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Ruthenium and Rhodium catalyzed C-N bond formation reactions in the synthesis of nitrogen containing heterocyclic compounds

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Why, for example, should a group of simple, stable compounds of carbon, hydrogen, oxygen and nitrogen struggle for billions of years to organize themselves into a professor of chemistry? What's the motive?

R. M. Pirsig

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I. Foreword

I.I. Transition metal catalysis

Since the last decades transition metal-mediated reactions have played an important role either in intermolecular and intramolecular level, leading to the formation of new bonds in mild conditions. Attractiveness of these reactions arises both from the possibility to start from easily accessible substrates, and from their capability to act with high selectivity, also in the case of rather complex molecules. These reactions allow a wide variety of synthetic transformations, arising from the broad class of reagents that could be employed, and leading to the formation of heterocyclic rings either through the formation of a carbon-heteroatom or a carbon-carbon bond. In the second case, the presence in the molecular chain of an heteroatom is needed (Figure 1).
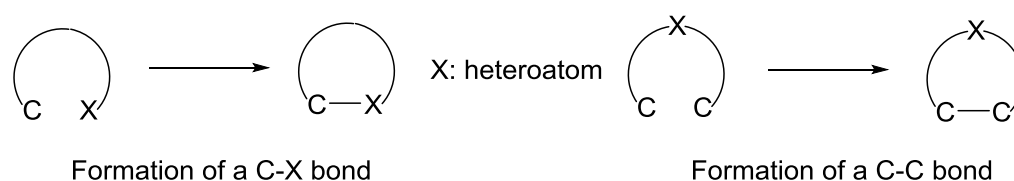

Formation of a C-X bond   Formation of a C-C bond

Figure 1

The possible use of substrates having the same properties, usually both electron rich reagents like alcohols, amines and carbon-carbon multiple bonds, is an important feature of this method. Coordination of the transition metal centre to electron rich substrates induces an *umpolung* of their classic reactivity, making possible a nucleophilic attack.

Request for green and sustainable chemistry has inspired chemists to search for efficient and cheaper ways to assemble chemical bonds during the synthesis of complex structures.[1] In particular, C-C, C-N and C-O bonds are essential links in most organic frameworks, and their construction constitutes a primary and essential aspect of synthetic chemistry. On the other hand, C-H bonds are pervasive within the structure of organic molecules. Thus, direct functionalisation of C-H to C-X (X = C, N, O) bonds emerge as one of the most relevant and straightforward methods available for the synthesis of complex molecules.[2] Mediation of a transition metal is often necessary, due to the high dissociation energy of C-H bonds (110 kcal mol^{-1} for benzene and 105 kcal mol^{-1} for methane).

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[1] P. T. Anastas, J. C. Warner, *Green Chemistry Theory and Practice*, Oxford University Press **1998**.
[2] D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.*, **2007**, 107, 174; E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.*, **2007**, 107, 5318; X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.,* **2009**, 48, 5094; D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.,* **2010**, 110, 624.

Strategies based on transition metal-catalyzed C-H activation are advantageous in that no previous activation of C-H bonds is needed, and through the formation of reactive organometallic intermediates we can realize an eco-friendly and step-economic pathway. Although the nature of C-H bonds cleavage and the formation of a M-C species (M = metal) can significantly change, depending on the solvent, substrate, additives, nature of the transition metals and of the ligands, we can identify four general mechanisms, depending on electronic properties of the substrate and/or of the metal: *i)* oxidative addition for electron rich metals of the late transition, *ii)* σ-bond metathesis for metals of the early transition, *iii)* electrophilic C-H activation for electron deficient late transition metals, *iv)* Lewis base-assisted C-H activation.[3] These different pathways allow the activation of C-H bonds in a multitude of substrates. Achieving regioselective C-H activation and functionalisation often represents an interesting trial for chemists, since several C-H bonds are present in many organic molecules and also in value-added structures.

I.II. Importance of selectivity

Coordination compounds are constituted by a central metal ion surrounded by a certain number of ligands, bounded in dative or coordinative manner, and the number of occupied coordination sites determines the coordination number of metals. The role of metal complexes used as catalysts in organic reactions is fundamental, since many processes only occur when the catalyst enables new reaction pathways.

Selectivity is a fundamental characteristic of chemical reactions, both speaking in terms of regioselectivity and stereoselectivity. Regioselectivity could be described as the preference of one direction in chemical bond making (or breaking) over all other possibilities, while stereoselectivity is the property of a chemical reaction in which a single reactant forms an unequal mixture of stereoisomers during the non-stereospecific creation of a new stereocenter or during the non-stereospecific transformation of a pre-existing one.

We can also distinguish between enantioselective reactions, when one enantiomer is formed in preference to the other, creating an optically active compound from an achiral starting material, and diastereoselective reactions, in which one diastereoisomer is preferentially formed establishing a preferred relative stereochemistry.

Since tetrahedral model for the carbon atom was introduced by van't Hoff and Le Bel to explain optical activity of some organic molecules, giving a structural basis for molecular stereochemistry,

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[3] J. Kim, M. Movassaghi, *Chem. Soc. Rev.*, **2011**, 38, 3035; J. A. Labinger, J. E. Bercaw, *Nature*, **2002**, 417, 507.

chemists have been intrigued by the challenge to achieve absolute stereocontrol in chemical reactions starting from achiral compounds.

In spite of its remarkable importance, since chirality is intimately related to the origin and evolution of life, asymmetric catalysis has not been considered as a major research area until 1968. At that time, only a few examples of enantioselective reactions were known, and because of the generally low enantiomeric excess obtained, a great number of chemists seriously doubted that man-made chiral catalysts could play an important role in asymmetric synthesis, contrary to already known enzymatic processes. But soon the situation greatly changed, when Horner, Knowles, Kagan and Noyori,[4] in the early seventies, made impressive progresses in the rhodium-catalyzed hydrogenation of olefins, until development of the famous Monsanto process for L-DOPA, and the selective epoxidation and dihydroxilation of olefins developed by Sharpless[5]. In 2001 Knowles was awarded of the Noble Prize in Chemistry for his work on chirally catalyzed hydrogenation reaction, also used in the synthesis of L-DOPA (Scheme 1).
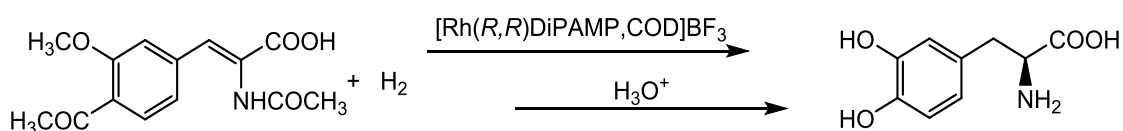
Scheme 1

The demand for enantiomerically pure compounds has sharply escalated in the last few years, particularly in the field of pharmaceuticals, but also for agricultural chemicals, flavours, fragrances and materials. Most of the commercially available drugs are chiral, and the majority of them are made up of a single enantiomer.

Some time later, about 40 years ago, the Russian chemist prof. N. Emanuel wrote in a review: "The high selectivity and rate of a chemical reaction have become the main criteria of the practical usefulness of a chemical process".[6] Certainly, non-selective reactions that usually lead to the formation of a huge variety of undesirable products are not worth to be used in practical chemistry. On the contrary, selective conversion of reagents to value-added products constitutes the final goal of contemporary catalytic chemistry.

Asymmetric catalysis could be a very powerful tool in chemist's hands. Great usefulness of this chemical approach arises from the possibility to obtain the maximum chiral efficiency by simply

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[4] W. S. Knowles, M. J. Sabacky, *Chem. Commun.*, **1968**, 22, 1445; W. S. Knowles, *Angew. Chem. Int. Ed.*, **2002**, 41, 3331998; L. Horner, H. Siegel, *Angew. Chem. Int. Ed. Engl.*, **1968**, 7, 941; H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.*, **1972**, 94, 6429; R. Noyori, *Adv. Synth. Cat.*, **2003**, 345, 15.
[5] M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc.*, **1991**, 113, 113; H. C. Kolb, M. S. van Nieuwenhze, K. B. Sharpless, *Chem. Rev.*, **1994**, 94, 2483.
[6] N. M. Emanuel, *Russ. Chem. Rev.*, **1978**, 47, 705.

combining proper molecular design and suitable reaction conditions. Reactions must show a high turnover number (TON) and high turnover frequency (TOF), while the enantioselectivity can range between 50:50 (nonselective) and 100:0 (completely selective). Along the years, different synthetic approaches were proved effective in selective transformations, like the use of a directing group, or the use of bulky substituent and steric hindrance; and also various transition metals have found broad application in stereo- and regioselective reactions as proper catalysts.

I.III. Content of this work

In this PhD thesis, we are going to discuss two main arguments. In the first section, we report an overview on amination and hydroamination reactions, and then we focus on the application of commercially available ruthenium and rhodium catalysts enabling new reaction pathways in the field of intramolecular hydroaminations of aminoallenes (Scheme 2).
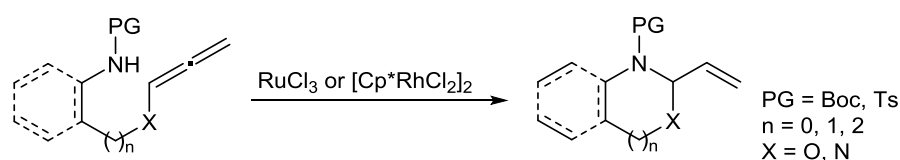
Scheme 2

In the second section we investigate the structure of a well-known commercially available rhodium catalyst in order to rationally develop new complexes that could act as selective catalysts in benchmark reactions. Different bidentate and tridentate phosphorus-, nitrogen- and oxygen-based ligands are employed. Reactivity of the so-obtained complexes is tested both on hydroamination reaction and on a well-known intermolecular amination benchmark reaction involving the presence of an internal oxidant (Scheme 3).
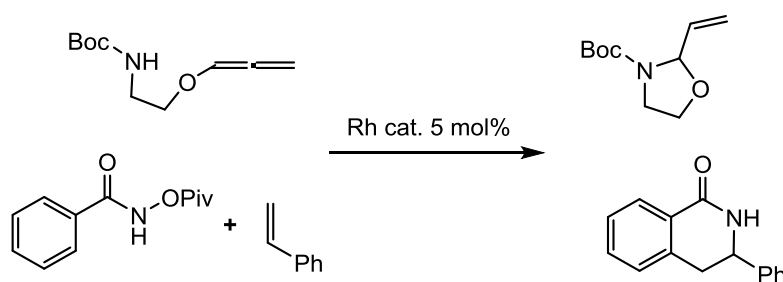
Scheme 3

Chapter 1: Introduction about Amination and Hydroamination Reactions

1.1. General considerations about amination and hydroamination reactions

Nitrogen is a key element in nature, found in several well known and important natural product families such as amino acids, alkaloids, porphyrins and penicillins. Its ability to carry a positive charge, as well as to act as a hydrogen bond donor and/or acceptor is an important feature for many applications. In this context, the development of novel C-N bond forming methodologies is an intensively investigated field of the utmost importance. While classical transformations range from nucleophilic displacement of leaving group to reductive carbonyl amination or imine alkylation, newly discovered processes have taken benefit from the advent of transition metal catalysis. Thus, modern amination methods include Buchwald-Hartwig C-N coupling,[7] hydroamination[8] and diamination[9] of multiple bonds.

The development of transition metal complexes has also helped to address the question of whether a hydrogen could be directly replaced by an amino group. This C-H functionalization process could offer unique opportunities,[10] complementary to those displayed by the above-mentioned reactions.

In the following section are reported recent developments in the field of C-H amination reactions and hydroamination reactions. Hydroamination is the reaction in which a N-H unit is added across a carbon-carbon multiple bond, with the cleavage of the N-H bond and formation of a C-N and C-H bond. Addition of amides and related compounds to multiple bonds should be more accurately designed as hydroamidations, but in this work we will refer also to them as hydroaminations, following a custom found in many literature papers.

1.2. Amination reactions

Inducing selective C-H functionalization is a real challenge that requires to find suitable conditions for the generation of highly active but sufficiently mild species, a challenge also due to high energy and ubiquity of C-H bonds in organic substrates.

The first examples of metal-mediated C-H amination was reported in the late 60s, by different works of Kwart and Kahn,[11] Breslow and Sloan,[12] and Turner et al.[13] More attention was given to the

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[7] D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2008**, 47, 6338.
[8] J. Hannedouche, E. Schultz, *Chem. Eur. J.*, **2013**, 19, 4972.
[9] R. Marcia de Figueiredo, *Angew. Chem. Int. Ed.*, **2009**, 48, 1190.
[10] G. Bergman, *Nature*, **2007**, 446, 391; K. Godula, D. Sames, *Science*, **2006**, 312, 67.
[11] H. Kwart, A. A. Kahn, *J. Am. Chem. Soc.*, **1967**, 89, 1951.
[12] D. S. Breslow, M. F. Sloan, *Tetrahedron Lett.*, **1968**, 5349.
[13] D. Carr, T. P. Seden, R. W. Turner, *Tetrahedron Lett.*, **1969**, 477.

studies involving iminoiodanes published by Breslow in the 80s,[14] on the capacity of iron porphyrins to efficiently catalyze intramolecular C-H aminations. Breslow clearly demonstrates the potential of nitrene C-H insertion for the synthesis of nitrogen-containing products, a field that has later considerably expanded. The reaction of commercially available hypervalent iodine reagents with various NH_2-containing substrates has lead to the development of efficient methodologies that has culminated in the total synthesis of Tetrodotoxin.[15]

Recent studies have allowed to overcome some of the limitations of catalytic hypervalent iodine-mediated nitrene C-H insertion, but more interestingly new amination protocols involving C-H activation have been developed. These transformations, with the C-H being broken in the first step of the catalytic cycle, differ mechanistically from the nitrene-based methodologies (Scheme 4).
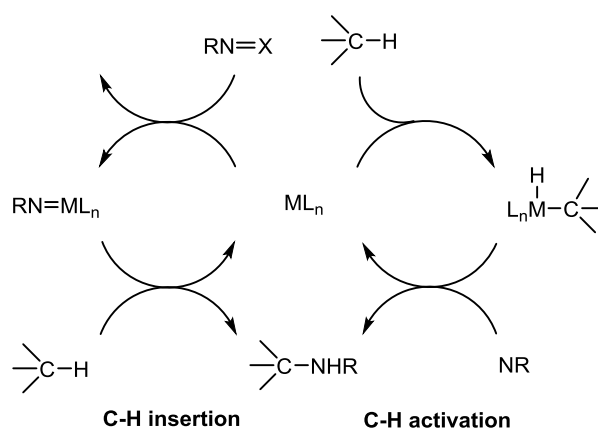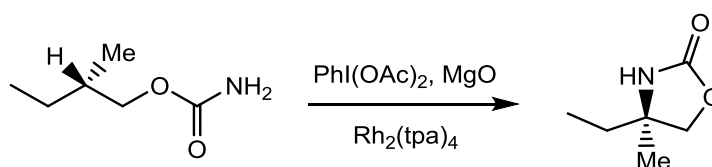

Scheme 4

1.2.1. Intramolecular amination reactions

In the field of intramolecular C-H amination, elegant solutions for the selective insertion of nitrogen into various C-H bonds have been devised. These reactions involve the regioselective internal delivery of a nitrene generated by using a combination of $PhI(OAc)_2$ and MgO in the presence of a Rh(II) catalyst, and carbamates or sulfamates as the substrate. In the case of carbamates insertion occurs in β-position (Scheme 5), while with sulfamates occurs in γ-position, affording homologous 6-membered rings.[16]

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[14] R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.*, **1983**, 105, 6728.
[15] A. Hinman , J. Du Bois, *J. Am. Chem. Soc.*, **2003**, 125, 11510.
[16] K. W. Fiori, J. J. Fleming, J. Du Bois, *Angew. Chem. Int. Ed.*, **2004**, 43, 4349; K. W. Fiori, C. G. Espino, B. H. Brodsky, J. Du Bois, *Tetrahedron,* **2009**, 65, 3042.

Scheme 5

The chemoselectivity observed in intramolecular C-H aminations is excellent. As a consequence of electronic effects, the preferred reacting positions are α-ethereal, tertiary and benzylic sites but functionalizing a secondary C-H bond is also feasible.[17] The chemoselectivity can, however, be less predictable with unsatured compounds.

Recently, attention has been paid to the design of either new catalysts and nitrene precursors, in order to improve the scope of intramolecular C-H aminations. Du Bois et al.[18] have developed a new Rh(II) catalyst, $Rh_2(esp)_2$, composed of two bidentate ligands derived from *m*-benzenedipropionic acid, extending C-H amination to ureas, guanidines and sulfamides. The question of catalytic asymmetric intramolecular C-H amination has also been addressed by the design of new ligands. This was met with limited success in previous studies, with enantioselectivities only up to 66% obtained with Rh(II) carboxylate complexes. Higher enantiomeric excess, in 65-99% range, have been recorded with Rh(II) carboxamidate complexes[19] and ruthenium porphyrins.[20]

In the issue of sustainable chemistry, a limitation attributed to hypervalent iodine-mediated generation of nitrene is the release of a stoichiometric amount of PhI. As a greener alternative, Lebel et al.[21] have proposed the use of *N*-tosylcarbamates. The nitrene is thus generated by treatment with an inorganic base, in the presence of a Rh(II) catalyst, and the residue salts can be easily removed through an aqueous workup. Also use of azides would be an atom-economical and environmental friendly alternative.

Intramolecular amination reactions have been reported for the synthesis of pyrrolidines and related heterocycles, usually under palladium catalysis. Stahl and coworkers[22] developed a Pd(OAc)$_2$/pyridine catalyst system that promotes the conversion of 4-hexenyltosylamide to the pyrrolidine product (Scheme 6).

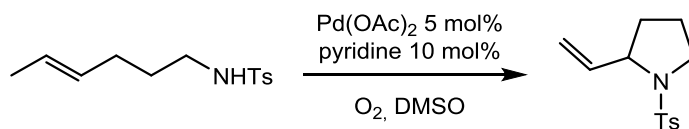[17] C. G. Espino, J. Du Bois, *Angew. Chem. Int. Ed.*, **2001**, 40, 598.
[18] T. Kurokawa, M. Kim, J. Du Bois, *Angew. Chem. Int. Ed.*, **2009**, 48, 2777.
[19] D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.*, **2008**, 130, 9220.
[20] J. L. Liang, S. X. Yuan, J. S. Huang, C. M. Che, *J. Org. Chem.*, **2004**, 69, 3610.
[21] K. Huard, H. Lebel, *Chem. Eur. J.*, **2008**, 14, 6222.
[22] S. R. Fix, J. L. Brice, S. S. Stahl, *Angew. Chem. Int. Ed.*, **2002**, 41, 164.

Pd(OAc)$_2$ 5 mol%
pyridine 10 mol%

O$_2$, DMSO

Scheme 6

The reaction proceeds well for both aromatic and aliphatic tosylamides and is tolerant to wide variations in solvent polarity, however nonpolar solvents appear to be optimal and permit the reaction to be performed at significantly reduced catalyst loading.

Both inter- and intramolecular C-H activation methodologies have been developed for the selective C-N bond formation. The first example of intramolecular reaction for C-N bond formation was reported by Buchwald et al.[23] in 2005 and involved a combination of catalytic Pd(OAc)$_2$ and Cu(OAc)$_2$ as the stoichiometric co-oxidant. This work lead to the development of a new protocol for the synthesis of carbazoles from biaryl acetamides (Scheme 7).

Pd(OAc)$_2$ 5 mol%
O$_2$ 1 atm

Cu(OAc)$_2$ 5 mol%
DMSO, 120°C
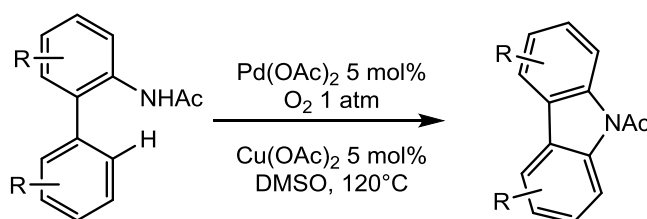
Scheme 7

Initial complexation of the catalyst to the nitrogen directs its regioselective addition on the other aromatic ring at the position *ortho* to the biaryl axis. Under these conditions, functionalisation of either Csp^2-or Csp^3-H bonds occurs in very good yields. Interestingly, contrary to the catalytic nitrene C-H insertion, the functionalisation has been shown to take place preferentially at the primary positions as a consequence of steric effects, a trend confirmed also in intermolecular reactions. In that case, products arising from multiple aminations have not been isolated.

1.2.2. Intermolecular amination reactions

While a high degree of chemo- and regioselectivity can be assured in the intramolecular reaction, devising a similar intermolecular C-H bond discriminating process is much more challenging. In C-H activation-based transformations, elegant solutions have arisen from application of the

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[23] W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.,* **2005**, 127, 14560.

chelate effect that brings the metal in close proximity to the C-H bond that must be cleaved. However, such a chelation has been rarely envisaged in C-H insertion, where the metal does not directly interact with the substrate.[24] Efficiency is also an issue to address due to high reactivity of metallanitrene, a drawback avoided in intramolecular C-H amination wherein the reacting centers are in close proximity. Finally, the formation of products resulting from over-oxidation must be minimized. Thus, several early examples of intermolecular nitrene C-H insertions lead to the expected product only when substrates were used in large excess.[25] These reactions were often directed towards the amination of "activated" C-H bonds, like benzylic and allylic positions of lower bond dissociation energy, which displays higher reactivity to the electrophilic metallanitrene. Che et al.[26] demonstrated the high capability of ruthenium and manganese porphyrin complexes to catalyze the amination of benzylic and allylic C-H bonds in high yields, using stoichiometric amounts of substrates (Scheme 8). Asymmetric transformations were also described, with enantiomeric excess up to 55%.
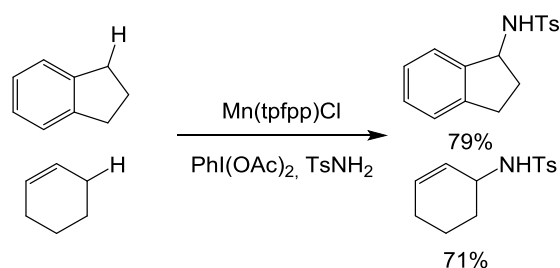
Scheme 8

In order to improve efficiency, selectivity and scope of these reactions, several transition metals were thoroughly investigated. While cobalt porphyrin,[27] zinc(II)[28] or iron(II)[29] showed a modest efficiency as catalysts in intermolecular C-H functionalization, the results reported with silver(I), copper and especially rhodium(II) complexes were more noteworthy.

Initially found by He et al. to catalyze intramolecular C-H amination of carbamates and sulfamates, dinuclear silver(I) complex $Ag_2(bp)_2(OTf)_2$ has also proved to be active for intermolecular

[24] S. Das, C. D. Incarvito, R. H. Crabtree, G. V. Brudvig, *Science,* **2006**, 312, 1941.
[25] A. R. Dick, M. S. Sanford, *Tetrahedron,* **2006**, 62, 2439.
[26] X. Q. Yu, J. S. Huang, X. G. Zhou, C. M. Che, *Org. Lett.*, **2000**, 2, 2233.
[27] J. D. Harden, J. V. Ruppel, G. Y. Gao, X. P. Zhang, *Chem. Commun.*, **2007**, 4644.
[28] B. Kalita, A. A. Lamar, K. M. Nicholas, *Chem. Commun.*, **2008**, 4291.
[29] Z. Wang, Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.*, **2008**, 10, 1863.

amination of various hydrocarbons.[30] Primary, secondary and tertiary benzylic positions, as well as cyclic hydrocarbons, can thus be aminated in good yields (Scheme 9).
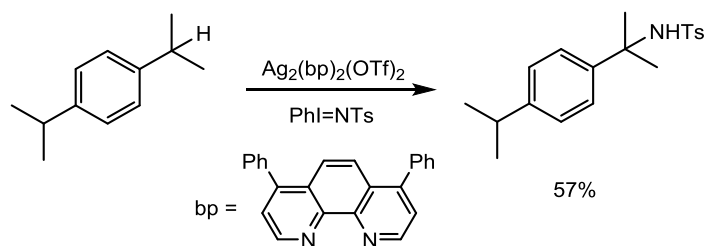
Scheme 9

Copper(I) complexes with scorpionate ligands were found able to induce unexpected regioselective aminations in the case of alkylaromatics such as *p*-ethyltoluene.[31] Nitrene insertion occurs at the secondary benzylic position, but also at the primary benzylic site. The study also reported the capability of copper(I) complexes to catalyze C-H nitrene insertion using chloramine-T, as previously observed by Taylor et al.,[32] thereby opening opportunities to develop efficient green procedures since NaCl is the sole by-product generated in this case. Bhuyan and Nicholas reported an efficient catalytic intermolecular C-H amination involving a stoichiometric amount of substrate and commercially available Cu catalysts.[33] The reaction occurs at primary, secondary and tertiary benzylic positions, as well as α-ethereal sites, although chemoselective allylic C-H amination has proved impossible so far (Scheme 10).
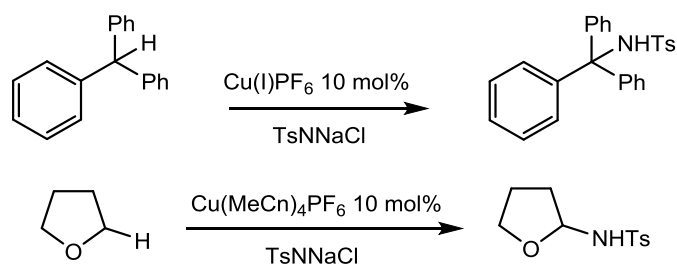
Scheme 10

Although these experiments highlighted the potential of chloramine-T as a C-H aminating agent, the efficiency of the process remains lower than that involving hypervalent iodine species. The

[30] Y. Cui, C. He, *Angew. Chem. Int. Ed.*, **2004**, 43, 4210; Z. Li, D. A. Capretto, D. Rahaman, C. He, *Angew. Chem. Int. Ed.*, **2007**, 46, 5184.

[31] M. R. Fructos, S. Trofimenko, P. J. Perez, *J. Am. Chem. Soc.*, **2006**, 128, 11784.

[32] D. P. Albone, S. Challenger, A. M. Derrick, S. M. Fillery, J. L. Irwin, C. M. Parsons, H. Takada, P. C. Taylor, D. J. Wilson, *Org. Biomol. Chem.*, **2005**, 3, 10.

[33] R. Bhuyan, K. M. Nicholas, *Org. Lett.*, **2007**, 9, 3957.

capability of copper to catalyze C-H aminations under a variety of different oxidizing conditions has been documented in several other studies. Use of halogenated and peroxide oxidants were found to be suitable for generating aminating species.[34]

Significant progress in intermolecular C-H amination were made with rhodium catalysts through the design of either ligands and new types of nitrene sources. First examples were reported by Muller et al.,[35] followed by asymmetric versions developed by Hashimoto et al.[36] and Reddy and Davies,[37] all based on the hypervalent iodine-mediated generation of nitrene from sulfamides. However, yields up to 95% and enantiomeric excess up to 94% were obtained only in the presence of an excess of substrate. Then, Fruit and Muller[38] and subsequently Du Bois[39] demonstrated that sulfamates can afford higher yields even with a stoichiometric amount of starting material. Thus, a combination of Rh$_2$(esp)$_2$ and trichloroethylsulfamate (TcesNH$_2$) gave up to 74% yields of C-H aminated products. Functionalisation of secondary benzylic and tertiary positions is favored. In the case of substrates having multiple reactive sites, the regioselectivity is governed by a combination of electronic and steric factors, (Scheme 11) and the more sterically accessible and/or electron rich C-H bond is preferentially aminated also in carbenoid chemistry.
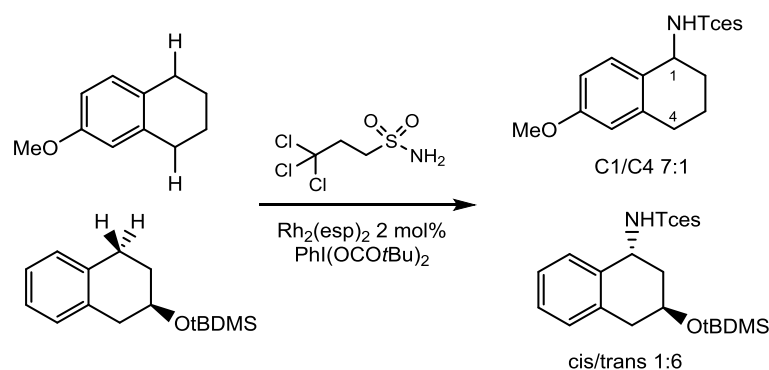
Scheme 11

Competition experiments indicated that inter- and intramolecular C-H aminations exhibit opposite selectivities in some instances. Benzylic positions are thus favored over tertiary sites in the intermolecular reaction, while the behaviour is reversed in the intramolecular version.

Due to good results obtained with Rh$_2$(esp)$_2$, Du Bois tried to develop a chiral version, but success of this attempt was limited, and the enantiomeric excess remained in the 20% range.

[34] J. S. Clark, C. Roche, *Chem. Commun.,* **2005**, 5175; X. Liu, Y. Zhang, L. Wang, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.,* **2008**, 73, 6207.
[35] I. Nageli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Muller, *Helv. Chim. Acta,* **1997**, 80, 1087.
[36] M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett.,* **2002**, 43, 9561.
[37] R. P. Reddy, H. M. L. Davies, *Org. Lett.,* **2006**, 8, 5013.
[38] C. Fruit, P. Muller, *Tetrahedron Asymmetry,* **2004**, 15, 1019.
[39] K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.,* **2007**, 129, 562.

Instead, devising a chiral nitrene precursor may appear conceptually less appealing than the design of chiral ligands for the development of stereoselective nitrene transfer, since the chirality carrier will be present in a stoichiometric amount.

Application of this strategy based on the design of chiral sulfur(VI) reagents analogous to sulfonamides lead to unprecedented results. Sulfonimidamide derived nitrenes thus display exceptionally high reactivity first revealed in transition metal-catalyzed aziridinations,[40] and then confirmed in the development of an efficient diastereoselective intermolecular benzylic C-H amination.[41] The preparation of less sterically-demanding chiral ligands for the rhodium catalyst allowed extension of the reaction to allylic substrates and to simple alkanes. An optically pure sulfonimidamide and a chiral rhodium catalyst are needed for a successful reaction (Figure 2).
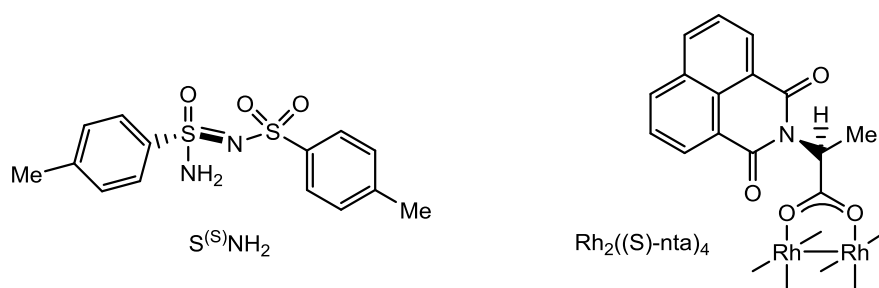

Figure 2

A strong matched effect results from their interaction, thus leading to intermolecular benzylic and allylic aminations with excellent yields and diastereoselectivity up to 92-99%, starting from stoichiometric amount of the C-H bond containing substrate. Even cyclic hydrocarbons can be efficiently functionalized under stoichiometric conditions (Scheme 12).
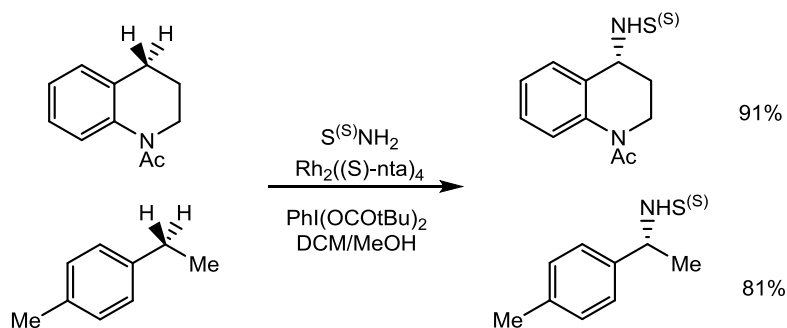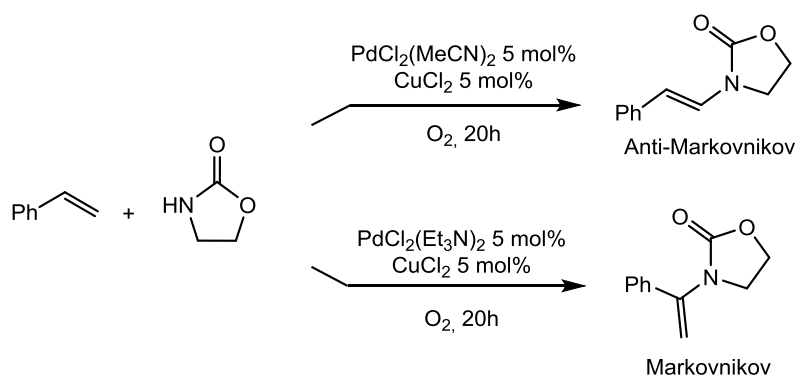

Scheme 12

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[40] P. Di Chenna, F. Robert-Paillard, P. Dauban, R. H. Dodd, *Org. Lett.,* **2004**, 6, 4503.
[41] C. Liang, F. Robert-Paillard, C. Fruit, P. Muller, R. H. Dodd, P. Dauban, *Angew. Chem. Int. Ed.,* **2006**, 45, 4641.

Another worth-mentioning point is the selectivity towards secondary benzylic and allylic sites as a consequence of the compromise in terms of electronic and steric effects, while branched alkanes such as 2-methylbutane reacted at the tertiary position. The nature of the interactions responsible for the high stereoselectivity observed are not yet clearly understood.

Intermolecular allylic C-H activation-amination was studied by Nicholas and Srivastava[42] since the early 90s. They demonstrated the ability of Mo(VI), Fe(II, III) and Cu(I) complexes to catalyze C-H amination with arylhydroxylamines as the nucleophiles. This reaction takes place regioselectively at the less substituted carbon of the starting alkene, but low reactivity limits the synthetic potential of this reaction. Lately, Reed and White[43] developed a catalytic heterobimetallic intermolecular protocol. They showed that a combination of Pd(OAc)$_2$-bis-sulfoxide and chromium(III) complex efficiently promotes the transformation of various terminal olefins used in stoichiometric amounts, with good regio- and stereoselectivities.

Pd(OAc)$_2$ and other palladium salts are widely employed in amination reactions for the well-known aza-Wacker process. Intermolecular version was reported in the formal oxidative conjugate addition of cyclic amides and carbamates to electron-deficient alkenes.[44] Styrene, which is mildly activated toward nucleophilic attack at the terminal C atom, also exhibited some reactivity under the catalytic conditions, yielding to the anti-Markovnikov amination product with oxazolidinone as the nucleophile. Stahl and coworkers reported several examples of intermolecular Pd-catalyzed aminations of alkenes,[45] including a Markovnikov or anti-Markovnikov amination of styrene that depends on the reaction conditions (Scheme 13).

Scheme 13

[42] R. S. Srivastava, K. M. Nicholas, *J. Org. Chem.*, **1994**, 59, 5365; R. S. Srivastava, N. R. Tarver, K. M. Nicholas, *J. Am. Chem. Soc.*, **2007**, 129, 15250.
[43] S. A. Reed, M. C. White, *J. Am. Chem. Soc.*, **2008**, 130, 3316.
[44] T. Hosokawa, M. Takano, Y. Kuroki, S. I. Murahashi, *Tetrahedron Lett.*, **1992**, 33, 6643.
[45] V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.*, **2007**, 46, 1910.

The ability to achieve catalyst-controlled regioselectivity in coupling reactions with alkenes represents an important goal in synthetic chemistry. In the reported example, the reaction yielding anti-Markovnikov amination products is limited in scope. Oxazolidinone was the most effective nucleophile and presence of electron-donating and -withdrawing substituents resulted in lower yields. In contrast, the reactions yielding Markovnikov products are more versatile. A number of nonbasic nitrogen nucleophiles and vinylarenes proceed to the enamide products in good yields.

Amination processes involving alkynes lead to the formation of ynamines and ynamides. Ynamines have a difficult preparation and handling, while ynamides, in which the donating ability of the nitrogen is diminished by the presence of an electron-withdrawing group, display an excellent balance between stability and reactivity. Ynamides were introduced in 1972 by Viehe[46], and since then various methods were developed for their preparation. In 1994 Stang[47] described a process involving the use of alkynyliodium triflates, in 2003 Hsung[48] reported the use of copper(I) cyanide with dimethylethylenediamine and K_3PO_4, and in 2012 Muniz and coworkers[49] developed an efficient metal-free direct amination of alkynes with bis(sulfonyl)amine-derived aryliodonium acetates (Scheme 14).
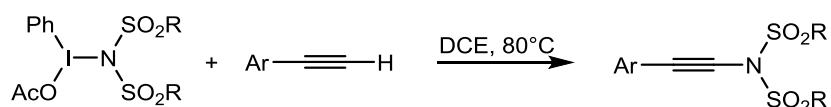
Scheme 14

Recently an increasing interest about the formation of C-N bonds via C-H activation in oxidative conditions lead to the development of intriguing methodologies, often in the presence of rhodium catalysts. Rh-catalyzed oxidative reactions have been much less explored in contrast to the huge amount of reports on the Pd-catalyzed ones. Despite the generally high cost of rhodium compounds, rhodium catalysis could be highly attractive if reaction systems that are inaccessible under palladium conditions can be efficiently developed. Indeed, in the last years remarkable progresses were made in this field.[50] Rhodium(III) catalyst, in particular $[RhCp*Cl_2]_2$ and $[RhCp*(MeCN)_3]^{2+}$, stand out in the functionalization of C-H bonds *via* C-H activation pathway owing to high efficiency, selectivity and functional group tolerance.

Some characteristics of rhodium-mediated oxidative reactions can be observed: *i)* rhodium-catalyzed C-H activation is mostly limited to $C(sp^2)$-H bonds; *ii)* formation of Rh-C bonds *via* C-H

[46] Z. Janousek, J. Collard, H. G. Viehe, *Angew. Chem. Int. Ed.,* **1972**, 11, 917.
[47] P. Murch, B. L. Williamson, P. J. Stang, *Synthesis,* **1994**, 1255.
[48] M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, *J. Am. Che. Soc.,* **2003**, 125, 2368.
[49] J. A. Souto, P. Becker, A. Iglesias, K. Muniz, *J. Am. Chem. Soc.,* **2012**, 134, 15505.
[50] D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.,* **2010**, 110, 624.

activation is generally limited to chelation assistance; *iii)* the coupling partner for the Rh-C functionalisation is mostly limited to unsaturated molecules.

