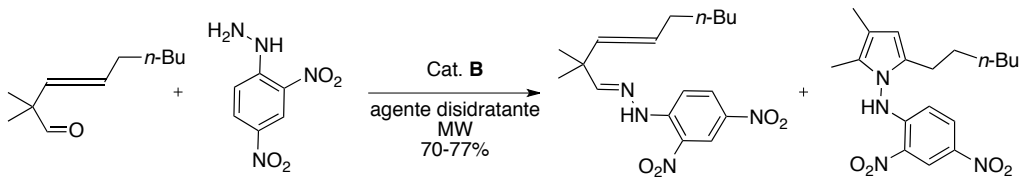
Schema 32. *Cicloisomerizzazioni con espansione d'anello*

Il meccanismo proposto per il processo di cicloisomerizzazione dei β-allenilidrazioni è riportato nello Schema 33. L'attivazione elettrofila dell'allene da parte del catalizzatore a base d'oro genera un intermedio zwitterionico via addizione nucleofila dell'azoto sull'atomo centrale dell'allene. Segue una migrazione intramolecolare di un gruppo alchilico o arilico, con conseguente aromatizzazione dell'intermedio risultante e formazione del prodotto osservato.



Schema 33. *Meccanismo di reazione*

Lo sviluppo di una versione *one-pot* della reazione per la rapida trasformazione di aldeidi β-alleniche in pirroli multisostituiti è attualmente in fase di ottimizzazione nel nostro laboratorio (Schema 34).



Schema 34. *Reazione one-pot*

CONCLUSIONI GENERALI

In conclusione, in questa tesi è stato dimostrato come le reazioni di metatesi, le carbonilazioni di Pauson-Khand e l'attivazione elettrofila di legami multipli C-C, catalizzata da iridio e oro, consentano un rapido aumento della complessità molecolare partendo da substrati a struttura relativamente semplice. Studi che descrivono l'ampia applicabilità di queste reazioni sono pubblicati a rapido ritmo, attestando l'interesse che questi processi ricoprono per la comunità chimica.

Nel prossimo futuro, con lo studio di nuove metodologie asimmetriche, le trasformazioni catalizzate da metalli di transizione, descritte in questo dattiloscritto, continueranno a occupare un ruolo centrale nella sintesi organica.

Summary in French

RÉACTIONS DE CYCLOISOMÉRISATION CATALYSÉES PAR LES COMPLEXES DES MÉTAUX DE TRANSITION. SYNTHÈSE DE COMPOSÉS HÉTÉROCYCLIQUES OXYGÉNÉS ET AZOTÉS.

INTRODUCTION GENERALE

Ces dernières années, le besoin de méthodes éco-compatibles pour la préparation d'une vaste gamme de produits chimiques requis par la société a poussé la recherche à développer de nouveaux procédés de synthèse qui soient plus efficaces et économiques.

Afin de minimiser l'utilisation de matières premières et la production de déchets, une réaction chimique devrait procéder selon les principes d'économie d'atomes. Plus précisément, une séquence synthétique devrait idéalement avoir lieu avec un contrôle complet de la stéréochimie, de manière quantitative et sans formation de produits secondaires.

Les réactions de cyclisation des systèmes polyinsaturés, catalysées par les métaux de transition, offrent une opportunité réelle d'atteindre les objectifs exposés ci-dessus. De plus, le potentiel synthétique des substrats polyinsaturés rend accessible une grande variété de composés, utilisables comme intermédiaires pour la préparation de molécules complexes, naturelles ou non.

Dans cette thèse, quatre différentes classes de réactions de cyclisation, catalysées par les métaux de transition, ont été traitées: (1) les réactions de métathèse, (2) les carbonylations de Pauson-Khand, (3) l'activation électrophile d'alcynes catalysée par l'iridium et (4) les cycloisomérisations d'allènes catalysées par l'or. Ces méthodologies, qui ont permis d'obtenir une haute complexité moléculaire en une seule étape de synthèse, ont été utilisées avec succès pour la formation de nombreux composés hétérocycliques oxygénés et azotés.

1. REACTIONS DE METATHESE

Initialement découverte en 1950, la métathèse des oléfines, qui procède par la rupture et la reformation de liaisons multiples carbone-carbone, est aujourd'hui considérée comme un des procédés les plus attractifs et utilisé en synthèse organique.

Grâce au développement de catalyseurs stables, réactifs et tolérants envers la plupart des groupements fonctionnels (Figure 1), les réactions de métathèse ont permis d'isoler une grande variété de molécules organiques, difficiles à obtenir en utilisant les stratégies conventionnelles de synthèse.

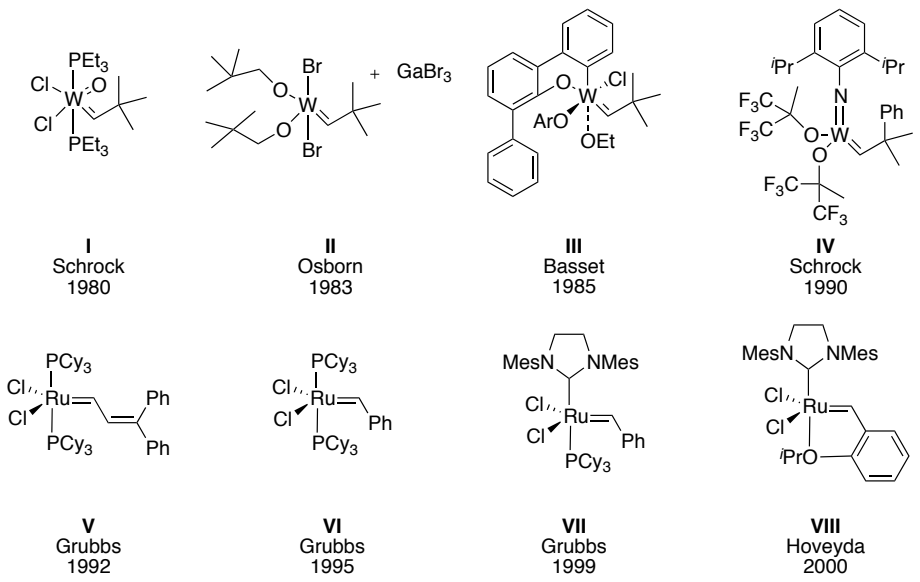


Figure 1. *Catalyseurs de métathèse*

Selon le type de liaison insaturée impliquée dans le processus, trois catégories de réaction peuvent être identifiées: les métathèses des dièns, des énynes et des diynes (Schéma 1). De plus, le changement structurel, qui se produit pendant le processus, peut être divisé à son tour en fermeture de cycle, ouverture de cycle et métathèse croisée (Schéma 1).

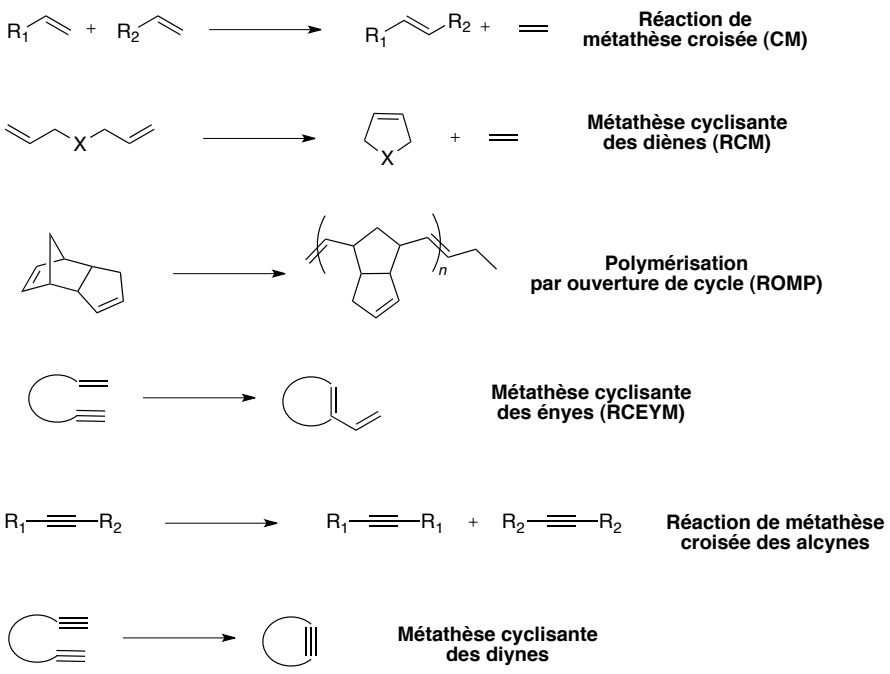


Schéma 1. *Différents types de réaction de métathèse*

Dans la première partie de cette thèse, nous avons décrit les applications des métathèses cyclisantes des diènes (RCM) et des énynes (RCEYM). Ces réarrangements de liaisons multiples C-C ont été utilisés pour obtenir les squelettes hétérocycliques les plus communs dans les produits naturels ou biologiquement actifs.

En focalisant notre attention sur les composés oxygénés et azotés, nous avons commencé notre étude en développant une procédure synthétique capable de former des éthers cycliques à cinq ou six chaînons.

Les précurseurs de la cyclisation ont été obtenus à partir de différents aldéhydes aromatiques disponibles dans le commerce, *via* l'addition de réactifs de Grignard sur le groupe carbonyle suivie par l'éthérification de Willamson des alcools secondaires résultants (Schéma 2).