In rhodium(III)-catalyzed coupling reactions between arenes and multiple bonds, two general reaction patterns have been reported. When a protic X-H (X = N, O) bond is present, and this anionic X atom acts as a sufficient directing group, typically 1:1 coupling with a multiple bond is followed leading to the formation of a five- or six-membered ring (Scheme 15).
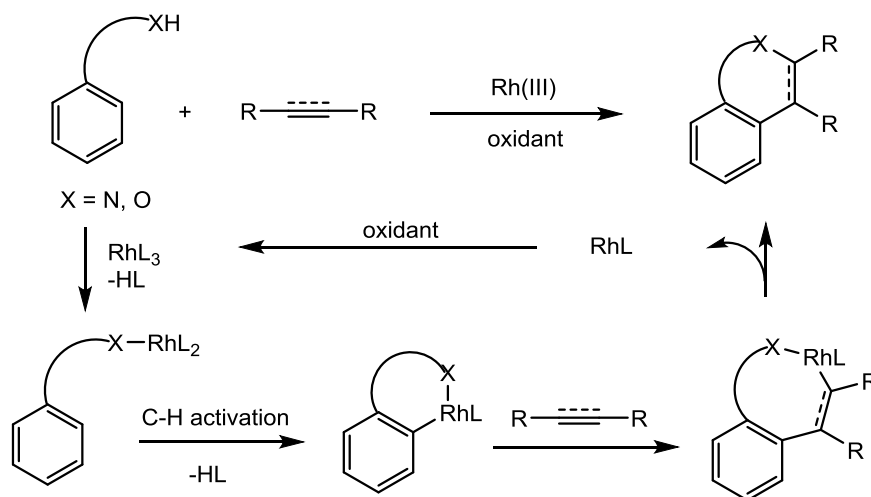
Scheme 15

In the proposed catalytic cycle, coordination of the anionic directing group X followed by ortho C-H activation affords a metallacycle. Subsequent ligation and insertion of a multiple bond (alkynes, alkenes, allenes) into the Rh-C bond gives an expanded rhodacycle. The final product is generated together with a Rh(I) species from the C-X reductive elimination, and the active Rh(III) catalyst is regenerated when Rh(I) is oxidized.

In contrast, when no X-H directing group is available, arenes functionalized by a neutral X atom typically undergo 1:2 coupling with multiple bonds, affording naphthalene derivatives. In this process, two-fold cyclometallation is involved, and the neutral X donor acts as a reversible chelator. These reactions apply to both electron-rich and -poor arenes,[51] which indicates that the electrophilic C-H activation mechanism should not be considered as the general pathway.

In the oxidative C-H functionalization, two different methodologies have been developed. The first one uses an external oxidant, while the second one involves the presence of an internal oxidizing group into the substrate structure. When an external oxidizing agent is employed, formation of the

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[51] Y. F. Han, H. Li, P. Hu, G. X. Jin, *Organometallics,* **2011**, 30, 905; Y. Boutadla, D. L. Davies, R. C. Jones, K. Singh, *Chem. Eur. J.,* **2011**, 17, 3438.

initial Rh-C species could occur *via* transmetalation and subsequent C-H activation, or through initial C-H activation.

Amides have been well studied in catalytic aminations using various transition metals. Rhodium can also mediate the *ortho* C-H activation of a variety of amides in coupling with alkenes and alkynes. Fagnou firstly reported the Rh(III)-catalyzed oxidative coupling of acetanilides with alkynes[52] (Scheme 16).
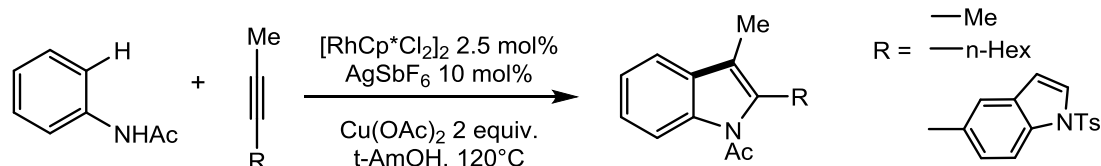
Scheme 16

Compared to acetanilides, the C-H activation of *N*-aryl benzamides can be more complicated with respect to chemoselectivity: either the C-aryl or *N*-aryl rings can potentially undergo C-H activation. Similar but complementary studies on oxidative coupling of alkynes and *N*-substituted benzamides at the *ortho* position of the C-ring were independently reported by Rovis[53] and Li[54] using [RhCp*Cl$_2$]$_2$ as the catalyst. They observed that the coupling process is favored by electron-withdrawing groups in both aryl rings of the *N*-aryl benzamides, and very likely this suggest *N*-metalation upon deprotonation as the first step.

Oxidative coupling reactions reported so far are carried out in the presence of an external oxidant, which is usually involved in the regeneration of the active catalyst. Consequently, the reduced product of the oxidant remains as a waste by-product. An alternative emerging green strategy is the use of an oxidizing directing group (an internal oxidant) that offers directing effect and regenerates the catalyst.[55]

A pioneering example of rhodium(III) catalyzed, overall redox neutral synthesis of NH isoquinolones was achieved by catalytic *ortho* C-H activation of *N*-methoxybenzamides with an alkyne.[56] Instead of acting as a simple directing group,[57] the *N*-methoxyamide group is both a directing group and an oxidant, and it was converted to an amide functionality after the reaction.

[52] D. R. Stuart, M. G. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.,* **2008**, 130, 16474.
[53] T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.,* **2010**, 132, 10565.
[54] G. Song, D. Chen, C. L. Pan, R. H. Crabtree, X. Li, *J. Org. Chem.,* **2010**, 74, 7487.
[55] F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.,* **2011**, 50, 1977; J. Wu, X. Cui, L. Chen, G. Jiang, Y. Wu, *J. Am. Chem. Soc.,* **2009**, 131, 13888.
[56] N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.,* **2010**, 132, 6908.
[57] M. Wasa, J. Q. Yu, *J. Am. Chem. Soc.,* **2008**, 130, 14058.

This methodology is complementary to previously reported procedures using an external oxidant. Screening of various substrates indicate that the N-pivalate and N-benzoate benzamides are even more reactive substrates, and the reaction can be performed at room temperature. Under these improved conditions, simple internal alkynes, alkynes bearing heteroatoms, sterically hindered alkynes and even terminal alkynes can be used, affording a broad spectrum of isoquinolones. Both electron-rich and electron-poor, internal and terminal olefins readily coupled with N-Piv benzamides, yielding dihydroisoquinolones (Scheme 17).
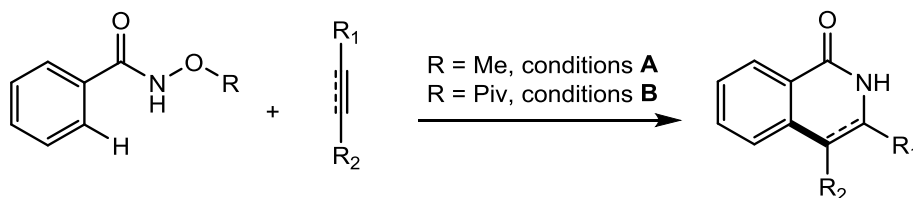
A: [RhCp*Cl$_2$]$_2$ 2.5 mol%, CsOAc 30 mol%, MeOH, 60°C, yields 30-50%
B: [RhCp*Cl$_2$]$_2$ 1 mol%, CsOAc 2 equiv., MeOH, rt, yields 70-90%

Scheme 17

These results indicate the powerful and extremely versatile coupling partners that enable rare room temperature C-H activation compatible with various functional groups.

On the basis of DFT studies, Guimond and coworkers[58] proposed a probable mechanism. Rhodium first coordinates to the nitrogen atom and gives cyclometallation. This step is followed by the insertion of an alkyne or alkene to give a seven-membered rhodacycle. Subsequently C-N reductive elimination gives a Rh(I) species chelated by the neutral nitrogen and the oxygen atom, which then undergoes N-O oxidative addition, leading to a rhodium(III)-OAc amido intermediate. Protonolysis of the Rh-N bond generates the final product and regenerates the Rh(III) catalyst.

Very recently, another type of redox-neutral C-N coupling under chelation-assistance was reported by Yu[59] and Glorius.[60] This new methodology differs from the previous system in that the oxidants are embedded in the partner that couples with the arene, instead of in the arene itself.

1.3. **Hydroamination reactions**

Nitrogen-containing compounds like amines, enamines and imines plays a fundamental role in the fine chemical, and are widely encountered in the scaffold of natural products or synthetic drugs.

[58] N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.,* **2011**, 133, 6449.
[59] K. H. Ng, Z. Zhou, W. Y. Yu, *Org. Lett.,* **2012**, 14, 272.
[60] C. Grohmann, H. Wang, F. Glorius, *Org. Lett.,* **2012**, 14, 656.

In addition to their relevance as part of bioactive naturally occurring products, enamines, imines and enamides are of substantial interest as building blocks for many reactions and processes. In the field of material sciences, enamides are widely used as monomers in polymerization processes.[61] Enamines, imines and enamides are used as starting material for asymmetric hydrogenations,[62] and they are also versatile building blocks for cycloadditions.[63] Further reaction modes are addition to electrophiles,[64] metal-catalyzed cross-couplings,[65] C-H functionalizations[66] and codimerizations.[67]

Among various synthetic procedures to achieve the formation of nitrogen-containing molecules, hydroamination reactions have a prominent role. As previously said, this kind of reactions involve the formal addition of a N-H group to a carbon-carbon multiple bond, generating a more substituted nitrogen-containing product.[68]

The first experimental evidence of a homogeneously catalyzed hydroamination of alkynes was reported by Kozlov[69] in 1936. He provided an addition of aniline to acetylene in the presence of mercury(II) chloride, leading to *N*-[(1E)-ethylidene]-aniline. Later, Loritsch et al.[70] developed a mercury oxide-catalyzed hydroamination of terminal and internal alkynes with aniline (Scheme 18).
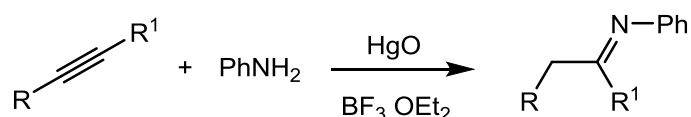
Scheme 18

The toxicity of mercury was not considered an awkward problem before the 1990s, and a lot of interesting Hg-based chemistry was developed between 1940 and 1990. However, the use of this toxic metal has become obsolete with the advent of modern transition metal-based catalysts. The first addition of amines to alkenes was reported in 1954 by Howk et al.[71] They found that ammonia can be added to ethylene in the presence of metallic sodium or lithium, or also in the presence of

[61] W. Reppe, H. Krzihalla, Ger. Patent DE000000851197B, **1944**.
[62] R. I. Storer, D. E. Carrera, Y. Ni, D. W. MacMillan, *J. Am. Chem. Soc.*, **2006**, 128, 84; A. V. Malkov, S. Stoncius, P. Kocovsky, *Angew. Chem. Int. Ed.*, **2007**, 46, 3722.
[63] K. C. Nicolau, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, **2002**, 41, 1668; C. Gaulon, R. Dhal, T. Chapin, V. Maisonneuve, G. Dujardin, *J. Org. Chem.*, **2004**, 69, 4192.
[64] R. Matsubara, N. Kawai, S. Kobayashi, *Angew. Chem. Int. Ed.*, **2006**, 45, 3814.
[65] J. Mo, L. Xu, J. Xiao, *J. Am. Chem. Soc.*, **2005**, 127, 751; G. Evano, A. C. Gaumont, C. Alayrac, I. E. Wrona, O. Delacroix, K. Jouvin, J. Gatignol, A. C. Silvanus, *Tetrahedron*, **2014**, 70, 1529.
[66] N. Gigant, I. Gillaizeau, *Org, Lett.*, **2012**, 14, 3304; Q. Gou, B. Deng, H. Zhang, J. Qin, *J. Org. Lett.*, **2013**, 15, 4604.
[67] H. Tsujita, Y. Ura, S. Matsuki, K. Wada, T. Mitsudo, T. Kondo, *Angew. Chem. Int. Ed.*, **2007**, 46, 5160.
[68] T. E. Muller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, 108, 3795.
[69] N. S. Kozlov, R. Dinaburskaya, T. Rubina, *J. Gen. Chem USSR*, **1936**, 6, 1341.
[70] J. A. Loritsch, R. R. Vogt, *J. Am. Chem. Soc.*, **1939**, 61, 1462.
[71] B. W. Howk, E. L. Little, S. L. Scott, G. M. Whitman, *J. Am. Chem. Soc.*, **1954**, 76, 1899.

their corresponding metal hydrides. In 1992, Bergman and Livinghouse[72] reported examples of hydroamination of alkynes with metallacene catalysts of zirconium and titanium, and Marks[73] with lanthanide catalysts. These results gave a hint for the development of various hydroamination protocols using early transition metal or lanthanide catalysts.

A broad range of useful product classes are accessible through catalytic hydroaminations (Scheme 19).
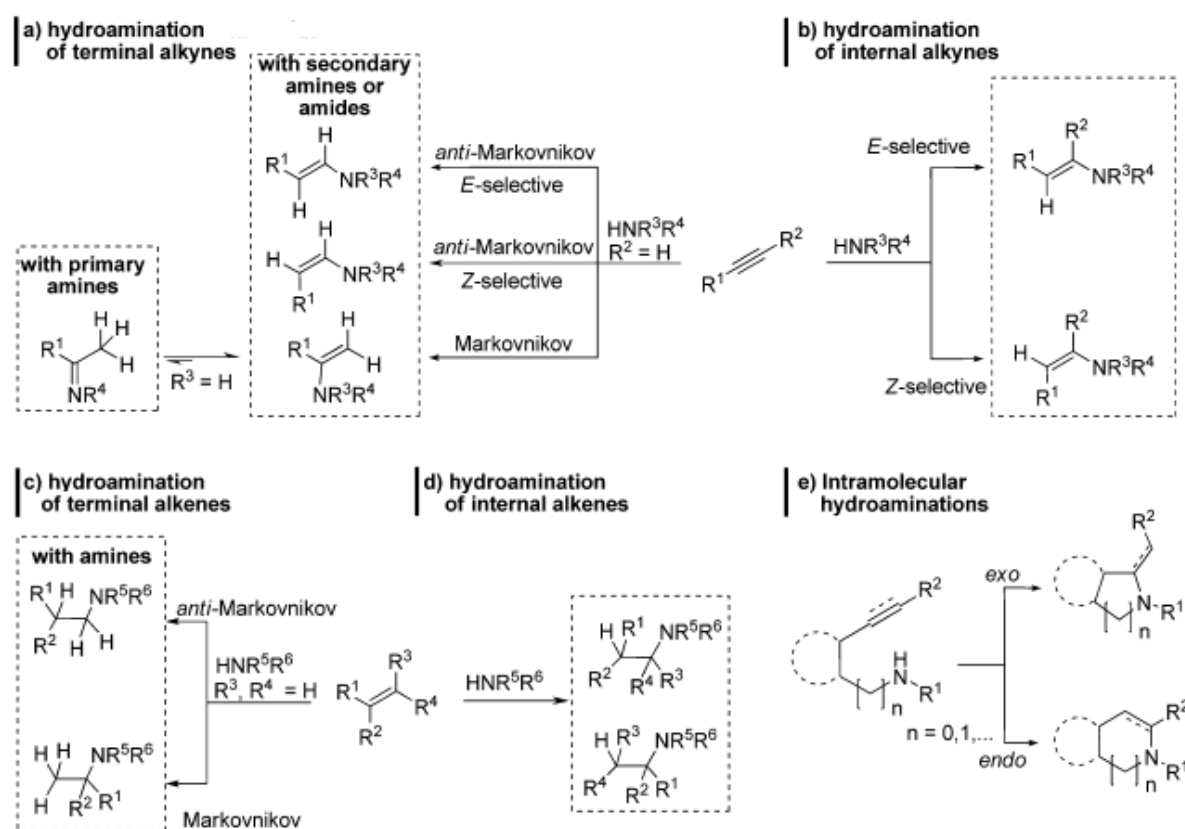
Scheme 19

Addition of primary amines to alkynes lead to the formation of imines, whereas the addition of secondary amines results in the formation of enamines (in E or Z configuration). In the presence of water, these products hydrolyze to the corresponding aldehydes or ketones. Addition of amides to alkynes produces enamides, that are hydrolytically stable and widely encountered in the scaffolds of natural products and materials. Protocols for the selective formation of both E and Z enamides from alkynes are known. In the case of terminal alkynes, the regioselectivity for the formation of Markovnikov or anti-Markovnikov product can be controlled by the catalytic system. Hydroamination

[72] P. L. McGrane, M. Jensen, T. Livinghouse, *J. Am. Chem. Soc.*, **1992**, 114,5459; P. J. Walsh, A. M. Baranger, R. G. Bergman, *J. Am. Chem. Soc.,* **1992**, 114, 1708.
[73] Y. Li, T. J. Marks, *J. Am. Chem. Soc.,* **1996**, 118, 9295.

of alkenes lead to alkylamines and alkylamides. Intramolecular hydroaminations with formation of five- or six-membered rings are catalyzed by various metals, and are widely employed in the formation of heterocycles. The synthetic potential of this reaction type is further enhanced by the ease of incorporating N-H addition steps into reaction cascades.

Attractiveness of these reactions arises from their inherent benefit of optimal atom economy, matching the principles of Green Chemistry, and from their capability to occur also on unsaturated and unactivated readily available and inexpensive starting materials. Furthermore, they do not require stoichiometric amounts of coupling or dehydrating agents. However, control of their chemo-, regio- and stereoselectivity is essential to establish them as "green".

Addition of a nucleophile such as an amine across a carbon-carbon multiple bond is slightly exothermic or approximately thermoneutral.[74] However, this transformation is kinetically difficult, since it suffers from a high activation energy barrier, due to electrostatic repulsion between the lone pair of the nucleophilic nitrogen atom and the π orbital of the electron-rich double bond. Moreover, the high temperatures required to cross the activation energy barrier induce a shift of the equilibrium toward the starting materials, because of the negative entropy associated with this reaction.[75] Running these reactions under mild conditions requires thus either multiple-bonds activation through metal coordination to limit the electron density, or σ N-H bond activation to increase the nucleophilicity. Noncatalytic hydroaminations could involve use of strong acids to protonate the C-C multiple bond, thus facilitating the attack of the N-nucleophile,[76] or use of strong bases for its deprotonation, generating highly nucleophilic metal amides.[77]

The presence of a transition metal can override the problem of electrostatic repulsion, since it induces an *umpolung* of substrates reactivity by coordinating to one of them and making possible the nucleophilic attack. Metal catalyst can coordinate to the carbon-carbon multiple bond, thereby reducing its electron density and enabling the C-N bond formation, or alternatively they can replace the nitrogen-bound proton and thus allow insertion of C-C multiple bonds. Addition of N-nucleophiles to alkene affords alkyl-metal species, which are prone to β-hydride elimination. Such oxidative processes lead to enamine, imine or enamide products rather than the saturated amines and amides that would result from a hydroamination of alkenes (Scheme 20). This pathway is favored for metal catalysts with a preference for β-hydride elimination, such as palladium.[78]

[74] F Pohlki, S. Doye, *Chem. Soc. Rev.,* **2003**, 32, 104.
[75] R. Severin, S. Doye, *Chem. Soc. Rev.,* **2007**, 36, 1407.
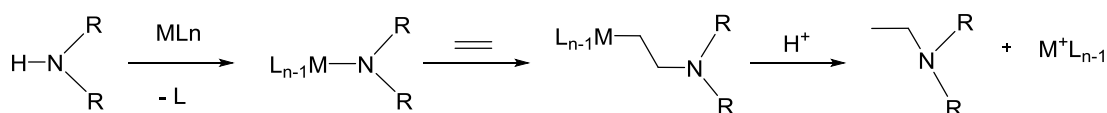[76] I. Dion, A. M. Beauchemin, *Angew. Chem. Int. Ed.,* **2011**, 50, 8233.
[77] M. T. Herrero, J. D. de Sarralde, R. SanMartin, L. Bravo, E. Dominguez, *Adv. Synth. Catal.,* **2012**, 354, 3054.
[78] P. S. Hanley, D. Markovic, J. F. Hartwig, *J. Am. Chem. Soc.,* **2010**, 132, 6302; R. I. McDonald, G. Liu, S. Stahl, *Chem. Rev.,* **2011**, 111, 2981.

Coordination of alkenes

Oxidative amination product
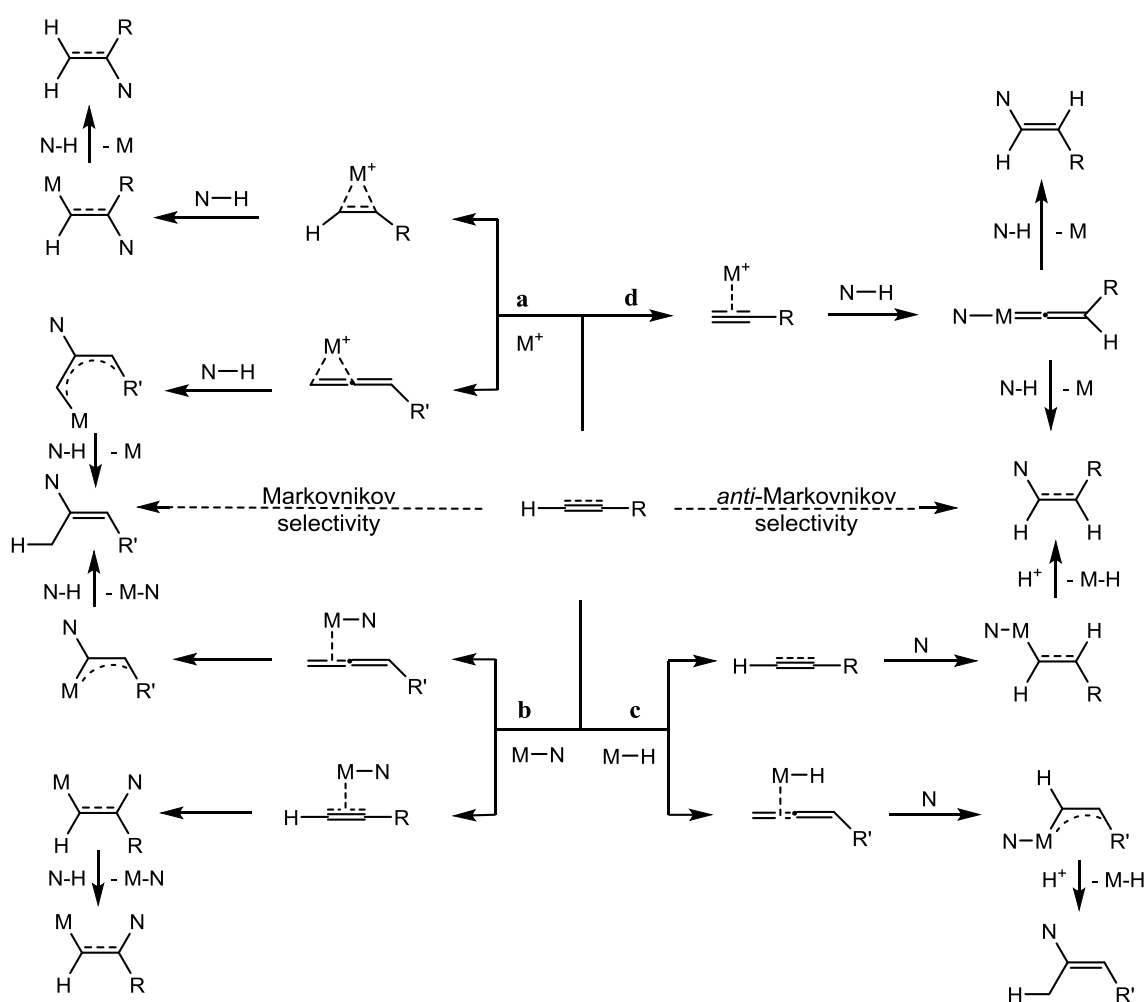
Hydroamination product
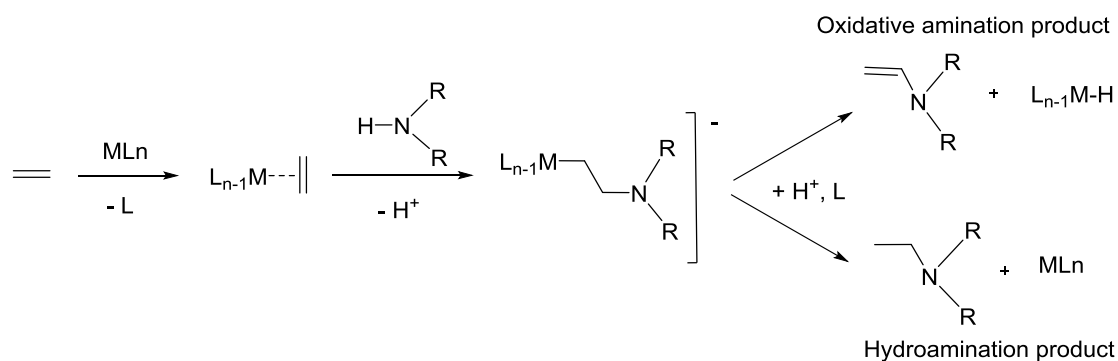
Coordination of amines

Scheme 20

Despite the fact that alkynes have more π-electron density than alkenes, which could be expected to result in an increase of the electrostatic repulsion of the nucleophile, metal-catalyzed addition reactions across carbon-carbon triple bonds are much easier to accomplish than those across double bonds. This can be explained by the formation of a weaker π-bond between the catalyst and the alkyne, compared to alkenes, thus allowing the activation of triple bonds toward nucleophilic attack without inhibiting the reaction by a strong π-coordination to the metal center. Alkynes are also less sterically hindered toward attack of the nucleophile.

Beyond achieving high catalytic activity, for making these reactions preparatively useful it is necessary to achieve also a good control over the chemo-, regio- and stereoselectivity. Tolerance to functional groups is the key to the broad applicability of a method, and also opens opportunities for further functionalizations. A first challenge is the difficult in the control of chemoselectivity. In the absence of a catalyst, N-H nucleophiles tend to react easier with electrophilic centers like carbonyl groups, than with C-C multiple bonds. To ensure the correct hydroamination pathway, a selective catalyst needs to preferentially coordinate to the N-H nucleophile and/or to the C-C multiple bond, and must not react with other functionalities. Later transition metals like ruthenium and palladium act as catalysts accordingly to these rules, in a better way than early transition metals, and the conditions employed are usually milder.

About regioselectivity, it is particularly challenging for internal olefins or alkynes with similar substituents on both sides. For internal C-C multiple bonds, the regioselectivity could be influenced by the introduction of strongly electron-withdrawing or extremely bulky substituents on one side of

the multiple bond.[79] In the intramolecular reaction, it is preferred the formation of five- or six-membered rings. In the presence of a catalyst, the preferred regioselectivity strongly depends from the catalytic pathway. The stereochemical outcome of the reaction is instead influenced by factors related both to the substrate, like acidity of the N-H bond, electronic properties of the multiple bond or steric effects, and to the catalyst, in particular electronic and steric properties of the transition metal complex. One strategy for the development of stereoselective hydroaminations is to design the ligand environment in order to block one side of the multiple bond, so that the nucleophile addition can only occur from the other side. Addition of amines, amides or other N-H nucleophiles across a carbon-carbon multiple bond can follow different mechanisms, efficiency and selectivity depending on the catalytic pathway involved (Scheme 21).

Scheme 21

[79] B. M. Trost, G. R. Dake, *J. Am. Chem. Soc.*, **1997**, 119, 7595.

The combination of substrate, catalyst and the reaction conditions together determine which mechanism is most favorable. Metal-catalyzed hydroamination pathways can be approximately divided into four categories depending on the initiating step: *a*) activation of the C-C multiple bond by π-coordination of a Lewis-acidic metal complex, and subsequent nucleophilic addition of the nucleophile; *b*) initial formation of a metal-nitrogen bond, followed by insertion of the multiple C-C bond into the M-N bond; *c*) first formation of a metal-hydride, and then migratory insertion of the multiple bond into the M-H bond; *d*) rearrangement of initially formed η^2-alkyne-metal species into a vinylidene complex, that is then attacked by the nucleophile.

Pathway *a)* is the most common. A Lewis-acidic catalyst metal activates the carbon-carbon multiple bond by withdrawing electron density via η^2-coordination. The hydroamination product is finally generated by direct protonolysis or protonation at the metal center, followed by reductive elimination. Both of these terminating steps occur with retention of configuration, meaning that the overall addition of the N-H group proceeds with *anti*-regioselectivity. The substrates most commonly prone to this pathway are electron-deficient alkenes or alkynes, in combination with electron-rich N-nucleophiles.

In pathway *b)*, that is equally common as path *a)*, the metal catalyst first activates the N-nucleophile either by ligand exchange or by oxidative addition of a low-valent transition metal to the N-H bond. The C-N bond is then formed by migratory insertion of the alkene, alkyne or allene into the M-N bond. In contrast to pathway *a)*, this type of reaction requires at least two coordination sites on the metal center, one for the N-nucleophile and one for the multiple bond. Liberation of the product via protonolysis again occurs with retention, leading to the formation of *syn*-addition products.

Pathway *c)* involves a migratory insertion of the multiple bond into a M-H rather than an M-N bond. This reaction mode has been described for low-valent Rh, Ir, Ru or Pd complexes. Migratory insertion of the alkene, alkyne or allene is influenced by steric factors, that will usually direct the metal to the less hindered carbon atom. The subsequent reductive elimination process, in which the C-N bond forms, will give rise to the *anti*-Markovnikov product. Pathway *d)* has been described for Ru-catalyzed hydroamination of alkynes. This pathway usually leads to the exclusive formation of Markovnikov products with high selectivity for *sin*-enamides.

Different strategies have been developed to avoid the formation of oxidative amination product arising from competitive β-hydride elimination, like the use of metals with a lower tendency for this

pathway,[80] or the addition of an excess of coordinating anions or bi- or tridentate ligands to block all coordination sites of the transition metal center, thus precluding metal-β-hydride interactions.[81]

Over the years, numerous metals have been found to promote the addition of N-H nucleophiles across C-C multiple bonds. Because of their inherent set of properties, the application range of various metals is diverse and often complementary. The appeal of a catalytic system is not only determined by its performance, but also by its availability and cost, its tolerance to functional groups, and certainly its toxicity. Because of their lower reactivity toward oxygen-containing functional groups, the use of late transition metals as the catalyst is desirable in particular for the last-stage functionalisation of complex molecules, and many new systems and catalysts have been developed within the last decade.

1.3.1. Intermolecular hydroamination reactions

A general overview for intermolecular hydroamination reactions involving alkenes, alkynes, allenes and dienes is given in Scheme 22. Critical feature for this transformation lies in the choice of the amine, which should possess a low basicity to avoid a tight coordination onto the metal center preventing the binding of the multiple bond substrate. Anilines, carboxamides, sulfonamides and other protected amines are therefore classical substrates engaged in those reactions.
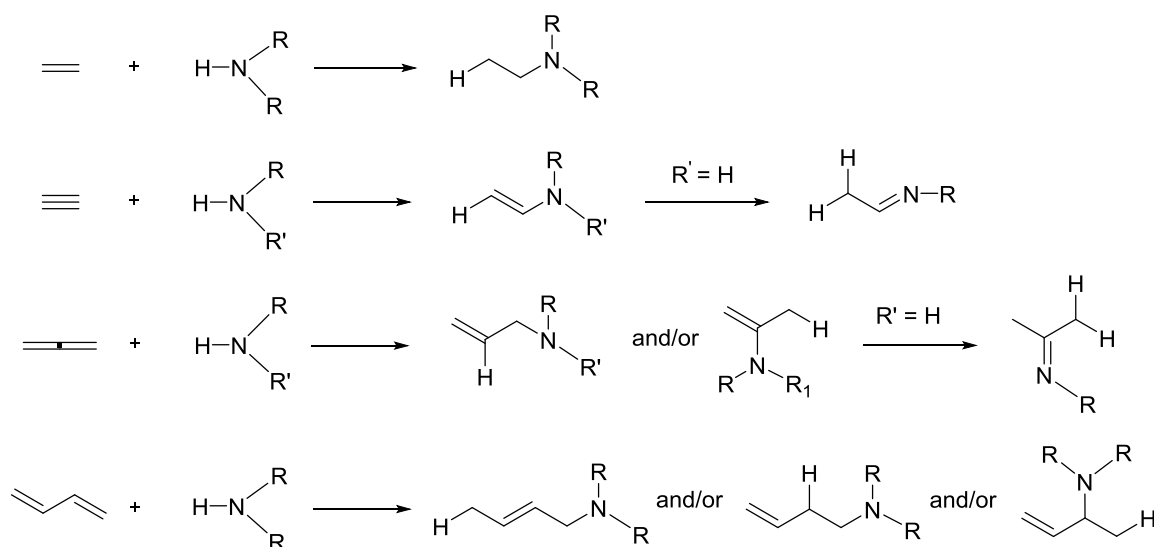
Scheme 22

[80] C. Liu, C. F. Bender, X. Han, R. A. Widenhoefer, *Chem. Commun.,* **2007**, 3607; H. Qian, R. A Widenhoefer, *Org. Lett.,* **2005**, 7, 2635.
[81] A. McGhee, B. M. Cochran, T. A. Stenmark, F. E. Michael, *Chem. Commun.,* **2013**, 49, 6800; B. M. Cochran, F. E. Michael, *Org. Lett.,* **2008**, 10, 329.

Addition of an amine to substituted alkenes bearing electron-withdrawal groups leads to β-amino substituted compounds, through an anti-Markovnikov pathway, while alkenes bearing alkyl or aryl substituents follow a Markovnikov addition. Because of the unfavorable competition between weakly coordinating alkenes and strongly coordinating aliphatic amines, the hydroamination of nonactivated alkenes is quite difficult to achieve. It is also understandable that the intermolecular version is much more challenging as compared to the intramolecular version. Catalytic systems based on rare-earth metals such as lanthanum complexes give the intermolecular Markovnikov hydroamination of nonactivated alkenes in good yields and moderate enantioselectivities.[82]

The first examples of transition metal-catalyzed homogeneous hydroamination of alkenes were reported by Coulson[83] in 1971 (Scheme 23). Both Rh(I) and Rh(III) complexes can effectively catalyze the hydroamination of ethylene with secondary aliphatic amines.
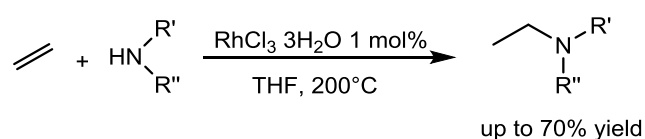
Scheme 23

In contrast to activated alkenes such as styrene, 1,3-dienes or strained cyclic olefins, nonactivated and unstrained 1-alkenes have low tendency to undergo hydroaminations. The main reason is the low affinity of 1-alkenes toward transition metals, so that they cannot compete for coordination sites with amines, which are much stronger donor ligands. Hull et al.[84] have incorporated a Lewis-basic, coordinating imine functional group into the alkenes, which directs the alkene moiety toward the metal center and induces hydroamination reactivity (Scheme 24). Other Lewis-basic groups, such as amines, amides and imides were unsuccessful in this method.
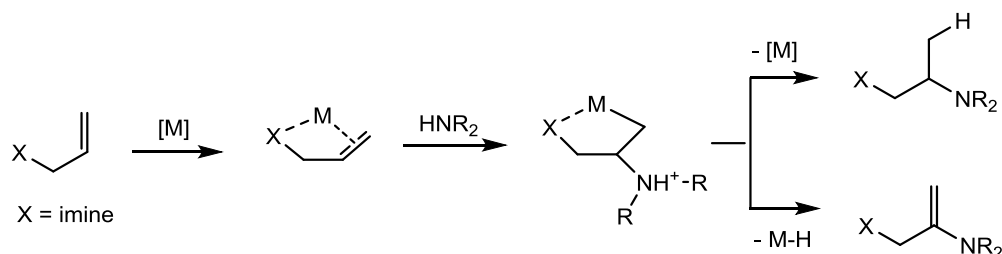
Scheme 24

[82] A. L. Reznichenko, H. N. Nguyen, K. C. Hultzsch, *Angew. Chem. Int. Ed.*, **2010**, 49, 8984.
[83] D. R. Coulson, *Tetrahedron Lett.*, **1971**, 12, 429.
[84] A. R. Ickes, S. C. Ensign, A. K. Gupta, K. L. Hull, *J. Am. Chem. Soc.*, **2014**, 136, 11256.

Intermolecular hydroaminations of activated alkenes such as vinylarenes with aliphatic or aromatic amines can lead to the formation of both Markovnikov or *anti*-Markovnikov products depending on the metal employed. While Rh and Ru complexes usually lead to the *anti*-Markovnikov products as reported by Beller[85] and Hartwig,[86] palladium-catalyzed transformations form the Markovnikov products exclusively.[87] The first intermolecular enantioselective hydroamination of alkenes was reported by Togni[88] in 1997. An Ir/diphosphine system was shown to effectively promote the reaction between norbornene and aniline with an enantiomeric excess up to 95% (Scheme 25).
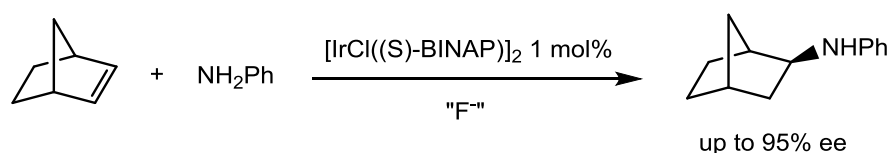
Scheme 25

A remarkable effect of fluoride ions on the activity and selectivity of the reaction was observed, and an important increase in turnover numbers was achieved by using KHDMS instead of fluoride as a base. Further development on unactivated and activated alkenes were reported by Shibata[89] and Hartwig.[90] Pd, Pt, Au and Ir complexes are used for intermolecular hydroamination of alkenes using amides as nucleophiles, leading to Markovnikov products, while no example is available so far for the *anti*-Markovnikov selectivity. Metal halides in combination with triflate salts or metal triflates are often employed as catalysts, and the in situ generated protic acid might function as the catalytically active species.[91]

Reaction between alkynes and primary amines lead to the formation of an enamine, that can easily isomerize leading to an imine. This reaction occurs easily than addition of amine to alkenes, due to an enhanced reactivity and also major electronic density of carbon-carbon triple bonds.[92] In late transition metal-catalyzed hydroamination of alkynes, aliphatic amines are less reactive than aromatic amines. This can be explained by their stronger coordination to the catalyst, which slows catalytic turnover. Many catalysts that are highly efficient for the intermolecular Markovnikov hydroamination of alkynes with anilines are unable to promote the transformation of aliphatic

[85] M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, T. E. Muller, *Eur. J. Inorg. Chem.,* **1999**, 1121.

[86] M. Utsonomiya, J. F. Hartwig, *J. Am. Chem. Soc.,* **2004**, 126, 2702.

[87] A. M. Johns, M. Utsonomiya, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.,* **2006**, 128, 1828.

[88] R. Dorta, P. Egli, F. Zurcher, A. Togni, *J. Am. Chem. Soc.,* **1997**, 119, 10857.

[89] S. Pan, K. Endo, T. Shibata, *Org. Lett.,* **2012**, 14, 780.

[90] M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.,* **2000**, 122, 9546.

[91] D. C. Rosenfeld, S. Shekhar, A. Takemiya, J. F. Hartwig, *Org. Lett.,* **2006**, 8, 4179.

[92] J. Haggins, *Chem. Eng. News*, **1993**, 71, 23.

amines. Primary and secondary amines can react with terminal alkynes leading both to *anti*-Markovnikov[93] and Markovnikov[94] products depending on the metal catalyst. By using internal alkynes, one obvious challenge is achieving satisfactory regioselectivity. One way to address this is to employ alkynes containing an electron-withdrawing group, which will force the amine to attack the less electron-rich side of the π-system,[95] while the regioselective addition of amines to nonactivated internal alkynes is much harder to accomplish. Examples with Au(I) complexes were reported by Bertrand[96] and Stradiotto,[97] in good yields and moderate selectivity.

Late transition metal-catalyzed hydroamination of terminal alkynes with primary aromatic amines usually lead to Markovnikov products. The enamines intermediately formed rapidly tautomerize to the imines. Wakatsuki et al.[98] first developed a method for the addition of primary amines to terminal alkynes to give imines. They found that the presence of amine adducts of acids with noncoordinating anions, such as NH_4PF_6, strongly enhances the activity of $Ru_3(CO)_{12}$ as the catalyst (Scheme 26).
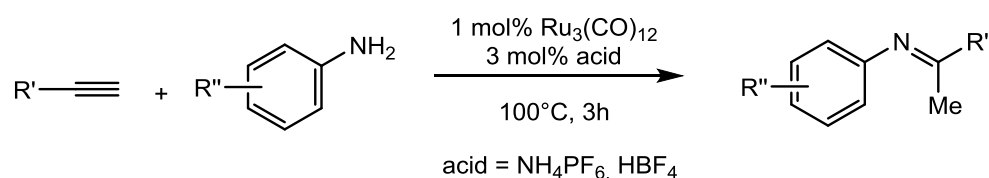
Scheme 26

The first example of an intermolecular *anti*-Markovnikov addition of primary anilines to terminal alkynes was achieved by Antinolo et al.,[99] with a cationic Rh(I) complex bearing iminopyridine-based bidentate nitrogen donor ligands. In comparison to primary arylamines, secondary derivatives are more challenging substrates. First of all, they are more nucleophilic than primary ones and coordinate more strongly to the metal, so their transfer to the carbon center is more difficult, second their electrostatic repulsion to the alkyne is stronger, and finally their greater steric bulk is disadvantageous in the reaction mechanism. Few examples of late transition metal-catalyzed hydroaminations with secondary amines are reported, and are usually mediated by strong bases, such as KOH or CsOH. These protocols usually provide *anti*-Markovnikov enamines with low E/Z

[93] Y. Fukumoto, H. Asai, M. Shimizu, N. J. Chatani, *J. A. Chem. Soc.,* **2007**, 129, 13792.

[94] H. W. Cheung, C. M. So, K. H. Pun, Z. Zhou, C. P. Lau, *Adv. Synth.Catal.,* **2011**, 353, 411.

[95] A. E. Panarina, A. Dogadina, V. I. Zhakarov, B. I. Ionin, *Tetrahedron Lett.,* **2001**, 42, 4365.

[96] X. Zheng, G. D. Frey, S. Kousar, G. Bertrand, *Chem. Eur. J.,* **2009**, 15, 3056.

[97] K. D. Hesp, M. Stradiotto, *J. Am. Chem. Soc.,* **2010**, 132, 18026.

[98] M. Tokunaga, M. Eckert, Y. Wakatsuki, *Angew. Che,. Int. Ed.,* **1999**, 38, 3222.

[99] C. Alonso-Moreno, F. Carrillo-Hermosilla, J. Romero-Fernandez, A. M. Rodriguez, A. Otero, A. Antinolo, *Adv. Synth.Catal.,* **2009**, 351, 881.

selectivities.[100] A high regio- and stereoselective example of *anti*-Markovnikov addition of azoles to terminal alkynes was achieved by Bhattacharjee in 2012, using a Ru(II) based cationic complex[101] (Scheme 27).
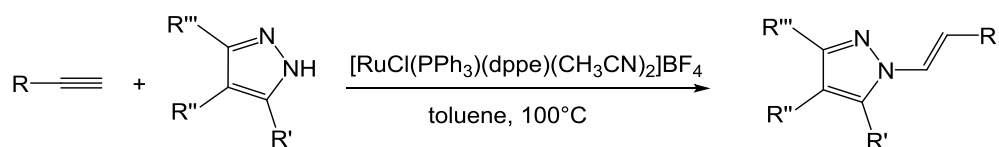
Scheme 27

Also the intermolecular addition of amides to alkynes usually requires strong bases or Brønsted acids.[102] Early transition metals do not seem to catalyze such reactions, and the first example of a late transition metal-catalyzed hydroamination was reported as late as 1995 by Watanabe et al.,[103] that observed the *anti*-Markovnikov addition of simple anilides to 1-octyne. This reaction was applicable only to a handful of rather special substrates, in rather extreme temperatures and with the use of a pressure reactor. The *anti*-Markovnikov addition of imides (pKa ≈ 15) to terminal alkynes was achieved with a catalyst system generated in situ, from $(cod)Ru(met)_2$ in the presence of scandium(III) triflate and tributylphosphine.[104] Under these conditions, products are formed with a high preference for the Z-isomers. If tri(isopropyl)phosphine is used as the ligand in place of tributylphosphine, the stereoselectivity is inverted, and the E-configured isomers become the major products.

By using allenes or conjugated dienes as substrate, hydroamination products can show different regioselectivity in the addition of the amine, that could be 1,2 and 2,1 for both the compounds and also 1,4 for conjugated diolefines. Late transition metals have been extensively used in intermolecular hydroaminations of allenes with anilines and aliphatic secondary amines. As a complementary strategy, the early transition metals could promote the intermolecular hydroamination of allenes with primary aliphatic amines.[105] Intermolecular processes usually requires Au or Pd complexes as the catalysts. Especially gold complexes are well known to catalyze intermolecular hydroaminations of internal allenes.

[100] M. Joshi, M. Patel, R. Tiwari, A. K. Verma, *J. Org. Chem.,* **2012**, 77, 5633; M. Patel, R. Saunthawal A. K. Verma, *Tetrahedron Lett.,* **2014**, 55, 1310.

[101] U. K. Das, M. Bhattacharjee, *Chem. Eur. J.,* **2012**, 18, 5180.

[102] H. Wang, J. Zhao, J. Zhang, Q. Zhu, *Adv. Synth. Catal.,* **2011**, 353, 2653.

[103] T. Kondo, A. Tanaka, S. Kotachi, Y. Watanabe, *J. Chem. Soc., Chem. Commun.,* **1995**, 413.

[104] L. J. Goossen, M. Blanchot, C. Brinkmann, K. Goossen, R. Karch, A. Rivas-Naas, *J. Org. Chem.,* **2006**, 71, 9506.

[105] R. O. Ayinla, L. L. Schafer, *Inorg. Chem. Acta,* **2006**, 359, 3097.

In 2007, Yamamoto and coworkers achieved the first gold-catalyzed hydroamination of allenes with morpholine as the only amine source, using a $Ar_3PAuCl/AgOTf$ system.[106] Aromatic amines can also perform a intermolecular hydroamination with monosubstituted, 1,1- and 1,3-disubstituted allenes in the presence of a mixture of Au salts/AgOTf.[107] Employing a mixture of a NHC-Au(I) complex and $KB(C_6F_5)_4$ lead to in situ formation of a cationic gold species, which exhibits a high reactivity for intermolecular hydroaminations of allenes with a variety of primary and secondary amines[108] (Scheme 28).
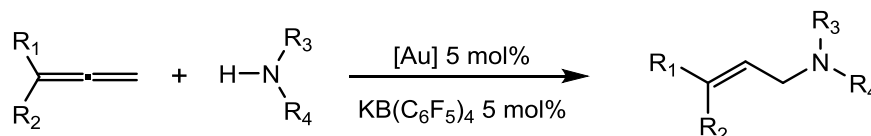
Scheme 28

The first intermolecular Markovnikov hydroamination of allenes was reported in the 1980s with equimolar amounts of Pt(II) and Hg(II) salts.[109] In 1995, Cazes et al.[110] demonstrated the palladium-catalyzed addition of amines to allenes in the presence of triethylammonium iodide via a Pd-H species. On the basis of the same strategy, Yamamoto et al.[111] developed another pathway for intermolecular hydroaminations by using Pd(0) and acetic acid as the catalytic system. In 2012, Breit et al.[112] reported a Rh(I)/Josiphos system for the first intermolecular asymmetric hydroamination of allenes, using anilines as nucleophiles (Scheme 29).
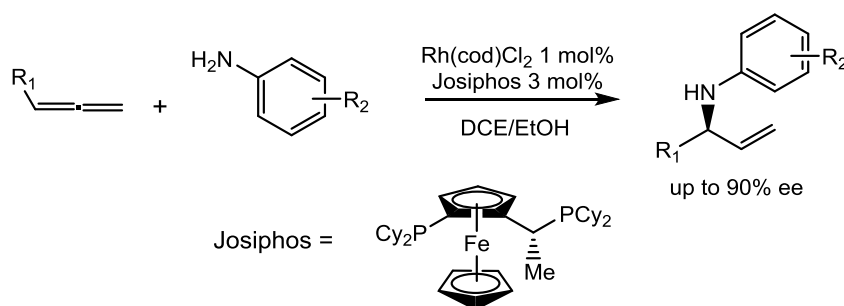
Scheme 29

[106] N. Nishina, Y. Yamamoto, *Synlett,* **2007**, 1767.

[107] A. Duncan, R. Widenhoefer, *Synlett,* **2010**, 419.

[108] X. Zeng, M. Soleilhavoup, G. Bertrand, *Org. Lett.,* **2009**, 11, 3166.

[109] A. De Renzi, P. Ganis, A. Panunzi, A. Vitagliano, G. Valle, *J. Am. Chem. Soc.,* **1980**, 102, 1722.

[110] L. Besson, J. Gorè, B. Cazes, *Tetrahedron Lett.,* **1995**, 36, 3857.

[111] M. Al-Masum, M. Meguro, Y. Yamamoto, *Tetrahedron Lett.,* **1997**, 38, 6071.

[112] M. L. Cooke, K. Xu, B. Breit, *Angew. Chem. Int. Ed.,* **2012**, 51, 10876.

Mechanistic studies suggested that the oxidative addition of aniline to Rh(I) leads to the formation of a Rh(III)-H intermediate. After hydrometalation of the allene, the corresponding π-allyl-Rh complex undergoes reductive elimination to afford branched allylic amines. The same catalytic system was employed using imidazoles and benzimidazoles.

Addition of nucleophiles to conjugate multiple bonds as dienes meets another significant problem related to the control of regioselectivity. Several transition metal catalysts have been used for the regioselective intermolecular hydroamination of 1,3-dienes to afford allylic amines. Some are effective for aliphatic amines,[113] while others are useful for aromatic ones.[114] However, there is still a lack of a general system that allows the addition of both aryl and alkyl amines to 1,3-dienes in good yields. Recently, the Beller group[115] reported the hydroamination of nonactivated 1,3-dienes with anilines, using Pd(cod)Cl$_2$ and DPEphos to give the 1,4-hydroamination product. Also asymmetric examples were reported by Hartwig et al.,[116] with good yields and high enantioselectivities.

1.3.2. Intramolecular hydroamination reactions

Intramolecular hydroamination reactions are a powerful tool for chemists since they permit to obtain heterocyclic N-containing structures. The use of different compounds containing multiple carbon-carbon bonds and a nucleophilic nitrogen atom, makes also possible to achieve both *exo* and *endo* cyclizations. Preference of a pathway over the other depends mainly on structural features of the chain linking reaction centers, in particular length and strain (Figure 3).
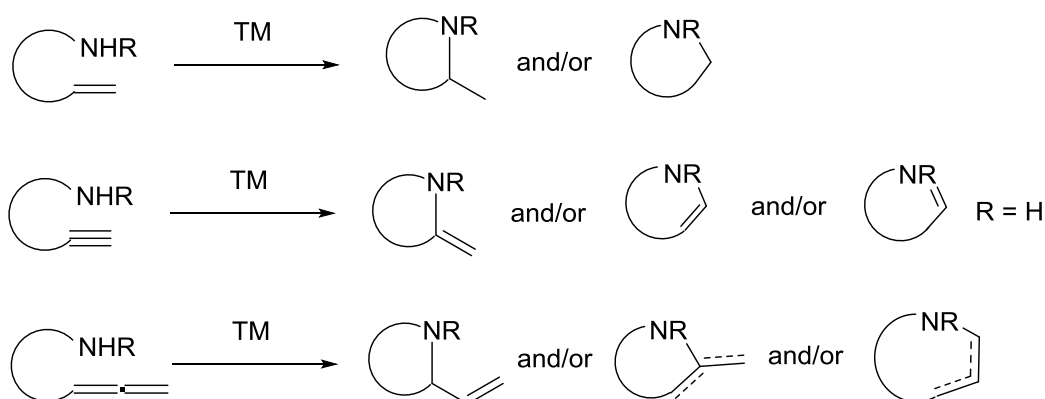
Figure 3

[113] G. Kuchenbeiser, A. R. Shaffer, N. C. Zingales, J. F. Beck, J. A. R. Schmidt, *J. Organomet. Chem.,* **2011**, 696, 179.
[114] A. Behr, L. Johnen, N. Rentmeister, *Adv. Synth. Catal.,* **2010**, 352, 2062.
[115] D. Banerjee, K. Junge, M. Beller, *Org. Chem. Front.,* **2014**, 1, 368.
[116] O. Lober, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.,* **2001**, 123, 4366.

Rare-earth metal complexes are highly efficient catalysts for intramolecular hydroaminations of various C-C multiple bonds such as alkenes, alkynes, allenes and dienes, while reduced rate are observed in intermolecular reactions. Attractive features of rare-earth metal catalysts include very high turnover frequencies and excellent stereoselectivities, rendering this methodology applicable to concise synthesis of naturally occurring alkaloids and other polycyclic azacycles. While the rare-earth metal complexes are very efficient catalysts for intramolecular hydroaminations, their sensitivity to oxygen and moisture have limited their use in many applications.

Intramolecular processes are easier to accomplish than intermolecular ones because of the close spatial proximity of the *N*-nucleophile and the carbon-carbon multiple bond. About hydroaminations of alkynes, since the early works a wide array of metals have been used to promote such reactions, including early and late transition metals and rare earths.[75] These reactions often employ as catalysts complexes of Rh(I), bearing *N,N*- and *N,P*-ligands. A drawback common to these systems is that they are generally suitable only to make five- or six-membered *N*-heterocycles, even in the presence of simple acid catalysts. The construction of seven-membered rings remain challenging, and that of four- or eight-membered rings has yet to be accomplished,[117] unless amides were used as *N*-nucleophiles. In that case, gold, silver and palladium catalysts allow accessing to entropically unfavorable four- and seven-membered heterocycles.[118] Muller et al. systematically investigated the late transition metal-catalyzed cyclization of a simple aminoalkyne (Scheme 30).
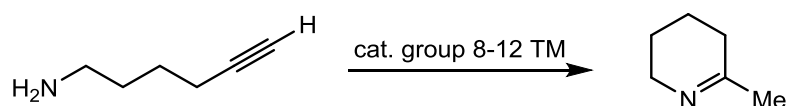
Scheme 30

In this reaction type, a free coordination site on the transition metal center is crucial for success. One extensively used strategy to form the active catalyst in situ is to abstract one anionic ligand from neutral metal complexes, using for example silver salts. Catalyst activation is also possible by dissociation of a labile ligand from the transition metal. Cationic Ir(I), Rh(I) and Ag(I) complexes were shown to be efficient catalysts for intramolecular *N*-alkyne compounds.[119] Most substrates appear to exhibit a preference for the formation of either *exo*- or *endo*- cyclization products.

In the case of amides, the choice of the metal catalyst also influences whether ring closure occurs *via* the amide nitrogen or oxygen. Late transition metals often activate the amides by

[117] H. Kim, T. Livinghouse, J. Shim, S. G. Lee, P. H. Lee, *Adv. Synth. Catal.,* **2006**, 348, 701.
[118] X. Zheng, *Chem. Rev.,* **2013**, 113, 6864; J. Weibel, A. Blanc, P. Pale, *Chem. Rev.,* **2008**, 108, 3149.
[119] L. D. Field, B. A. Messerle, S. L. Wren, *Organometallics,* **2003**, 22, 4393; S. R. Beeren, S. L. Dabb, B. A. Messerle, *J. Organomet. Chem.,* **2009**, 694, 309.

intermediate formation of metal-amido complexes, thereby increasing the reactivity of the nitrogen nucleophile toward carbon-carbon multiple bond. Dinuclear transition metal complexes were proved to be efficient catalysts for the intramolecular hydroamination, and also examples of transition metals on solid supports have been reported as useful hydroamination catalysts.[120]

Catalytic intramolecular hydroaminations of alkynes leading to five- and six-membered rings have been used to efficiently construct complex ring systems. Interestingly, many of these are *endo-*cyclizations. Examples of the synthetic usefulness of these reactions are the synthesis of polycyclic lamellarin derivatives by Xu[121] and synthesis of benzazepines derivatives by Kundu[122] (Scheme 31).
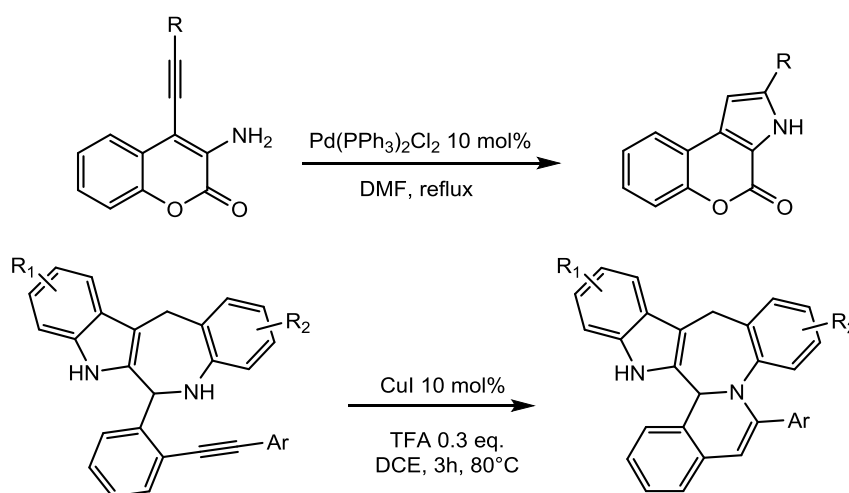
Scheme 31

Another worth-to-mention application is the indole synthesis, via intramolecular hydroamination of *ortho*-alkynyl anilines. Wu et al. reported some cases in which regioselectivity of the products can be tuned by using different metals. Thus, while using a silver catalyst like silver triflate a *6-endo*-cyclization was achieved on α-amino (2-alkynylphenyl)methylphosphonate, a palladium catalyst leads to *5-exo-dig* cyclization.[123]

In comparison with alkynes, the hydroamination of nonactivated olefins remains challenging, although the attack of nucleophiles across olefins complexed to Pt(II) has been known since about a century.[124] Recently, Widenhoefer[125] and Hartwig[126] reported Pt- and Rh-mediated hydroaminations

[120] M. K. Richmond, S. L. Scott, H. Alper, *J. Am. Chem. Soc.,* **2001**, 123,10521.

[121] L. Chen, M. Xu, *Adv. Synth. Catal.,* **2009**, 351, 2005.

[122] S. Samala, M. Saifuddin, A. Mandadapu, B. Kundu, *Eur. J. Org. Chem.,* **2013**, 3797.

[123] Q. Ding, Y. Ye, R. Fan, J. Wu, *J. Org. Chem.,* **2007**, 72, 5439.

[124] R. Palumbo, A. De Renzi, A. Panunzi, G. Paiaro, *J. Am. Chem. Soc.,* **1969**, 91, 3874.

[125] C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.,* **2005**, 127, 1070.

[126] Z. Liu, J. F. Hartwig, *J. Am. Chem. Soc.,* **2008**, 130, 1570.

of nonactivated alkenes with primary and secondary alkylamines, with good product yields (Scheme 32).
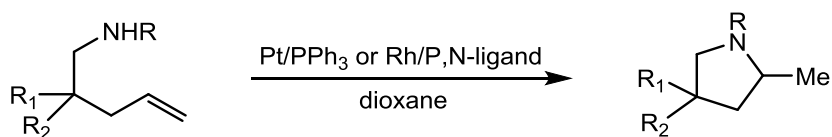
Scheme 32

Side-products deriving from the competitive oxidative amination were not observed, and many functional groups were tolerated, such as hydroxy, halogen, cyano and carboalkoxy. In the Rh(I)-catalyzed reaction of nonactivated alkenes the authors found that the nucleophilic addition of the amine toward the coordinated olefin is the rate-determining step. Usually, basic *N*-nucleophiles are not suitable for such reactions because they are strong coordinating to the electrophilic metal center, inactivating the catalyst.

Various gold complexes exhibit strong activity toward intramolecular hydroamination of alkenes, also by using dinuclear gold complexes, that were found to significantly accelerate the cyclization process via proximal and bimetallic activation of both the olefin and the *N*-nucleophile.[127] Besides sterically hindered, electron-rich phosphines such as P(*t*Bu)$_2$(*o*-biphenyl), highly sterically hindered *N*-heterocyclic carbenes, which are strong σ-donors, are also particularly effective ligands for gold-catalyzed hydroaminations, as reported by Widenhoefer[128] in 2006. He reported an intermolecular *5-exo*-hydroamination of *N*-alkenyl ureas catalyzed by a NHC-Au complex in the presence of silver triflate, allowing the formation of the corresponding *N*-heterocycles at room temperature in good yields.

One early example of hydroamination involving amides and nonactivated alkenes was reported by Sandford and Groves[129] using a Rh-H species as the catalyst, leading to the *anti*-Markovnikov product. In 2006 Michael reported a palladium-catalyzed method.[130] Because of the strong tendency of alkyl-palladium species to undergo β-hydride elimination, he employed a tridentate ligand to block free coordination sites at the metal center, thus steering the reactivity toward a desired protonation of the C-Pd bond. By using coordinating solvents it is possible to inhibit the reaction occupying all free coordination sites on the palladium center (Scheme 33). The same catalytic system could be applied to different substrates.

[127] M. Kojima, K. Mikami, *Synlett,* **2012**, 57.
[128] C. F. Bender, R. A. Widenhoefer, *Org. Lett.,* **2006**, 8, 5303.
[129] M. S. Sanford, J. T. Groves, *Angew. Chem. Int. Ed.,* **2004**, 43, 588.
[130] F. E. Michael, B. M. Cochran, *J. Am. Chem. Soc.,* **2006**, 128, 4246.
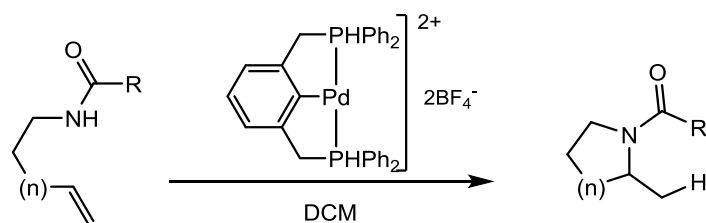
Scheme 33

As compared to intermolecular version, intramolecular nucleophilic additions to allenes with transition metals received more attention. Gold, silver and platinum catalyst have been extensively used in the intramolecular hydroaminations between nitrogen nucleophiles and allenes, due to their soft and carbophilic character.[131] Ag(I) salts are widely employed to generate five- or six-membered heterocycles. Such a protocol can also be applied for the synthesis of chiral products if chiral allenes or chiral auxiliaries are used.[132] Also copper salts are known to be efficient catalysts. In the field of gold catalysis, great improvements were made by Hashmi and coworkers.[133]

Recent progress in the development of new catalyst systems was achieved by using gold as the preferred metal for hydroamination of allenes. Starting from 2004, Krause and coworkers reported different Au(I)- and Au(III)-catalyzed reactions for the synthesis of pyrrolines in excellent yields.[134] They also found that the amine protecting group has a significant influence on the reactivity and selectivity of the transformation. Intermolecular hydroaminations of amidoallenes were initially performed mostly using silver tetrafluoroborate as catalyst. Starting from allenyl sulfonamides, the use of sliver nitrate allows for *5-endo*-trig hydroaminations in acetone at room temperature.[135]

This introduction tried to demonstrate that the addition of NH nucleophiles to either C-H bonds and C-C multiple bonds is a field that attracts great attention. Amination and hydroamination processes have evolved over the past decade into broadly applicable methodologies that give convenient access to various product classes of considerable synthetic value. Reported reactions often proceed with high regio-, chemo- and stereoselectivity, at low temperatures and under mild conditions. The starting material (alkanes, alkenes, alkynes, allenes, amides and amines) are readily available in great structural diversity, and for hydroaminations the reaction concept is inherently atom-economic.

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[131] B. Alcaide, P. Almendros, *Adv. Synth. Catal.,* **2011**, 353, 2561; P. M. Munoz, *Chem. Soc. Rev.,* **2014**, 43, 3164.

[132] R. K. Dieter, H. Yu, *Org. Lett.,* **2001**, 3, 3855; I. W. Davies, T. Gallagher, R. B. Lamont, D. I. Scopes, *J. Chem. Soc., Chem. Commun.,* **1992**, 335.

[133] D. Pflasterer, P. Dobundalchok, S. Rafique, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.,* **2013**, 355, 1383.

[134] N. Morita, N. Krause, *Org. Lett.,* **2004**, 6, 4121; N. Morita, N. Krause, *Eur. J. Org. Chem.,* **2006**, 4643.

[135] M. O. Amombo, A. Hausherr, *Synlett.,* **1999**, 1871.

Chapter 2: Ruthenium and Rhodium-catalyzed Hydroamination reactions of aminoallenes

2.1. Reactivity of allenes

If we consider allenes, the presence of two double bonds close together, both permit an enhancement of reactivity and to obtain products with interesting structure, still having a free double bond available for further reactions. 1,3-Disubstituted allenes possess an innate chirality, and they could be synthesized in an optically active form. This peculiarity permit to carry out stereoselective reactions. Allenes could react in different ways (showed in Figure 4) but in most cases their reactivity resemble that of analogues olefins, like Diels-Alder reactions, 1,3 dipolar cycloaddition, and reactions with electrophiles.[136]
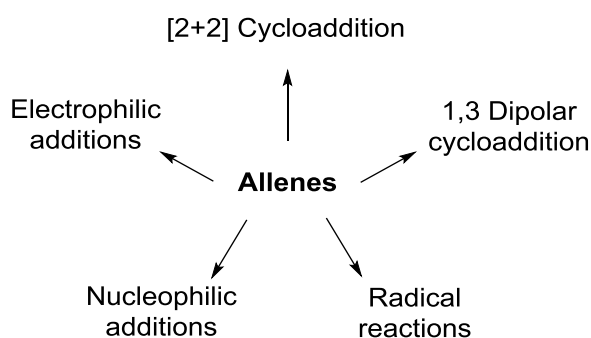
Figure 4

It is well known that 1,2-propadienes could give intramolecular reactions with nucleophiles also in the absence of transition metals. For this reason, they were widely employed in the synthesis of various heterocyclic systems, both saturated and unsaturated. However, hydroamination reactions carried out in these conditions could not allow a good control about selectivity of the process. On the other hand, more innovative and selective reaction pathways[137] could be achieved by operating through transition metal-mediated homogeneous catalysis, as reported in Scheme 34 for optically active allenamides derived from alpha aminoacids.[138]

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[136] N. Krause, A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH: Weinheim, **2004.**
[137] R. W. Bates, V. Satcharoen, *Chem. Soc. Rev.*, **2002**, 31, 12.
[138] G. Broggini, S. Galli, M. Rigamonti, S. Sottocornola, G. Zecchi, *Tetrahedron Lett.*, **2009**, 50, 1447; E. M. Beccalli, G. Broggini, F. Clerici, S. Galli, C. Kammerer, M. Rigamonti, S. Sottocornola, *Org. Lett.*, **2009**, 11, 1563; A. M. Manzo, A. D. Perboni, G. Broggini, M. Rigamonti, *Tetrahedron Lett.*, **2009**, 50, 4696.
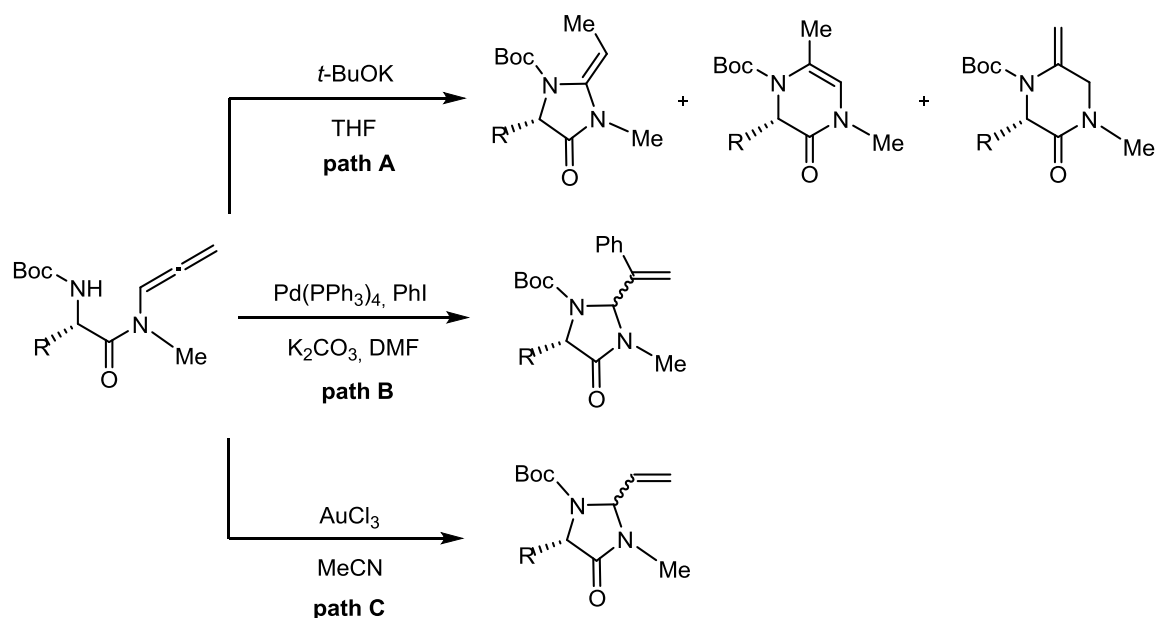
Scheme 34

In the field of homogeneous catalysis, palladium and gold are the most efficient transition metals either for the variety of synthetic methods developed and for the applicability to many different substrates.[139] In the last few years, in literature were reported a huge amount of gold-catalyzed synthetic procedures involving various nitrogen functional groups.[140] Most of them were hydroamination reactions, and many of them also involve allenes.

2.2. Palladium catalyzed hydroamination reactions of aminoallenes

Palladium is the most versatile between transition metals and its reactivity could involve nearly every leaving group and also hydrogen atoms, but hydroamination reactions occurs only in few cases. A common feature of all palladium-catalyzed reactions involving amino compounds is the need of specific nitrogen sources like amides, ureas, carbamates and sulphonamides. This need is due to the irreversible coordination of free amines to palladium, that give birth to stable complexes inhibiting the aminopalladation route.[141] In the case of palladium, carboamination reactions shows

[139] R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.*, **2000**, 100, 3067; R. A. Widenhoefer, H. Xiaoquing, *Eur. J. Org. Chem.*, **2006**, 4555.
[140] T. E. Muller, M. Beller, *Chem. Rev.*, **1998**, 98, 675.
[141] L. M. Venanzi, B. Pugin, *J. Organomet. Chem.*, **1981**, 214, 125.

general and simple application, while hydroaminations occur only sometimes and in particular conditions, with limited applications[142] (path A and B, Figure 5).
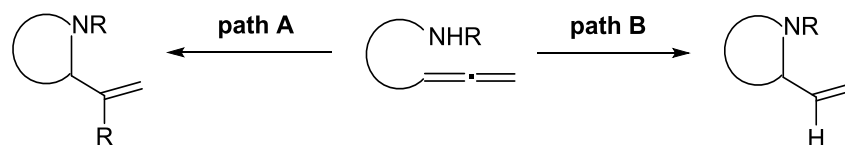
Figure 5

Previously in our research group, palladium-catalyzed cyclization conditions on allenamides of 2-indolcarboxylic acid as the substrate were reported.[143] Reaction conditions involve the use of a palladium(0) catalyst and proceed with microwaves activation, leading to imidazo[1,5-*a*]indoles (Scheme 35).
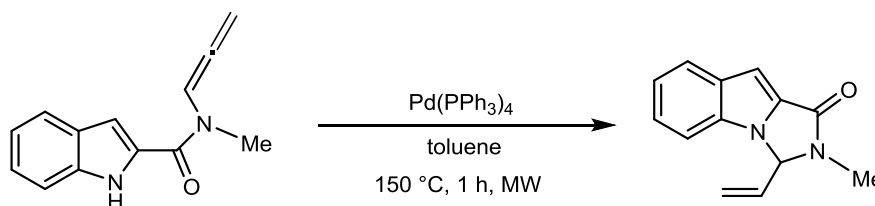
Scheme 35

Different aminoallenes were investigated in the same conditions as above, but the expected hydroamination products were obtained in low yields. Better results were achieved by operating a change in the reaction conditions, thus using a different source of palladium and milder conditions of temperature, and also reducing the reaction time (Scheme 36).

[142] S. Qiu, Y. Wei, G. Liu, *Chem. Eur. J.*, **2009**, 15, 2751; M. Meguro, Y. Yamamoto, *Tetrahedron Lett.*, **1998**, 39, 5421; M. Al-Masun, M. Meguro, Y. Yamamoto, *Tetrahedon Lett.*, **1997**, 38, 6071; L. Besson, J. Gorè, B. Cazes, *Tetrahedron Lett.*, **1995**, 36, 3857.
[143] E. M. Beccalli, A. Bernasconi, E. Borsini, G. Broggini, M. Rigamonti, G. Zecchi, *J. Org. Chem.*, **2010**, 75, 6923
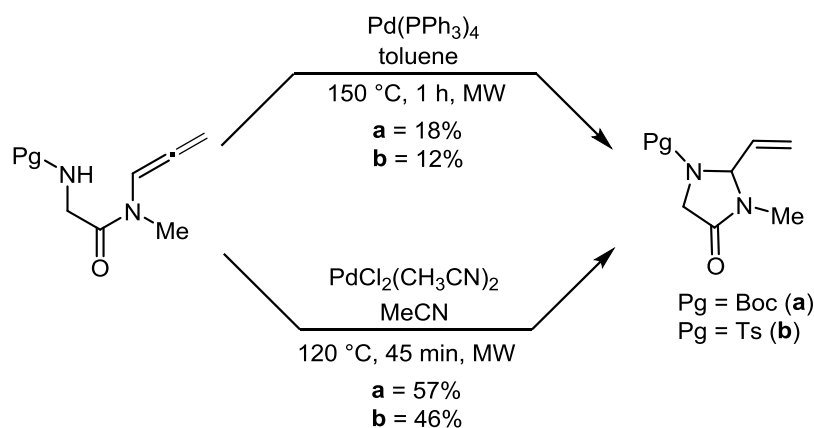
Scheme 36

These conditions were found able to promote both *5-endo* and *6-endo* reaction pathways, and a great variety of starting allenes with different structures can be used as substrates. The presence of a benzene ring between reaction centers, that gives structural rigidity, did not incapacitate the reaction. Whether five and six member rings can be obtained, either in the presence or in the absence of an heteroatom close to the allenic function. In the second case, presence of a base is requested due to lower reactivity of the allene (Scheme 37).
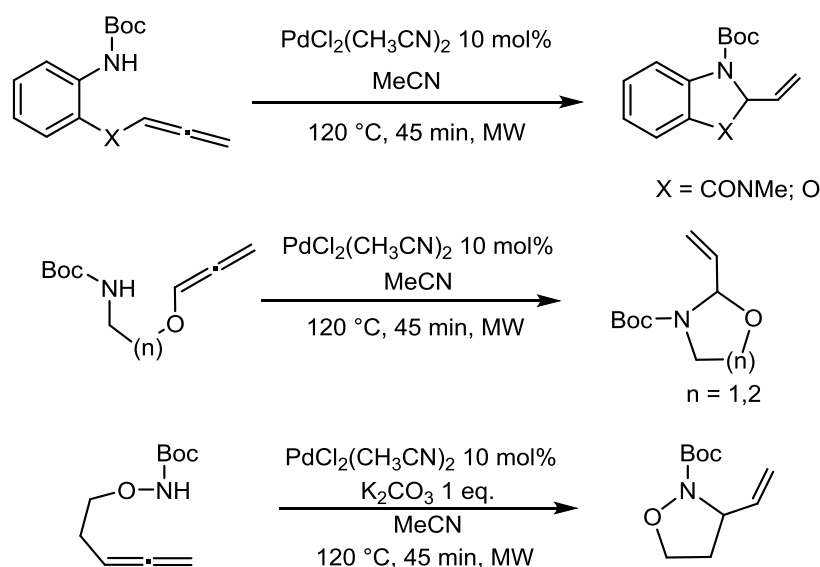
Scheme 37

A valid interpretation of the mechanism, based on literature data about *N-H* groups in amines and amides, displays that probably palladium(0) catalyst initially coordinates to the nitrogen atom, generating a palladium(II)-hydride complex **I** (Scheme 38). This intermediate undergoes to insertion of the allenic function in the Pd-H bond giving a π-allyl-palladium(II) complex that subsequently

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generates a new intramolecular carbon-nitrogen bond through reductive elimination of palladium(0). Then palladium(0) catalyst is regenerated and the resulting vinyl-substituted nitrogen-containing heterocycle is formed.

n = 0, 1
R = Boc, Ts, CONHR, COR
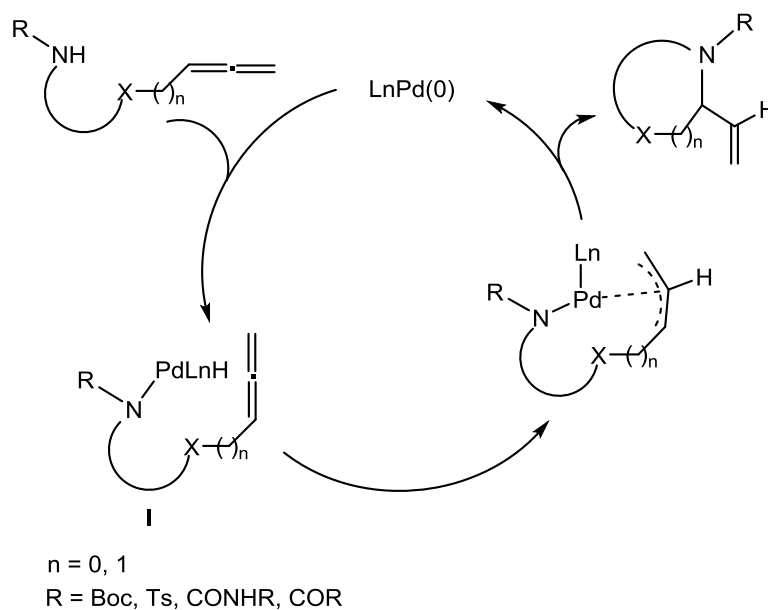
Scheme 38

2.3. Ruthenium catalyzed hydroamination reactions of aminoallenes

As previously demonstrated, intramolecular hydroaminations represent a powerful tool for the synthesis of nitrogen-containing heterocycles.[144] Indeed, through this reaction is possible to achieve the formation of a carbon-nitrogen and a carbon-hydrogen bond *via* N-H addition across a double bond in a direct and efficient way. In particular, transition metal-mediated aminoallene cyclizations[145] exhibit an elegant chemistry and represent a very good choice to this synthetic purpose. In literature various metals found application in this field, with a special mention to palladium, silver and gold catalysis.[146]

Ruthenium complexes have been recently appreciated as useful tools for the synthesis and functionalisation of heterocycles through C-H bond activation. Ru-catalyzed allene cyclizations have

[144] K. D. Hesp, M. Stradiotto, *ChemCatChem*, **2010**, 2, 1192; K. C. Hultzsch, *Adv. Synth. Cat.*, **2005**, 347, 367.

[145] T. Lu, Z. Lu, Z. X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.*, **2013**, 113, 4862; L.L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.*, **2003**, 36, 773.