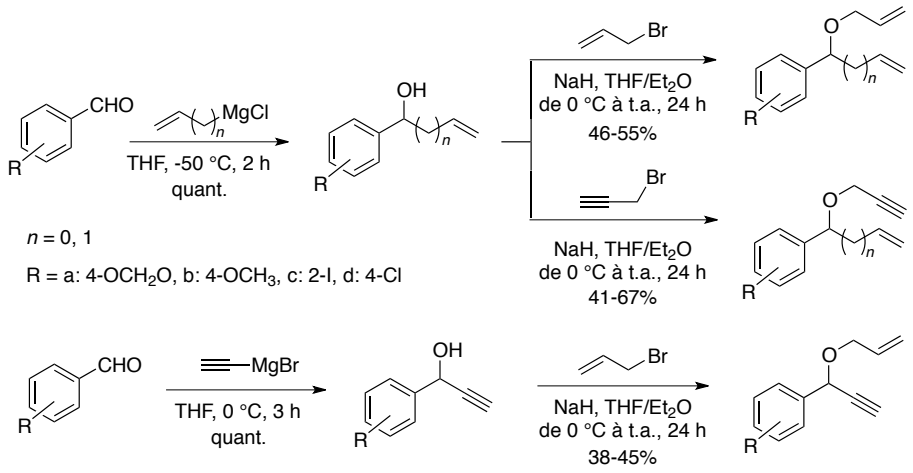
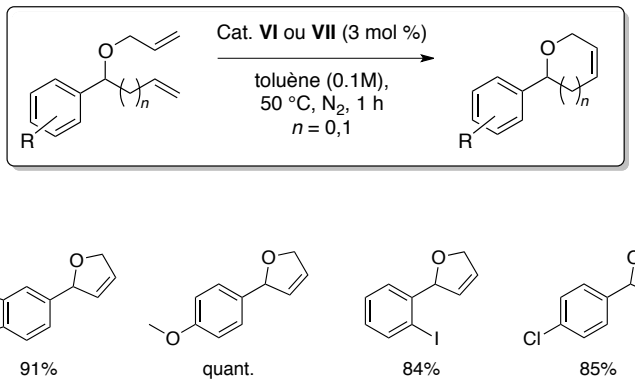


Schéma 2. *Synthèse de dienes et énynes 1,6 et 1,7*

Les réactions de cyclisation des diènes, effectuées en utilisant les catalyseurs de Grubbs **VI** et **VII** (3% mol), dans le toluène à 50 °C, ont permis la formation de dihydropyranes et dihydrofuranes avec des excellents rendements (Schéma 3).



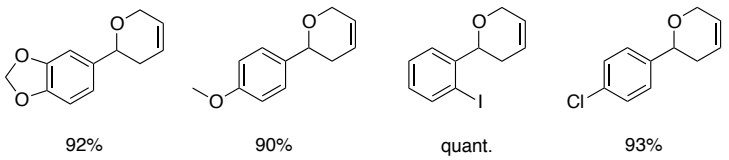


Schéma 3. *RCM des dienes 1,6 et 1,7*

Les énynes 1,6 et 1,7 ont également réagi en présence du catalyseur de métathèse **VI**, générant les 1,3-diènes correspondants avec des rendements de modérés à bons (Schéma 4). Toutes les réactions de RCM et de RCEYM ont toléré la présence de groupements fonctionnels électro-donneurs, ainsi que électro-attracteurs, sur le cycle aromatique des substrats de départ.

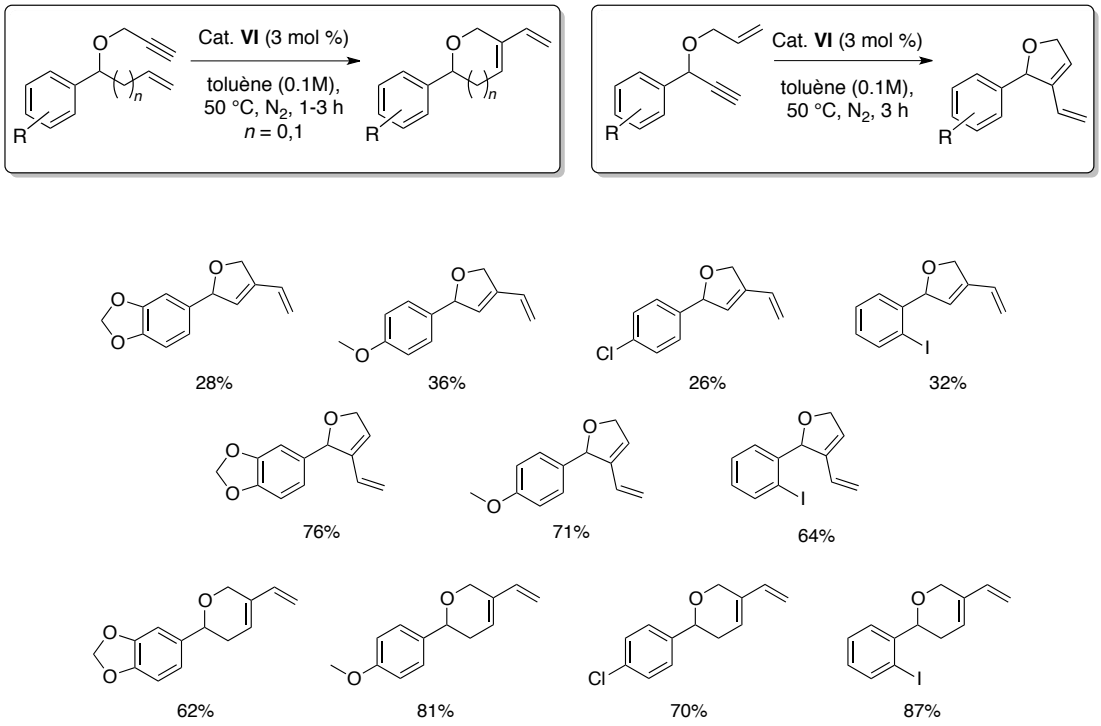


Schéma 4. *RCEYM des énynes 1,6 et 1,7*

Les lactones sont des unités structurales fondamentales, communes à de nombreux produits, qui généralement possèdent des propriétés anticancéreuses intéressantes.

Afin d'obtenir des esters cycliques à cinq et six chaînons, une stratégie de synthèse différente a été développée. Les alcools allyliques, homoallyliques et propargyliques, précédemment isolés, ont été engagés dans une réaction d'estérification classique avec le chlorure d'acryloyle, afin de générer les acrylates désirés rapidement et avec des rendements acceptables (Schéma 5).

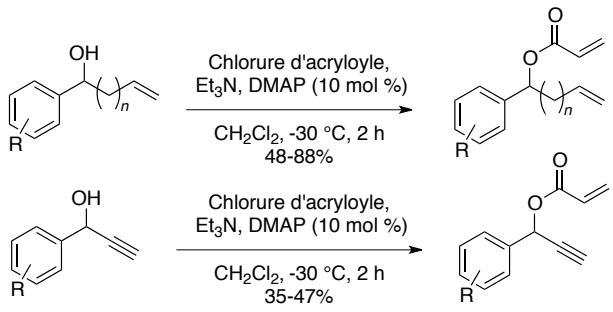
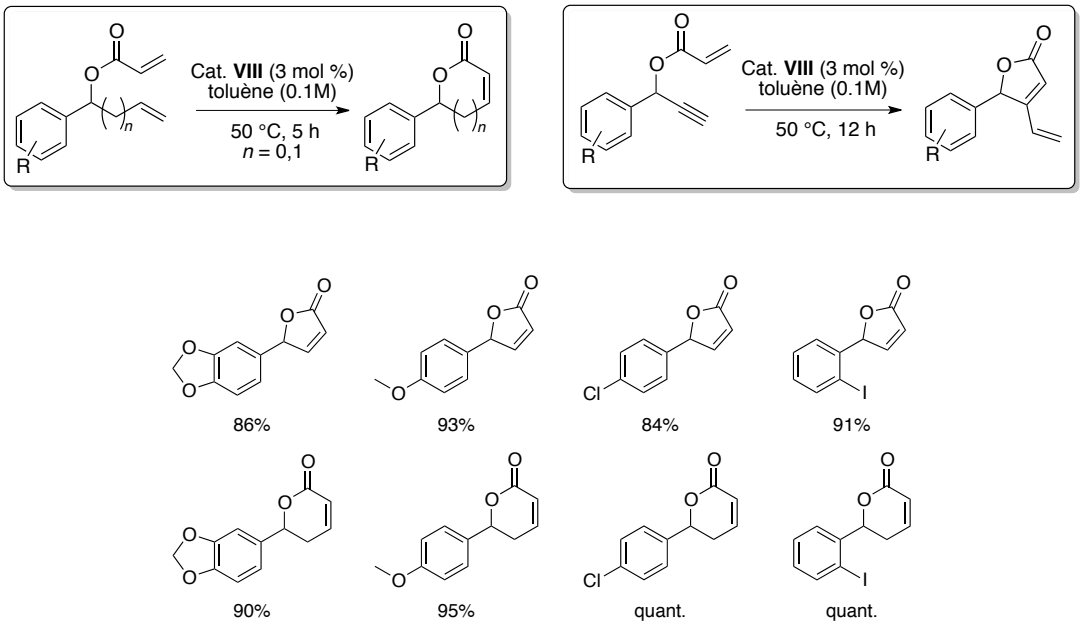


Schéma 5. *Synthèse des esters acryliques*

Les résultats préliminaires, obtenus en soumettant un substrat modèle aux conditions de métathèse, ont clairement démontré que le catalyseur de Grubbs de première génération (**VI**) est inefficace pour promouvoir la cyclisation des acrylates. Par conséquent, plusieurs catalyseurs ont été testés et le complexe **VIII** s'est avéré être le plus efficace pour la synthèse des lactones.

Tous les produits de RCM ont été isolés avec des rendements excellents, alors que la formation de produits de RCEYM nécessite des temps de réaction plus longs et s'effectue avec des rendements modérés. Dans ce dernier cas, la rigidité structurelle du groupement acryloyle, ainsi que la conjugaison entre la double liaison et le carbonyle, résulte en une affinité réduite de cette chaîne latérale pour le catalyseur électrophile à base de ruthénium.



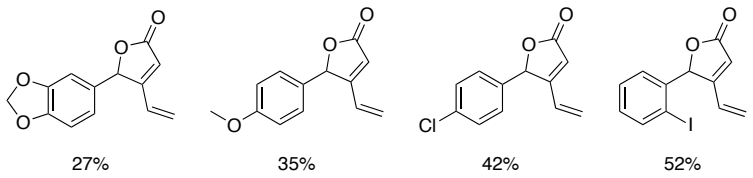


Schéma 6. *Synthèse des lactones*

Les lactames sont d'autres éléments structurels de base dans les composés biologiquement actifs. Des précurseurs de RCM, spécifiquement conçus pour générer des lactames benzyliques, ont été synthétisés en utilisant une réaction de condensation entre des aldéhydes benzyliques et l'allylamine, suivie par la réduction des imines intermédiaires par le borohydrure de sodium. Les amines ainsi isolées ont servi à générer les acrylamides correspondants *via* une réaction d'acylation avec le chlorure d'acryloyle (Schéma 7).

Des substrats de départ avec l'atome d'azote directement lié au cycle aromatique ont également été préparés à partir de plusieurs anilines disponibles dans le commerce. Dans ce cas, une voie de synthèse en deux étapes a été utilisée, composée d'une réaction d'alkylation classique suivie d'une acylation avec le chlorure d'acryloyle (Schéma 7).

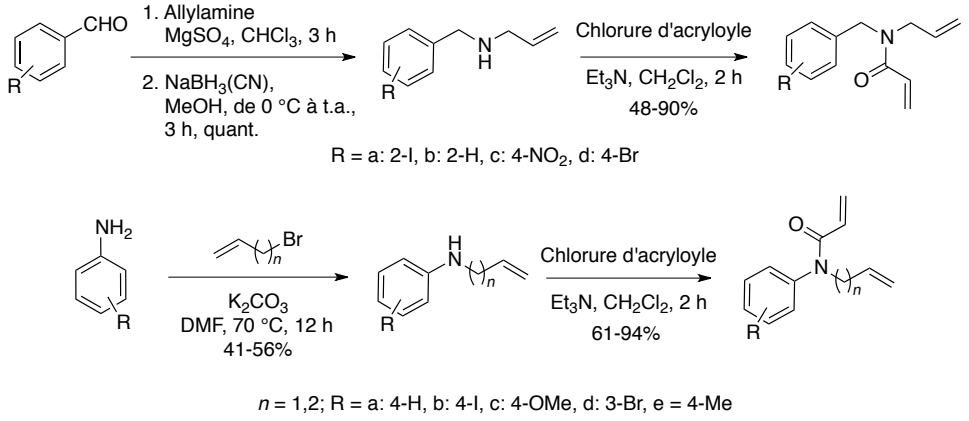


Schéma 7. *Synthèse des acrylamides*

La RCM des acrylamides, effectuée en utilisant le catalyseur **VIII** (3% mol), dans le toluène à 70 °C, a conduit à la formation rapide de lactames à cinq et six chaînons, qui ont été isolés avec des excellents rendements après purification sur gel de silice. Dans ce cas, des solutions diluées des substrats de départ (0,05 M) ont été indispensables pour minimiser la formation de sous-produits résultant de réactions de métathèse croisée.

Malheureusement, toute tentative d'accès aux lactames *via* RCEYM s'est avérée infructueuse, car seul le substrat de départ a pu être récupéré après la réaction.

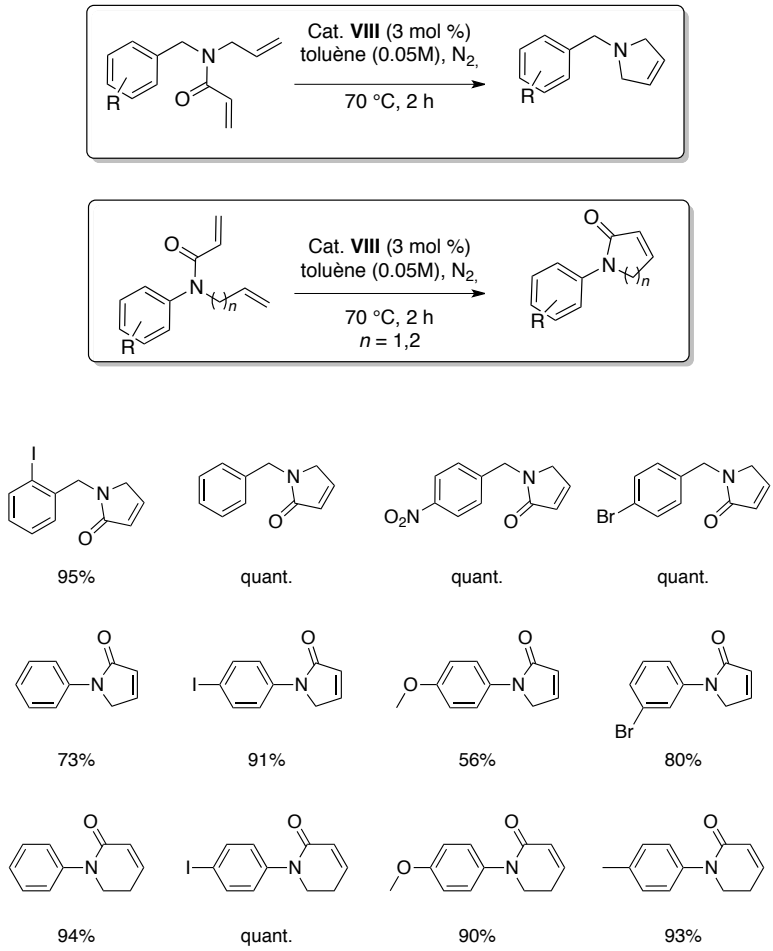


Schéma 8. *RCM des acrylamides*

Ces dernières années, les composés azotés, constitués de cycles à sept chaînons fusionnés avec des substrats aromatiques, ont suscité un intérêt croissant en raison de leur activité biologique.

Les 1- et 2-benzoazépines, qui font partie de cette classe de molécules, ont été peu étudiée, bien que ces deux composés soient des éléments clés pour la découverte de nouveaux médicaments.

Nous avons donc développé de nouvelles réactions de RCEYM, pour accéder rapidement à ce type de structures.

Les précurseurs de cyclisation ont été obtenus à partir de la *N*-allylaniline, en utilisant le réarrangement de aza-Claisen et l'alkylation de la 2-allylaniline résultante avec le bromure de propargyle. Plusieurs substrats fonctionnalisés sur l'atome d'azote ont ensuite été synthétisés par substitution nucléophile (Schéma 9).

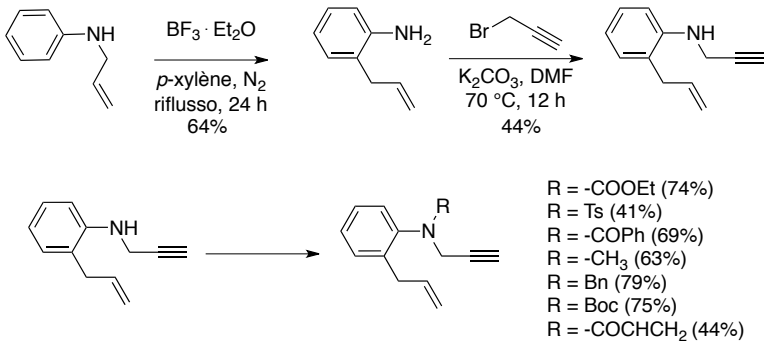


Schéma 9. *Synthèse des énynes 1,8 différemment fonctionnalisés sur l'atome d'azote*

En utilisant le catalyseur **VIII** (3 mol %) dans le toluène à 70 °C, plusieurs 1-benzoazépines différemment substituées ont été isolées *via* la cyclisation des précurseurs ényniques correspondants (Schéma 10).

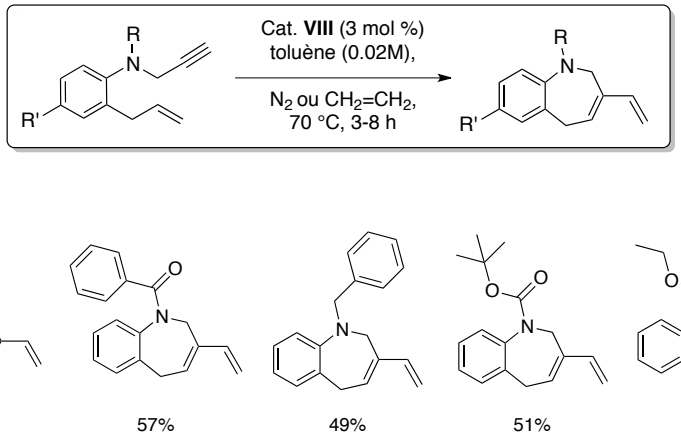


Schéma 10. *Synthèse de 1-benzoazépines*

Dans certains cas, une atmosphère d'éthylène a été nécessaire pour empêcher la formation de sous-produits, dérivants d'un processus tandem RCEYM/homo-CM (Figure 2).

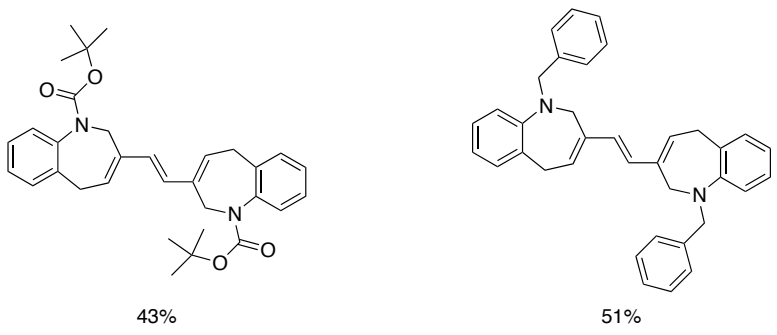


Figure 2. *Sous produits dérivants d'un processus tandem RCEYM/homo-CM*

Nous avons ensuite analysé le comportement des précurseurs ayant un groupement acryloyle lié à atome d'azote. Dans ce cas, trois voies de réaction différentes peuvent être envisagées (Figure 3): 1) la formation d'un cycle à cinq chaînons *via* RCEYM (énone-yne), 2) la synthèse d'un cycle à sept chaînons *via* RCM (énone-ène) et 3) l'obtention d'un cycle à sept chaînons *via* RCEYM (ène-yne).