[146] L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.*, **2004**, 126, 1622; N. T. Patil, L. M. Lutete, H. Wu, N. K. Pahadi, I. D. Gridnev, *J. Org. Chem.*, **2006**, 71, 4270; N. Krause, C. Winter, *Chem. Rev.*, **2011**, 111, 1994; N. Morita, N. Krause, *Org. Lett.*, **2004**, 6, 4121; M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *Tetrahedron Lett.*, **1991**, 32, 6359.

also been reported by different research groups. However, only in rare cases intramolecular reactions of aminoallenes were concerned, such as in the case of cyclocarbonylations and domino reactions[147] (Scheme 39).
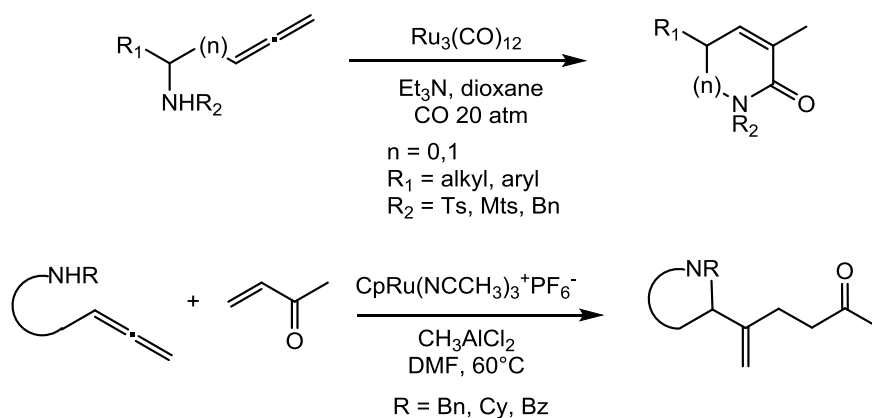
Scheme 39

Since poor examples of ruthenium catalyzed intramolecular hydroaminations of aminoallenes were reported in the literature, we started our investigation on this topic.

One of the advantageous feature in using ruthenium is constituted by its price. In fact, the cost of this metal favorably compares with that of most other noble metals, and the catalyst we used, $RuCl_3 \cdot xH_2O$ is quite cheap. In September, 2015 quotation of ruthenium was about 42 USD/ozt, as shown in Figure 6, reporting ruthenium and rhodium prices between 1992 and 2015. For comparison, nowadays rhodium price is about 700 USD/ozt and platinum about 550 USD/ozt.
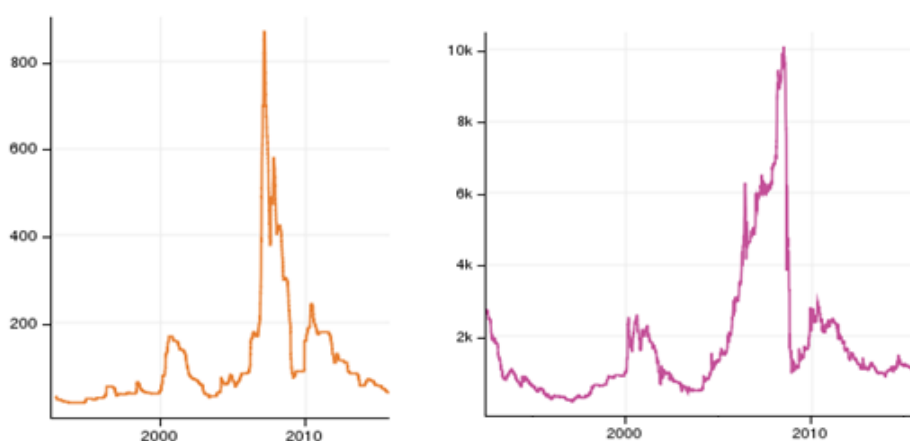
Figure 6

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[147] S. K. Kang, K. J. Kim, C. M. Yu, Y. K. Do, *Org. Lett.*, **2001**, 3, 2851; B. M. Trost, A. B. Pinkerton, D. Kremzow, *J. Am. Chem. Soc.*, **2000**, 122, 12007.

Purpose of this investigation was to develop a concise method for the synthesis of vinyl substituted 1,3-diaza- and 1,3-oxaza- heterocyclic structures, resulting from the selective intramolecular hydroamination of aminoallenes at the internal unsaturation of the allene function (Scheme 40).
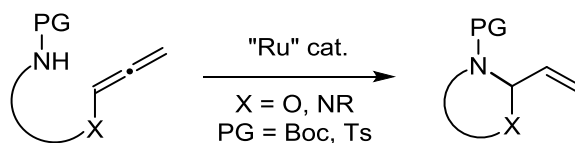
Scheme 40

First screening of reaction conditions were accomplished on *O*-allenyl *N*-Boc-2-aminoethanol **1a**, obtained from the corresponding alkyne *via* prototropic isomerization, which was submitted to the conditions collected in Table 1.
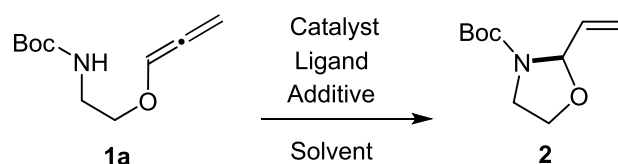
Entry	Catalyst / ligand[a]	Additive	Solvent	T (°C)	t (h)	Yield of **n**
1	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), allylacetate (4 equiv.)	MeCN	60	2	80%
2	RuCl$_3$ (1 mol%)	K$_2$CO$_3$ (2 equiv.), allylacetate (4 equiv.)	MeCN	60	24	5%
3	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.)	MeCN	60	24	-
4	**RuCl$_3$ (1 mol%), dppe**	**K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)**	**MeCN**	**60**	**2**	**90%**
5	dppe	K$_2$CO$_3$ (2 equiv.), allylacetate (4 equiv.)	MeCN	60	24	-
6	dppe	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	MeCN	60	2	-
7	RuCl$_3$ (1 equiv.), dppe	K$_2$CO$_3$ (2 equiv.), N$_2$	MeCN	60	2	-
8	RuCl$_3$ (1 mol%), dppp	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	MeCN	60	2	86%
9	RuCl$_3$ (1 mol%), PPh$_3$	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	MeCN	60	24	-
10	RuCl$_3$ (1 mol%), (-)chiraphos	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv	MeCN	60	2	47%
11	RuCl$_3$ (1 mol%), dppe	CuCl$_2$ (1 equiv.)	MeCN	60	2	-
12	RuCl$_3$ (1 mol%), dppe	allylacetate (4 equiv.)	MeCN	60	2	-
13	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	THF	60	18	41%
14	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	dioxane	90	6	8%
15	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	DMF	100	18	5%

16	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), CuCl$_2$ (1 equiv.)	DCE	80	18	5%
17	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), O$_2$	MeCN	60	24	20%
18	RuCl$_3$ (1 mol%), dppe	K$_2$CO$_3$ (2 equiv.), PhI(OAc)$_2$ (1 equiv.)	MeCN	60	2	69%

[a]1 mol%

Table 1

Taking a cue from literature data involving intramolecular aminations of carbon-carbon multiple bonds, the first experiments were carried out with the system formed by RuCl$_3$ (1 mol%), dppe (1 mol%), K$_2$CO$_3$ (2 equiv.), allylacetate (4 equiv.) in acetonitrile at 60 °C. Ru(II)-catalyzed oxidative processes usually generate a Ru dihydride complex, but by using allylacetate as additive the metal is brought back to its original oxidation state, with simultaneous development of propene and acetic acid.[148] In these conditions was possible to observe a clean *exo*-hydroamination of the internal allenic unsaturation of **1a**, leading to the formation of 2-vinyl-oxazolidine **2** in 80% yield (Table 1, entry 1).

Despite the good result showed in this first attempt, we proceeded with a screening of the reaction conditions. Further experiments proved that the hydroamination reaction did not proceed in the absence of either the bidentate phosphine ligand (Table 1, entry 2), or of allylacetate (Table 1, entry 3). Replacement of allylacetate with a stoichiometric amount of CuCl$_2$ lead to a slight yield improvement to 90% (Table 1, entry 4).

As expected, presence of RuCl$_3$ was also essential (Table 1, entries 5 and 6). Besides, use of RuCl$_3$ in stoichiometric amounts but in the absence of allyl acetate or CuCl$_2$ did not permit the hydroamination to occur (Table 1, entry 7). While the use of dppp instead of dppe provided the product in analogous yield, the substitution of the diphosphine with PPh$_3$ totally precluded the reaction (Table 1, entries 8 and 9). Use of a chiral enantiopure phosphine like (-)-chiraphos afforded the expected product in good yields, but in a virtually racemic form (Table 1, entry 10). Thus, dppe was confirmed as the ligand of choice, although enantioselection could not be controlled.

The presence of the base was also demonstrated to be crucial for the successful conversion of the substrate (entries 11 and 12). Use of different solvents, like dioxane, THF, DMF or dichloroethane (DCE) instead of acetonitrile did not improve the yield of the reaction (Table 1, entries 13-16). As a consequence, acetonitrile was chosen as the most suitable solvent. Other additives such as molecular oxygen, or PhI(OAc)$_2$ combined with the system [RuCl$_3$ / dppe / K$_2$CO$_3$] were able to act as oxidizing agents and promote the cyclization, although in lower yields (Table 1, entries 17-18).

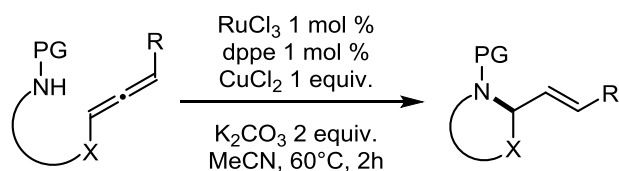[148] T. Kondo, T. Mukai, Y. Watanabe, *J. Org. Chem.*, **1991**, 56, 487.

Summarizing the results, we found that: *i)* simultaneous use of a base and of an oxidizing agent is essential for the reaction, *ii)* presence of a bidentate phosphine as a ligand is necessary to obtain satisfactory yields, *iii)* acetonitrile was the most suitable solvent.

The optimized conditions (Table 1, entry 4) were then applied to the intramolecular hydroamination of a series of amino-allenamides or amino-alkoxyallenes showed in Figure 7. All these allenes were obtained through conversion of the corresponding terminal alkyne *via* base-promoted prototropic isomerization with *t*-BuOK.

1b   **1c**   **1d**

1e: n = 2
1f: n = 3

1g: PG = Boc, R = Me, R^1 = H
1h: PG = Ts, R = Me, R^1 = H
1i: PG = Boc, R = Me, R^1 = Cl
1j: PG = Boc, R = Bn, R^1 = H

1k
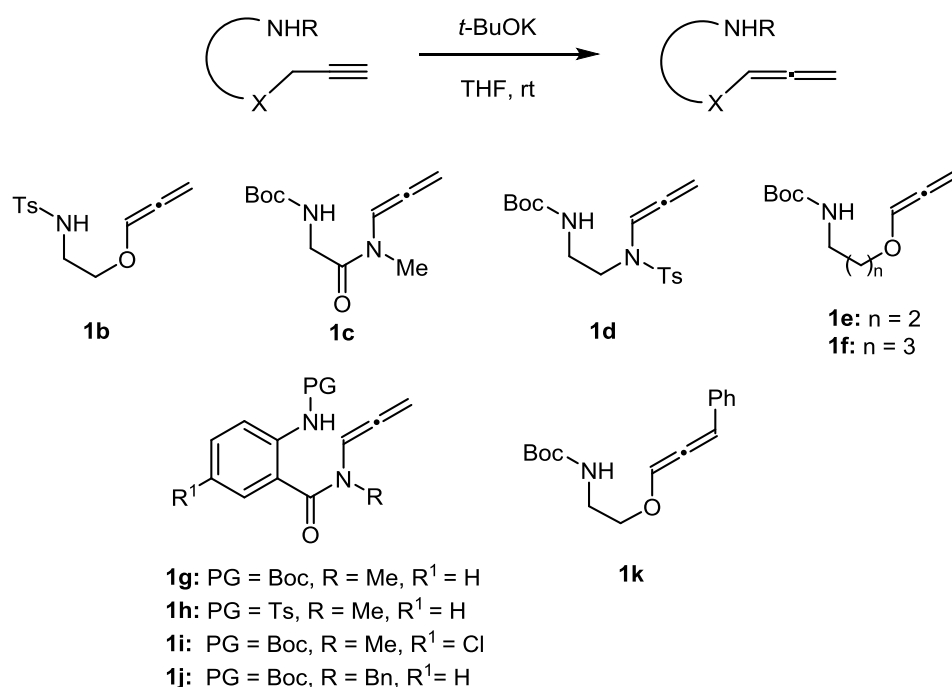
Figure 7

In Scheme 41 are reported the optimized cyclization conditions, while in Figure 8 are displayed the resulting vinyl-substituted heterocycles and the newly formed bond is highlighted.

Scheme 41

3 (89%)   **4** (80%)   **5** (61%)   **6** (71%)   **7** (crude product)

8 (90%)   **9** (72%)   **10** (68%)   **11** (61%)   **12** (63%)
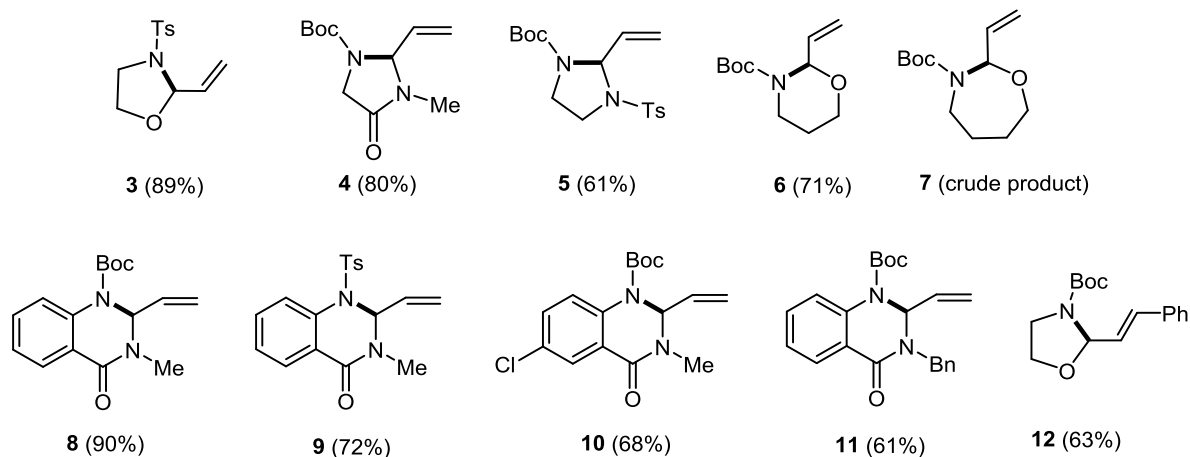
Figure 8

As expected, allenamides **1c,d** gave the corresponding imidazolidine derivatives. These conditions are effective also for *N*-tosyl-protected aminoallenes, as disclosed by the formation of the 2-vinyl-oxazole **3**. The same catalytic system allowed also 6-*exo*-allylic hydroaminations, as proven by the isolation of the *N*-terbutoxycarbonyl 2-vinyl-1,3-oxazine **6** from allenamide **1e** and by the formation of the quinazolin-4-one products **8-11** starting from anthranilic allenamides **1g-j**. The cyclization of allene **1f** into the 1,3-oxazepine **7** highlights that 7-*exo*-allylic processes are also possible, although in this case it was not possible to obtain the pure product by column chromatography. Finally, internal allenes undergo the intramolecular hydroamination too, as evidenced by transformation of **1k** into (*E*)-alkenyl oxazolidine **12** as the only product.

In order to obtain 3-vinylmorpholine, allene **1l,** generated via Crabbe's reaction, was submitted to optimized conditions. In this case, catalytic system was ineffective in the hydroamination reaction, and unreacted product was recovered (Scheme 42). In comparison to the previous allenes, the sole structural difference was the absence of an heteroatom close to 1,2-propadienic function.
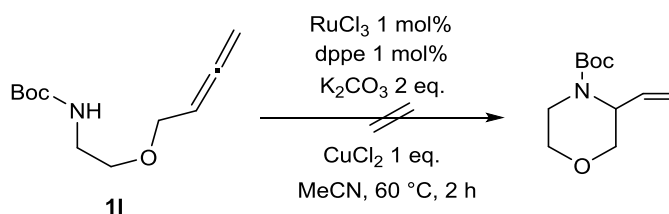
Scheme 42

Structures of unreactive allene **1l** and reactive allene **1e** differ barely for the mutual exchange of the oxygen atom and methylene group, which suggests that the unresponsiveness of the C-substituted allenes is likely due to electronic effects more than conformational reasons.

Importance of this structural feature was verified on allenes **1m,n**, that in theory could give 5-*exo*-allylic cyclization in the ruthenium-mediated hydroamination (Scheme 43).
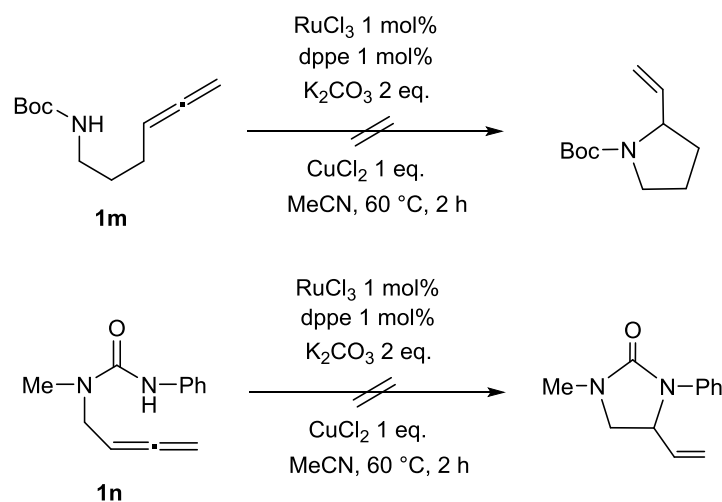
Scheme 43

In contrast to the previously described heterosubstituted allenes, the corresponding C-substituted allenes failed to react when submitted to the same reaction conditions as above. Presence of an heteroatom close to allenic function was then confirmed as a fundamental structural feature for ruthenium-catalyzed hydroamination reactions. Use of harsh reaction conditions for longer time lead only to product degradation.

In order to gain further information on the role of the additives, some additional experiments were performed. First, the cyclization was conducted using a catalytic system based on a well-defined ruthenium(II) species. Thus, allene **1a** was submitted to [RuCl$_2$(p-cymene)]$_2$ and dppe under the otherwise optimized conditions, in the presence as well as in the absence of CuCl$_2$ (Scheme 44, *path a* and *path b*). Only the latter conditions allowed the reaction to take place (87% yield), so confirming the crucial role of CuCl$_2$ as additive.
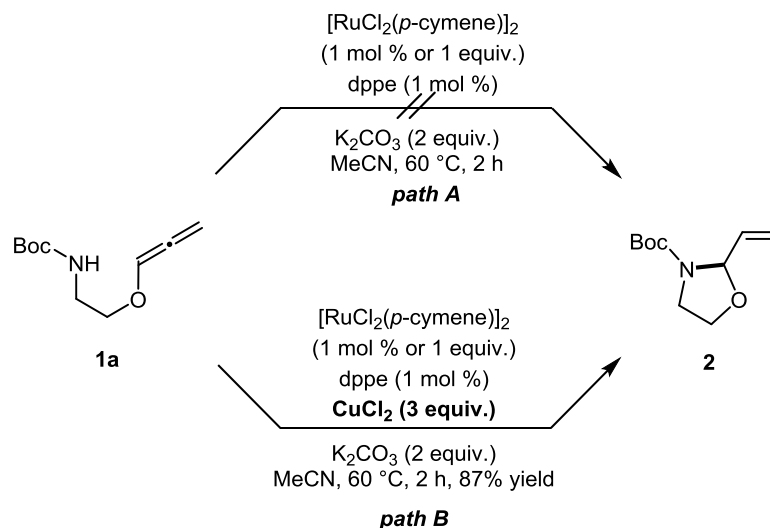
Scheme 44

A catalytic system containing RuCl$_3$ and CuCl$_2$ in sub-stoichiometric amount was subsequently tested (Scheme 45, *path a*). These conditions lead to the formation of the expected product, although the reaction became more sluggish and gave a reduced yield (48%). Finally, CuCl$_2$ was replaced by LiCl in the system [RuCl$_2$(*p*-cymene)]$_2$ / dppe / LiCl / K$_2$CO$_3$ in acetonitrile at 60 °C, that provided **2** in 51% yield (Scheme 45, *path b*).
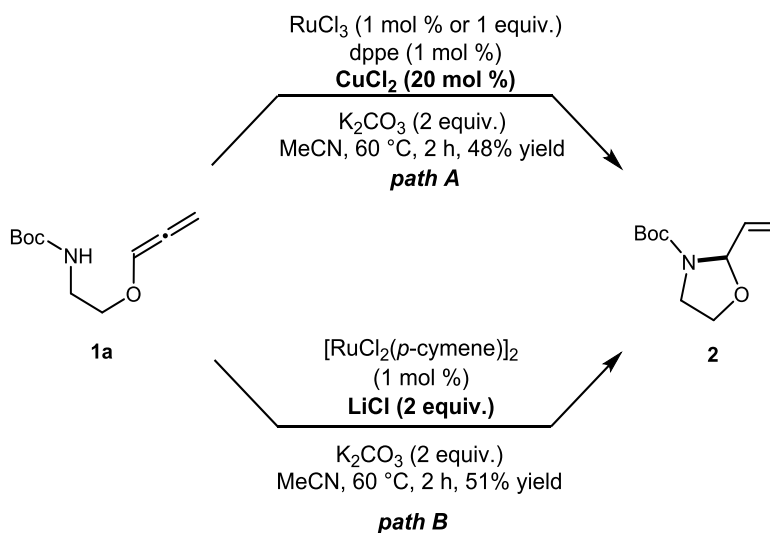
Scheme 45

The ensemble of these results provide us with several hints about the possible mechanism of this transformation: *a)* an active catalytic system could be obtained either starting from [Ru(II)Cl$_2$(p-cymene)]$_2$, or RuCl$_3$ in the presence of dppe, which is expected to reduce the metal to Ru(II).[149] As a consequence, the starting catalyst is believed to be a Ru(II) complex; *b)* besides the metal complex, also the base, the phosphine, as well as CuCl$_2$ (or LiCl) were all found to be necessary for the success of the reaction. The diphosphine is expected to coordinate the metal via a κ^2 coordination, while the copper or the lithium salt additives provide extra chloride coordination to Ru, so as to generate a monomeric reactive Ru complex. As to the role of K$_2$CO$_3$, it probably plays a proton shuttle from the nitrogen atom.

Although additional studies will be needed to further elucidate the details of this transformation, we can hypothesize the mechanism depicted in Scheme 46 for the transformation **1a → 2**. Interaction between the Ru(II) source, the diphosphine and the chloride additive generates the active monomeric catalyst LLRu(II)MCl, that will form a complex through the allene function giving the zwitterionic complex **II**, through complex **I** (Scheme 46, steps a and b). Involvement of intermediate **II** is supported by the fact that non heterosubstituted allenes (for which such intermediate is not plausible) are not reactive. Subsequent intramolecular addition of the nitrogen atom onto the oxycarbenium function produces the heterocyclic structure **III** (Scheme 46, step c). The subsequent K$_2$CO$_3$ mediated proton transfer from the nitrogen atom could take place according to two alternative mechanisms. N-to-Ru 1,3-H transfer generates the Ru(IV) hydride **IV**,[150] whose reductive elimination gives the product and regenerates the catalyst. Alternatively, the product can be formed via N-to-C 1,3'-H transfer from **III** (Scheme 46, step f), to produce the Ru carbenoid species **V**, followed by a 1,2-H shift (Scheme 46, step g) and final Ru decomplexation (Scheme 46, step h).[151]

[149] B. Godin, A. Jutand, F. Lemaitre, *Chem. Eur. J.,* **2007**, 13, 2002; M. Rohr, J. D. Grunwaldt, A. Baiker, *J. Mol. Catal.,* **2005**, 226, 253.
[150] H. Nagashima, K. Mukai, Y. Shiota, K. Yamaguchi, K. Ara, T. Fukahori, H. Suzuki, M. Akita, K. Itoh, *Organomeyallics,* **1990**, 9, 799.
[151] R. X. Zhu, D. J. Zhang, J. X. Guo, J. L. Mu, C. G. Duan, C. B. Liu, *J. Phys. Chem.,* **2010**, 114, 4689.
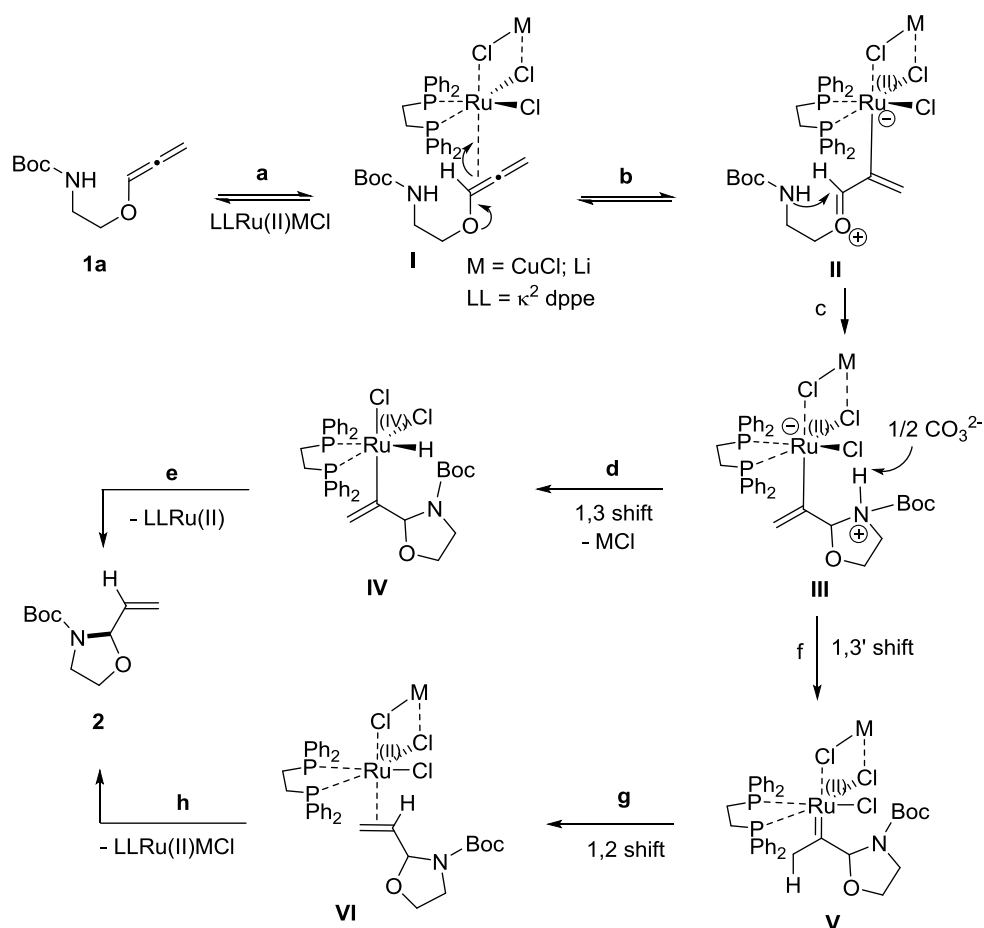
Scheme 46

In summary, a ruthenium-catalyzed synthesis of vinyl-substituted heterocycles involving intramolecular hydroamination of amino-allenamides and amino-alkoxyallenes has been developed. Further experiments are required to completely understand the reaction mechanism. This synthetic protocol, although it shows some restrictions for the cyclization of allenes without an heteroatom in α-position, is a valuable and less expensive alternative to other catalytic systems already reported in the literature.

2.4. Rhodium catalyzed hydroamination reactions of aminoallenes

As a natural consequence of our previous work about ruthenium catalyzed hydroamination reactions, we asked ourselves if this kind of reactivity could be achieved also by using other transition metals. As we previously said, palladium and gold, and as demonstrated also ruthenium, were

proved effective for the conversion of aminoallenes in the corresponding vinyl derivatives (Scheme 47).
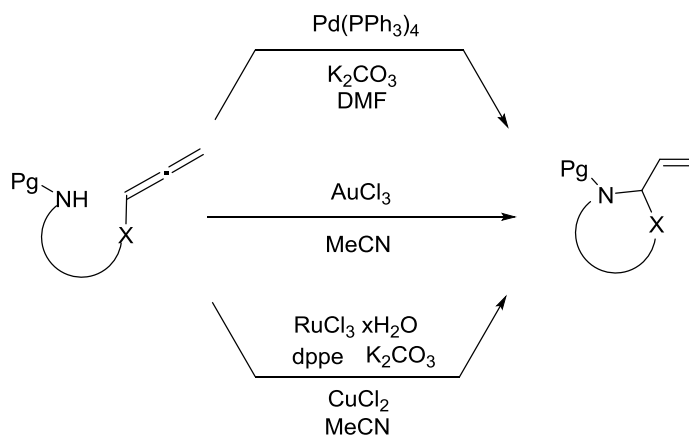
Scheme 47

In the literature there were no mention about intramolecular rhodium-catalyzed hydroamination reactions involving the previously displayed aminoallenes as the substrate, and leading to heterocyclic vinyl derivatives. Only examples of rhodium-catalyzed intramolecular hydroamination reaction involving alkenes and alkynes, or intermolecular reactions involving allenes are reported.

Examples of rhodium-catalyzed direct functionalisation of C-H bonds are widely reported as an attractive step-economic approach to value-added molecules from readily available starting materials, also showing high functional group tolerance, high reactivity and selectivity. In most cases, a directing group is necessary to effect high selectivity, and the directing group include hydroxyl, carbonyl, amide and imine. Amides are widely present as important building blocks in organic synthesis.

Metal-catalyzed intramolecular hydroamination of olefins is one of the most conceptually simple and atom-economical approaches to the construction of nitrogen heterocycles. Recently, Buchwald and coworkers[152] displayed an example of rhodium-catalyzed asymmetric intramolecular addition of amines to olefins for the synthesis of a variety of 2-methylpyrrolidines with good enantioselectivity. Operating with a commercially available Rh(I) catalyst like $[Rh(cod)_2]BF_4$ in the presence of a chiral ligand like KenPhos or analogues oxygen, phosphorus and nitrogen- based binaphthyl ligands, was possible to achieve the formation of different pyrrolidines in 50-90% yield and 60-85% ee (Scheme 48).

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[152] X. Shen, S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2010**, 49, 564.
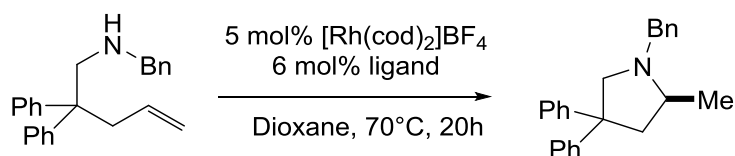
Scheme 48

Similarly, Mascarenas and coworkers[153] reported examples of intramolecular annulations involving amide-directed C-H activation in the presence of an internal alkyne. These reactions lead to the formation of tricyclic molecules with good yields, operating under oxidative conditions. Commercially available $[RhCp^*Cl_2]_2$ was used as the catalyst (Scheme 49). DFT calculations suggested that the migratory insertion of the alkyne into the rhodacycle resulting from the initial C-H activation step takes place into the Rh-N instead of the Rh-C bond.
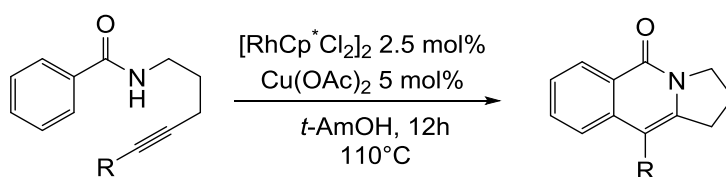
Scheme 49

A very interesting procedure was reported by Glorius and coworkers.[154] Heteroannulation of allenes, pioneered by Larock, has proven to be a valuable method for the synthesis of a variety of heterocycles. Contrary to previously reported procedures, Glorius developed a Rh(III) catalyzed C-H functionalisation under mild conditions, without the presence of an oxidant (Scheme 50). This was made possible by using benzohydroxamic acid derivatives as directing group and internal oxidant. In this way, the synthesis of 3,4-dihydroisoquinolones was achieved with high regio- and stereoselectivity.
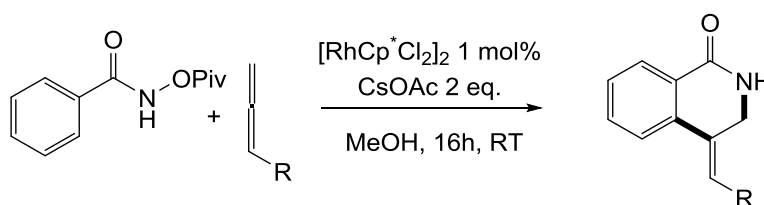
Scheme 50

[153] N. Quinones, A. Seoane, R. Garcia-Fandino, J. L. Mascarenas, M. Gulìas, C*hem. Sci.*, **2013**, 4, 2874.
[154] H. Wang, F. Glorius, *Angew. Chem. Int. Ed.*, **2012**, 51, 7318.

Taking a hint from these works, we started our investigation on the feasibility of rhodium-catalyzed intermolecular hydroamination reactions of aminoallenes. As we did previously for ruthenium-catalyzed hydroaminations, first screening of the reaction conditions was carried out on *O*-allenyl *N*-Boc-2-aminoethanol **1a** in the condition reported in Table 2 and Table 3.
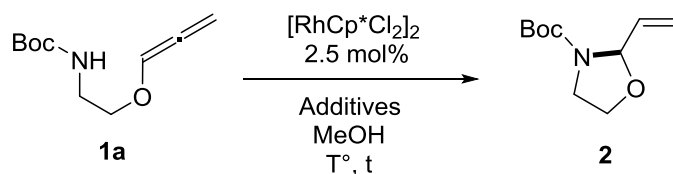
Entry	Oxidant	Base	t(h)	T (°C)	Yield of **2**
1	-	CsCO$_3$ 2eq.	16	50	-
2	DBPO 2.5 mol%	CsCO$_3$ 2eq.	16	50	15%
3	DBPO 2.5 mol%	K$_2$CO$_3$ 2eq.	16	50	14%
4	DBPO 2.5 mol%	KOAc 2eq.	12	50	27%
5	DBPO 2.5 mol%	KOAc 1.2eq.	12	50	28%
6	NCS 2.5 mol%	KOAc 1.2eq	12	50	12%
7	Ag$_2$CO$_3$ 2.5 mol%	KOAc 1.2eq.	12	50	19%
8	PhI(OAc)$_2$ 2.5 mol%	KOAc 1.2eq.	12	50	17%
9	DBPO 2.5 mol%	-	12	50	-
10[a]	DBPO 2.5 mol%	KOAc 1.2eq.	12	50	-

[a]: reaction carried out in the absence of catalyst

Table 2

Taking a cue from literature data, we decided to use as catalyst the commercially available [RhCp*Cl$_2$]$_2$. The first experiment was carried out with the system ([RhCp*Cl$_2$]$_2$ 2.5 mol% and Cs$_2$CO$_3$ 2 eq.), in methanol for 16 hours at 50°C. Previous test proved that the reaction did not work at room temperature. Also this system failed the conversion of *O*-allenyl *N*-Boc-2-aminoethanol in the desired vinylderivative, probably due to the absence of an oxidizing agent. In fact, the addition of an oxidant (Table 2, entries 2-8) lead to the formation of the expected product, either in low yields. Among different oxidizing agents tested, DBPO was found to be the most appropriate, utilized in co-catalytic amount. Different bases were also tested (Table 2, entries 2-5), and KOAc was found to be appropriate in slightly more than stoichiometric amount. Entries 9 and 10 proved that both the base and the catalyst are necessary for successful conversion of the starting aminoallene.

1a → **2**

Reagents above arrow: [RhCp*Cl$_2$]$_2$ 2.5 mol%, DBPO 2.5 mol%, KOAc 1.2eq., solvent, T°, t
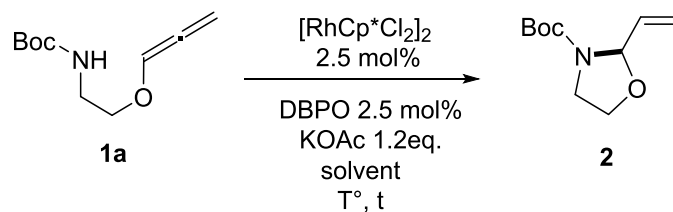
Entry	Solvent	t(h)	T (°C)	Yield of **2**
1	THF	12	60	-
2	MeCN	12	70	32%
3	DMF	12	90	65%
4	DMF	6	90	60%
5[a]	DMF	12	90	-
6[b]	DMF	12	90	9%
7[c]	DMF	12	90	-

[a]: reaction carried out in the absence of catalyst

[b]: reaction carried out in the absence of oxidizing agent

[c]: reaction carried out with RhCl$_3$ 2.5 mol% as the catalyst

Table 3

The use of methanol as the solvent do not allow us to reach good yields, so we did a screening of different solvents (Table 3, entries 1-3) simultaneously increasing the temperature, using the loading of oxidant and base corresponding to Table 2, entry 5. THF was not able to promote the cyclization, while acetonitrile did not improve significantly reaction yield. On the opposite, operating in dimethylformamide at 90°C, even for a shorter time, greatly affect the vinylderivative formation. As a consequence, we choose DMF as the most suitable solvent. As expected, [RhCp*Cl$_2$]$_2$ was essential for the successful conversion of the substrate (Table 3, entry 5) and also the oxidizing agent (Table 3, entry 6) although the highly-reactive aminoallene partially reacts anyway. The use of different rhodium(III) catalyst (Table 3, entry 7) did not allow the reaction to occur.

Summarizing the results, we found that: *i)* simultaneous use of a base and of an oxidizing agent is essential for the reaction, and the most suitable base and oxidizing agent were found to be KOAc and DBPO respectively, *ii)* DMF was found to be the most suitable solvent in terms of yield.