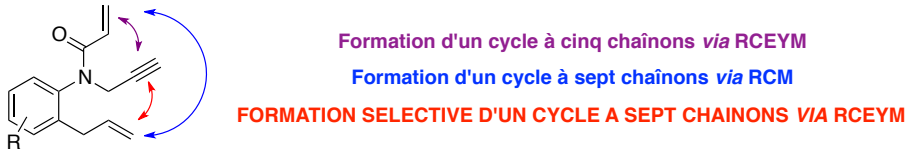


Figure 3. *Trois possibilités différentes de métathèse cyclisante*

Seule la formation du cycle à sept chaînons *via* la métathèse d'ényne a été observée, ce qui mène à l'obtention de produits hautement fonctionnalisables avec de bons rendements (Schéma 11). La régiosélectivité de cette réaction pourrait provenir d'une réactivité élevée des liaisons doubles et triples C-C *vs* une très faible affinité du groupement acyloyle pour le catalyseur de métathèse employé.

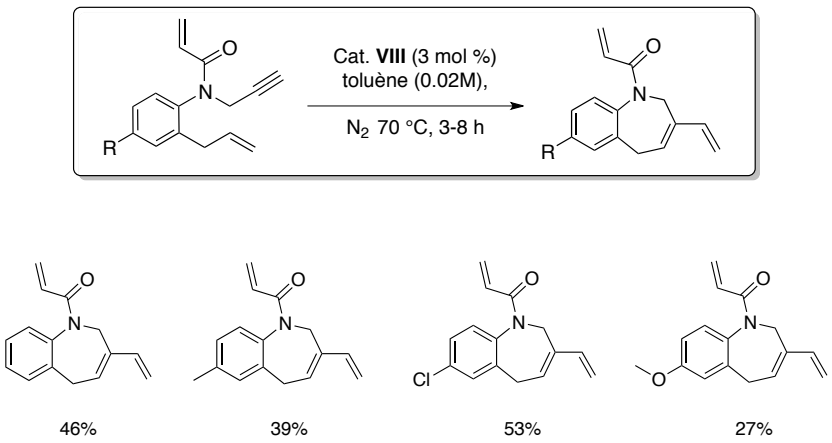


Schéma 11. *Synthèse régiosélective de 1-benzoazépines*

Ces résultats nous ont incités à étudier le comportement d'un 5-aza-1,8-ényne, facilement synthétisé à partir de la 2-iodo aniline (Schéma 12). Ce composé soumis à l'action du catalyseur **VIII** (3 mol%) a rapidement généré le diène 1,3 désiré avec 83% de rendement.

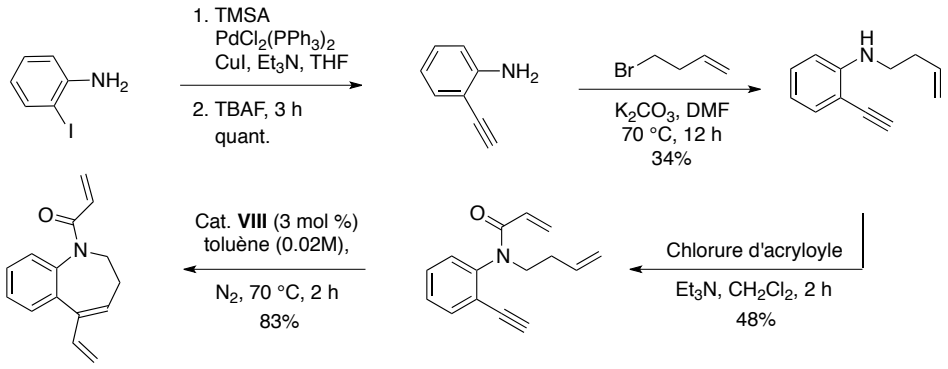


Schéma 12. *Synthèse et réactivité d'un 5-aza-1,8-ényne*

En utilisant les mêmes conditions opérationnelles, le squelette d'une 2-benzoazépine a été obtenu avec 74% de rendement, à partir du 4-aza-1,8-ényne correspondant (Schéma 13).

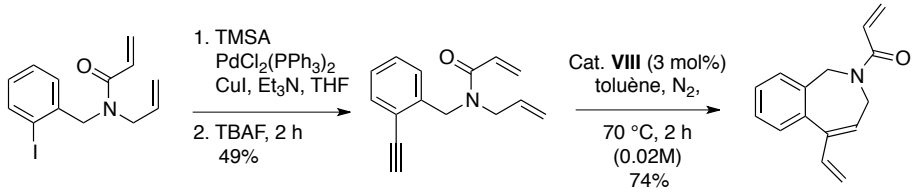


Schéma 13. *Synthèse et réactivité d'un 4-aza-1,8-ényne*

Les produits de RCEYM obtenus régiosélectivement incorporent au moins deux groupements fonctionnels qui peuvent être ultérieurement derivatisés (le 1.3-diène et l'acrylamide).

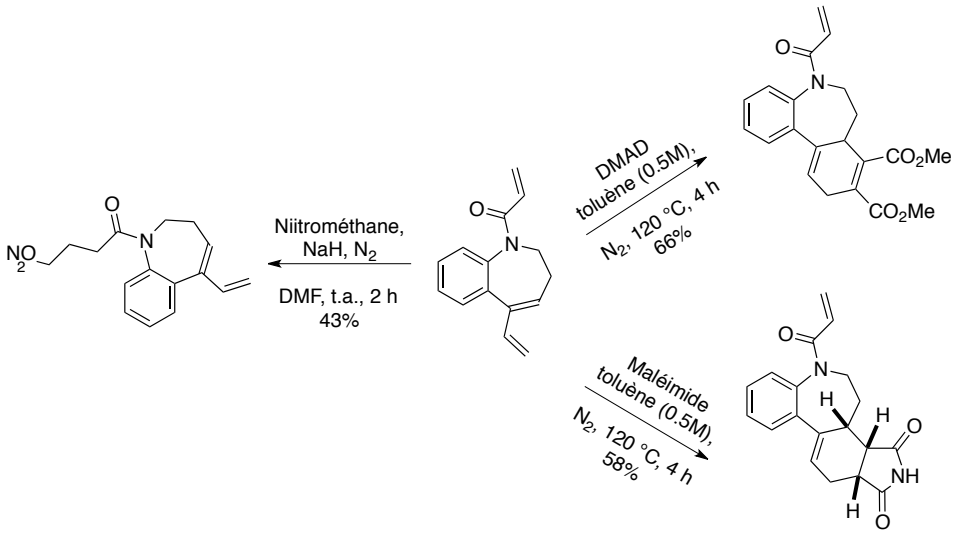


Schéma 14. *Réactivité des composés cycliques obtenus*

Une addition de Michael, ainsi que des réactions de Diels-Alder, ont été conduites avec succès à partir d'une bénzazepine choisie comme substrat modèle (Schéma 14). Pour cette raison, tous les produits synthétisés peuvent être considérés des versatiles intermédiaires de synthèse, pour la préparation de substrats à complexité moléculaire élevée.

Le complexe **VIII** a, enfin, été utilisé comme catalyseur dans la synthèse d'un cycle à huit chaînons fusionné à un composé aromatique (Schéma 15). Dans ce cas, le précurseur de la cyclisation a été obtenu à partir du 2-iodo benzaldéhyde, en utilisant une réaction d'amination réductrice avec de la butenylamine et du $NaBH_3CN$. L'amine secondaire résultante de ce processus a réagit avec du chlorure d'acryloyle, générant l'amide correspondant avec 87% de rendement. Un ényne 1,9 a ensuite été préparé en utilisant une réaction de Sonogashira suivie par la déprotection du groupement TMS avec du TBAF.

Comme observé dans le cas des benzoazépines, une réaction de RCEYM a permis la formation de la benzazocine désirée avec 69% de rendement (Schéma 16). Aucun sous-produit n'a été observé dans le brut réactionnel.

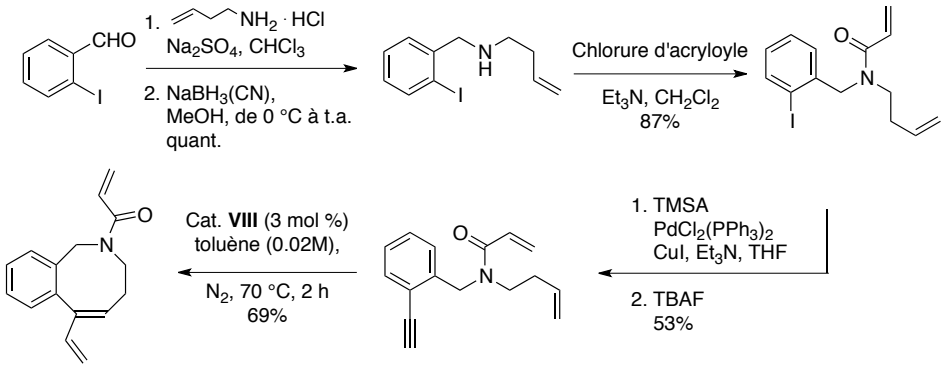


Schéma 15. *Synthèse d'une benzazocine via RCEYM*

Ce dernier résultat suggère que, dans le futur, la procédure de métathèse développée pourrait être utilisé comme protocole général pour la préparation régiosélective d'hétérocycles azotés de dimensions diverses.

2. REACTIONS DE PAUSON-KHAND

La réaction de Pauson-Khand (PKR) peut être considérée une cycloaddition [2+2+1] formelle dans laquelle une liaison double, une liaison triple et du monoxyde de carbone réagissent pour générer une cyclopentenone. Ce processus implique la formation de trois liaisons C-C, d'un cycle dans la version intermoléculaire ou deux cycles dans la version intramoléculaire (Schéma 16).

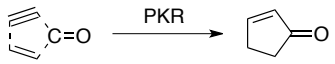


Schéma 16. *Réaction de Pauson-Khand*

Peux de processus peuvent concurrencer la PKR pour la construction de molécules complexes en une seule étape de synthèse.

Les premiers exemples de cette réaction, qui a été initialement réalisée en utilisant des conditions sévères, remontent aux années 70 (Schéma 17). Bien que jusqu'au milieu des années 90, le dicobalt-octacarbonyle ait été le seul complexe utilisé pour promouvoir la réaction, de nombreux catalyseurs mono-et bi-nucléaires sont maintenant disponibles pour la réalisation de ce processus.

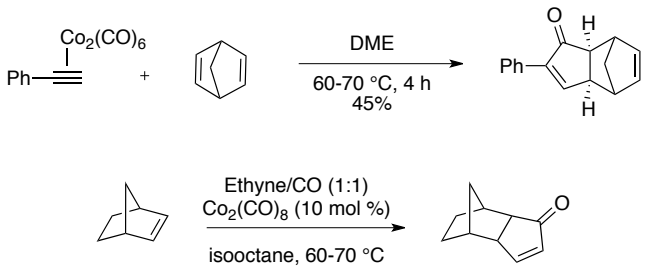
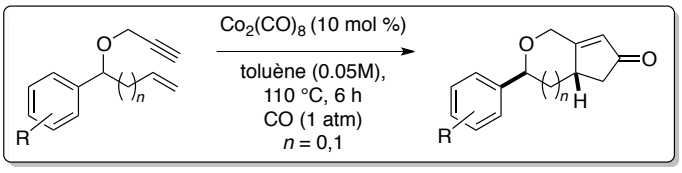
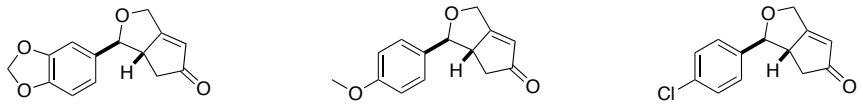


Schéma 17. *Premiers exemples de PKR*

Dans le deuxième chapitre de cette thèse nous avons décrit les réactions de Pauson-Khand des énynes, qui mènent à la formation de squelettes bicycliques. Alors que la RCEYM des énynes 1,5 et 1,6 est une méthode particulièrement efficace pour la synthèse de dihydrofuranes et dihydropiranes, les PKR ont quant à elles permis d'obtenir des composés bicycliques oxygénés 5,5 et 5,6 fusionnés.

Les réactions de carbonylation ont été réalisées dans le toluène à 110°C, en utilisant $Co_2(CO)_8$ (10 mol%) comme catalyseur et une atmosphère de CO (Schéma 18).





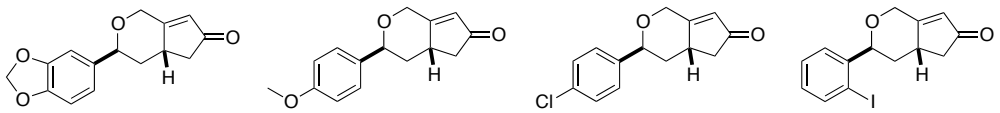


Schéma 18. *Synthèse de composés bicycliques oxygénés via PKR*

Dans ces conditions de réaction, les systèmes bicycliques desirés ont été isolés avec des rendements acceptables après purification sur gel de silice.

La faible conversion des produits de PKR dépend principalement de la formation de complexes stables entre le catalyseur à base de cobalt et les substrats de départ.

Tous les composés bicycliques figurant dans le Schéma 17 ont été obtenus sous la forme d'un seul diastéréoisomère. La configuration relative *cis* de ces produits a été déterminée par analyse RMN (NOESY). L'origine du stéréocontrole a été rationalisée en invoquant la tendance du métal à se lier préférentiellement à un seul côté de la liaison double du substrat de départ (Schéma 19), ce qui est dû à l'encombrement stérique généré par le substituant R sur le centre stéréogénique.

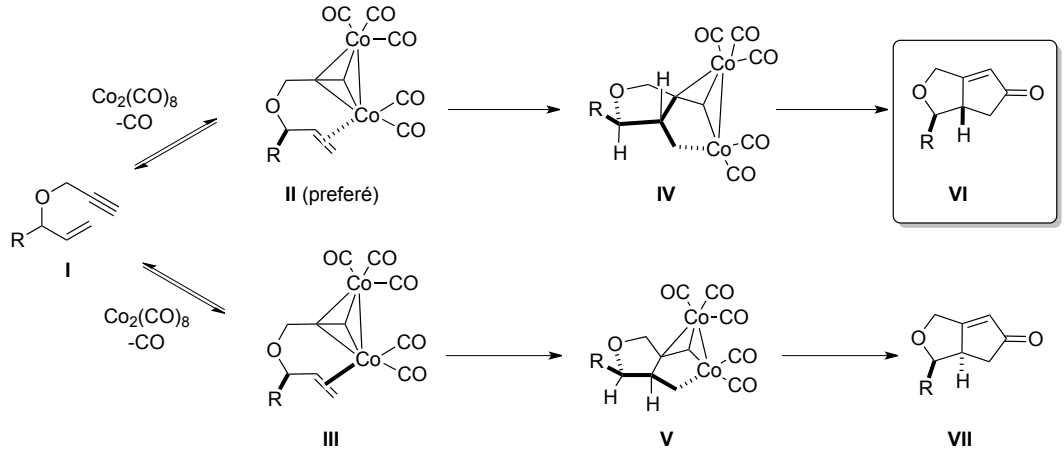


Schéma 19. *Origine du stéréocontrôle des PKR*

En collaboration avec le groupe de recherche de Sannicolò (Université de Milan), nous avons ensuite examiné la possibilité d'utiliser de nouveaux ligands chiraux contenant du phosphore, pour développer une version énantiosélective de la PKR catalysées par le cobalt.

Des résultats préliminaires ont montré une faible activité des ligands testés. Dans le futur, nous tâcherons de tester les mêmes ligands à des PKR catalysée par des complexes de rhodium. Ceci dans le but d'évaluer toute relation entre énantiosélectivité et densité électronique du ligand phosphoré utilisé.

3. ACTIVATION ELECROPHILE DES ALCYNES CATALYSEE PAR LES METAUX DE TRANSITION

L'attaque des nucléophiles sur les alcynes activés par les métaux de transition est l'une des stratégies les plus utilisées pour la synthèse de structures cycliques et acycliques, d'origine naturelle ou non.

Parmi les complexes à base de métaux de transition qui peuvent catalyser l'activation électrophile des alcynes, les composés à base de platine et d'or ont démontré une capacité exceptionnelle à promouvoir différentes transformations organiques, générant une large gamme de produits structurellement différents dans des conditions de réaction douces. Tous ces processus sont issus des propriétés acides (d'acidité de Lewis) provenant des complexes de platine et d'or, ainsi que de leur capacité d'interaction sélective avec des liaisons π carbone-carbone.

Ces dernières années, l'attaque intramoléculaire (**I**) et intermoléculaire (**II**) de nombreux nucléophiles, sur les alcynes activés, ont été énormément étudiés (Schéma 20). Dans ce contexte et malgré la réactivité élevée des complexes à base d'or et de platine, l'amélioration des systèmes catalytiques reste un objectif majeur.

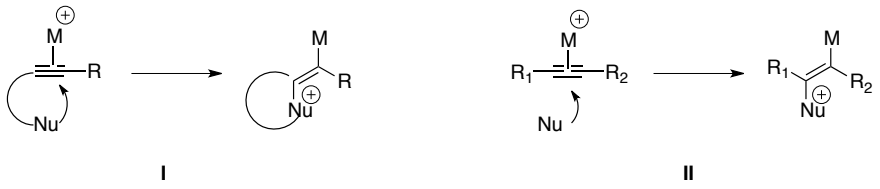


Schéma 20. *Attaque des nucléophiles sur les alcynes activés par les métaux de transition*

Dans la troisième partie de cette thèse, l'utilisation d'un catalyseur à base d'Iridium (III) a été décrite, ce qui a permis la synthèse de composés hétérocycliques avec des rendements élevés et des temps de réaction très courts.

Initialement, la grande efficacité des réactions d'hydroalcoxylation d'alcynes décrites dans la littérature, nous a encouragés à synthétiser différents diols homopropargyliques pour les tester dans des cyclisations catalysés par l'Ir (III).

Les alcools désirés ont été obtenus en utilisant une procédure en deux étapes, impliquant l'alkylation de malonates commerciaux et la réduction successive des groupements ester avec du $LiAlH_4$ (Schéma 21).

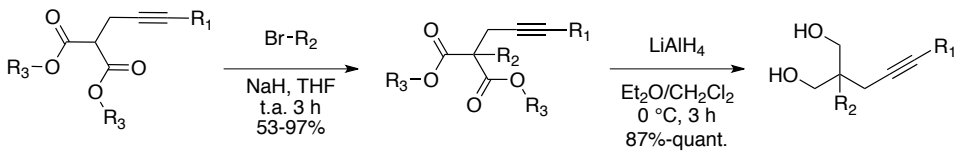
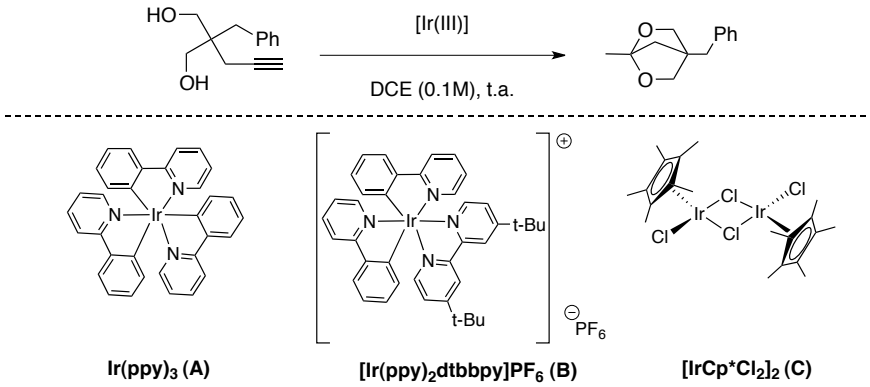


Schéma 21. *Synthèse des diols homopropargyliques*

A partir d'un substrat modèle, différents complexes d'iridium III on été employés. Cependant, en utilisant l'$IrCl_3$ et les catalyseur **A** et **B** (Tableau 1) dans le DCE a température ambiante, nous n'avons observé aucune formation du produit désiré : seul le substrat de départ a pu être isolé après la réaction.