The optimized conditions were then applied to the intramolecular hydroamination of a series of amino-allenamides or -alkoxyallenes showed in Figure 9. These allenes shows differences in the distance between the amine and allene functional group, in the rotational capability of the chain and

in the nature of protective group on the nitrogen atom. As told in paragraph 2.3, all the allenes were obtained through conversion of the corresponding terminal alkyne *via* prototropic isomerization except allenes **1l** and **1n** that were obtained by Crabbè's reaction.
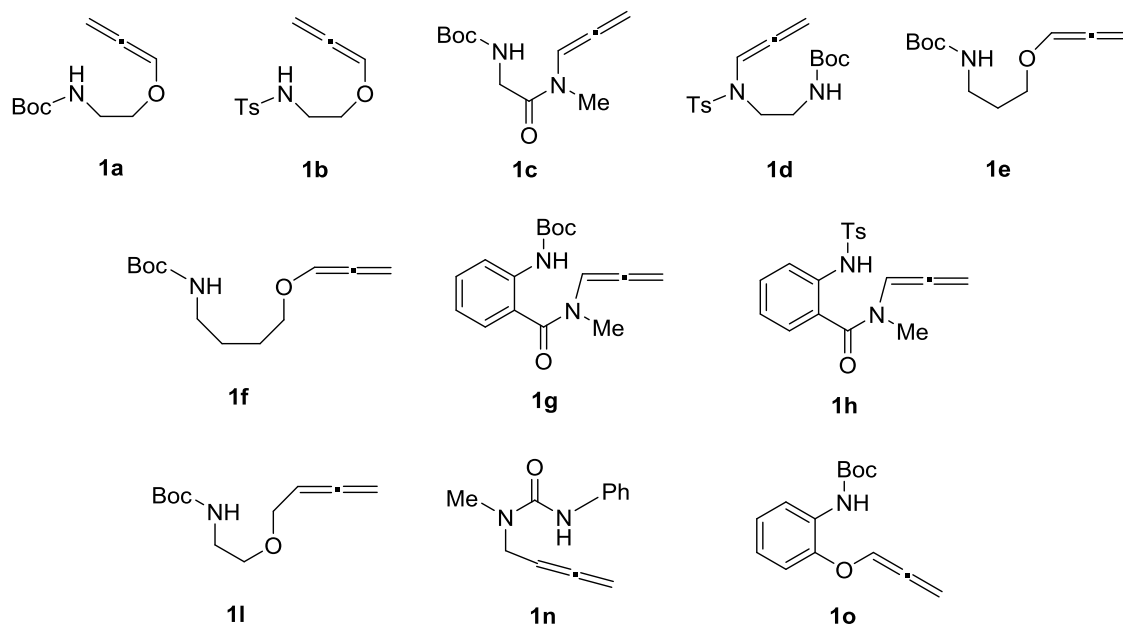
Figure 9

In Scheme 51 are reported the optimized cyclization conditions and the resulting vinyl-substituted products. These heterocycles belong to different classes and were obtained in good yield.
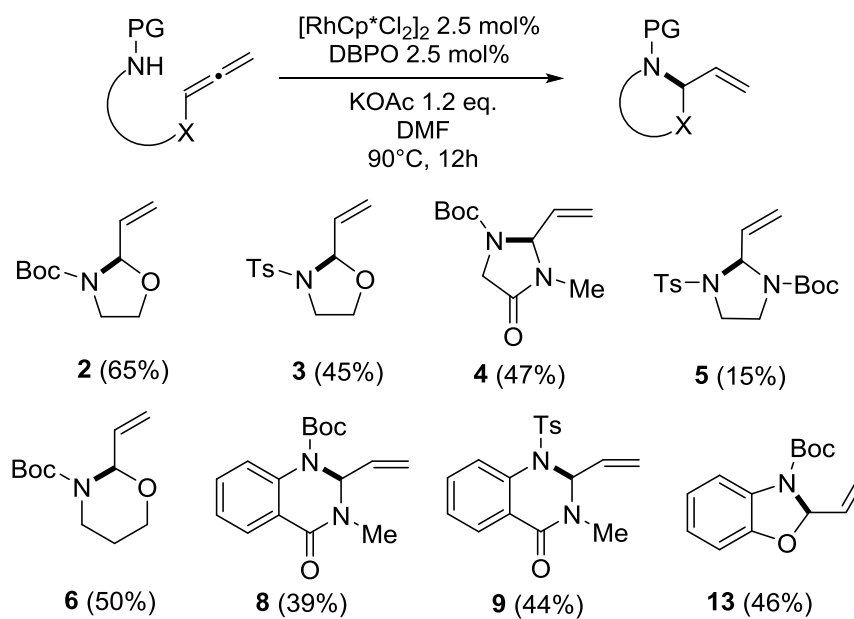
Scheme 51

These conditions are effective both for *N*-terbutoxycarbonyl-protected and *N*-tosyl-protected aminoallenes, as disclosed by the formation of the 2-vinyl-oxazole **3**. These results showed that the catalytic system allowed 5-*endo*- and also 6-*exo*-allylic hydroaminations, resulting by the isolation of the *N*-terbutoxycarbonyl 2-vinyl-1,3-oxazine **6** and by the formation of the quinazolin-4-one derivatives starting from anthranilic allenamides. Lower isolation yield of *N*-Boc-*N'*-tosyl-2-vinyl-imidazolidine is probably due to steric hindrance.

In contrast to ruthenium-catalyzed hydroaminations, rhodium-mediated reactions seems to not allow 7-*exo*-allylic processes, since we did not observe the conversion of allene **1f** into the corresponding 1,3-oxazepine under the usual reaction conditions (Scheme 52).
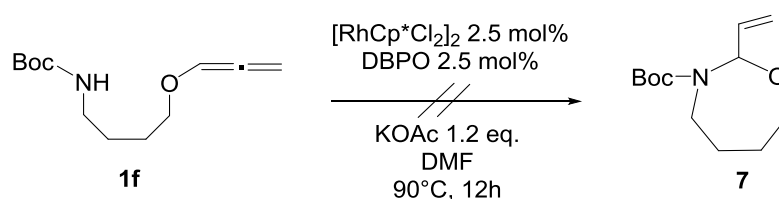
Scheme 52

Accordingly to results displayed for ruthenium mediated hydroaminations, also by using rhodium complex as the catalyst, C-substituted allenes failed to react when submitted to the same reaction conditions as above. This was the case for allenes showed in Scheme 53, that were generated via Crabbè's reaction. Thus, presence of an heteroatom in α-position to the allene functional group is proven to be a necessary structural feature for successful reactions.
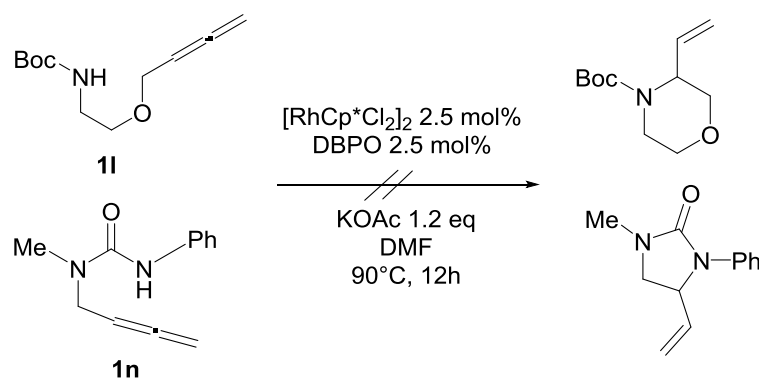
Scheme 53

During the screening of the reaction conditions, we run into an unexpected result. In fact, when CuCl$_2$ was employed as the oxidizing agent in co-catalytic amount with ([RhCp*Cl$_2$]$_2$, and methanol as

the solvent, the reaction did not lead to the desired 2-vinylsubstituted oxazolidine. From NMR spectra of the product we recognized the presence in the structure of a methoxy substituent in α-position on the vinyl double bond, as shown in Scheme 54.
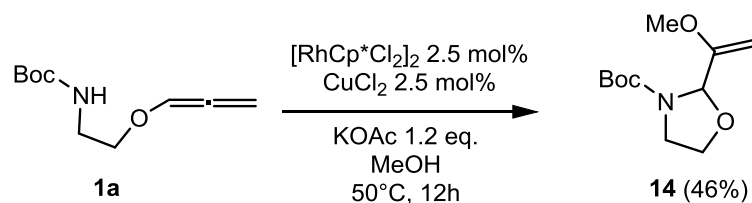
Scheme 54

This unexpected behaviour was confirmed by submitting allenes **1e** and **1o** to the same reaction conditions, similarly leading to the formation of the sole "methoxy-substituted vinylderivatives" in quite good yield for the oxazine product, while presence of the dihydro-benzoxazole was observed in the crude of reaction, but it was not possible to purify it through column chromatography (Scheme 55).
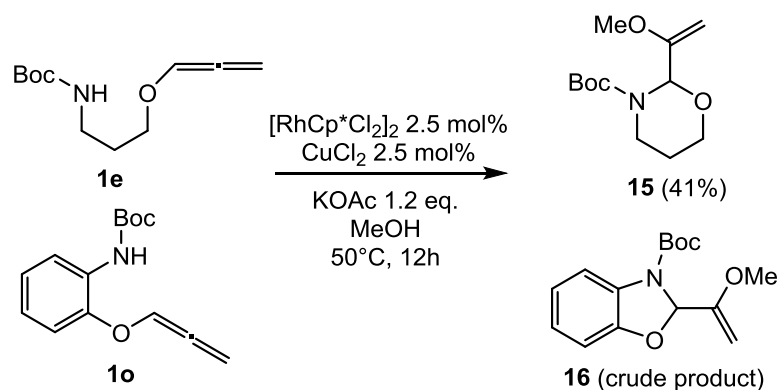
Scheme 55

2.5. Conclusions

We developed two different methodologies for intramolecular hydroamination reactions using aminoallenes as the substrate. Both approaches were found successful for the promotion of *exo*-allylic cyclization reactions, leading to N-containing vinyl-substituted heterocycles. Summarizing, we found that:

i)   both ruthenium- and rhodium-catalyzed hydroaminations requires aminoallenes with an heteroatom in α-position to the allene for a successful reaction

ii)   ruthenium-catalyzed reactions allows the formation of five-, six- and seven-membered rings, while the rhodium-mediated process did not permit the formation of 1,3-oxazepines

iii)   the ruthenium-based catalytic system is cheaper than rhodium, and also the reaction yields are better

2.6. Experimental section

General remarks

The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Melting point were determined on a Büchi B-540 instrument. IR spectra were measured on FT-IR 550 Nicolet instrument. Flash column chromatography was performed using silica gel (60 Å, particle size 40-64 µm) as stationary phase. ^{1}H- and ^{13}C-NMR spectra were recorded measured on a Bruker DRX 400MHz. Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl$_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded with a 400 MHz spectrometer operating at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard (CDCl$_3$, δ = 77.23 ppm).

Mass spectra were measured with a HPLC-MS LCQ-Advantage Thermo Finnigan instrument. Chiral HPLC analysis were performed with a Shimadzu instrument equipped with a Diode Array detector. Commercially available reagents were used as received, unless indicated otherwise.

General procedure for the preparation of allenes 1a- k, 1o
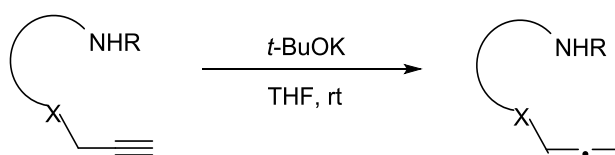
Tert-BuOK (2 mmol) was slowly added to a solution of alkynyl derivative (1 mmol) in THF. The solution was vigorously stirred at room temperature for the appropriate time and suddenly filtered on a thin silica gel layer with 250 mL of AcOEt. Solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography.

N-(*tert*-Butoxycarbonyl)-*O*-(1,2-propadienyl)-aminoethanol 1a
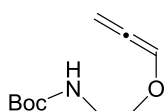
Reaction time: 30 min. Eluent: (9:1 light petroleum/AcOEt); Yield: 76%. Colourless oil. IR: 3287, 1956, 1704 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.38 (s, 9H), 3.32 (dd, J = 10.2, 5.1 Hz, 2H), 3.55 (dd, J = 10.2, 5.1 Hz, 2H), 4.98 (br s, 1H, missing after deuteration), 5.37 (d, J = 5.9 Hz, 2H), 6.66 (t, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 39.8 (t), 67.7 (t), 79.2 (s), 91.1 (t), 121.3 (d), 155.8 (s), 200.9 (s). MS: m/z 199 (M$^+$). Anal. calcd for C$_{10}$H$_{17}$NO$_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.32; H, 8.39; N, 6.78.

N-Tosyl-O-(1,2-propadienyl)-aminoethanol 1b
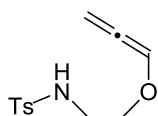
Reaction time: 10 min. Eluent: (6:4 light petroleum/AcOEt);Yield: 74%. Colourless oil. IR: 3292, 1946 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 2.42 (s, 3H), 3.28 (t, J = 5.3 Hz, 2H), 3.69 (t, J = 5.3 Hz, 2H), 4.20 (s, 1H, missing after deuteration), 5.32 (d, J = 6.2 Hz, 2H), 6.87 (t, J = 6.2 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.6 (q), 37.9 (t), 39.8 (t), 88.3 (t), 100.3 (d), 127.3 (d), 127.4 (d), 129.6 (d), 129.9 (d), 134.7 (s), 144.1 (s), 199.8 (s). MS: m/z 253 (M$^+$). Anal. calcd for C$_{12}$H$_{15}$NO$_3$S: C,56.90; H, 5.97; N, 5.53. Found: C, 57.13; H, 5.75; N, 5.67.

N-Methyl-N-(1,2-propadienyl)-2-($tert$-butoxycarbonylamino)-acetamide 1c
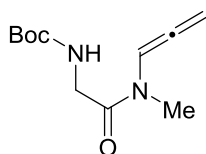
Reaction time: 1 min. Eluent: (6:4 light petroleum/AcOEt); Yield: 85%. Yellow oil. IR: 3460, 1925, 1709, 1644 cm^{-1}; Mixture of two rotamers in ratio 3:2; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.38 (s, 9H), 2.98 (s, 3H), 4.04 (br s, 2H), 5.35-5.37 (m, 2H), 5.50 (br s, 1H, missing after deuteration), 7.40-7.43 (m, 1H) (major rotamer); 1.38 (s, 9H), 2.99 (s, 3H), 4.05 (br s, 2H), 5.35 (d, J = 2.5 Hz, 2H), 5.36 (d, J = 2.5 Hz, 1H), 5.50 (br s, 1H, missing after deuteration), 6.54-6.59 (m, 1H) (minor rotamer); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.2 (q), 31.5 (q), 42.3 (t), 79.6 (s), 87.6 (t), 99.6 (d), 155.8 (s), 166.9 (s), 202.0 (s) (major rotamer); 28.2 (q), 31.3 (q), 42.8 (t), 79.2 (s), 86.9 (t), 99.5 (d), 156.6 (s), 171.0 (s), 201.2 (s) (minor rotamer). MS: m/z 226 (M$^+$). Anal. calcd for C$_{11}$H$_{18}$N$_2$O$_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.11; H, 8.32; N, 12.28.

### N-(tert-Butoxycarbonyl)-N'-tosyl-(1,2-propadienyl)-ethylenediamine 1d
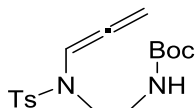
Reaction time: 4 min. Eluent: (6:4 light petroleum/AcOEt); Yield: 63%. Colourless oil. M. p. 95 °C. IR: 1950, 1634 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.45 (s, 9H), 2.41 (s, 3H), 3.27 (br s, 2H), 3.47 (br s, 2H), 4.92 (br s, 1H), 5.34 (dd, J = 12.6, 6.2 Hz, 2H), 6.83 (t, J = 6.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.5 (q), 28.3 (q), 37.7 (t), 38.6 (t), 80.6 (s), 88.2 (t), 100.4 (d), 127.1 (d), 127.6 (d), 129.2 (d), 129.8 (d), 134.5 (s), 143.9 (s), 154.6 (s), 200.1 (s). MS: m/z 352 (M$^+$). Anal. calcd for C$_{17}$H$_{23}$N$_2$O$_4$S: C, 58.67; H, 7.66; N, 7.06. Found: C, 58.15; H, 8.12; N, 7.28.

N-(tert-Butoxycarbonyl)-O-(1,2-propadienyl)-1,3-aminopropanol 1e
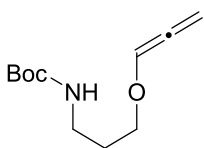
Reaction time: 20 min. Eluent: (8:2 light petroleum/AcOEt); Yield: 71%. Colourless oil. IR: 3287, 1955, 1704 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.44 (s, 9H), 1.79-1.85 (m, 2H), 3.23 (t, J = 6.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 4.73 (br s, 1H, missing after deuteration), 5.43 (d, J = 5.9 Hz, 2H), 6.71 (t, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 29.4 (t), 37.6 (t), 66.6 (t), 80.1 (s), 90.7 (t), 121.5 (d), 155.9 (s), 202.0 (s). MS: m/z 213 (M$^+$). Anal. calcd for C$_{11}$H$_{19}$NO$_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.24; H, 8.83; N, 6.27.

N-(tert-Butoxycarbonyl)-O-(1,2-propadienyl)-1,4-aminobutanol 1f
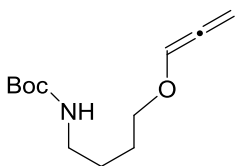
Reaction time: 15 min. Eluent: (9:1 light petroleum/AcOEt); Yield: 79%. Colourless oil. IR: 3252, 1954, 1702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.45 (s, 9H), 1.55-1.64 (m, 4H), 3.15 (t, J = 6.5 Hz, 2H), 3.54 (t, J = 6.2 Hz, 2H), 4.61 (br s, 1H, missing after deuteration), 5.42 (d, J = 5.9 Hz, 2H), 6.69 (t, J = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 26.4 (t), 28.3 (q), 40.2 (t), 68.3 (t), 78.9 (s), 90.5 (t), 121.5 (d),

155.9 (s), 201.4 (s). MS: m/z 227 (M$^+$). Anal. calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 62.98; H, 9.07; N, 6.34.

N-Methyl-*N*-(1,2-propadienyl)-(*tert*-butoxycarbonyl)-anthranilamide 1g
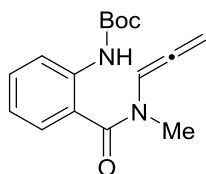
Reaction time: 1 min. Eluent: (4:1 light petroleum/AcOEt). Yield: 97%. Yellow oil. IR: 3326, 1953, 1701, 1652 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.52 (s, 9H), 3.13 (s, 3H), 5.40 (d, J = 6.3, 2H), 6.78 (bs, 1H), 7.04 (ddd, J = 7.9, 6.5, 1.2 Hz, 1H), 7.28 (dd, J = 7.7, 1.5 Hz, 1H), 7.39 (ddd, J = 7.9, 6.2, 1.6 Hz, 1H), 7.90 (br s, 1H), 8.16 (dd, J = 8.4, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 30.3 (q), 80.6 (s), 87.3 (t), 103.2 (d), 115.7 (s), 121.9 (d), 121.7 (d), 128.7 (d), 131.3 (d), 137.9 (s), 152.7 (s), 168.4 (s), 200.1 (s). MS: m/z 288 (M$^+$). These data are in good agreement with those reported in the literature.[155]

N-Methyl-*N*-(1,2-propadienyl)-tosylanthranilamide 1h
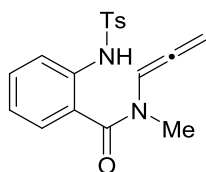
Reaction time: 1 min. Eluent: (7:3 light petroleum/AcOEt); Yield: 64%. Grey solid. M.p.: 125 °C IR: 3302, 1962, 1701 cm^{-1}; Mixture of two rotamers in 7:3 ratio; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 2.35 (s, 3H), 2.51 (s, 3H), 5.37 (br s, 2H), 6.04 (br s, 1H, missing after deuteration), 7.13-7.27 (m, 4H), 7.42 (t, J = 8.28 Hz, 1H), 7.60 (d, J = 6.8 Hz, 2H), 7.71 (d, J = 8.12 Hz, 1H), 8.40 (br s, 1H) (major rotamer); 2.35 (s, 3H), 2.99 (s, 3H), 5.37 (br s, 2H), 6.04 (br s, 1H, missing after deuteration), 7.13-7.27 (m, 4H), 7.42 (t, J = 8.28 Hz, 1H), 7.60 (d, J = 6.8 Hz, 2H), 7.71 (d, J = 8.1 Hz, 1H), 8.40 (br s, 1H) (minor rotamer); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.5 (q), 30.3 (q), 87.4 (t), 102.9 (d), 124.6 (d), 125.7 (d), 126.9 (d), 127.1 (d), 127.8 (d), 129.5 (d), 131.5 (d), 132.7 (d),133.3 (s), 144.0 (s), 144.8 (s), 160.9 (s), 167.3 (s), 199.8 (s) (major rotamer); 21.5 (q), 33.0 (q), 87.4 (t), 102.9 (d), 124.6 (d), 125.7 (d), 126.9 (d), 127.1 (d), 127.8 (d), 129.5 (d), 131.5 (d), 132.7 (d),133.3 (s), 144.0 (s), 144.8 (s), 160.9 (s), 167.3 (s), 199.8 (s) (minor

[155] G. Broggini, E. Borsini, A. Fasana, G. Poli, F. Liron, F. *Eur., J. Org. Chem.* **2012**, 3617-3624

rotamer). MS: *m/z* 342 (M$^+$). Anal. calcd for C$_{18}$H$_{18}$N$_2$O$_3$S: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.95; H, 5.42; N, 8.51.

**N-Methyl-N-(1,2-propadienyl)-(tert-butoxycarbonyl)-4-chloro-anthranilamide 1i**
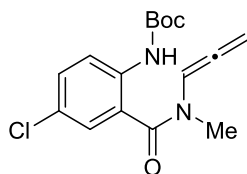
Reaction time: 1 min. Eluent: (9:1 light petroleum/AcOEt). Yield: 94%. Pale yellow oil. IR: 3345, 1954, 1701, 1652 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.52 (s, 9H), 3.15 (s, 3H), 5.42 (d, *J* = 6.0 Hz, 2H), 6.77 (br s, 1H), 7.26 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.27 (s, 1H), 7.91 (s, 1H), 8.14 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 31.9 (q), 80.9 (s), 87.5 (t), 102.9 (d), 126.9 (s), 122.3 (d), 129.3 (s), 131.2 (d), 136.5 (s), 152.6 (s), 167.0 (s), 200.2 (s). MS: *m/z* 321 (M$^+$). These data are in good agreement with those reported in the literature.[155]

N-Benzyl-N-(1,2-propadienyl)-(tert-butoxycarbonyl)-anthranilamide 1j
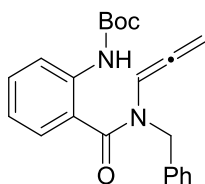
Reaction time: 1 min. Eluent: (9:1 light petroleum/AcOEt). Yield: 89%. Pale yellow oil. IR: 3360, 1947, 1702, 1652 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.53 (s, 9H), 4.90 (br s, 2H), 5.29 (d, *J* = 6.1 Hz, 2H), 6.73 (br s, 1H), 7.00-7.42 (m, 8H), 7.97 (br s, 1H), 8.15 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 47.7 (t), 80.6 (s), 87.6 (t), 102.4 (d), 121.3 (d), 122.0 (d), 125.3 (s), 127.2 (d), 127.8 (d), 128.5 (d), 131.3 (d), 137.1 (s), 137.6 (s), 152.8 (s), 168.4 (s), 200.5 (s). MS: *m/z* 364 (M$^+$). These data are in good agreement with those reported in the literature.[155]

N-(tert-Butoxycarbonyl)-O-[3-phenyl-(1,2-propadienyl)]-1,2-aminoethanol 1k
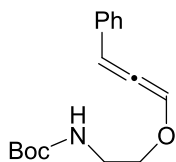
Reaction time: 15 min. Eluent: (9:1 light petroleum/AcOEt); Yield: 73%. Colourless oil. IR: 3287, 1967, 1704 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.30 (s, 9H), 3.05-3.21 (m, 2H), 3.58-3.73 (m, 2H), 5.09 (br s, 1H, missing after deuteration), 6.77 (d, J = 5.6 Hz, 1H), 7.04 (d, J = 5.6 Hz, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.4 (q), 39.9 (t), 65.8 (t), 79.3 (s), 108.8 (d), 123.5 (d), 127.1 (d), 128.2 (d), 128.8 (d), 134.9 (s), 155.8 (s), 194.7 (s). MS: m/z 275 (M$^+$). Anal. calcd for C$_{16}$H$_{21}$NO$_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.71; H, 7.43; N, 5.38.

N-(*tert*-Butoxycarbonyl)-*O*-(1,2-propadienyl)-2-aminophenol 1o
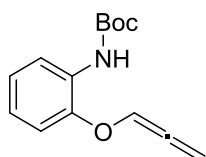
Reaction time: 5 min. Eluent: (4:1 light petroleum/AcOEt). Yield: 84%. Colourless oil. IR: 3510, 1962, 1522 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.52 (s, 9H), 5.48 (d, J = 5.9 Hz, 2H), 6.81 (t, J = 5.9 Hz, 1H), 6.94-7,09 (m, 4H), 8.11 (d, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.6 (q), 80.7 (t), 90.4 (s), 115.7 (d), 118.4 (d), 119.1 (d), 112.4 (d), 123.7 (d), 129.6 (s), 145.4 (s), 152.8 (s), 202.7 (s). MS: m/z 247 (M$^+$). Anal calcd for C$_{14}$H$_{17}$NO$_3$: C, 68.02; H, 6.93; N, 5.66. Found: C, 67.93, H, 7.01; N, 5.71.

General procedure for the preparation of allenes 1l-n
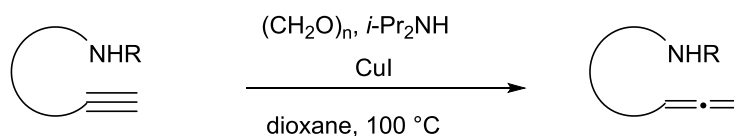
Diisopropylamine (2 mmol), paraformaldehyde (2 mmol) and CuI (0.2 mmol) were added to a suspension of the corresponding alkynyl derivative (1 mmol) in dioxane (20 mL). The solution was stirred under reflux for 5 hours. The solvent was removed under reduced pressure and the crude mixture purified by silica gel column chromatography.

**N-(*tert*-Butoxycarbonyl)-*O*-(buta-2,3-dien-1-yl)-aminoethanol 1l**
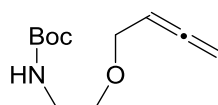
Eluent: (7:3 light petroleum/AcOEt); Yield: 34%. Yellow oil. IR: 3326, 1632, 1534 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.46 (s, 9H), 3.30-3.33 (m, 2H), 3.51 (t, J = 5.1 Hz, 2H), 4.02 (dt, J = 6.7, 2.5 Hz, 2H), 4.80 (dt, J = 6.7, 2.5 Hz, 2H), 4.89 (br s, 1H, missing after deuteration), 5.19-5.23 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.4 (q), 29.7 (t), 40.4 (t), 68.7 (t), 75.8 (t), 79.3 (s), 87.5 (d), 155.9 (s), 209.2 (s). MS: m/z 213 (M$^+$). Anal. calcd for C$_{11}$H$_{19}$NO$_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.49; H, 9.17; N, 6.64.

N-(tert-Butoxycarbonyl)-hexa-4,5-dienylamine 1m
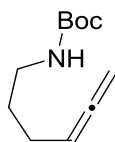
Eluent: (7:3 light petroleum/AcOEt); Yield: 24%. Colourless oil. IR: 3330, 1695, 1526 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.42 (s, 9H), 1.54-1.67 (m, 4H), 2.28-2.35 (m, 2H), 4.53 (br s, 1H, missing after deuteration), 4.69-4.72 (m, 2H), 5.52-5.54 (m, 1H),; ^{13}C NMR (100 MHz, CDCl$_3$) δ = 25.4 (t), 28.4 (q), 29.3 (t), 40.9 (t), 75.2 (t), 80.6 (s), 89.2 (d), 157.3 (s), 199.5 (s). MS: m/z 197 (M$^+$). Anal. calcd for C$_{11}$H$_{19}$NO$_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.59; H, 10.01; N, 7.39.

N′-Phenyl-N-methyl-N-(buta-2,3-dien-1-yl)urea 1n
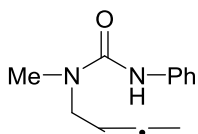
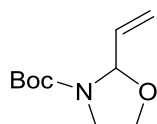Eluent: (7:3 light petroleum/AcOEt); Yield: 43%. Yellow oil. IR: 1715, 1595 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.02 (s, 3H), 3.98 (dt, J = 6.1, 2.9 Hz, 2H), 4.88 (dt, J = 6.1, 2.9 Hz, 2H), 5.12-5.29 (m, 1H), 6.51 (br s, 1H, missing after deuteration), 7.03 (t, J = 7.3 Hz, 1H), 7.17-7.32 (m, 2H), 7.37 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 34.7 (q), 47.8 (t), 77.1 (t), 86.8 (d), 119.8 (d), 123.0 (d), 128.9 (d), 129.2 (d), 139.1 (s), 155.4 (s), 208.7 (s). MS: m/z 201 (M$^+$). Anal. calcd for C$_{12}$H$_{14}$N$_2$O: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.13; H, 7.24; N, 13.57.

**General procedure for the ruthenium-catalyzed hydroamination of the allenes**

X = O, NR
PG = Boc, Ts
n = 0, 1, 2
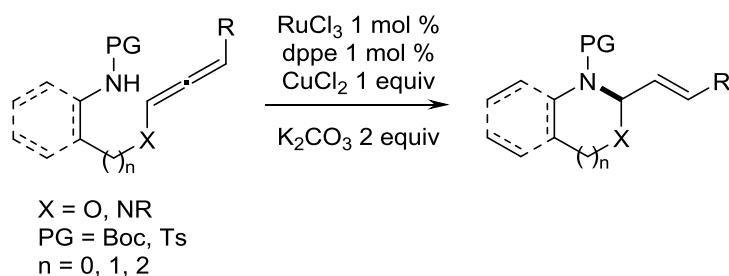
RuCl$_3$ (0.01 mmol), dppe (0.01 mmol), K$_2$CO$_3$ (2 mmol) and CuCl$_2$ (1 mmol) were added to a solution of the corresponding allene (**1a-k,** 1 mmol) in acetonitrile (5 mL). The solution was heated to reflux for 2 hours and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography.

3-(*tert*-Butoxycarbonyl)-2-vinyl-oxazolidine 2

Eluent: (7:3 light petroleum/AcOEt); Yield: 90%. Colourless oil. IR: 1685 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.40 (s, 9H), 3.30-3.35 (m, 1H), 3.56-3.60 (m, 1H), 3.89-3.98 (m, 2H), 5.21 (d, *J* = 10.3 Hz, 1H), 5.29-5.40 (m, 2H), 5.70-5.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 44.2 (t), 65.3 (t), 80.2 (s), 88.2 (d), 117.7 (t), 134.7 (d), 152.9 (s). MS: *m/z* 199 (M$^+$). Anal. calcd for C$_{10}$H$_{17}$NO$_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.67; H, 8.43; N, 7.39.

3-Tosyl-2-vinyl-oxazolidine 3
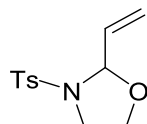
Eluent: (9:1 light petroleum/AcOEt); Yield: 89%. Yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 2.42 (s, 3H), 3.40-3.53 (m, 3H), 3.83-3.87 (m, 1H), 5.31 (dt, *J* = 10.3, 1.2 Hz, 1H), 5.51 (dt, *J* = 15.8, 1.2 Hz, 1H), 5.59 (d, *J* = 4.3 Hz, 1H), 5.78-5.86 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 24.5 (q), 46.1 (t), 65.1 (t), 90.2 (d), 116.6 (s), 118.5 (t), 127.8 (d), 129.8 (d), 134.5 (d), 144.2 (s). MS: *m/z* 253 (M$^+$). Anal. calcd for C$_{12}$H$_{15}$NO$_3$S: C, 56.90; H, 5.97; N, 5.53. Found: C, 57.19; H, 5.77; N, 5.69.

1-(*tert*-Butoxycarbonyl)-3-methyl-2-vinyl-imidazolidin-4-one 4
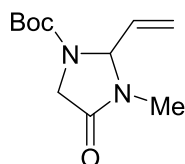
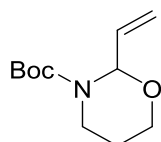Eluent: (7:3 light petroleum/AcOEt); Yield: 80%. Yellow oil. IR: 1708, 1671 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.47 (s, 9H), 2.80 (s, 3H), 3.86 (dd, J = 16.0, 0.4 Hz, 1H), 4.01 (d, J = 16.0 Hz, 1H), 5.21 (d, J = 7.2 Hz, 1H), 5.43 (dd, J = 9.9, 0.4 Hz, 1H), 5.45 (dd, J = 17.0, 0.4 Hz, 1H), 5.63 (ddd, J = 17.0, 9.9, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 26.5 (q), 28.3 (q), 47.8 (t), 76.2 (d), 81.2 (s), 121.3 (t), 133.9 (d), 152.0 (s), 167.7 (s). MS: *m/z* 226 (M$^+$). Anal. calcd for C$_{11}$H$_{18}$N$_2$O$_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.71; H, 7.78; N, 11.94.

1-(*tert*-Butoxycarbonyl)-3-tosyl-2-vinyl-imidazolidine 5
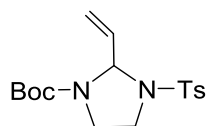
Eluent: (8:2 light petroleum/AcOEt); Yield: 61%. Colourless oil. IR: 1689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.42 (s, 9H), 2.42 (s, 3H), 2.93 (br s, 1H), 3.15 (t, J = 6.9 Hz, 1H), 3.42-3.49 (m, 1H), 3.72 (br s, 1H), 5.24 (d, J = 9.8 Hz, 1H), 5.33 (d, J = 16.8 Hz, 1H), 5.76-5.83 (m, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.28 (br s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.6 (q), 28.3 (q), 43.3 (t), 45.4 (t), 73.2 (d), 80.7 (s), 116.9 (t), 127.1 (d), 127.4 (d), 129.7 (d), 129.9 (d), 133.9 (s), 144.4 (s), 152.2 (s). MS: *m/z* 352 (M$^+$). Anal. calcd for C$_{17}$H$_{24}$N$_2$O$_4$S: C, 57.93; H, 6.86; N, 7.95. Found: C, 58.13; H, 6.58; N, 8.06.
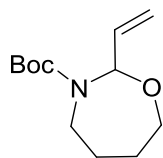
3-(*tert*-Butoxycarbonyl)-2-vinyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine 6

Eluent: (7:3 light petroleum/AcOEt); Yield: 71%. Colourless oil. IR: 1699 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.47 (s, 9H), 1.76-1.98 (m, 2H), 3.10 (dt, J = 13.0, 3.2 Hz, 1H), 3.72-3.76 (m, 1H), 3.88 (dt, J = 11.7, 2.7 Hz, 1H), 3.99-4.03 (m, 1H), 5.28 (d, J = 17.5 Hz, 1H), 5.38 (d, J = 10.7 Hz, 1H), 5.83-5.91 (m, 1H), 6.01-6.05 (br s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 25.2 (t), 28.4 (q), 37.6 (t), 60.6 (t), 79.9 (s),
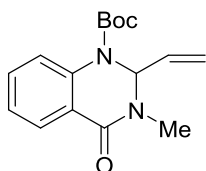
81.4 (d), 118.8 (t), 134.3 (d), 153.7 (s). MS: m/z 213 (M$^+$). Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.33; H, 8.57; N, 6.87.

3-(*tert*-Butoxycarbonyl)-2-vinyl-2,3,4,5,6,7-hexahydro-1,3-oxazepine 7

Yellow oil. IR: 1689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.46 (s, 9H), 1.54-1.61 (m, 4H), 3.11-3.14 (m, 2H), 3.38-3.44 (m, 1H), 3.52-3.61 (m, 1H), 5.16 (d, J = 9.6 Hz, 1H), 5.23-5.46 (m, 2H), 5.72-5.83 (m, 1H).

1-(*tert*-Butoxycarbonyl)-3-methyl-2-vinyl-1,2-dihydro-quinazolin-4(3*H*)-one 8

Eluent: (4:1 light petroleum/AcOEt). Yield: 90%. White solid. M.p.: 121 °C. IR: 1702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.50 (9H, s), 3.15 (3H, s), 5.20 (dd, J = 0.7, 6.8 Hz, 2H), 5.64-5.73 (m, 1H), 6.11 (d, J = 3.7 Hz, 1H), 7.16-7.19 (m, 1H), 7.41-7.44 (m, 1H), 7.50 (d, J = 6.0 Hz, 1H), 8.01 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.2 (q), 32.9 (q), 70.9 (d), 83.0 (s), 118.6 (t), 122.4 (s), 123.7 (d), 124.5 (d), 127.7 (d), 131.6 (d), 132.2 (d), 137.5 (s), 155.0 (s), 162.3 (s). MS: m/z 288 (M$^+$).

These data are in good agreement with those reported in the literature.[155]

3-Methyl-1-tosyl-2-vinyl-1,2-dihydro-quinazolin-4(3*H*)-one 9
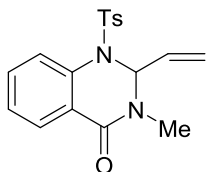
Eluent: (9:1 light petroleum/AcOEt); Yield: 72%. Colourless oil. IR: 1705 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 2.35 (s, 3H), 2.83 (s, 3H), 5.13 (dd, J = 17.0, 1.6 Hz, 1H), 5.21 (dd, J = 10.3, 1.6 Hz, 1H), 5.70 (ddd, J = 17.0, 10.3, 4.4 Hz, 1H), 5.92 (d, J = 4.4 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H),

7.11 (td, J = 7.6, 1.1 Hz, 1H), 7.57 (td, J = 7.5, 1.6 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 21.6 (q), 33.1 (q), 73.2 (d), 119.1 (t), 124.9 (s), 126.9 (d), 127.4 (d), 127.9 (d), 129.6 (d), 131.7 (d), 132.9 (d), 133.0 (d), 134.2 (s), 135.9 (s), 144.8 (s), 161.1 (s). MS: m/z 343 (M$^+$). Anal. calcd for C$_{18}$H$_{18}$N$_2$O$_3$S: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.87; H, 5.46; N, 8.32.


1-(*tert*-Butoxycarbonyl)-6-chloro-3-methyl-2-vinyl-1,2-dihydro-quinazolin-4(3*H*)-one 10
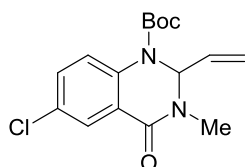
Eluent: (4:1 light petroleum/AcOEt). Yield: 68%. White solid. M.p.: 120 °C. . IR: 1706, 1655 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.53 (s, 9H), 3.47 (s, 3H), 5.15-5.21 (m, 2H), 5.66 (ddd, J = 15.5, 10.3, 3.6 Hz, 1H), 6.05 (br s, 1H), 7.38 (dd, J = 8.7, 2.5 Hz, 1H), 7.50 (d, J = 6.3 Hz, 1H), 7.97 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.2 (q), 33.1 (q), 70.0 (d), 83.4 (s), 118.9 (t), 123.7 (s), 125.2 (d), 127.5 (d), 130.2 (s), 131.3 (d), 131.9 (d), 136.0 (s), 151.4 (s), 161.3 (s). MS: m/z 322 (M$^+$).
These data are in good agreement with those reported in the literature.[155]

**3-Benzyl-1-(*tert*-butoxycarbonyl)-2-vinyl-1,2-dihydro-quinazolin-4(3*H*)-one 11**
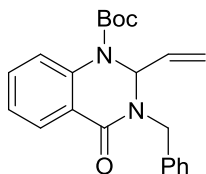
Eluent: (4:1 light petroleum/AcOEt). Yield: 61%. Yellow oil. . IR: 1705, 1644 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.34 (s, 9H), 5.17-5.21 (m, 2H), 5.59 (br s, 2H), 5.70 (ddd, J = 16.8, 8.9, 5.4 Hz, 1H), 6.05 (br s, 1H), 7.21-7.25 (m, 2H), 7.31-7.37 (m, 4H), 7.47 (ddd, J = 7.5, 6.0, 1.6 Hz, 1H), 7.60 (br s, 1H), 8.07 (dd, J = 7.8, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 27.9 (q), 47.7 (t), 68.3 (d), 82.6 (s), 118.6 (t), 122.6 (s), 123.5 (d), 124.5 (d), 127.8 (d), 128.1 (d), 128.3 (d), 128.8 (d), 131.8 (d), 132.3 (d), 136.6 (s), 137.6 (s), 152.0 (s), 164.9 (s). MS: m/z 364 (M$^+$). These data are in good agreement with those reported in the literature.[155]

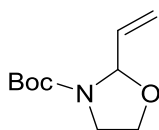### 3-(*tert*-Butoxycarbonyl)-2-(beta-styryl)-oxazolidine 12
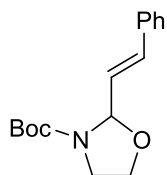
Eluent: (4:1 light petroleum/AcOEt); Yield: 63%. Yellow oil. IR: 1674 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.48 (s, 9H), 3.43-3.48 (m, 1H), 3.66-3.74 (m, 1H), 3.57-4.02 (m, 1H), 4.07-4.13 (m, 1H), 5.66 (d, *J* = 5.6 Hz, 1H), 6.15 (dd, *J* = 15.8, 5.6 Hz, 1H), 6.70 (d, *J* = 15.8 Hz, 1H), 5.25-5.41 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.4 (q), 44.4 (t), 65.5 (t), 80.4 (s), 88.2 (d), 125.9 (d), 126.8 (d), 128.1 (d), 128.6 (d), 133.0 (d), 136.1 (s), 153.1 (s). MS: *m/z* 275 (M$^+$). Anal. calcd for C$_{16}$H$_{21}$NO$_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.38; H, 7.41; N, 4.80.