En considérant sa capacité d'interaction avec les alcynes dans des conditions douces, le complexe $[IrCp^*Cl_2]_2$ (**C**) a été également testé dans la cyclisation. En effet, en mettant en présence le substrat modèle et le catalyseur **C** (5 mol%) dans le dichloroéthane (DCE), à température ambiante, nous avons isolé le cétal bicyclique correspondant avec un rendement quantitatif. La quantité de catalyseur a été réduite jusqu'à 1 mol% sans observer de diminution du rendement. Néanmoins des temps de réaction plus longs ont été nécessaires pour obtenir la conversion complète du substrat de départ (Tableau 1).



Catalyseur	Quantité catalytique (mol %)	t (h)	Rendement (%)
$IrCl_3{\cdot}3H_2O$	10	1	0
$IrCl_3$	10	1	0
$Ir(ppy)_3$	5	1	0
$[Ir(ppy)_2dtbbpy]PF_6$	5	1	0
$[IrCp^*Cl_2]_2$	5	0.25	quant.
$[IrCp^*Cl_2]_2$	2.5	0.25	quant.
$[IrCp^*Cl_2]_2$	1	0.5	quant.

Tableau 1. *Optimisation des conditions de réaction*

Beaucoup de cétals bicycliques ont été synthétisés avec de très bons rendements, en utilisant les conditions de réaction décrites ci-dessous (Schéma 22).

A partir de substrats contenant des groupements allyles, la cyclisation s'est révélée chimiosélective envers les alcynes, puisque les chaînes allyliques n'ont pas donné lieu à des réactions secondaires.

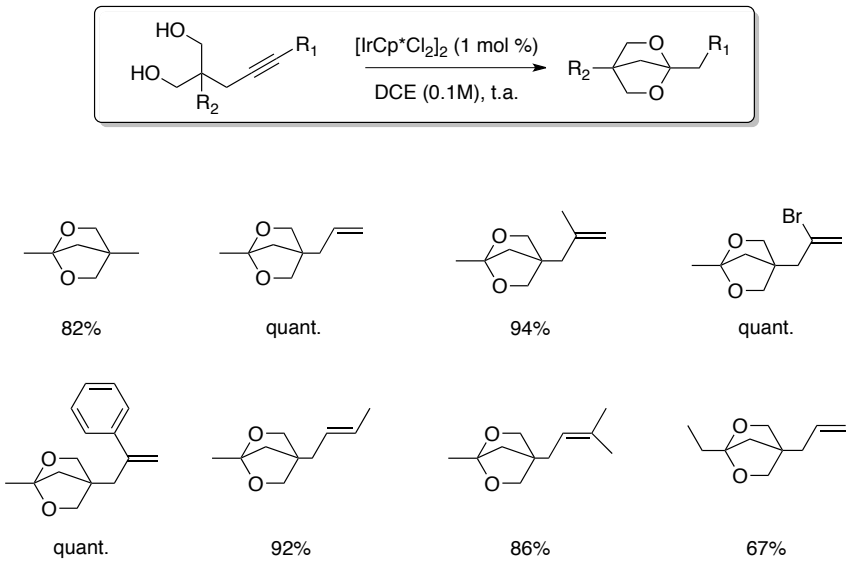


Schéma 22. *Réactivité des diols homopropargyliques*

Un mécanisme est proposé dans le Schéma 23 pour expliquer la formation des cétals bicycliques. Dans un premier temps, l'interaction π entre la triple liaison et le catalyseur pourrait générer le complexe métallique **I**. Une première addition nucléophile intramoléculaire du groupement hydroxyle sur l'alcyne activé conduirait alors à la formation de l'intermédiaire **II**. La protodemétallation de **II** suivie par l'addition du deuxième hydroxyle sur l'éther vinylique résultant pourrait enfin générer le cétal bicyclique observé (**III**).

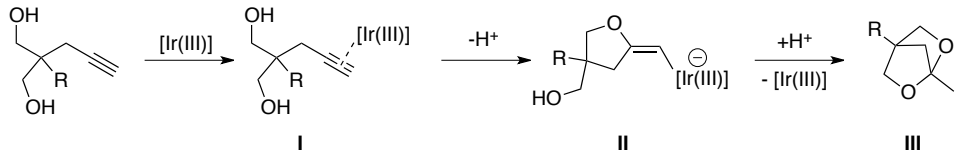


Schéma 23. *Mécanisme des réactions d'hydroalcoxylation*

Les rendements élevés et les conditions douces des hydroalcoxylations catalysées par l'Ir(III), nous ont poussés à étudier d'autres types de cyclisations pour la synthèse de produits ayant

une structure différente. Dans cette perspective, l'application de notre système catalytique aux énynes 1,6 azotés a été envisagée, afin de développer des réarrangements impliquant simultanément les liaisons double et triple des substrats de départ. Par conséquent, plusieurs énynes 1,6 azotés ont été synthétisés et testés dans les réactions catalysées par l'Ir(III).

Deux tosylamides ont été obtenus à partir de la *N*-Boc-*p*-toluènesulfonamide, en utilisant une réaction d'alkylation suivie par la déprotection de l'atome d'azote. Ces composés ont ensuite réagi avec des alcools allyliques dans une réaction de Mitsunobu, afin de générer les énynes désirées avec de bons rendements (Schéma 24).

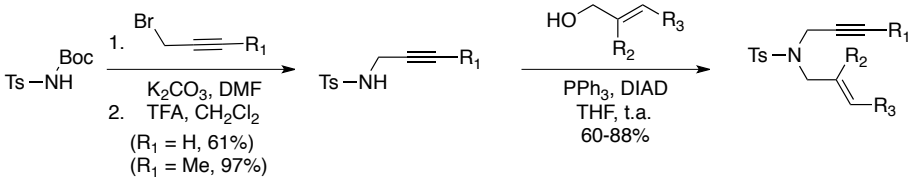
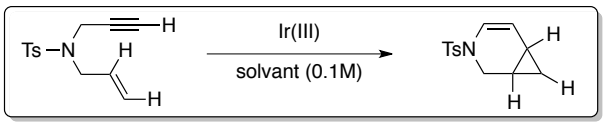


Schéma 24. *Synthèse d'ényne 1,6 azotés*

Les conditions de réaction développées pour les hydroalcoxylations des diols homopropargyliques ont tout d'abord été appliquées à la cyclisation des énynes 1,6 (Tableau 2) mais se sont avérées inefficaces. Différentes conditions opérationnelles ont ensuite été examinées et l'utilisation du catalyseur $[IrCp^*Cl_2]_2$ (5% mol) dans la DCE à reflux, a conduit à la formation d'un dérivé cyclopropanique avec 55% de rendement. Un résultat similaire a été obtenu en employant le toluène comme solvant de réaction.



Quantité catalytique (mol%)	Solvant	T (°C)	t (h)	Rendement (%)
1	DCE	r.t.	24	0
2.5	DCE	r.t.	24	0
5	DCE	r.t.	24	30
5	DCE	reflux	3	55
5	Toluène	reflux	3	53

Tableau 2. *Optimisation des conditions de réaction*

Une fois optimisée, la cyclisation a été appliquée avec succès à une grande variété de composés ényniques azotés et un certain nombre de produits bicycliques ont été isolés sous la

forme d'un seul diastereoisomère (Schéma 25). Les groupements alkyles et aryles, ainsi que les alcynes internes, ont été tolérés dans les conditions de réaction.

Il faut noter que le complexe $[IrCp^*Cl_2]_2$ a été efficace en faible quantité catalytique et en absence de tout autre additif. Pour cette raison, le protocole que nous avons développé semble avoir une applicabilité remarquable par rapport à d'autres procédures précédemment décrites dans la littérature

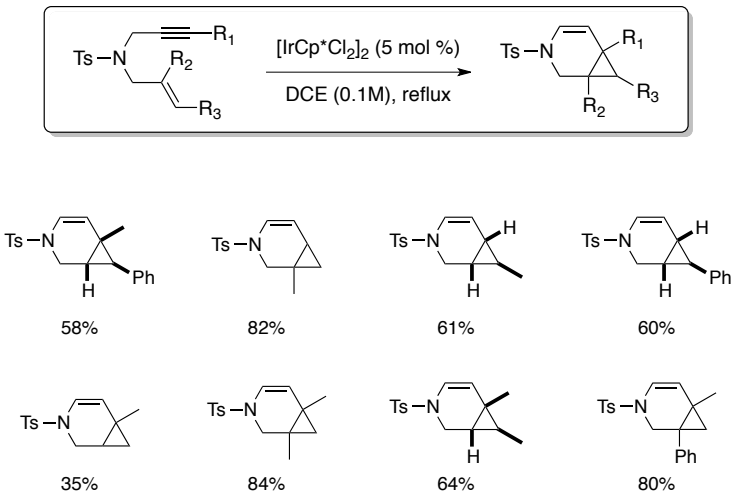


Schéma 25. *Réactivité d'ényne 1,6 azotés*

La formation des 2-aza-bicyclo[4.1.0]heptènes peut être expliquée par analogie avec la réactivité des complexes d'or(I) et de platine (II) décrite dans la littérature (Schéma 26). Tout d'abord il y aurait la formation d'un complexe π entre l'iridium et l'alcyne suivi par la formation d'un Ir-carbène, stabilisé par l'atome donneur.