### General procedure for the rhodium-catalyzed hydroamination of the allenes

X = O, NR
PG = Boc, Ts
n = 0, 1, 2
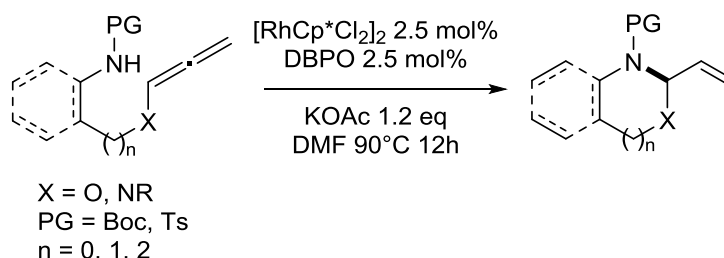
[RhCp*Cl$_2$]$_2$ (0.025 mmol), DBPO (0.025 mmol) and KOAc (1.2 mmol) were added to a solution of the corresponding allene **1a-e, 1g-h, 1o** (1 mmol) in dimethylformamide (5 mL). The solution was heated for 12 hours at 90°C and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography.

3-(*tert*-Butoxycarbonyl)-2-vinyl-oxazolidine 2

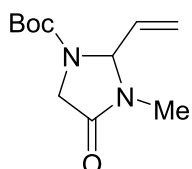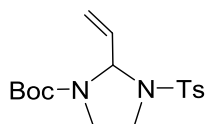

Yield: 65%

3-Tosyl-2-vinyl-oxazolidine 3
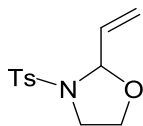
Yield: 45%

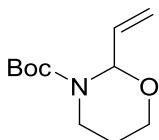**1-(*tert*-Butoxycarbonyl)-3-methyl-2-vinyl-imidazolidin-4-one 4**

Yield: 47%

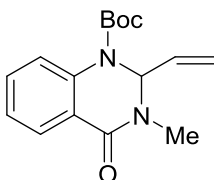**1-(*tert*-Butoxycarbonyl)-3-tosyl-2-vinyl-imidazolidine 5**

Yield: 15%

3-(*tert*-Butoxycarbonyl)-2-vinyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazine 6
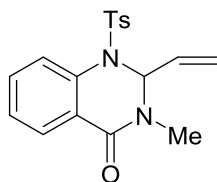

Yield: 50%

1-(*tert*-Butoxycarbonyl)-3-methyl-2-vinyl-1,2-dihydro-quinazolin-4(3*H*)-one 8

Yield: 39%

3-Methyl-1-tosyl-2-vinyl-1,2-dihydro-quinazolin-4(3H)-one 9

Yield: 44%

3-(tert-Butoxycarbonyl)-2-vinyl-2,3-dihydro-benzoxazole 13
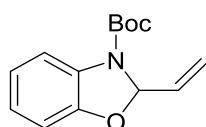
Eluent: (4:1 light petroleum/AcOEt). Yield: 46%. Colourless oil. IR: 1702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.49 (s, 9H), 5.39 (d, J = 10.3 Hz, 1H), 5.50 (d, J = 16.9 Hz, 1H), 5.96 (ddd, J = 16.9, 10.3, 6.1 Hz, 1H), 6.47 (d, J = 6.1 Hz, 1H), 6.95-6.84 (m, 3H), 7.36 (br s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.7 (q), 82.6 (s), 93.8 (d), 109.5 (d), 114.4 (d), 120.6 (t), 122.2 (d), 124.2 (d), 131.2 (s), 133.8 (d), 150.5 (s). MS: m/z 247 (M$^+$). Anal calcd for C$_{14}$H$_{17}$NO$_3$: C, 67.89; H, 6.73; N, 5.96. Found: C, 67.96, H, 6.95; N, 5.81.

General procedure for the rhodium-catalyzed amino-alcoxylation of the allenes
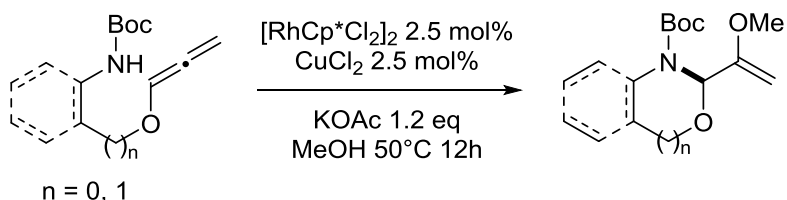
[RhCp*Cl$_2$]$_2$ (0.025 mmol), CuCl$_2$ (0.025 mmol) and KOAc (1.2 mmol) were added to a solution of the corresponding allene (1 mmol) in methanol (4 mL). The solution was heated for 12 hours at 50°C and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography.

3-(*tert*-Butoxycarbonyl)-2-(1-methoxy-vinyl)-oxazolidine 14
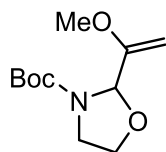

Eluent: (7:3 light petroleum/AcOEt); Yield: 46%. Colourless oil. IR: 1704, 1150cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.59 (s, 9H), 3.35-3.37 (m, 5H), 3.55-3.57 (m, 1H), 3.61-3.65 (m, 1H), 4.82 (s, 1H), 5.52 (s, 1H), 5.68 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 28.3 (q), 44.2 (t), 56.5 (q), 65.3 (t), 80.2 (s), 88.2 (d), 117.7 (t), 134.7 (d), 152.9 (s). MS: *m/z* 229 (M$^+$). Anal. calcd for C$_{11}$H$_{19}$NO$_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 58.13; H, 7.99; N, 6.34.

3-(*tert*-Butoxycarbonyl)-2-(1-methoxy-vinyl)-3,4,5,6-tetrahydro-2*H*-1,3-oxazine 15
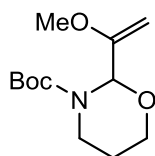
Eluent: (7:3 light petroleum/AcOEt); Yield: 41%. Yellow oil. IR: 1698, 1143 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.44 (s, 9H), 1.78-1.81 (m, 2H), 3.25-3.27 (m, 2H), 3.35 (s, 3H), 3.52-3.55 (m, 1H), 3.61-3.67 (m, 1H), 4.19 (d, *J* = 2.4 Hz, 1H), 4.41 (d, *J* = 2.4 Hz, 1H), 4.73 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 25.2 (t), 28.4 (q), 37.6 (t), 56.2 (q), 60.6 (t), 79.9 (s), 81.4 (d), 118.8 (t), 134.3 (d), 153.7 (s). MS: *m/z* 243 (M$^+$). Anal. calcd for C$_{12}$H$_{21}$NO$_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.87; H, 8.61; N, 5.92.

3-(*tert*-Butoxycarbonyl)-2-(1-methoxy-vinyl)-2,3-dihydro-benzoxazole 16

Yellow oil. IR: 1694, 1163 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ = 1.54 (s, 9H), 3.33 (s, 3H), 4.97 (s, 1H), 5.45 (s, 1H) 5.53 (d, *J* = 1.4 Hz, 1H), 6.47 (m, 1H), 6.95-6.84 (m, 3H).

Chapter 3: Synthesis of new Rhodium(III) complexes and their application to Amination and Hydroamination reactions

3.1. About rhodium and its complexes

Rhodium is the 45th element of the periodic table, naturally occurring as the free metal, alloyed with similar metals and rarely in minerals. It is a noble metal belonging to palladium group and it was discovered in 1803 by W. H. Wollaston. Rhodium is a relatively rare and expensive metal, yet its organometallic complexes have played an extremely important role in transition-metal catalysis and organic synthesis. The use of rhodium catalysts in synthetic organic chemistry has been one of the most active research areas of the last fifty years and continues to be extensively investigated at the present time. Among the most important reactions are hydrogenation, hydroformylation, oligomerization, isomerization, hydroboration and hydrosilation of multiple bonds, which are extremely useful in organic synthesis in order to obtain a great variety of different structures.[156] In industry, a number of processes currently used for the syntheses of pharmaceuticals as well as fine chemicals are based on the catalytic activity of rhodium complexes.

Organorhodium complexes are normally encountered in oxidation states +1 or +3, although complexes of other oxidation states between +4 and -3 have also been synthesized. Complexes of rhodium(I) (d^8) often possess either tetra-coordinate square-planar or penta-coordinate trigonal-bipyramidal structures, while those of rhodium(III) (d^6) are usually octahedral (Figure 10).

Rh (I)   **Rh (III)**

Figure 10

Ligand dissociation of penta- to tetra-coordinate complexes is often proposed as a means of generating open-coordination sites for binding of substrates in catalytic reactions. A key feature of organorhodium chemistry is the facile oxidative addition to tetra-coordinate rhodium(I) and the reductive elimination from octahedral rhodium(III). It is the reversibility of such reactions connecting the rhodium(I) and rhodium(III) oxidation states that brings about the powerful catalytic activity of

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[156] P. Hofmann, C. Meier, W. Hiller, *J. Organomet. Chem.,* **1995**, 490, 51; K. Riener, M. Hogerl, P. Gigler, *ACS Catal.,* **2012**, 2, 613; A. Carroll, T. O'Sullivan, T. Guiry, *Adv. Synth. Cat.,* **2005**, 347, 609; I. Piras, R. Jenneriah, M. Beller, *J. Organomet. Chem.* **2010**, 695, 479.

organorhodium complexes to promote a wide range of organic transformations. The transition between oxidation states (I) and (III) differentiate the behaviour of rhodium complexes from that of other classically employed transition metals such as palladium or ruthenium, whose complexes usually shifts between oxidation states (0) and (II).

Most rhodium(III) and many rhodium(I) complexes are relatively air-stable. However, in many instances, reactions involving presumably "air-stable" rhodium complexes give inconsistent results. Thus, it is highly recommended that all rhodium complexes to be used in catalytic reactions should be stored in an inert atmosphere.

The toxicity of rhodium complexes has not been thoroughly investigated. However, it appears that most organorhodium complexes are not particularly toxic, although some of them have been shown to exhibit antitumor activity and have been used in cancer chemotherapy (Figure 11).
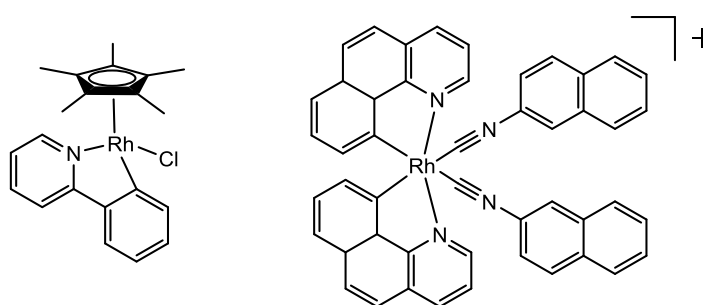
Figure 11

Ruiz et al.[157] recently reported that rhodium(III) complexes with the *C,N*-chelating ligand ppy (2-phenyl-pyridine) showed interesting citotoxicity and anticancer activity, in addition they are cathepsin B inhibitors. Leung et al.[158] synthesized cyclometalated rhodium complexes, that exhibited citotoxicity toward human erythroleukemia (HEL) cancer cells.

Rhodium-mediated reactions are also attractive in the outlook of Green Chemistry, since they could tolerate processes in which water acts as co-solvent, or even as the sole solvent.

3.1.1. Cyclopentadienyl rhodium complexes

Among commercially available rhodium(III) catalysts, those bearing a cyclopentadienyl ligand are of remarkable importance, since cyclopentadienyl and pentamethylcyclopentadienyl ligands are

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[157] J. Ruiz, V. Rodriguez, N. Cutillas, K. G. Samper, M. Capdevila, O. Palacios, A. Espinosa, *Dalton Trans.*, **2012**, 41, 12847.
[158] C. H. Leung, H. Yang, V. P. Ma, D. S. Chan, H. J. Zong, Y. W. Li, W. F. Fong, *Med. Chem. Commun.*, **2012**, 3, 696.

ubiquitous in organotransition-metal chemistry. Complexes of these ligands are well known for all transition and most of the f-block metals,[159] owing to the great stability of the η^5-cyclopentadienyl binding mode. In most organometallic reactions of transition-metal complexes the η^5-cyclopentadienyl ligand plays the role of spectator, staying tightly bound to the metal center throughout the curse of the reaction.

There are many methods for preparing cyclopentadienylrhodium complexes. Most of these methods rely on the acidity of cyclopentadiene ($pK_a = 9$) and often involve reactions of cyclopentadienyl anions with rhodium halide complexes.

Between cyclopentadienyl complexes of rhodium, a large portion displays a "half-sandwich" structure, referring to complexes that contain only one cyclopentadienyl group together with other ligands. It is worth to remember that cyclopentadienyl anions tricoordinatively bound to rhodium. The most important complex of this series is dicarbonyl(cyclopentadienyl)rhodium, which has been used as catalyst in a number of organic reactions including hydroformylation, hydrogenation, and cyclotrimerization of alkynes.[160] As mentioned, the primary method for synthesizing cyclopentadienylrhodium complexes involves nucleophilic displacement of rhodium halides with cyclopentadienyl anions. The simplest method to prepare half-sandwich complexes is from dicarbonylchlororhodium(I) dimer and lithium (or sodium) cyclopentadienide (Scheme 56).

$$Rh_2Cl_2(CO)_4 \xrightarrow{\ C_5H_4^- \ } $$
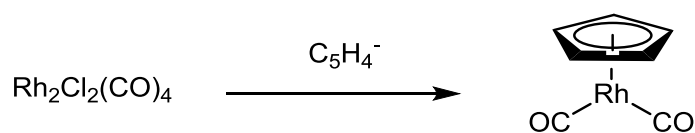
Scheme 56

It is possible to replace one of the carbonyl ligands of this complex by Lewis base ligands, like phosphines, phosphites or isocyanides under thermal conditions,[161] leading to a huge number of different complexes. The rate of these reactions are slow because $RhCp(CO)_2$ is coordinatively saturated, but can be enhanced by the presence of electron-withdrawing substituents on the cyclopentadienyl ring, which increase the stability of the "ring-slipped" intermediate.[162]

Similarly, sandwich complexes can also be prepared. The first one was synthesized by reacting tris(acetylacetonato)rhodium(III) with cyclopentadienyl anion.[163] A later preparation using

[159] T. J. Marks, *Prog. Inorg. Chem.*, **1979**, 25, 223.
[160] E. O. Fischer, K. Z. Bittler, *Naturforsch, Teil B.*, **1961**, 16, 225.
[161] H. G. Schuster-Woldan, F. J. Basolo, *Am. Chem. Soc.*, **1966**, 88, 1657.
[162] D. L. Lichtenberger, S. K. Renshaw, F. J. Basolo, M. Cheong, *Organometallics*, **1991**, 10, 148.
[163] F. A. Cotton, R. O. Whipple, J. Wilkinson, *J. Am. Chem. Soc.*, **1953**, 75, 3586.

rhodium(III) chloride in place of tris(acetylacetonato)rhodium(III) provides a cleaner synthesis (Scheme 57).

RhCl$_3$ + CpMgBr

X = BF$_3$, PF$_6$
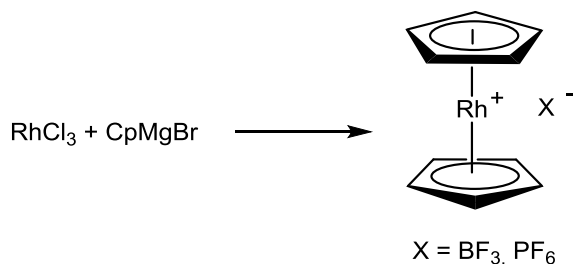
Scheme 57

The pentamethylcyclopentadienyl ligand is widely utilized in transition-metal complexes compared to its less substituted analogues as a consequence of the greater binding stability of the pentamethylcyclopentadienyl ligand. This stability may be attributed to the electron-donating effect of the five methyl groups that help stabilize the cationic species. The steric bulk of the pentamethyl cyclopentadienyl ligand presumably also adds some kinetic stability to the otherwise reactive rhodium center. Thus, while the cyclopentadienyl ligand is easily removed from the rhodium center under acidic conditions or in the presence of hydrogen, the corresponding more substitute ligand survives both under acidic and basic, as well as reductive and oxidative, conditions.[164] The pentamethyl cyclopentadienyl rhodium complexes, particularly in the +3 oxidation state, are normally air stable.

The forefather of this class of complexes is pentamethyl cyclopentadienyl rhodium dichloride dimer, that can be utilized in the preparation of many others. It was first synthesized by Kang and Moseley in 1969, through the reaction of rhodium trichloride trihydrate with hexamethyl substituted Dewar benzene[165] (Scheme 58). Discovery of this synthetic route was something serendipitous.

RhCl$_3$·3H$_2$O   +

MeOH, 65°C, 15h
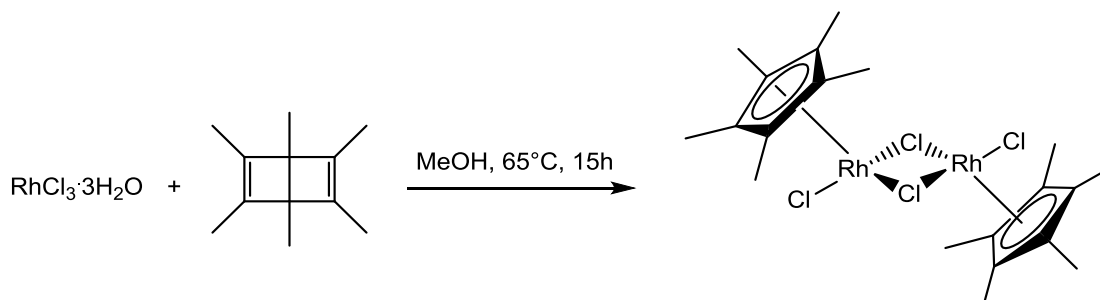
Scheme 58

[164] P. M. Maitlis, *Acc. Chem. Res.*, **1978**, 11, 301.
[165] J. W. Kang, K. Moseley, P. M. Maitlis, *J. Am. Chem. Soc.*, **1969**, 91, 5970.

In the dimeric structure both metal centers are coordinatively saturated, so during the reactions the dimer splits in order to show a free coordination site on the rhodium atoms, giving rise to catalytic activity. Pentamethyl cyclopentadienyl rhodium dichloride dimer has been used as a catalyst for hydrogenation of alkenes and alkynes, disproportionations, aminations and many others.[166]

The dimeric framework can also be cleaved by bridge splitting reactions upon treatment with donor ligands like phosphines, pyridine, phosphates, isocyanides, to give neutral monomeric Cp* rhodium complex.[167]

3.2. Synthesis of new rhodium complexes

In principle, asymmetric catalysis is the most efficient strategy to produce enantiopure compounds, requiring only catalytic amounts of metal complexes bearing chiral ligands. These ligands must possess suitable three-dimensional structure and functionality to generate the desired reactivity and selectivity. In this way, a chiral catalyst can permit kinetically precise discrimination among the enantiotopic atoms, groups or faces in chiral molecules.[168]

Two significant challenges pertain to asymmetric catalysis: discovering new catalytic reactions and inventing effective chiral catalysts. In this chapter we tried to deal with the second one.

As previously reported, the catalytic activity of [RhCp*Cl$_2$]$_2$ arise from the splitting of the dimeric complex when added to the reaction media, releasing a free coordination site on each rhodium center (Figure 12). Observing the structure of the "catalytically active" RhCp*Cl$_2$ complex, it is possible to identify two different ways to introduce a chiral moiety into its structure, possibly without affecting the activity of the catalyst. The first one is to replace the chloride atoms with an enantiopure bidentate ligand, while the second one deals with the modification or the substitution of the cyclopentadienyl ligand.
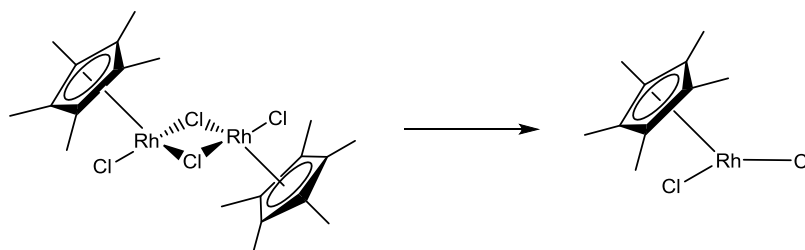

Figure 12

[166] J. Cook, J. E. Hamlin, A. Nutton, P. M. Maitlis, *J. Chem. Soc., Chem. Commun.*, **1980**, 144.
[167] W. Rigby, J. A. McCleverty, P. M. Maitlis, *J. Chem. Soc., Dalton Trans.*, **1979**, 382; J. A. McCleverty, J. Williams, *Transition Met. Chem.*, **1978**, 3, 201.
[168] P. Espinet, K. Soulantica, *Coord. Chem. Rev.*, **1999**, 193, 499.

Reactivity and selectivity of the newly synthesized rhodium(III) complexes were investigated in two reactions involving the formation of a new stereocenter. The first one is the intramolecular cyclization of O-allenyl N-Boc-2-aminoethanol through an hydroamination pathway, described in the previous chapter under both ruthenium and rhodium catalysis, in which the stereocenter is formed at the carbon atom in 2-position. The second one is a benchmark reaction, reported by Guimond and coworkers using [RhCp*Cl$_2$]$_2$ as the catalyst, that involves the formation of a 3,4 dihydroisoquinolone by intermolecular reaction of a protected hydroxamic acid with styrene. This kind of reaction, involving the presence of an internal oxidant, have been deeply investigated by the groups of Cramer, Glorius and Fagnou, and lead to the formation of a new stereocenter at the carbon atom in 3-position (Scheme 59).
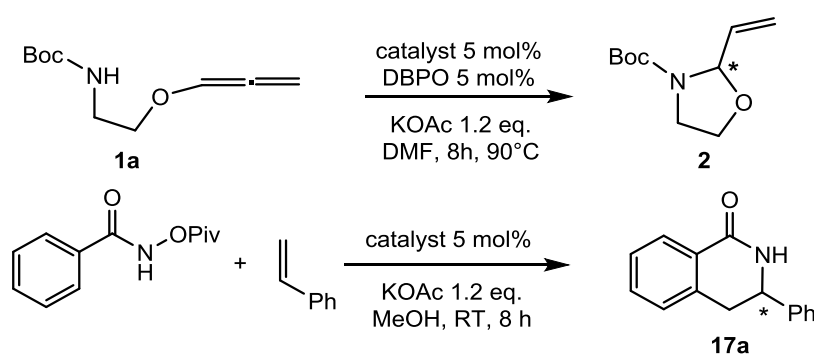
Scheme 59

3.2.1 Replacement of chlorides

A common approach to the control of stereoselectivity has relied on the use of molecules that possess only symmetry elements of pure rotation, belonging to the C_n or the D_n symmetry groups. These molecules could allow the prediction of enantioselectivity, due to the presence in the reaction environment of only a single defined reactive species. Under these assumptions, in the last thirty years interest in the application of chiral atropoisomers, especially binaphtalene systems, has greatly blossomed.[169]

However, to achieve the desired selectivity for a catalytic reaction of interest, the catalyst must be optimized and adjusted to the particular problem. Especially in the field of metal-complex catalysis, the choice of the most suitable ligand, shaping the microenvironment at the catalytically active metal centre, is crucial. Despite significant progress in the field of theoretical and

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[169] C. Rosini, L. Franzini, A. Raffaelli, P. Salvadori, *Synthesis*, **1992**, 503; M. Slany, P. J. Stang, *Synthesis*, **1996**, 1019.

computational chemistry, there is still no rational way to model from scratch the best ligand for a given reaction and selectivity problem. So far, finding the optimal ligand is an unpredictable high-risk endeavor, which is driven to a large extent by various combinations of intuition, experience, hard labor, and in some cases serendipity.

For bidentate ligands, the concept of bite-angle is of great importance. The bite angle is defined as the angle formed by two bonds existing between a metal center and two ligand atoms. It is well known that catalytic activity of the final catalyst is depending on the bite angle, but despite many studies have been undertaken in order to understand how exactly reactions are affected by variations of the bite angle[170] it is still not possible to exactly predict the activity and selectivity of a catalytic system.

Bidentate ligands containing a binaphthyl moiety are widely employed in asymmetric reactions. Use of BINAP and BINOL phosphorus- and oxygen-based ligands has greatly blossomed through the years, representing very powerful tools for asymmetric reactions. The importance of these ligands is confirmed by the huge number of papers about their chemistry, and synthesis and activity of many substituted analogs. In this perspective, we chose simple BINAP and BINOL ligands as adequate replacement of chloride atoms and chiral inducers in the RhCp* complex. After obtaining the new rhodium(III) complexes, their activity and selectivity could be tested in the two selected benchmark reactions previously reported. In this section, we will consider the synthesis of simple and/or substituted BINAP and BINOL systems, and the synthesis and behaviour of the BINAP- and BINOL-RhCp* complexes.

3.2.1.1. Bidentate P,P and O,O ligands: BINAP and BINOL

BINAP and its derivatives

BINAP is one of the rare chiral ligands produced on an industrial scale. It was discovered by Noyori in 1980,[171] and immediately found successful applications both from scientific and economic point of view, resulting in a huge number of papers dealing with the use or the synthesis of BINAP itself. Several large-scale asymmetric synthesis are now carried out with BINAP, like for example the Takasago synthesis of (-)-menthol by asymmetric isomerization (Scheme 60). This process could be

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[170] S. Otsuka, *J. Organomet. Chem.,* **1980**, 200, 191; P. Dierkes, P. W. N. M. van Leeuwen, *J. Chem. Soc., Dalton Trans.,* **1999**, 1519; Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.,* **2003**, 1890; R. Fazaeli, A. Ariafard, S. Jamshidi, E. S. Tabatabaie, K. A. Pishro, *J. Organomet. Chem.,* **2007**, 692, 3984.
[171] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.*, **1980**, 102, 7932.

considered as one of the first demonstrations of large-scale industrial feasibility of asymmetric catalysis.
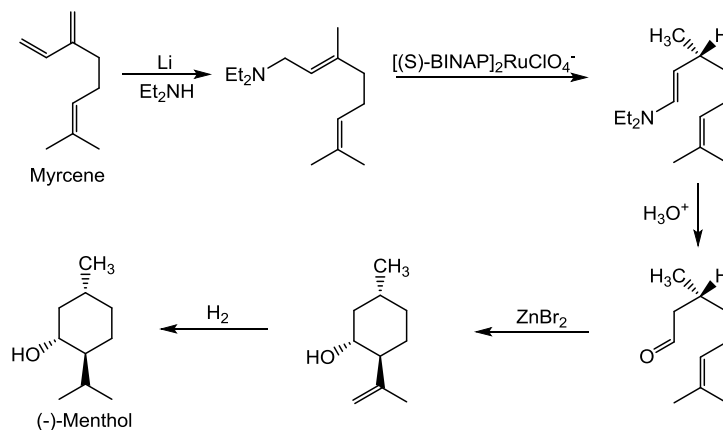
Scheme 60

Preparation of (-)-menthol is made starting from myrcene, and the catalyst [(S)-BINAP]$_2$RuClO$_4^-$ is used for the asymmetric isomerization of diethylgranylamine to 3-(R)-citronellal enamine before classical conversion to menthol. This was the first way patented by Takasago, more recently the manufacture of menthol has switched to the use of SEGPHOS.

In the first synthesis of BINAP reported by Noyori, as well as all the industrial methods for BINAP synthesis, the starting point was BINOL. In this case, the racemate was used. This was then converted under harsh conditions to dibromide with at best a moderate yield. Then through a Grignard coupling the bis-phosphine oxide was formed. This was resolved by fractional crystallization with camphorsulphonic acid or 2,3-di-*O*-benzoyltartaric acid into its optically pure isomers. A silane reduction lead then to BINAP (Scheme 61).
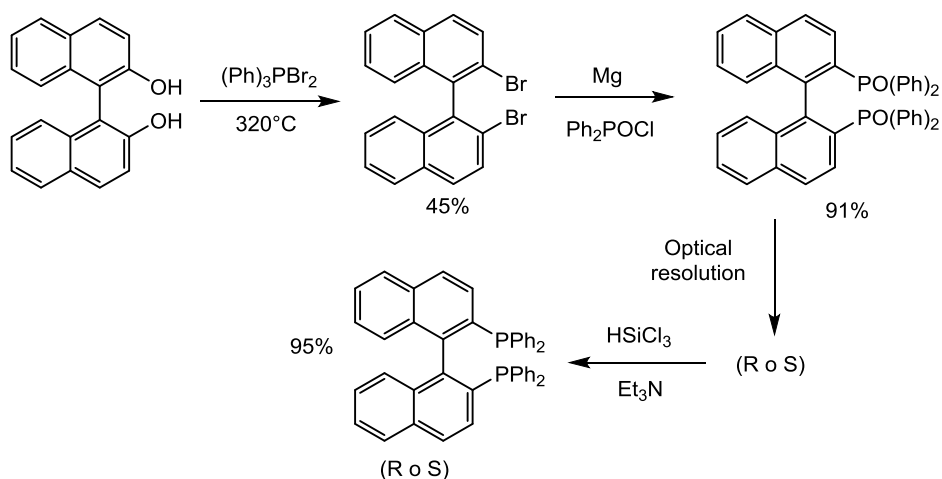
Scheme 61

This synthetic scheme represents the first successful way to obtain BINAP on a moderate scale. However, from a production point of view it is relatively long-winded compared to more recent methods. Also, the loss of more than half of the BINOL backbone in the bromination step means that the overall yield is poor. Similarly, the optical resolution near the end of the synthetic route implies that yield is halved again for each enantiomer.

A more recent method developed by Monsanto,[172] has the advantage of using industrially available diphenylchlorophosphine as starting material. In this case zinc metal is used as a reductant to generate the active Ni(0) catalyst. The phosphine is then reacted with chiral BINOL ditriflate in the presence of excess zinc to give the desired BINAP (Scheme 62).
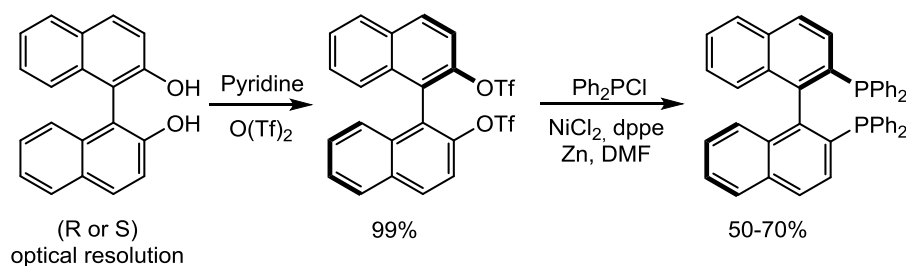
Scheme 62

The major advantage of the Monsanto process is the availability and ease of handling of the raw materials. The batch time is also shorter than that of Takasago route. The disadvantage of the system is that the yield is still quite low, however safety and efficiency advantages are predominant, so this method was implemented and became the largest scale route to BINAP. This route has been exclusively licensed to Rhodia for the production of hundred kilograms scale of BINAP.

Recently Merck Gmbh proposed another route,[173] that is indeed only a variation on the Monsanto route. In this path, they exploited the omission from Monsanto's patent of longer chain homologues of the triflate group. Thus, the substrate of the coupling reaction was no longer BINOL ditriflate but BINOL dinonaflate, and the process is extremely similar with the only different being the addition of DABCO as a base.

BINAP has been commercially available for several years now, but researchers are still working to find easier and cheaper synthetic methods for this important ligand. Moreover, many modifications of the structure of BINAP have been done to increase both efficiency (turnover) and selectivity (ee%), but also to facilitate separation from the bulk of the reaction. Aiming to this

[172] S. A. Laneman, *Chem. Commun.*, **1997**, 2359; Monsanto, U.S. Patent US 5,902,904, **1997**.
[173] Merck Darmstadt. PCT Int. Appl. WO 99/36387, **1999**.

objective, and taking into account BINAP's industrial potential, it is not surprising that many modern technologies that pursue easy separation and recycling are currently explored with BINAP.

Homogeneous supported catalysts with BINAP grafted onto organic or inorganic supports have been described, and polymers including the BINAP structure in the main chain have been proved to be efficient as well as selective catalytic precursors. In 2004, Kumar[174] grafted the (S,S)-1,2-diphenylethylenediamine (SDPEN) inside chloro-functionalized mesoporous silica (MCM) with high surface area and an ordered pore structure with a narrow pore size distribution, and then anchoring a Ru-(S)-BINAP complex (Scheme 63).
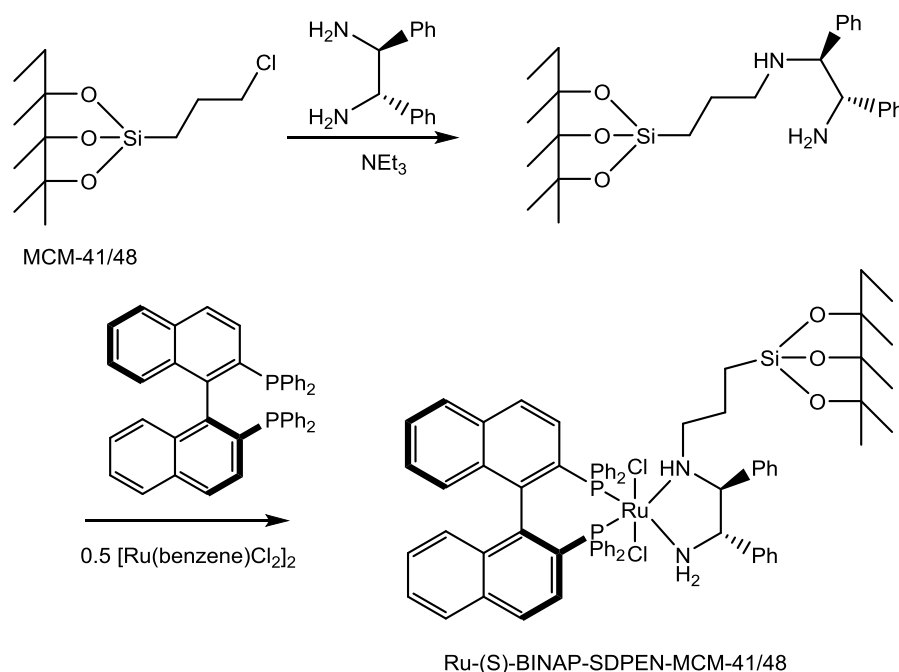
Scheme 63

A second possible approach in the development of supported catalysts is to functionalize the BINAP skeleton in order to anchor the diphosphine ligand onto the surface of silica support.

BINAP has been found to have astounding chiral recognition ability and large applicability in various transition-metal-catalyzed asymmetric reactions[175] such as hydrogenation,[176] hydrosilylation,[177] 1,3-hydrogen migration,[178] and much more. BINAP ruthenium catalysts are well recognized to be highly efficient in asymmetric hydrogenation of various functionalized olefins and

[174] A. Ghosh, R. Kumar, *J. Catal.*, **2004**, 228, 386.
[175] S. Akutagawa, *Appl. Catal. A.*, **1995**, 128, 171.
[176] I Ojima, *Catalytic Asymmetric Synthesis*, VCH Publishers New York, **1993**.
[177] S. H. Bergens, P. Nohada, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.*, **1992**, 114, 2121.
[178] K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, *J. Am. Chem. Soc.*, **1984**, 106, 5208.

ketones such as acrylic acids,[179] enamides,[180] allylic and homoallylic alcohols,[181] alkylidene lactones[182] and β-cheto esthers.[183]

But even if BINAP has shown excellent efficiency, its industrial applications remain relatively limited (about 20 applications).[184] Actually the reasons are due to the royalties to be paid to Noyori and Takasago. To avoid this problem, different approaches have been developed to increase activity of the catalyst and its recycling. In most cases, these approaches need BINAP functionalization to tune its steric and electronic properties and/or to heterogenize the catalyst. In order to functionalize BINAP many routes are possible. Both the phenyl groups and the naphtyl skeleton could be modified. Although modifications on phenyl groups has lead to success with increasing activity and selectivity, the naphtyl skeleton was mainly used to obtain easy separation and recycling of the catalyst from the bulk of the reaction.

BINAP ligands allow the formation of catalytic sites in which the chiral environment is controlled by classical steric and electronic factors, but also by the dihedral angle between the two aromatic cycles of the skeleton. The interest in modifying phenyl substituents generally results in the modification of the electronic properties of the phosphorus ligand. Both electronic effects and steric hindrance could be modified.

The first (R)- or (S)-BINAP derivatives were obtained from 2,2'-dibromo-1,1'-binaphthyl and diarylphosphinyl chloride, in a similar way than the first industrial synthesis of BINAP. With this method Noyori describes the synthesis of *p*-Tol-BINAP and *p*-t-Bu-BINAP.[185] These derivatives were tested as ruthenium complexes, and gave excellent results in the hydrogenation of citronellol with same selectivity and better activity than BINAP. Other derivatives were synthesized and compared to BINAP[186] (Figure 13).
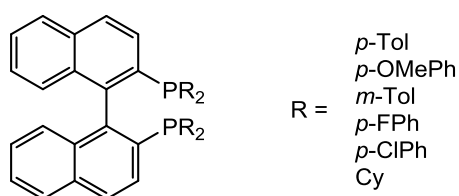
Figure 13

[179] W. D. Lubel, M. Kitamura, R. Noyori, *Tetrahedron Asymmetry*, **1991**, 2, 543.
[180] T. Ohta, H. Takaya, R. Noyori, *Tetrahedron Lett.*, **1990**, 112, 7189.
[181] M. Kitamura, Y. Hsiao, H. Takaya, *J. Org. Chem.,* **1994**, 59, 297.
[182] H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, I. Kasahara, *J. Am. Chem. Soc.*, **1987**, 109, 1596.
[183] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya. N. Sayo, *J. Am. Chem. Soc.*, **1987**, 109, 5856.
[184] H. U. Blaser, F. Spindler, M. Studer, *Appl. Catal.*, **2001**, 221, 119.
[185] H. Takaya, R. Noyori, European Patent Appl. EP 0245959, **1987**.
[186] K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Takaya, *J. Org. Chem.*, **1994**, 59, 3064; K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, T. Ishizaki, H. Takaya, *J. Chem. Soc. Chem. Commun.*, **1991**, 609.

The electronic donor-acceptor properties of BINAP and its derivatives were investigated by comparison of the spectral data of the carbonyl stretching frequencies of [RhCl(BINAP)(CO)] complexes. It was realized that *p*-FPh-BINAP and *p*-ClPh-BINAP have more π-acidic character than BINAP itself. After performing an asymmetric hydrogenation on methyl-2-(benzamidomethyl)-3-oxobutanoate with cationic Ru(II) complexes as catalysts, it was also found that no remarkable changes in activity and stereoselectivity were observed with electron-donating substituents, while introduction of electron withdrawing substituents in *para* position resulted in a loss in catalytic activity and stereoselectivity.

In 1995, a patent by Hoffman-La Roche[187] described water-soluble BINAP derivatives, synthesized using the following method (Scheme 64).
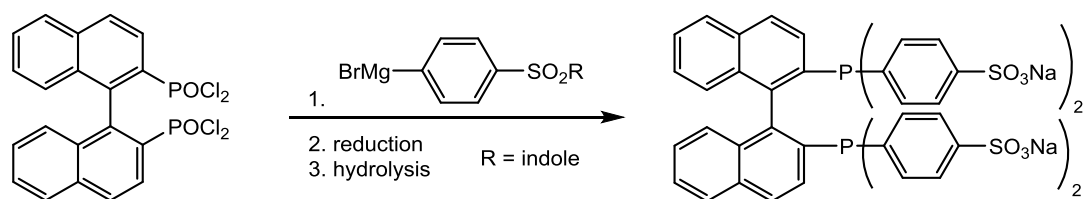
Scheme 64

An aqueous biphasic system represents a very attractive and powerful technology if catalyst separation and recycling are required. Since the first industrial application of the rhodium-TPPTS (trisulfonated triphenylphosphine) system by Hoechst, the development of water-soluble organometallic catalysis has expanded significantly,[188] also in the field of chiral catalyst for biphasic applications. High turnover and easy recycling render this technology of particular interest also from an economic point of view.

Also the synthesis of analogues of BINAP with alkyl and heterocyclic substituents was developed. In 1991, in an attempt to provide complexes with an improved performance as catalysts for asymmetric reactions, Kumobayashi et al. from Takasago synthesized 2,2'-bis-(dicyclopentylphosphino)-1,1'-binapthyl (Cp-BINAP)[189] (Figure 14) in a quite poor overall yield (4%). Cp-BINAP has been used with rhodium metal complexes to perform the asymmetric hydrogenation of nerol to (S)-(-)-citronellol at a total conversion, with 99% selectivity and 70% ee. Under these specific conditions, the cyclopentyl group introduced in place of the phenyl group of BINAP exhibits greatly improved selectivity and conversion.

[187] M. F. Lalonde, European PAtent Appl. EP 0667350, **1995**.
[188] B. Cornils, W. A. Herrman, Eds. *Acqueous-phase Organometallic Catalysis*, Wiley-VCH, Weinheim, Germany, **1998**
[189] Y. Hori, H. Kumobayashi, European Patent Appl. EP 0466405, **1992**.
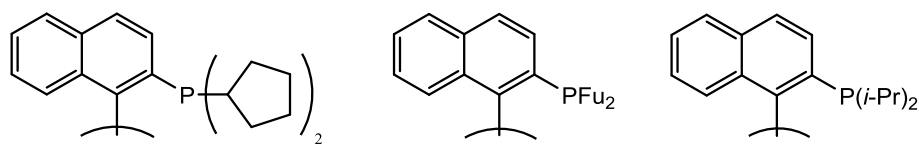
Figure 14

In 2001 the Canadian group of Keay synthesized 2,2'-bis-(di-2-furylphosphino)-1,1'-binaphtalene (Tet-Fu-BINAP),[190] (Figure 14). This time the two phosphorus atoms were found to be less electron rich and less basic than in BINAP. This ligand was tested in the asymmetric Heck arylation of 2,3-dihydrofuran with phenyl triflate, as palladium complex, but was found to form a less reactive Pd catalyst than the corresponding BINAP, and provided a lower level of isomer selectivity. Finally, in 2003 Pregosin et al. described a Ru(II) alkyl-BINAP complex.[191](Figure 14). They synthesized *i*-Pr-BINAP by treating 2,2'-dibromo-1,1'-binaphtalene with *t*-BuLi followed by an addition of chlorodiisopropylphosphine. Activity of this complex was not tested.

Also for modifications on the naphtyl skeleton different pathways are viable. Generally the modification of the binaphthyl moiety was performed to facilitate separation, because the large conjugated naphthyl rings are less sensitive to the electronic effects of the substituent, while modification of the phenyl substituents could influence more strongly both the electronic properties and the steric hindrance around the coordinating phosphorus atoms. Several positions of the naphthyl skeleton can be modified: the 3, 4, 5 and 6 positions have been the subject of most of the research described so far, probably due to a more difficult introduction of substituents in position 7 and 8. Moreover, introducing substituents on positions 7 or 8 of BINAP would modify the dihedral angle and therefore the ligand properties.

3 and 3' are the positions for which modifications could most influence both the electronic density on the phosphorus atoms and the steric hindrance around the catalytic site, thanks to the strong ortho-directing effect[192] of the phosphine group. The 3,3'-positions could be directly functionalized by first deprotonation of BINAP oxide with butyllithium or LDA,[193] then halogenation or alkylation or arylation with different substituent groups as reported by Zhang. Further studies showed that the introduction of 3,3'-substituted groups can restrict the rotation of phenyl groups on the phosphorus atoms, and therefore generating a well-defined chiral pocket around the transition metal when the complex is formed. Conformational rigidity is crucial for achieving high enantioselection in asymmetric reactions.

[190] N. G. Andersen, R. McDonald, B. A Keay, *Tetrahedron Asymmetry*, **2001**, 12, 263.
[191] T. J. Geldbach, P. S. Pregosin, A. Albinati, *Organometallics*, **2003**, 22, 1443.
[192] P. J. Cox, W. Wang, V. Snieckus, *Tetrahedron Lett.* **1992**, 33, 2253.
[193] X. Zhang, PCT Int. Appl. WO 02/40491, **2002**.

Functionalisation of the 4,4'-positions was not described before the synthesis of 4,4'-dibromo BINAP by Kockritz and Kant group.[194] They presented a method using Br_2 and pyridine in dichloromethane to brominates BINAP oxide (BINAPO) in positions 4 and 4' (Scheme 65).
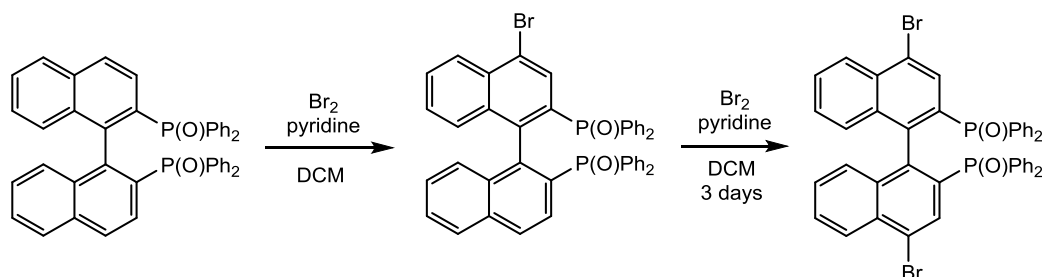
Scheme 65

This reaction is extremely regioselective, and only monobromo and dibromo BINAPO in the 4,4'-positions were formed. Moreover, the optical purity of the initial BINAPO was conserved in the reaction, but the slow reaction rate could be a limiting factor. This 4,4'-dibromo intermediate could be used as starting material for the preparation of other derivatives by introduction of phosphonate groups, aminomethyl groups[195] or polyfluorinated groups.[196]

BINAP derivatives substituted in the 5,5'-positions are the most exemplified, probably due to the possibility of electrophilic substitution onto this position of the BINAPO. Three major methods may be noted to synthesize 5,5'-substituted BINAP. Indeed nitration,[197] sulfonation[198] and halogenation of the BINAPO permit the BINAP to be obtained directly in these positions when acidic media are used instead of neutral or basic media as described above (Scheme 66).
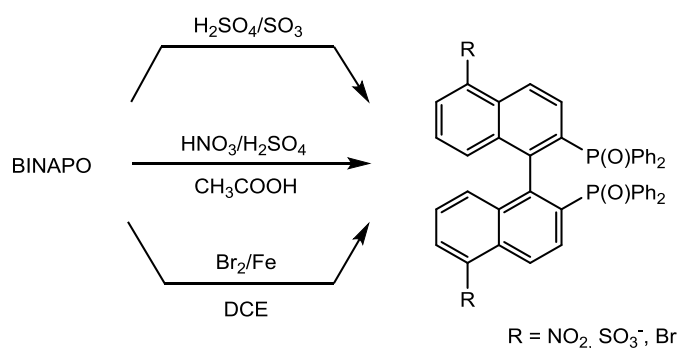
Scheme 66

[194] M. Kant, S. Bischoff, R. Siefken, E. Grundemann, A. Kockritz, *J. Org. Chem.*, **2001**, 477.
[195] M. Berthod, C. Saluzzo, G. Mignani, M. Lemaire, *Tetrahedron Asymmetry*, **2004**, 15, 639.
[196] M. Berthod, G. Mignani, M. Lemaire, *Tetrahedron Asymmetry*, **2004**, 15, 1121.
[197] H. Kumobayashi, European Patent Appl. EP 0235450, **1986**.
[198] H. Kumobayashi, European Patent Appl. EP 0544455, **1992**.

The nitro derivative was reduced by Kumobayashi to the 5,5'-diamino BINAP, which was used as rhodium complex in the asymmetric isomerization of diethylgeranylamine, leading to excellent conversion rate. The 5,5'-disulfonate derivative was tested as ruthenium complex in the two-phase hydrogenation of ethyl acetoacetate in water, showing excellent yields and enantiomeric excess, better than BINAP itself. Finally, 5,5'-dihalogenated BINAP showed the same activities and enantioselectivities as 4,4'-dihalogen derivative and BINAP itself.

The 6,6'-positions of BINAP or BINAPO are not accessible via electrophilic substitution. These positions cannot be substituted directly as shown before for 3,3', 4,4' and 5,5' positions. Nevertheless, these positions have been frequently studied, thanks to the reactivity of the BINOL precursor. Contrary to those of BINAP, the 6,6'-positions are more reactive in BINOL and protected BINOL, and many electrophilic substitutions can be conducted such as Friedel-Crafts acylation or bromination. A phosphination step is then necessary to obtain the BINAP derivatives. Jedlinski et al.[199] first reported in 1976 the preparation of 6,6'-dibromo BINOL in a single-stage process with excellent yields (96%). Also in this case, as previously reported for 4,4'-dibromo BINAP, the dibromo compound could be used as starting material for the preparation of many other derivatives.

Recently also some BINAP substituted in the 7,7'-positions were reported. Best results were obtained in the synthesis of 7,7'-dimethoxy BINAP, reported separately by Cai and Keay.[200] Efficiency of the corresponding palladium complex was evaluated performing asymmetric Heck reactions, and the results indicate that activity and selectivity of the new ligand are similar to those of BINAP.

BINOL and its derivatives

Since 1990 the enantiomeric atropoisomers of 1,1'-binaphtyl-2,2'-diol (BINOL) have become among one of the most widely used ligands for both stoichiometric and catalytic asymmetric reactions. BINOL, together with BINAP, is the best known representative of axially chiral molecules,[201] and was first prepared as a racemate in 1873 by von Richter.[202] Since this date, the preparation of racemic BINOL has been widely studied, leading to a well-established method for its preparation that involves an oxidative coupling of 2-naphtol using $FeCl_3$, $K_3Fe(CN)_6$, $Mn(acac)_3$, Cu-amine complexes or

[199] W. Pradellok, A. Kotas, W. Walczyk, Z. Jedlinski, PL 87054, **1976**.
[200] D. W. Cai, U.S. Patent US 6,333,435, **2001**; D. Che, N. G. Andersen, S. Y. Lau, B. A. Keay, *Tetrahedron Asymmetry*, **2000**, 11, 1919.
[201] H. Akimoto, S. Yamada, *Tetrahedron*, **1971**, 27, 5999.
[202] V. von Richter, *Chem. Ber.*, **1873**, 6, 1252.

TiCl$_4$ as coupling agents.[203] This methods imply the formation of a radical species from a one-electron oxidation with the metal, and allow to reach yields up to 90% (Scheme 67). Usually, these coupling reactions are not catalytic processes and require more than stoichiometric amount of the metal salts.
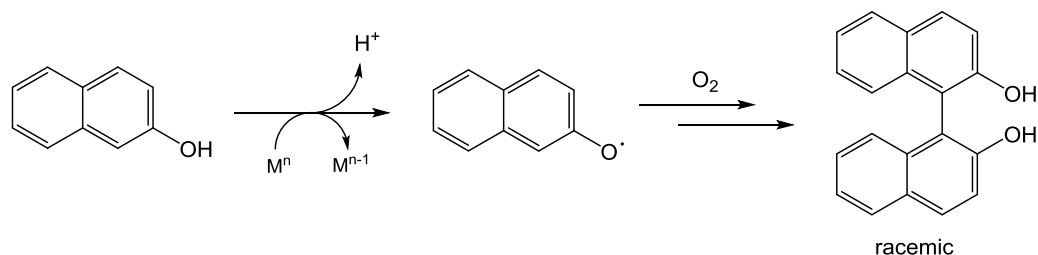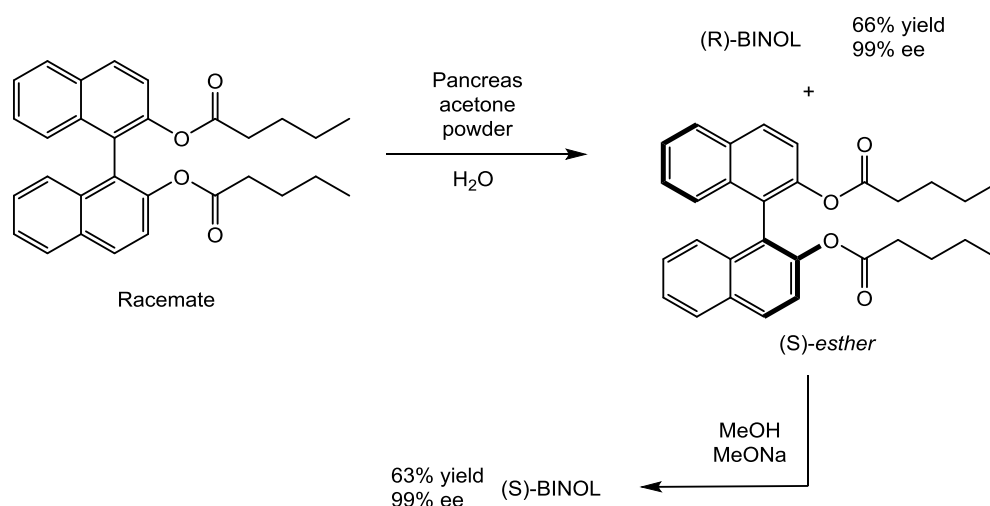

Scheme 67

Use of these ligands as chirality inducers in asymmetric reactions is enabled by the great stability of the enantiomers, with rotation barriers ranging from 23.8 kcal/mol for BINOL to more than 50 kcal/mol for more substituted derivatives.

Synthesis of enantiomerically pure (R)- or (S)- BINOL has been extensively studied. It is possible to approach the preparation of the different enantiomers in two ways: chemical or enzymatic resolution of racemic BINOL, or direct stoichiometric or catalytic oxidative coupling synthesis.

One of the first efficient methods for enzymatic resolution of *rac*-BINOL was described by Kazlauskas in 1989[204] (Scheme 68).

Scheme 68

[203] F. Toda, K. Tanaka, S. Iwata, *J. Org. Chem.*, **1989**, 54, 3007; D. Villemin, F. Sauvaget, *Synlett*, **1994**, 435; M. O. Rasmussen, O. Axelsson; D. Tanner, *Synth. Commun.*, **1997**, 27, 4027; P. Mastrorilli, F. Muscio, G. P. Suranna, C. F. Nobile, M. Latronico, *J. Mol. Catal. A. Chem.*, **2001**, 165, 81.
[204] R. J. Kazlauskas, *J. Am. Chem. Soc.*, **1989**, 111, 4953.

This mthod was based on the cholesterol esterase-catalyzed enantiospecific hydrolysis of binaphthol esters, using as the catalyst an inexpensive enzyme like bovine pancreatic acetone powder (PAP). Each enantiomer was obtained in more than 60% yield and 99% enantiomeric purity.

Many other enzymatic resolution methods have been later developed, by using enzymes from bovine serum, porcine pancreas, Pseudomonas and Camellia, reported by Lin,[205] Cavazza,[206] and Tanaka.[207]

The chemical resolution of *rac*-BINOL has been extensively reported in the literature, and in all cases the methods are based on the easy separation of the pair of diastereomers derived from the reaction of the racemate with a chiral auxiliary, often through selective crystallization of diastereoisomeric salts. The use of cinchonine salts was reported by Jacques and coworkers.[208] With this method, the overall resolved yield was only moderate, and the enantiomeric purity was not satisfactory. Moreover, cinchonine is quite expensive. Other resolution procedures with chiral auxiliaries that permit better results reported the use of (R)-2-aminobutanol,[209] optically active phenetylamines[210] or (S)-proline.[211]

Enantioselective oxidative coupling of 2-naphtol with chiral catalyst apparently provides one of the simplest route to synthesize optically active BINOL, but only a few attempts to develop such an approach have been reported. Wynberg et al.[212] were the first to describe an oxidative coupling of 2-naphtol by stirring a mixture of cupric-(S)-phenylethylamine and 2-naphtol in equimolar quantities at room temperature under a nitrogen atmosphere (Scheme 69). Although BINOL was obtained in 63% yield the enantiomeric excess was only 3%.
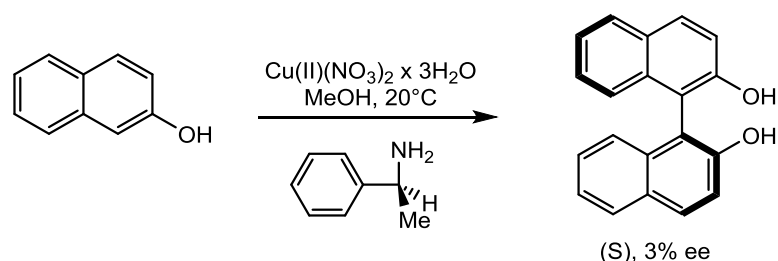
Scheme 69

[205] G. Lin, S. H. Liu, S. J. Chen, F. C. Wu, *Tetrahedron Lett.*, **1993**, 34, 6057.

[206] M. Cavazza, M. Zandomeneghi, A. Ouchi, Y. Koga, *J. Am. Chem. Soc.*, **1996**, 118, 9990.

[207] M. Takemoto, Y. Suzuki, K. Tanaka, *Tetrahedron Lett.*, **2002**, 43, 8499.

[208] J. Jacques, C. Fouquey, *Org. Synth.*, **1988**, 67, 1.

[209] Y. Tamai, P. Heung-Cho, K. Iizuka, A. Okamura, S. Miyano, *Synthesis,* **1990**, 222.

[210] D. Fabbri, G. Delogu, O. De Lucchi, *J. Org. Chem.*, **1995**, 60, 6599.

[211] Z. Shan, Y. Xiong, W. Li, D. Zhao, *Tetrahedron: Asymmetry,* **1998**, 9, 3985.

[212] B. Feringa, H. Wynberg, *Bioorg. Chem.*, **1978**, 7, 397.

Further work allowed to achieve better enantiomeric excesses, but often with a decrease in term of yields. A remarkable result was obtained using an enantioselective electrocatalytic oxidative coupling of 2-naphtol on a TEMPO-modified graphite felt electrode in the presence of (-)-sparteine.[213] This procedure allowed the synthesis of (S)-BINOL in 94% yield and 99% enantiomeric excess.

Two approaches can be followed in the synthesis of BINOL derivatives, substituted on different positions: by asymmetric oxidative coupling of 2-naphtol derivatives or by functionalisation of the BINOL skeleton (Scheme 70).
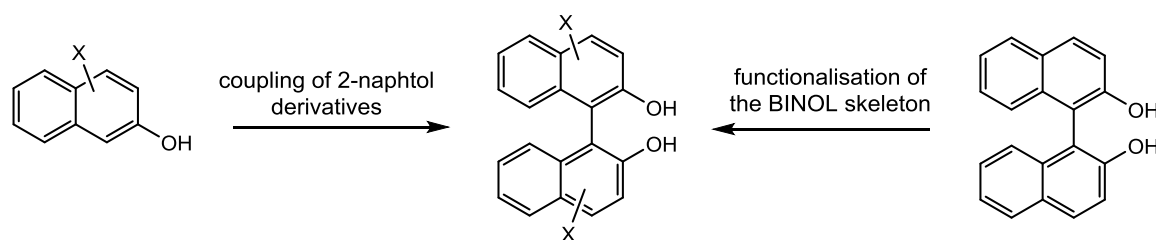
Scheme 70

The first approach permit to avoid laborious resolution procedures, and excellent results have been reported by Gong and coworkers[214] employing a dinuclear oxavanadium(IV) catalyst, and also by Nakajima and coworkers with a chiral analogue of [CuClOH(tmda)] catalyst.[215]

Ligands based on the BINOL framework can also be prepared starting from the parent BINOL compound. One of the major advantage of this approach is that both enantiomers of BINOL are commercially available in an enantiopure form. Many synthetic protocols have been devised for derivatization of the BINOL skeleton, and selective functionalisation of the 3,3'-, 4,4'- and 6,6'-positions are widely employed.[216] Also functionalisations in the other positions are possible, although less studied. Functionalisation methods for BINOL are similar and in some cases the same as for BINAP derivatization, since BINOL derivatives are often the starting material for the synthesis of substituted BINAPs. Also general considerations about electronic and steric effects of different substituent groups on the behaviour of BINAP can be reported for BINOL. Widely employed examples concern substitution in the 6,6'- and 3,3'-positions. Bromination of BINOL by Br_2 gives 6,6'-dibromo-BINOL in quantitative yield, while reaction with $C_2Br_2Cl_4$/BuLi at low temperature gives the 3,3'-

[213] T. Osa, Y. Kashiwagi, Y. Yanagisawa, J. M. Bobbit, *J. Chem. Soc., Chem. Commun.,* **1994**, 2535.
[214] Z. Luo, Q. Liu, L. Gong, X. Cui, A. Mi, Y. Yiang, *Angew. Chem. Int. Ed.,* **2002**, 41, 4532.
[215] M. Nakajima, I. Miyoshi, K. Kanayama, S. I. Hashimoto, M. Noji, K. Koga, *J. Org. Chem. Soc.,* **1999**, 64, 2264.
[216] L. Pu, *Chem. Rev.,* **1998**, 98, 2405.

dibromo derivative.[217] Once the BINOL skeleton is brominated at the desired positions, ligating groups can be introduced directly (e.g. by coupling reactions), or further derivatization gives access to alternative functional groups (e.g. carboxyaldehyde). Reaction at the BINOL oxygen atoms also provides straightforward access to BINOL derivatives.

We started our investigation about bidentate O,O and P,P ligands by insertion of the simple BINAP or BINOL ligand in the structure of [RhCp*Cl$_2$]$_2$. These ligand were expected to replace two chloride atoms at the metal center, generating rhodium(III) complexes.

First we prepared a cationic BINAP complex, by reaction of [RhCp*Cl$_2$]$_2$ with enantiopure (R)-BINAP in dichloromethane under nitrogen atmosphere. Due to the presence of AgBF$_4$ the reaction was carried out in the absence of light. After purification steps, complex **18** was recovered in a quite good yield (Scheme 71).
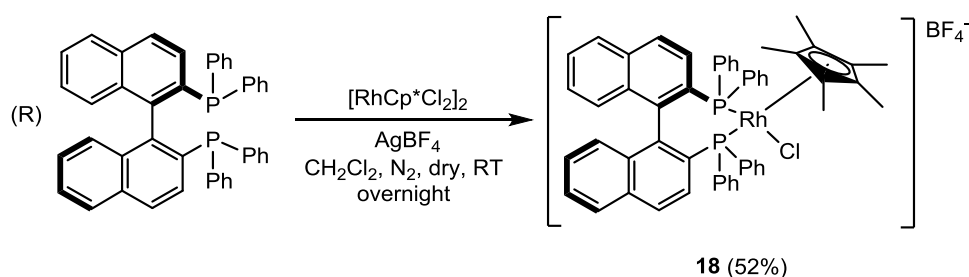
Scheme 71

Similarly complex **19** was prepared by reaction of [RhCp*Cl$_2$]$_2$ with enantiopure (R)-BINOL in dichloromethane, in the presence of triethylamine. In this case no concern derived from exposure to light or air, and after purification steps the complex was obtained in a quite satisfactory yield (Scheme 72).
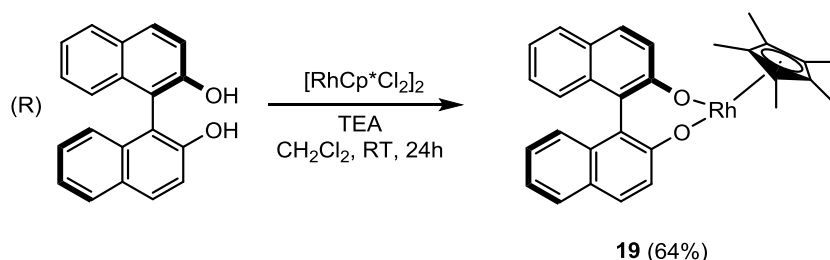
Scheme 72

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[217] J. M. Chong, L. Shen, N. J. Taylor, *J. Am. Chem. Soc.*, **2000**, 122, 1822; H. J. Deussen, E. Hendrickx, C. Boutton, D. Krog, K. Clays, K. Bechgaard, A. Persoons, T. Bjornholm, *J. Am. Chem. Soc.*, **1996**, 118, 6841.

In both cases, from NMR spectra we were able to recognize the presence of the cyclopentadienyl moiety. Structure of the complexes was also confirmed by mass analysis.

Behaviour of both complexes was then investigated in the chosen benchmark reactions. Results were very different for the two complexes: while the BINOL-containing complex **19** successfully lead to the formation of the expected product, with yields slightly lower than the [RhCp*Cl$_2$]$_2$-catalyzed reactions, presence of the BINAP complex **18** did not allow the hydroamination reaction to occur, and also the 3,4-dihydroisoquinolone product was obtained in low yield (Scheme 73).

After a purification step on column chromatography, products **2** and **17a** were submitted to an HPLC analysis to determine the percentage of both enantiomers. Unfortunately, use of the complexes did not allow the detection of any enantiomeric excess.
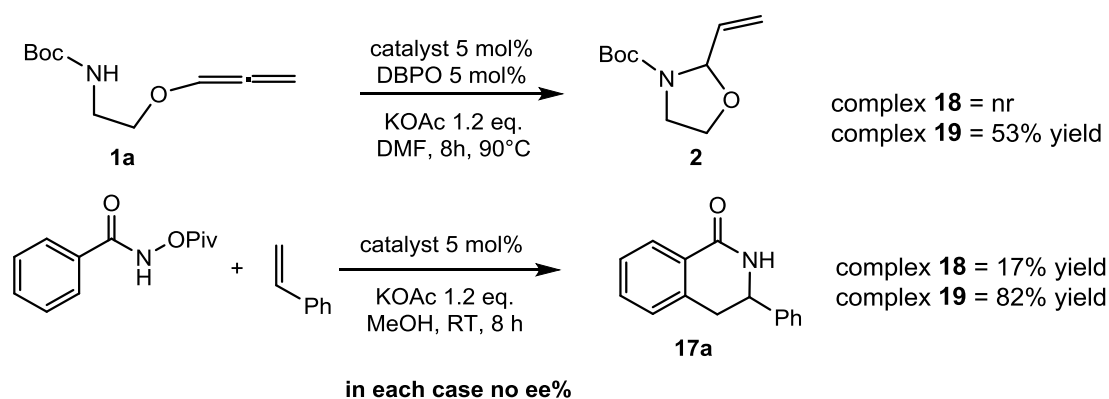
Scheme 73

Starting from the good results in term of yields achieved with complex **19**, we prepared a bulkier BINOL derivative bearing two methoxy substituents in 3,3' positions. In this way, we tried to enhance the selection theorically arising from the enantiopure ligand. In Scheme 74 is reported the synthesis of ligand **23**, prepared in four steps starting from (R)-BINOL.

Lithiation of bis(methoxymethyl) ether **20** with BuLi in THF and trapping of the resulting dianion with B(OMe)$_3$, gave the corresponding boronate, which was oxidized to the 3,3' dihydroxy derivative **21** in one pot by H$_2$O$_2$ in benzene. After protection of the hydroxy functionality as the methyl ether, selective deprotection of the methoxymethyl group was conducted under acidic conditions affording the desired ligand **23**.
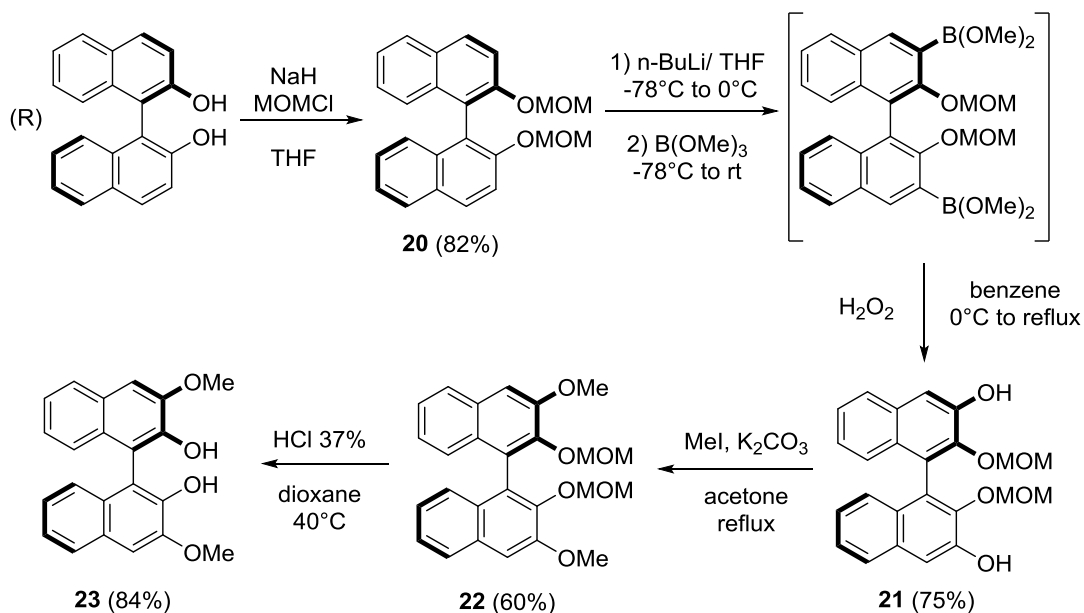
Scheme 74

With the ligand in our hand, we prepared the corresponding rhodium(III) complex **24** by the same reaction conditions previously employed for the BINOL ligand, and we tested its behaviour as catalyst in the usual benchmark reactions. The complex was recovered in quite satisfactory yield (Scheme 75).
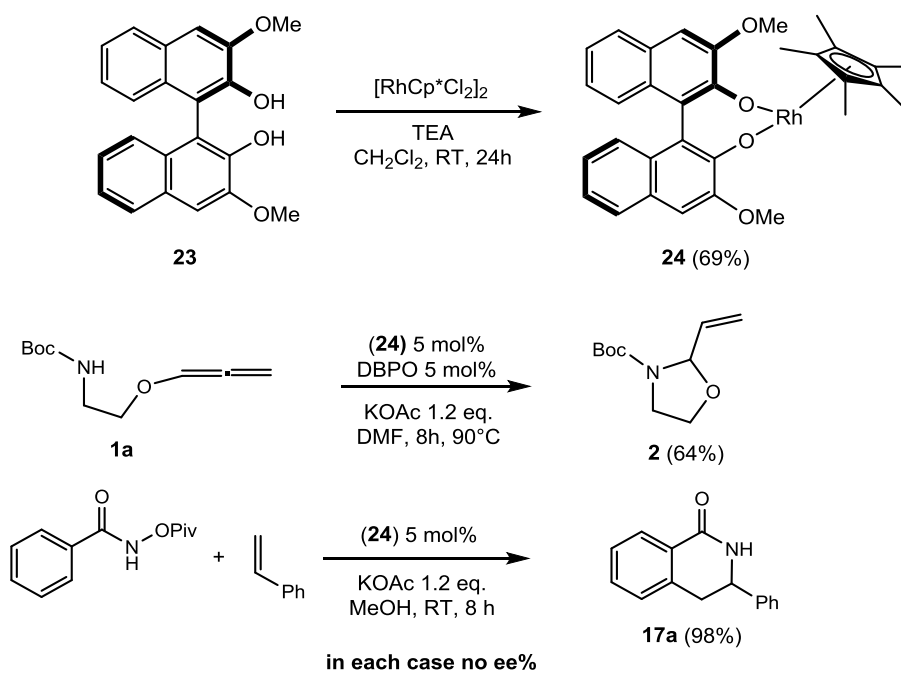
Scheme 75

Complex **24** showed an enhanced reactivity compared to the unsubstituted analogue, leading to the formation of the expected products in very good yields. Unfortunately, presence of the substituents in the 3,3'-positions did not affect selectivity of the complex toward the reactions, and we were still unable to detect any enantiomeric excess.

Despite the lack in selectivity, we extended the reactivity of the complex to the synthesis of other aminoallenes and dihydroisoquinolones in the same conditions previously reported. Results confirmed the good reactivity of complex **24** in these reactions (Figure 15).

3 (43%)   **6** (46%)   **8** (39%)   **17b** (91%)   **17c** (94%)
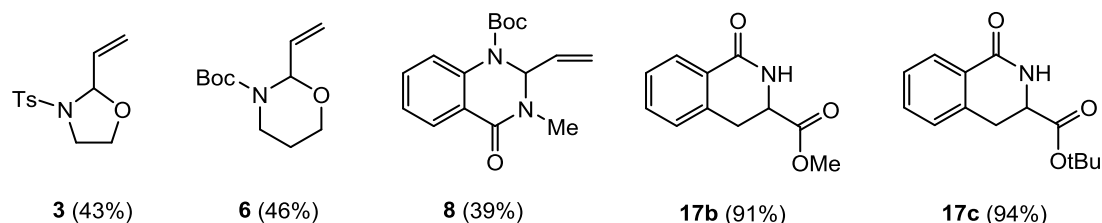
Figure 15

3.2.2. Replacement of the cyclopentadienyl ligand

As previously reported, cyclopentadienyl anions mimic monoanionic ligands tricoordinatively bound to the rhodium metal center in a facial way. In order to replace the cyclopentadienyl moiety, tridentate monoanionic ligands have been used. These ligands can mimic the coordination behaviour of the cyclopentadienyl anion, and they might be expected to exhibit similar reactivity.

A famous and widely studied class of tridentate ligands are scorpionates, that shows a N,N,N bonding mode to the metal center. Also ligands with a N,O,N coordinating mode are suitable for this scope, permitting a simple way to develop an anion on the oxygen atom.

For the synthesis of complexes bearing tridentate ligands instead of cyclopentadienyl anion, it is not viable to start from [RhCp*Cl$_2$]$_2$ removing the cyclopentadienyl moiety. Instead, we will use the commercially available RhCl$_3$ or other rhodium salts.

3.2.2.1. Tridentate ligands: tris(pyrazolyl)borates and methanes

Among the different types of tridentate ligands, we focused our attention on scorpionates, because they exhibit the peculiar features typical of cyclopentadienyl ligands. These tripodal ligands

appeared for the first time in 1966, discovered by Trofimenko,[218] and have in their structure three pyrazole rings attached to a central atom (in the first examples boron, then extended to other atoms), and resembles the posture of a scorpion in their way to clamp the metal center. In fact, they bind the metal with nitrogen atoms from two pyrazole rings, while the third pyrazole rotates forward like a scorpion's tail; hence their name (Figure 16).

Figure 16

Over the years, the definition of scorpionates has been extended to tripodal ligands analogs to tris(pyrazol-1-yl)borates with different donor groups and bridging atoms. Central atoms other than boron, such as carbon, silicon, tin, germanium, indium, gallium, phosphorus and nitrogen have been reported.[219] Among them, the most studied classes of scorpionates involves B-centered and C-centered derivatives.[220]

These ligands are commonly six electron donors and occupy three coordination sites as capping ligands when binding to the metal (Figure 17).

X = B Tris(pyrazolyl)borate
X = C Tris(pyrazolyl)alkene
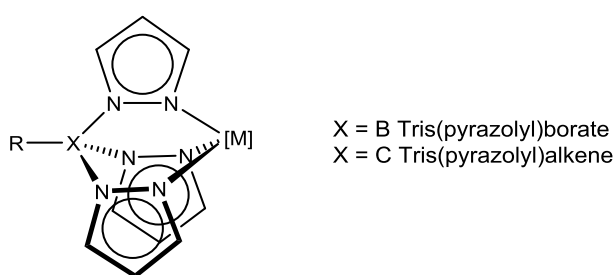
Figure 17

[218] S. Trofimenko, *J. Am. Chem. Soc.*, **1966**, 88, 1842.
[219] E. E. Pullen, A. L. Rheingold, D. Rabinovich, *Inorg. Chem. Commun.*, **1999**, 2, 194; A. Steiner, D. Stalke, *Inorg. Chem.*, **1995**, 34, 4846; K. R. Breakell, D. J. Patmore, A. Storr *J. Chem. Soc., Dalton Trans.* **1975**, 749; T. N. Sorrell, W. E. Allen, P. S. White, *Inorg. Chem.*, **1995**, 34, 952.
[220] S. Trofimenko, *J. Am. Chem. Soc.*, **1970**, 92, 5118; D. L. Reger, *Common. Inorg. Chem.*, **1999**, 21,1; C. Pettinari, R. Pettinari, *Coord. Chem. Rev.*, **2005**, 249, 525.

Tris(pyrazolyl)borates and tris(pyrazolyl)alkanes have been extensively investigated in inorganic, bioinorganic and organometallic chemistry,[221] and their coordination properties have been widely studied.

Scorpionates are among the most often used complex ligands. This is true for various main group elements as well as numerous transition metals, lanthanoids, and actinoids. These ligands are so popular due to their reliability and accountability as spectator ligands, which normally do not interfere with the reaction scenarios occurring at the metal centers.

In general, apart the nature of the bridging atom, two main types of scorpionates can be identified: *homoscorpionates* and *heteroscorpionates*, depending on the presence of one or more types of metal binding groups. In this section we will consider only the first type.

The naming of homoscorpionates follow some general rules, described by Trofimenko.[222] First of all, when R is H (Figure 17), abbreviations Tp for tris(pyrazolyl)borates and Tm for tris(pyrazolyl) methanes are used. Briefly, the main rules can be summarized as following: *i)* substituents are denoted by superscripts; *ii)* the "default" position is the 3-position on pyrazole ring, which is denoted with a superscript R (e. g. Tp^{Me}); *iii)* the 5-substituent follows the 3-substituent in the superscript, separated by a comma, if they are identical, the superscript is followed by a 2; *iv)* substituent in the 4-position is denoted as a 4R superscript.

Coordination properties of scorpionate ligands are correlated to steric and electronic effects that originate from the substituents on pyrazoles.[223] In general, scorpionates shows a wide set of coordination modes, starting from the typical k^3-N,N',N''.[224] In addition to this, they can also behave as tridentate k^3-N,N',XH donors, with a borohydride moiety linked to the metal, as bidentate ligands k^2-N,N' or k^2-N,XH, and rarely as k^1 or k^0 as uncoordinated counterion.[225] Higher hapticities (k^4, k^5 or k^6) are possible if the substituents in the 3-position on the pyrazole rings contain additional donor atoms.

With respect to its steric bulk, tris(pyrazolyl)hydroborate anion (Tp^{Me2})$^-$ is regarded as a steric equivalent of the pentamethylcyclopentadienyl (Cp*) ligand. However, conflicting reports can be found in the literature on the electron-donating properties of Tp^{Me} and Tp^{Me2} in comparison to Cp

[221] S. Trofimenko, *Scorpionates: The Coordination Chemistry of Poly(pyrazolyl)borate Ligands.* Imperial College Press: London **1999**; C. Pettinari, *Scorpionates II: Chelating Borate Ligands.* Imperial College Press: London **2008**.

[222] S. Trofimenko, *Chem. Rev.*, **1993**, 93, 943.

[223] N. Kitajima, W. B. Tolman, *Progr. Inorg. Chem.*, **1995**, 43, 419.

[224] F. T. Edelmann, *Angew. Chem. Int. Ed.*, **2001**, 40, 1656.