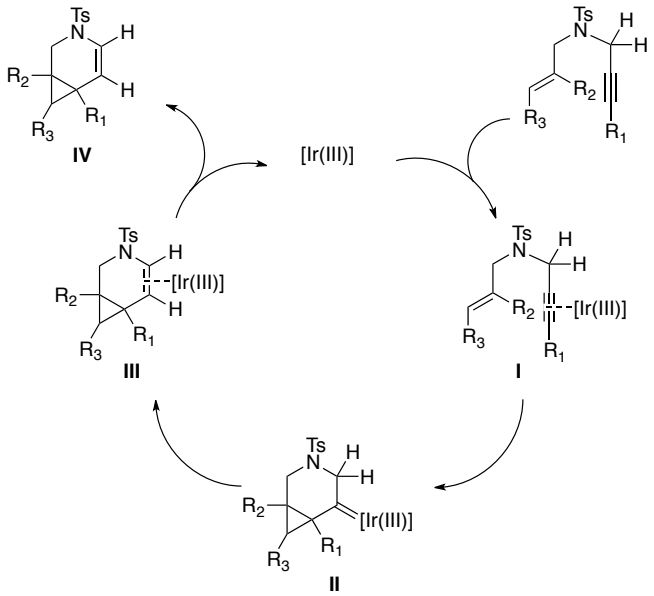


Schéma 26. *Mécanisme des réactions de cyclopropanation*

Une migration 1,2 d'hydrure ainsi que la décomplexation du métal permettraient enfin obtenir le composé bicyclique observé.

Dans un futur proche, l'extraordinaire réactivité du complexe $[IrCp^*Cl_2]_2$, ainsi que les conditions de cyclisation douces, pourraient entraîner des applications intéressantes de notre système catalytique dans la synthèse de produits naturels et d'autres hétérocycles biologiquement activfs.

4. CYCLOISOMERISATION D'ALLENES CATALYSEES PAR L'OR

Les complexes de platine, d'iridium et d'or, comme décrit précédemment, sont de faibles acides de Lewis, qui peuvent activer les liaisons multiples C-C pour former des nouvelles liaisons C-C ou C-hétéroatome *via* l'attaque de différents nucléophiles. Parmi divers substrats sensibles à l'activation, les alcynes jouent un rôle dominant, tandis que les réactions des alcènes ou des allènes ont été étudiées moins fréquemment.

Ces dernières années, les catalyseurs à base d'or se sont avérés particulièrement réactifs pour l'activation sélective des allènes en présence d'autres groupements fonctionnels et plusieurs réactions d'addition nucléophile intramoléculaire ont été décrites. Le catalyseur peut en effet coordonner les deux liaisons doubles conjuguées qui caractérisent la fonction allène, donnant lieu à différentes possibilités de cyclisation (Schéma 27). La régiosélectivité de l'attaque dépend de plusieurs facteurs tels que les propriétés du catalyseur, la structure du substrat de départ et les caractéristiques du nucléophile qui piège l'espèce déficiente en électrons.

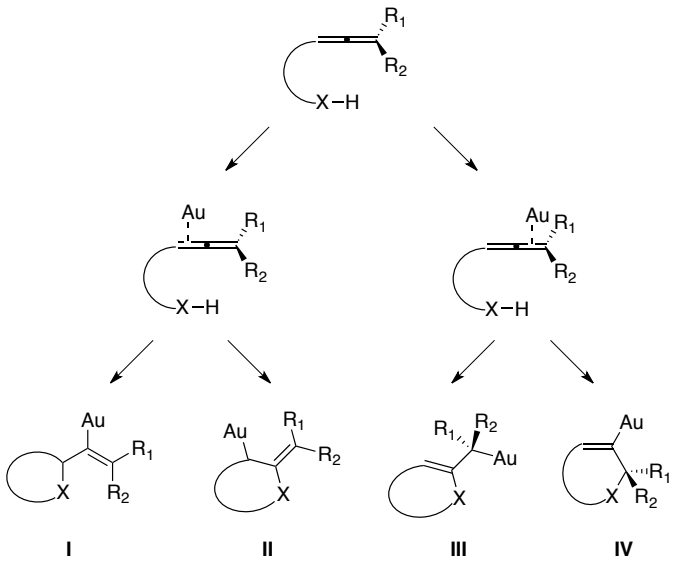


Schéma 27. *Régiosélectivité de l'attaque nucléophile sur les allènes activés*

Dans la dernière partie de cette thèse, une nouvelle réaction de cyclisation de β-allenylimines et β-allenylhydrazones a été présentée, ce qui conduit à la formation de pyrroles hautement substitués *via* la migration 1,2 de groupements alkyles ou aryles.

Les précurseurs de la cyclisation ont été synthétisés en utilisant la procédure en deux étapes décrite dans le Schéma 28. Initialement, la réaction entre des aldéhydes énolisables et des alcools propargyliques commerciaux nous a permis d'isoler différents aldéhydes β-alléniques avec des rendements modérés à bons. Dans la deuxième étape, la condensation de ces aldéhydes avec de l'aniline a conduit à la formation des imines correspondantes avec des rendements quantitatifs. En utilisant une réaction de condensation similaire, un certain nombre d'hydrazones différemment substituées ont enfin été isolés après purification rapide sur gel de silice.

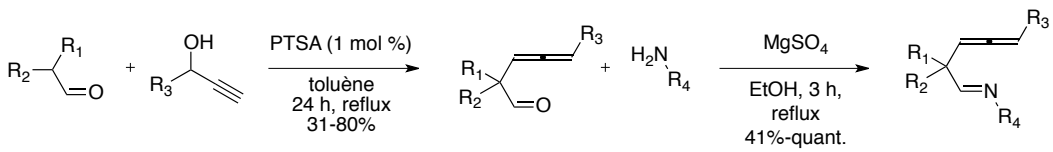


Schéma 28. *Synthèse des précurseurs de cyclisation*

La cyclization a tout d'abord été réalisée à partir d'une β-allenylimine modèle. Le précurseur choisi a été traité avec 5 mol% d'AuCl, d'$AuCl_3$ et de catalyseur **A**, dans le CH_2Cl_2 à température ambiante, mais aucune réaction n'a été observée. Malgré ce premier résultat décevant, différentes conditions réactionnelles ont été étudiés et le complexe **A** s'est avéré être un catalyseur efficace sous irradiation micro-ondes, dans le DCE, à 100 °C pendant 20 minutes. Le pyrrole désiré a ainsi été isolé avec 15% de rendement (Schéma 29).

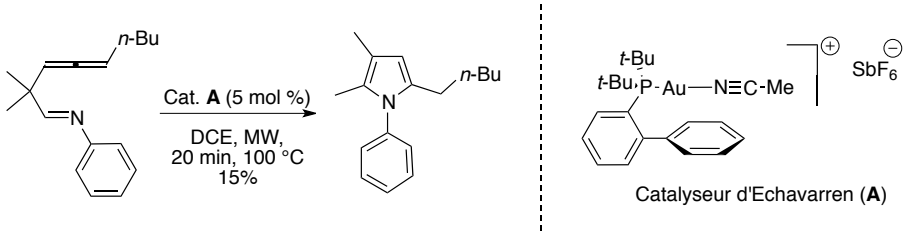
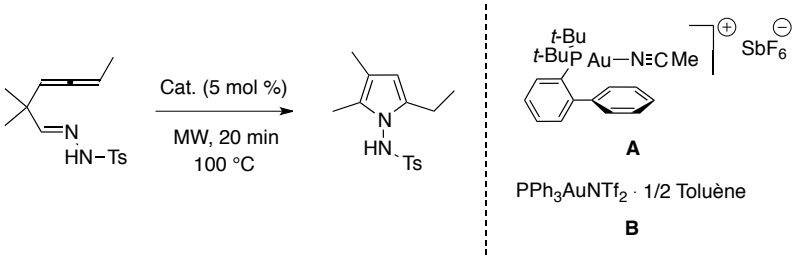


Schéma 29. *Réactivité des β-allenylimines*

L'instabilité et la faible réactivité des imines nous ont encouragé à examiner le comportement des β-allenylhydrazones.



Catalyseur	Solvant	Rendement
A	THF	51%
A	DCE	57%
$AuCl_3$	DCE	n.r.
AuCl	DCE	n.r.
B	DCE	55%
$AgNO_3$	DCE	n.r.
$AgSbF_6$	DCE	traces
AgOTf	DCE	n.r.
CuI	DCE	n.r.
$Cu(OTf)_2$	DCE	n.r.
$FeCl_3$	DCE	n.r.
TfOH	DCE	n.r.
$HN(OTf)_2$	DCE	n.r.

Tableau 3. *Activité de différents catalyseurs*

La réaction a été réalisée à partir d'un substrat modèle avec le catalyseur **A** (5 mol%), sous irradiation micro-ondes, à 100 °C pendant 20 minutes. En utilisant DCE en tant que solvant, le pyrrole désiré a été obtenu avec 57% de rendement (Tableau 3). D'autres composés capables de promouvoir les réactions d'isomérisation ont été testés, mais seuls le catalyseur **A** et le complexe **B** se sont révélés actifs dans ce type de processus (Tableau 3).

Nous avons donc réalisé les cycloisomérisations des différentes tosylhydrazones en utilisant 5 mol% de catalyseur **A** ou **B**, dans le DCE sous microondes, en chauffant à 100 °C pendant 20 minutes (Schéma 30). Les pyrroles désirés ont été obtenus avec de bons rendements. La réaction tolère et les groupements alkyles et les aryles sur l'allène de départ.

A partir des hydrazones qui contiennent les groupements éthyle-méthyle et phényle-méthyle sur le carbone en α de l'allène, nous avons observé une migration 1,2 sélective des groupements éthyle et phényle par rapport aux méthyles. Dans tous les cas, les produits ont été obtenus avec de très bons rendements.

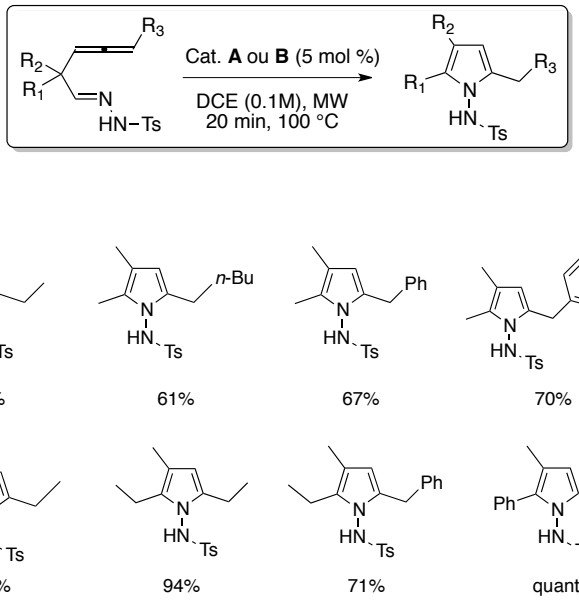


Schéma 30. *Réactivité des tosylhydrazones*

L'influence des substituants sur l'atome d'azote a ensuite été étudiée en plaçant différentes 2,4-dinitrophényl-hydrazones dans les mêmes conditions de cyclisation (Schéma 31). Dans ce cas, la réaction se déroule avec une grande efficacité, générant les pyrroles souhaités avec des rendements excellents.

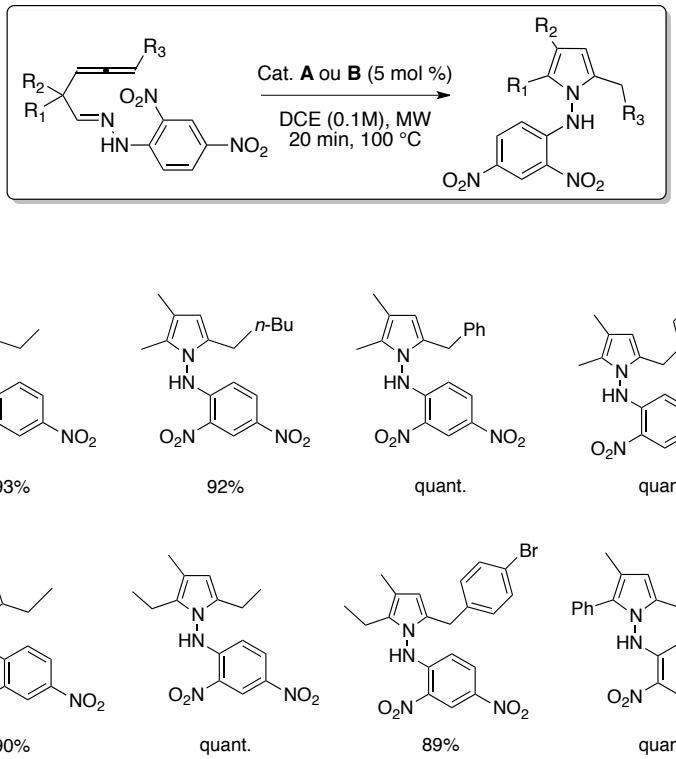


Schéma 31. *Réactivité des 2,4-dinitrophényl-hydrazones*

De plus, un pyrrole fusionné avec un cycle à six chaînons, qui dérive de l'agrandissement d'un cyclopentane, a été isolé avec un rendement quantitatif (Schéma 32). Nous avons même réussi à former un pyrrole fusionné avec un cycle à sept chaînons, thermodynamiquement moins favorable, qui dérive de l'agrandissement d'un cyclohexane. Dans ce cas, le produit a été obtenu avec 83% de rendement (Schéma 32).

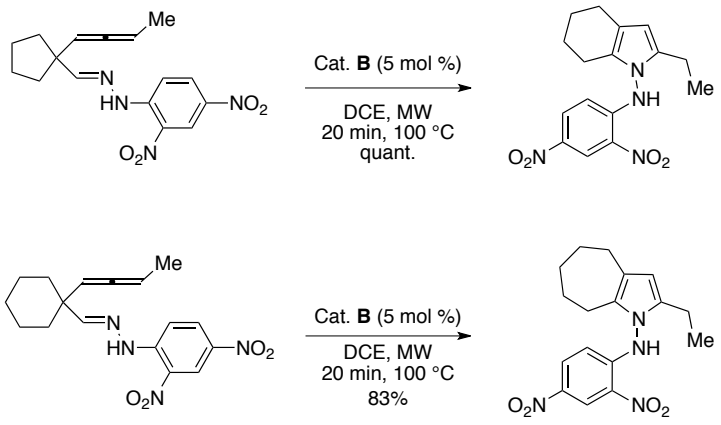


Schéma 32. *Agrandissement de cycles*

Le mécanisme proposé pour le processus de cycloisomérisation des β-allenylhydrazones est représenté dans le Schéma 30. Le complexe électrophile d'or(I) permettrait tout d'abord l'activation de l'allène, en formant un complexe π (**I**). Celui-ci subirait une attaque nucléophile de l'azote sur l'atome central. On formerait ainsi un ion iminium cyclique (**II**) sur lequel s'effectue la migration d'un groupement R, générant un composé (**III**) qui se réaromatise spontanément.

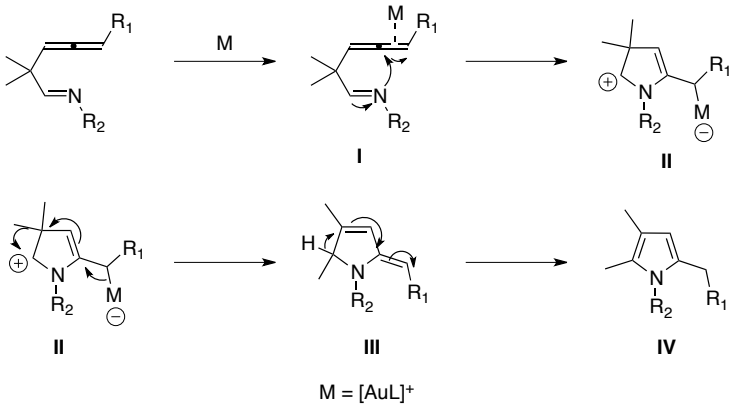


Schéma 33. *Mécanisme de réaction*

Actuellement, le développement d'une version *one-pot* de la réaction est en cours d'optimisation dans notre laboratoire, afin d'obtenir les pyrroles directement des aldéhydes β-alléniques sans avoir à isoler et purifier les hydrazones intermédiaires (Schéma 34).

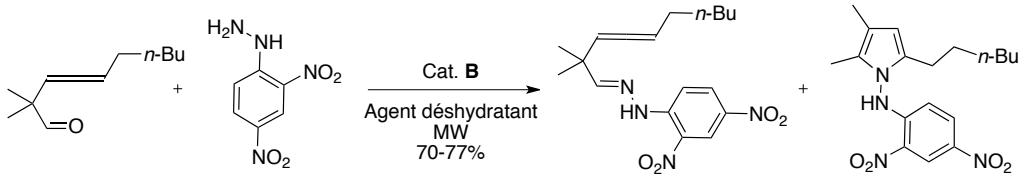


Schéma 34. *Réaction one-pot*

CONCLUSIONS GENERALES

En conclusion, cette thèse a montré que les réactions de métathèse, la carbonylation de Pauson-Khand et l'activation électrophile de liaisons multiplex C-C, catalysée par l'iridium et l'or, permettent une augmentation rapide de la complexité moléculaire à partir de substrats relativement simples.

Des études, qui décrivent la large applicabilité de ces réactions, sont publiées avec un rythme très rapide.

Dans le futur, la découverte de nouvelles transformations catalysées par les métaux de transition continuera sûrement à occuper un rôle central dans la synthèse organique.

PUBLISHED WORKS

Posters and Communications

Synthesis of *O*-heterocyclic compounds via ene-yne metathesis and Pauson-Khand reaction, *16th International Symposium on Homogeneous Catalysis*, Firenze (ITALY), July 2008 (Poster).

Synthesis of *O*-heterocyclic compounds *via* metathesis and Pauson–Khand reactions, *XXXIV edition of the "Attilio Corbella" Summer School on Organic Synthesis*, Gargnano (ITALY), June 2009 (Poster).

Synthesis of heterocyclic compounds *via* metathesis and Pauson–Khand reactions, *8ème Rencontre de Chimie Organique*, Paris (FRANCE), April 2010 (Poster).

Gold(I)-catalyzed cyclization of β-allenylhydrazones: an efficient synthesis of multisubtituted pyrroles, *6ème Rencontre de Chimie Organique de Marseille*, Marseille (FRANCE), May 2010 (Oral communication).

$[IrCp^*Cl_2]_2$: A novel efficient catalyst for the synthesis of oxygen and nitrogen containing bicyclic compounds, *17th European Symposium on Organic Chemistry*, Crete (GREECE), July 2011 (Poster).

Regioselective ring-closing ene-yne metathesis reactions for the synthesis of highly functionalizable benzazepine scaffolds, *8th International School of Organometallic Chemistry*, Camerino (ITALY), August 2011 (Flash presentation).

Publications

Gold(I)-catalyzed cyclization of β-allenylhydrazones: an efficient synthesis of multisubtituted *N*-amino pyrroles, Benedetti, E.; Lemière, G.; Chapellet, L.-L.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Org. Lett.* **2010**, *12*, 4396.

(Pentamethylcyclopentadienyl)iridium dichloride dimer {$[IrCp^*Cl_2]_2$}: a novel efficient catalyst for the cycloisomerizations of homopropargylic diols and *N*-tethered enynes, Benedetti, E.; Simonneau, A.; Hours, A.; Amouri, H.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard J. -P.; Fensterbank L. *Adv. Synth. Catal.* **2011**, *353*, 1908.

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