[225] N. Kitajima, T. Koda, S. Hashimoto, T. Kitagawa, *J. Am. Chem. Soc.*, **1991**, 113, 5664; R. G. Ball, C. K. Ghosh, J. K. Hoyano, A. D. McMaster, *J. Chem. Soc., Chem. Commun.*, **1989**, 341; F. Malbosc, P. Kalck, J. C. Daran, M. Etienne, *J. Chem. Soc., Dalton Trans.*, **1999**, 271; M. Paneque, S. Sirol, M. Trujillo, E. Gutierrez-Puebla, M. A. Monge, E. Carmona, *Angew. Chem. Int. Ed.*, **2000**, 39, 218.

and Cp*.[226] Some researchers claimed that the ligand Tp^{Me} and Tp^{Me2} are stronger electron donors than Cp and Cp*, but in a recent study on C-H activation reactions by $[Tp^{Me2}Ir]$complexes Bergman et al. were able to show the opposite effect.

Homotris(pyrazolyl)borates can be synthesized in many different ways, but most easily they are prepared by reaction of the proper pyrazole with a borohydride anion in the absence of solvent (Scheme 76).
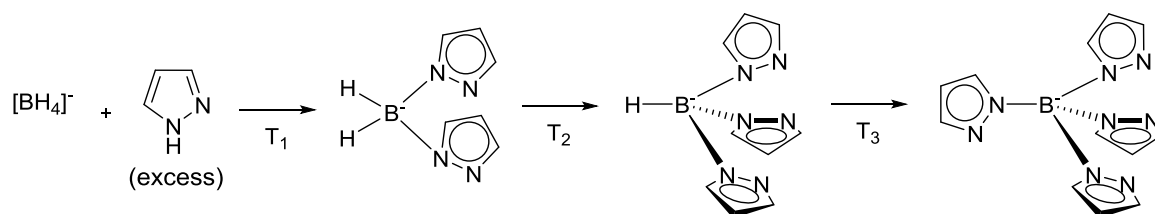
Scheme 76

As shown in Scheme 76, it is possible to control reaction progress through temperature control in order to produce selectively one of the above products. A huge variety of pyrazoles can be employed to synthesize poly(pyrazolyl)borates in this way. An obvious exception concern those pyrazoles containing functionalities incompatible with the borohydride ion.

Instead, homoleptic tris(pyrazolyl)methanes are mainly prepared as reported in Scheme 77.
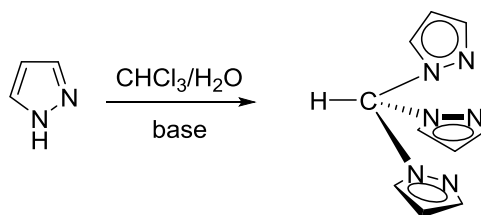
Scheme 77

Many examples of iron-poly(pyrazolyl)borates or methanes have been synthesized, studied and successfully applied to various reactions after they were for the first time synthesized in the sixties. In Figure 18 are reported some examples of Fe(II)-complexes ($Tp^{tBu,Me}FeCl$, $Tp^{Ph,Me}FeCl$, $Tp^{iPr2}FeCl$) obtained from $FeCl_2$ and one equivalent of the Tp ligand.[227] Also complexes that resembles structures of metalloenzymes such as hemerythrin, rubrerythrin, and methane momo-oxygenase were

[226] D. M. Tellers, S. J. Skoog, R. G. Bergman, T. B. Gunnoe, W. D. Harman, *Organometallics,* **2000**, 19, 2428; J. K. Koch, P. A. Sharpley, *Organometallics*, **1997**, 16, 4071.
[227] F. A. Jové, C. Pariya, M. Scoblete, G. P. A. Yap, K. H. Theopold, *Chem. Eur. J.* **2011**, 17, 1310; T. Tietz, C. Limberg, R. Stößer, B. Ziemer, *Chem. Eur. J.* **2011**, 17, 10010.

prepared. These complexes contain in their structure oxo-bridged diiron centers, like in $Tp_2Fe_2(\mu$-O)(μ-O_2CCH_3).[228] The five-coordinate iron(III) complex $Tp^{iPr}Fe(OAc)$ is another example of Tp-iron complex, that acts as a mimic for non-heme metalloprotein hemoglobin and cytochrome P-450.[229]

a: R_1 = Me, R_2 = tBu
b: R_1 = Me, R_2 = Ph
c: R_1 = iPr, R_2 = iPr
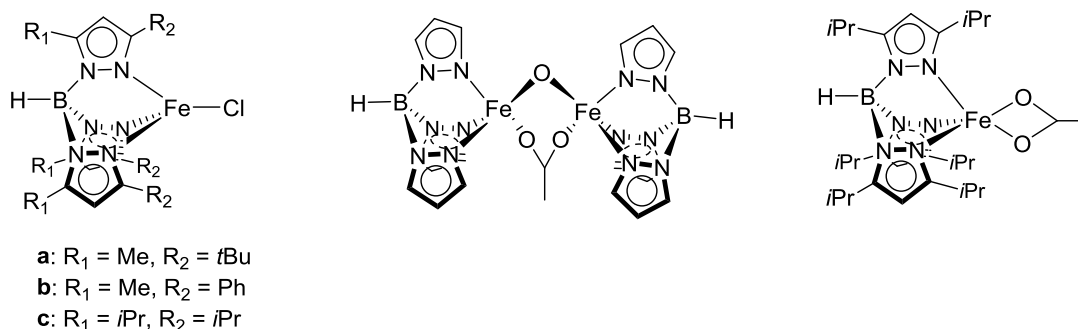
Figure 18

In literature only poor examples of tris(pyrazolyl)borate or methane complexes of rhodium were reported, together with fewer application examples. One of them is the rhodium dicarbonyl complex of C_3-symmetric Tp^{Menth} ligand (Figure 19), that under photolysis illustrate the capability of these scorpionates to exhibit a high degree of regio- and stereocontrol in reactions involving intramolecular attack of ligand substituent C-H bonds.[230]
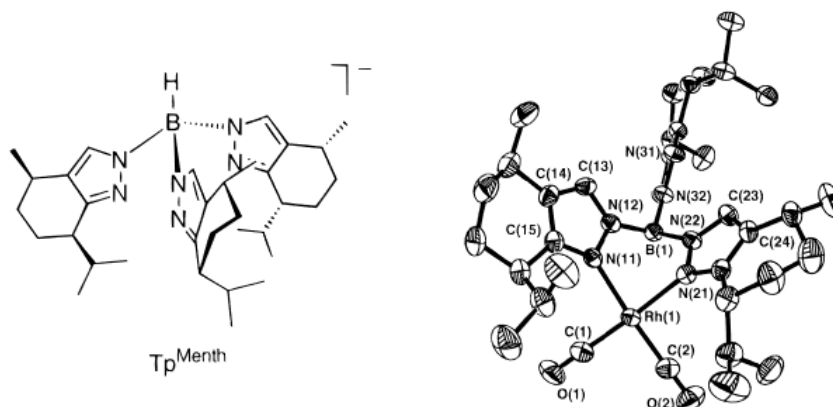
Figure 19

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[228] J. S. Loehr, W. D. Wheeler, A. K. Shiemke, B. A. Averill, T. M. Loehr, *J. Am. Chem. Soc.* **1989**, *111*, 8084.
[229] N. Kitajima, N. Tamura, H. Amagai, H. Fufui, Y. Moro-oka, Y. Mizutani, T. Kitagawa, R. Mathur, K. Heerwegh, C. A. Reed, C. R. Randall, L.J. Que, K. Tatsumi, *J. Am. Chem. Soc.* **1994**, *116*, 9071.
[230] M. C. Keyes, V. G. Young, W. B. Tolman, *Organometallics*, **1996**, 15, 4133.

Our aim in this work was to synthesize some new scorpionate rhodium complexes, bearing both tris(pyrazolyl) borates and methanes, and to test their applicability as catalysts in an intermolecular amination reaction and in an intramolecular hydroamination reaction, for which no examples have been ever reported.

All the chosen pyrazoles are commercially available. Tris(pyrazolyl)borates were prepared through a neat reaction at high temperature, from an excess of pyrazoles (more than 3 equivalents) and KBH_4, running for an hour. The borates were obtained in quite low yield. Instead, tris(pyrazolyl) methanes were prepared by reacting 3 equivalents of the desired pyrazoles in a basic mixture of $H_2O/CHCl_3$ with TBAB and Na_2CO_3, running for three days. Also these ligands were obtained in low yield. Despite our efforts, we never obtained yields higher than 40%, accordingly to literature data.

From tris(pyrazolyl)borate **25** we synthesized a neutral $Tp^{Me2}RhCOD$ complex **26**, by reaction of 2 equivalent of the chosen pyrazole and 1 equivalent of $(RhCODCl)_2$, in DCM at room temperature (Scheme 78).
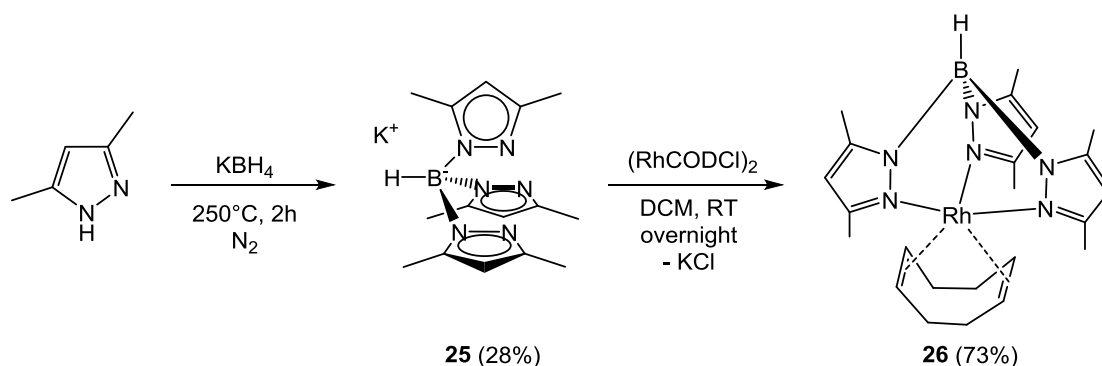
Scheme 78

We synthesized also two tris(pyrazolyl)methane complexes: neutral $Tm^{Me2}RhCl_3$ **28** from the corresponding ligand **27a** and $RhCl_3$ trihydrate, in EtOH under reflux conditions; and cationic $[Tm^{Ph}RhCOD]BF_4$ **29**, from Tm^{Ph} ligand **27b**, $(RhCODCl)_2$ as the rhodium source and $AgBF_4$, in DCM at room temperature in the absence of light (Scheme 79).
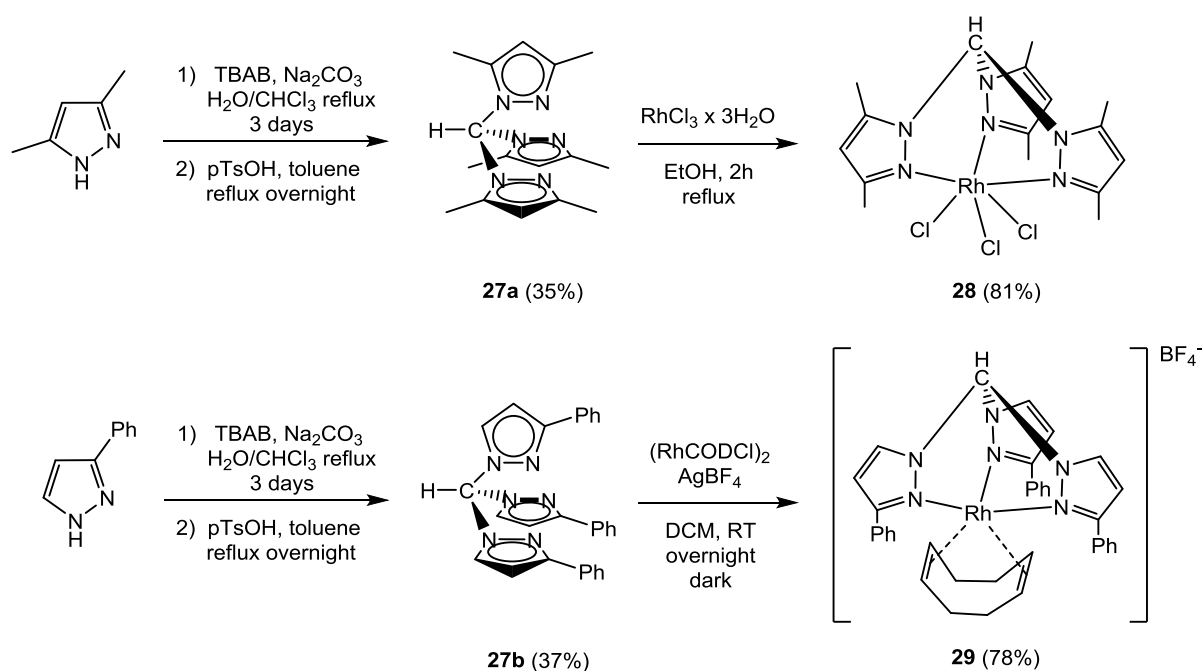
Scheme 79

While in the $Tp^{Me2}RhCOD$ and $[Tm^{Ph}RhCOD]BF_4$ complexes rhodium has oxidation number (I), in the $Tm^{Me2}RhCl_3$ complex it shows oxidation state (III). Tris(pyrazolyl)methane complexes were found to be moderately air-stable, as we saw from an NMR spectra registered after leaving the complexes in the presence of air for about 2 days, while boron-containing complexes were very air-sensitive. All the complexes were recovered in quite satisfactory yields after purification steps, which consist of a filtration over a celite pad and washing with DCM and hexane, and drying under vacuum.

These complexes in particular do not bear any chiral portion in their structure, but their activity was investigated in the aforementioned benchmark reactions. Despite different reaction conditions, reported in Scheme 80 and Table 4, no one of our complexes was able to promote the transformations under investigation.
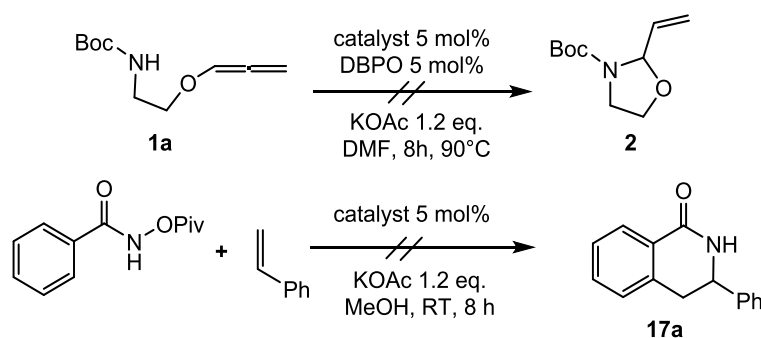
Scheme 80

Different reaction conditions were tested for the synthesis of 3,4-dihydroisoquinolone with styrene, as reported in Table 4, but the expected cyclic product was never obtained. Instead, addition of $CuCl_2$ as oxidizing agent resulted in the detachment of the -OPiv group from the nitrogen atom, exposing the free amide **I**.
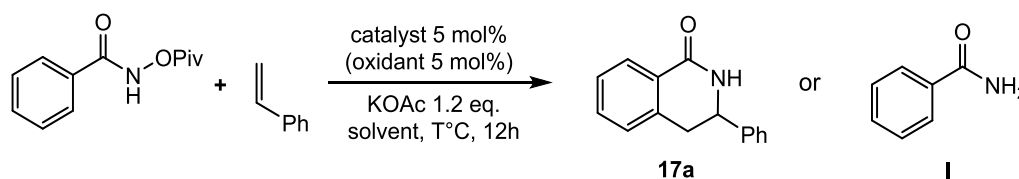
Entry	Catalyst	Temperature	Solvent	Oxidant	Yield of I
1	[Tm^{Ph}RhCOD]BF$_4$	rt	MeOH	-	-
2	[Tm^{Ph}RhCOD]BF$_4$	rt	DCM	-	-
3	[Tm^{Ph}RhCOD]BF$_4$	50°C	MeOH	-	-
4	[Tm^{Ph}RhCOD]BF$_4$	50°C	MeOH	DBPO	-
5	[Tm^{Ph}RhCOD]BF$_4$	50°C	MeOH	NCS	-
6	[Tm^{Ph}RhCOD]BF$_4$	rt	MeOH	CuCl$_2$	78%
7	Tm^{Me2}RhCl$_3$	rt	MeOH	CuCl$_2$	72%
8	-	rt	MeOH	CuCl$_2$	75%

Table 4

3.2.2.2. Salen ligands

Rising from a limitation of the Sharpless enantioselective epoxidation, that was the failure to induce enantioselectivity in simple alkenes lacking allylic hydroxy groups, the report by Jacobsen and Katsuki that chiral salen-Mn(III) complexes act as a highly enantioselective catalysts for the same reaction constituted a breakthrough in the field of asymmetric catalysis.[231] The outcome of this body of research is that metal complexes derived from chiral salen ligands are among the most powerful enantioselective catalysts. Importance of chiral salens in enantioselective catalysis arises from the high enantiomeric excess that can be achieved, and from their general applicability to many different reaction types.

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[231] E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, *J. Am. Chem. Soc.*, **1991**, 113, 7063; R. Irie, Y. Ito, T. Katsuki, *Synlett.*, **1991**, 265; R. Irie, K. Noda, Y. Ito, T. Katsuki, *Tetrahedron Lett.*, **1991**, 32, 1055.

Apparently, chiral salen ligands with bulky substituents can create a strongly stereogenic environment at the active metal center, generating a considerable discrimination between the two transition states leading to each enantiomer. This results in a very effective transmission of chirality to the reaction product for a broad range of substrates and reaction types.

"Salen" is an acronym widely used to denote a group of bis-imine compounds that shows a peculiar structure derived from *N,N'*-bis(salicylidene)ethylenediamine. The first salen-metal complex was probably reported by Pfeiffer in 1933.[232] Chiral salen ligands are generally obtained in an easy way by the uncatalyzed condensation between enantiomerically pure diamines and a suitable salicylaldehyde derivative (Scheme 81). 1,2-Cyclohexanediamine and 1,2-diphenylethylene-1,2-diamine are the two chiral diamines most frequently used.
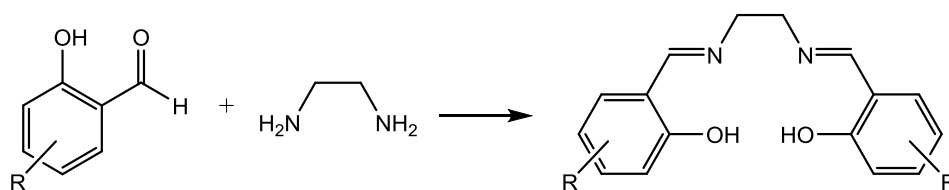
Scheme 81

The imine functional group is generally known as Schiff base. Schiff bases are among the most general N ligands, because of the basicity of the lone pair on the sp^2 N atom, although lower than that of amines (hybridized sp^3), that is adequate to form complexes with metal ions.[233] In the presence of water, the salicylidene imine group has a tendency to undergo an acid-catalyzed hydrolysis, reverting to the corresponding salicylaldehyde and diamine. However, the stability of the Schiff base group increases considerably upon coordination with metal ions and formation of the complex. Thus, in contrast to the ligand alone, the salen-metal complex can be used also in aqueous media without undergoing hydrolysis.

Synthesis of metal complexes bearing salen ligands has been widely investigated in organic chemistry. Symmetrical metal-salen compounds have been found to be catalytically active in many important reactions, like for example in asymmetric Diels-Alder reaction, in the ring opening of epoxides, the oxidation of sulfides, aziridination, hydrogenation, cyclopropanation and most notably the epoxidation of olefins.[234]

These complexes have shown a huge diversity in chemical reactivity, illustrating the ability of the salen ligand environment to accommodate many metals with diverse oxidation states as well as the

[232] P. Pfeiffer, E. Breith, E. Lubbe, T. Tsumaki, *Justus Liebigs Ann. Chem.*, **1933**, 503, 84.
[233] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* Wiley: New York, **2000**.
[234] L. Canali, D. C. Sherrington, *Chem. Soc. Rev.*, **1999**, 28, 85.

versatility of these ligands in homogeneous catalysis. Salen ligands have been successfully metalated by many transition metals, like Mn, Cr, Co, V, Cu, Ti, Ru, Pd, Au, Zn, as well as elements belonging to main group.[235] Depending on the tetradentate N_2O_2 or pentadentate N_2O_2X coordination around the metal center, the complex could exhibit a distorted square planar or square pyramidal geometry.[236] Distorted octahedral $N_2O_2X_2$ coordination has been very frequently postulated for many intermediates. Structure of many of these complexes was successfully characterized by X-ray crystallography.

In octahedral metal-salen complexes three different configurations are possible: *trans* (planar), *cis-α* and *cis-β* (Figure 20).

trans   cis-α   cis-β
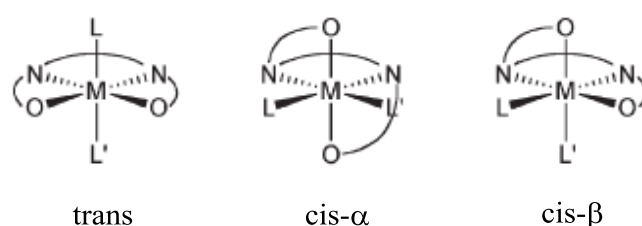
Figure 20

For the relatively rigid planarity of the salen skeleton, ligands showing *trans*-geometry are more stable than those of *cis*-geometry, and complexes usually adopt *trans* configuration. In most of the known metal-salen complexes, salen ligands adopt an almost planar geometry. In spite of this structural feature of the ligand, a chiral and/or sterically bulky group can be introduced near the donor atoms, setting a highly asymmetric atmosphere around the metal center. On the other hand, it is well known that metal-salen complexes could adopt a *cis*-configuration under particular conditions, for example the coordination of a bidentate ligand forces the metal-salen complex to choose a *cis*-configuration.[237] Although there are two possible *cis* configurations (α and β), the *cis-β* one is generally more stable than the *cis-α* one. Only few stable *cis-α* metal-salen complexes are known.[238]

Different from *trans* complexes, the metal atom of *cis*-complexes is chiral (Δ or Λ) thus the complexes are expected to be very efficient asymmetric catalysts. In addition, *cis*-complexes have

[235] S. M. Crawford, *Spectrochim. Acta*, **1963**, 19, 255; W. H. Leung, E. Y. Y. Chan, I. D. Williams, S. M. Peng, *J. Chem. Soc. Dalton Trans.*, **1996**, 1229.

[236] P. J. Pospisil, D. H. Carsten, E. N. Jacobsen, *Chem. Eur. J.*, **1996**, 2, 974; R. Irie, T. Hashihayata, T. Katsuki, M. Akita, *Chem. Lett.*, **1998**, 1041.

[237] M. Calligaris, G. Manzini, G. Nardin, L. Randaccio, *J. Chem. Soc., Dalton Trans.*, **1972**, 543; M. Nakamura, H. Okawa, T. Inazu, S. Kida, *Bull. Chem. Soc. Jpn.*, **1982**, 2400.

[238] P. R. Woodman, I. J. Munslow, P. B. Hitchcock, P. Scott, *J. Chem. Soc., Dalton Trans.*, **1999**, 4069.

two coordination sites in *cis* position, permitting them to capture a bidentate ligand or two monodentate ligands. (Figure 21).

Δ cis-α   Λ cis-α

Δ cis-β   Λ cis-β
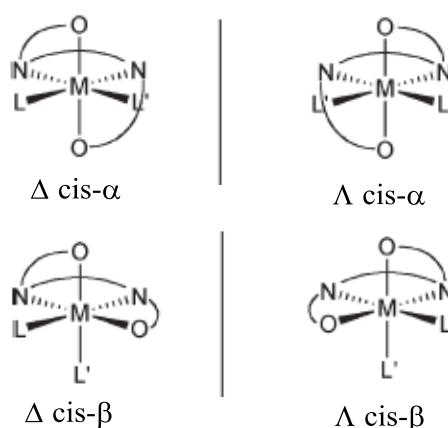
Figure 21

It is distinctive that, in *cis-β* metal-salen complexes, L and L' ligands are non-equivalent and they differ in steric and electronic nature. These characteristics offer advantages in the construction of asymmetric catalysts using *cis-β* metal-salen complexes. Actually, use of these *cis-β* complexes remarkably expanded the scope of metal-salen catalyzed asymmetric reactions.

The studies of *cis* metal-salen complexes set off those of the relate complexes, half-reduced salen (called salalen) and reduced salen (called salan) complexes (Figure 22), which also enabled asymmetric reactions.[239]

Salalen   R = H or alkyl   Salan
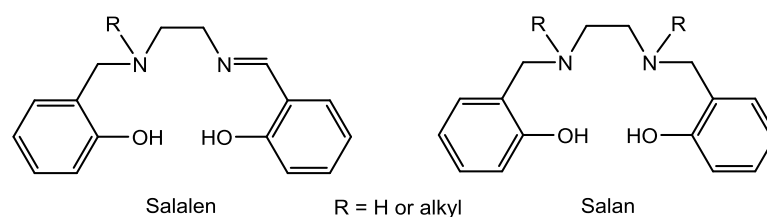
Figure 22

Examples of reaction types that can proceed using chiral salen-metal complexes are alkene epoxidation,[240] alkene aziridination,[241] epoxide ring opening,[242] hetero Diels-Alder,[243] epoxide kinetic

[239] K. Matsumoto, B. Saito, T. Katsui, *Chem. Commun.*, **2007**, 3619.
[240] E. N. Jacobsen, W. Zhang, M. L. Guler, *J. Am. Chem. Soc.*, **1991**, 113, 6703.
[241] Z. Li, K. R. Conser, E. N. Jacobsen, *J. Am. Chem. Soc.*, **1993**, 115, 5326.
[242] L. E. Martinez, J. L. Leighton, D. H. Carsten, *J. Am. Chem. Soc.*, **1995**, 117, 5897.
[243] S. E. Schaus, J. Branalt, E. N. Jacobsen, *J. Org. Chem.*, **1998**, 63, 403.

resolution,[244] cyclopropanations,[245] and Bayer-Villiger reactions.[246] All these reactions proceed with enantiomeric excess up to 90% and very good yields, depending on the metal center. The most employed metals are Mn, Cu, Co, Cr and Zn.

Organometallic rhodium complexes with tetradentate salen ligands coordinating to the Rh metal center in the N_2O_2 mode are known. In the early 1970s, West et al. reported the synthesis of octahedral Rh(III) salen complexes containing pyridine as neutral axially bound ligand.[247] Later, Eisenberg reported the synthesis of square pyramidal Rh(III) salen alkyl complexes from Rh(I) precursors.[248]

The synthesis of rhodium(III) dichloro complexes with unsymmetrically bound salen ligands was also reported in the literature.[249] This mode of binding left one intact phenol group coordinating to the rhodium center, and was never been observed before in salen-metal chemistry. Peculiarity of this work was also to be the first reported process in which direct combination of $RhCl_3x3H_2O$ and the salen ligand in the absence of a nucleophilic base was achieved. In this example the coordination mode can be expressed as N, N, O, O⁻, thus leading to the formation of a monoanionic ligand.

The synthesis of the (salcen)Rh(III) dichloride complex **31** (salcen is the abbreviation for *trans*-1,2-diaminocyclohexane-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)) was performed by combining the free imine ligand **30**, previously obtained through the reaction between 3,5-(*tert*-butyl)salicylaldehyde and trans-1,2-diaminocyclohexane, with rhodium trichloride trihydrate in reflux ethanol (Scheme 82).
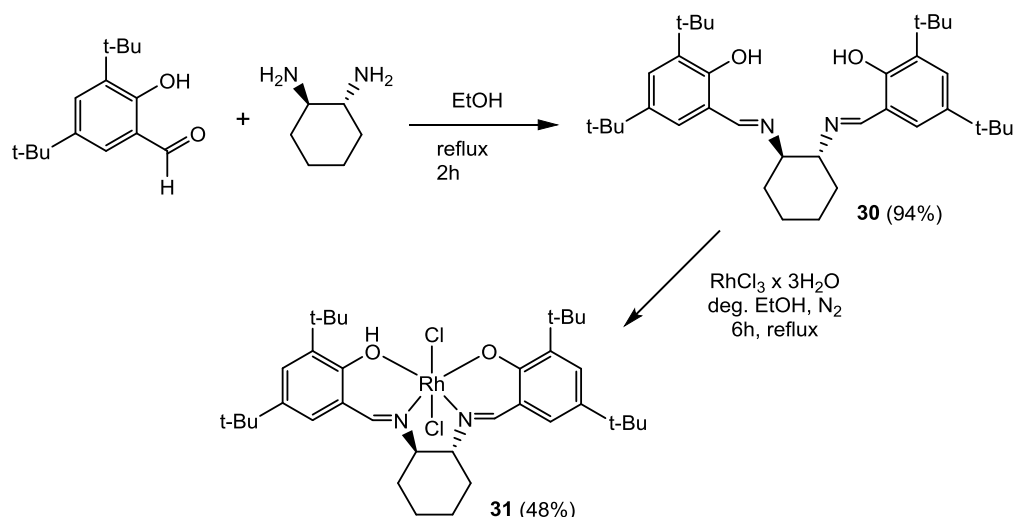
Scheme 82

[244] M. Tokunaga, J. F. Larrow, F. Kakiuchi, *Science* **1997**, 277, 936.

[245] J. A. Miller, W. C. Jin, S. T. Nguyen, *Angew. Chem. Int. Ed.*, **2002**, 41, 2953.

[246] A. Watanabe, T. Uchida, K. Ito, *Tetrahedron Lett.*, **2002**, 43, 4481.

[247] R. J. Cozens, K. S. Murray, B. O. West, *J. Chem. Soc. Chem. Commun.*, **1970**, 1262; C. A. Rogers, B. O. West, *J. Organomet. Chem.*, **1974**, 70, 445.

[248] D. J. Anderson, R. Eisenberg, *Inorg. Chem.*, **1994**, 33, 5378.

[249] R. A. Stinziano, S. T. Nguyen, L. M. Liable-Sands, A. L. Rheingold, *Inorg. Chem.*, **2000**, 39, 2452.

Formation of the complex was confirmed by an X-ray crystal structure (Figure 23, ORTEP diagram). The rhodium(III) center lies slightly above the salcen plane in an octahedral geometry with axial chloride ligands. The Rh-O(2) bond is 2.143 Å, quite a bit longer than the Rh-O(1) bond, that is 1.996 Å, and is consistent with a dative OH ligation mode.
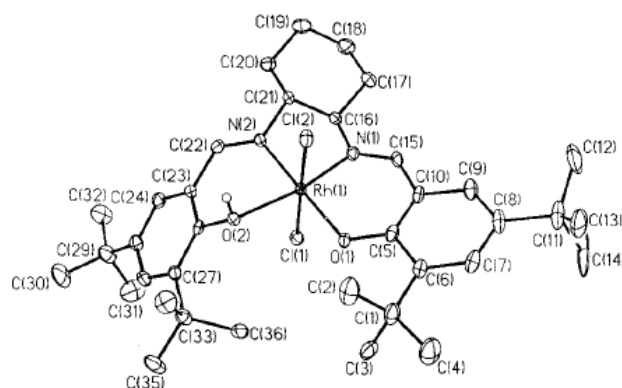
Figure 23

Complex **31** is the starting material for the synthesis of the (salcen)Rh(III) monochloride complex **32**, resulting from the first loss of HCl from the RhCl$_3$ and the salcen ligand. As such, it is remarkably stable toward the thermal elimination of a second molecule of HCl, and it is also air- and moisture-stable.

Conversion of complex **31** in the corresponding monochloro complex can be achieved through the reaction with metal carbonates, such as Cs$_2$CO$_3$, Na$_2$CO$_3$ or Ag$_2$CO$_3$, that was found to be the best choice in terms of yield (Scheme 83).
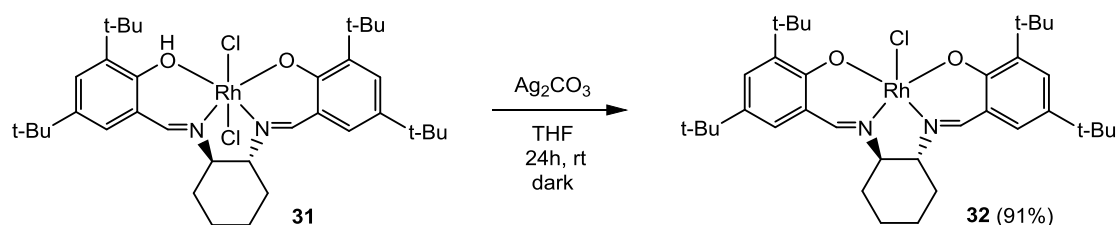
Scheme 83

We prepared complex **32** and tested its reactivity in the isoquinolone synthesis and in the hydroamination reaction of aminoallenes. Unfortunately, the complex showed no reactivity in both reactions, maybe due to excessive hindrance at the metal center. We planned therefore to reduce the sterical hindrance of the complex and contemporarily release another coordination site on the rhodium atom by removing a second chloride atom.

First attempt of chloride removal with Ag_2CO_3 failed, so we used instead $AgSbF_6$ in the same reaction conditions as above. In this way, we finally achieved the formation of the desired (salcen)Rh(III) complex **33** (Scheme 84).
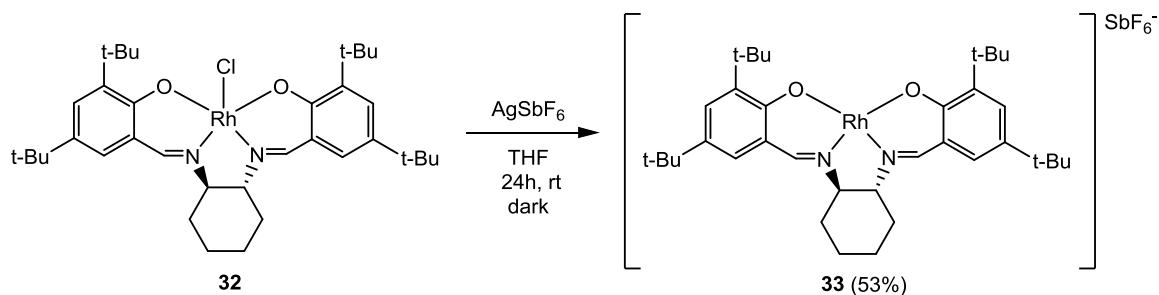
Scheme 84

Presence in this complex of two free binding site on the rhodium center should in theory enhance its reactivity in comparison to the monochlorinated analogue. Hoping that complex was more reactive, we tested it in the usual benchmark reactions. Unfortunately, also in this case results were lower than our expectations. The complex was not able to promote the hydroamination reaction; by contrast the formation of the dihydroisoquinolone product was successfully achieved, but in quite poor yields and without showing any enantiomeric excess (Scheme 85).
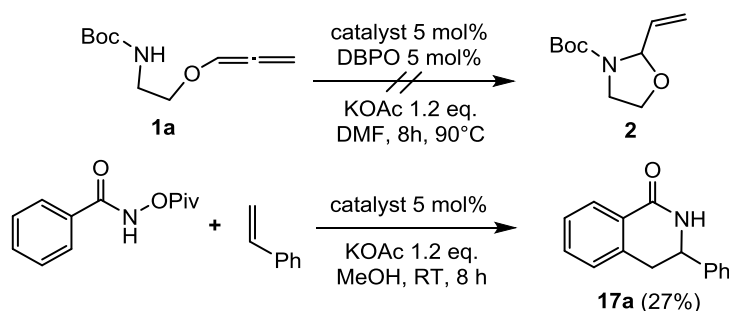
Scheme 85

Since the salen complex did not afford promising results, probably due to steric hindrance of the ligand, we decided to study another class of monoanionic oxazolines-containing tridentate ligands.

3.2.2.3. Oxazoline-containing tridentate ligands

Nitrogen ligands have played important roles in asymmetric catalysis, and among the most widespread nitrogen ligands (amines, Schiff bases, oxazolines, etc.) bis(oxazolines) are the most

successful ligands. Oxazolines are five-membered heterocycles, whose synthesis was first reported in 1884,[250] although ligands containing oxazolines groups have been extensively applied since 1970.

Use of chiral oxazolines as ligands in asymmetric catalysis was reported for the first time by Wimmer[251] in 1986, and thereafter a wide range of ligands having one, two, or more oxazoline rings incorporating various heteroatoms, additional chiral motifs and specific structural features have been successfully used in many asymmetric reactions.

C_2-symmetric bis(oxazolines) (BOX) are one of the most versatile and popular classes of chiral ligands in asymmetric catalysis, since C_2-symmetric ligands, when coordinated to the metal centre, form complexes that show a suitable orientation to favor a selective attack to one specific face and induce a good level of enantioselection.[252] In chiral oxazolines-containing complexes, the stereocenters on the oxazoline rings lies in close proximity to the coordination sphere at the metal center, thus having a huge influence on the stereochemical outcome of the reaction. These ligands are very attractive also because chiral oxazolines can be readily prepared starting from enantiomerically pure amino alcohols. Many different enantiomerically pure amino alcohols are commercially available, or can be easily obtained from the corresponding α-aminoacids by reduction,[253] making it easy to vary the ligand structure.

Bis(oxazolines) have become one of the most useful ligand classes for the synthesis of asymmetric complexes thanks to their ability to coordinate a huge variety of metal ions, as well as the excellent results in terms of reactivity and selectivity which can be accomplished in a number of enantioselective reactions.[254] In 1986 Pfaltz and coworkers[255] developed semicorrins (Figure 24), a new class of bidentate ligands having a rigid structure defined by the planar π-system and the two heterocyclic rings, making them attractive as ligands for asymmetric catalysis.
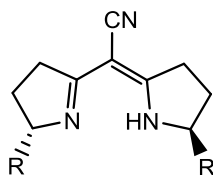
Figure 24

[250] R. Andreasch, *Monatsh. Chem.,* **1884**, 5, 33.
[251] H. Brunner, U. Obermann, P. Wimmer, *J. Organomet. Chem.,* **1986**, 316.
[252] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry,* **1998**, 9, 1; G. Helmchen, A. Pfaltz, *Acc. Chem. Res.,* **2000**, 33, 336; O. B. Sultcliffe, M. R. Bryce, *Tetrahedron: Asymmetry,* **2003**, 14, 2297.
[253] M. J. McKennon, A. I. Meyers, *J. Org. Chem.,* **1993**, 58, 3568.
[254] G. C. Hargaden, P. J. Guiry, *Chem. Rev.,* **2009**, 109, 2505; R. Rasappan, D. Laventine, O. Reiser, *Coord. Chem. Rev.,* **2008**, 252, 702.
[255] H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem. Int. Ed.,* **1986**, 25, 1005.

These complexes showed a very high enantioselectivity in copper-catalyzed asymmetric cyclopropanation of olefins[256] and in the cobalt-catalyzed conjugate addition of α,β-unsaturated esters and amides.[257] The electron-rich vinylogous amidine group imparts an electron-donating character to the ligands, reducing the electrophilicity of the metal center. This is useful for some kind of reactivity, but in other cases it is preferable to have a weak electron-donating character or even a π-acceptor ligand. In order to decrease this effect, in the early 90s different research groups independently reported the synthesis of neutral analogs of the semicorrins, the bis(oxazolines) (Figure 25).
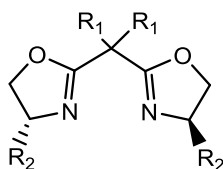
Figure 25

Bis(oxazolines) were then successfully applied with excellent results to a wide range of reactions, including cyclopropanation of olefins and Diels-Alder reaction. Modifications on the nature, size and flexibility of the linker and substituents on the two oxazolines, have led to the development of a great variety of BOX ligands that were used in many reactions such as aziridinations, cyclopropanations, allylic substitutions, Mukayama, Michael and many others.[258]

The C_2-symmetric bis(oxazoline) ligands are constituted of two homochiral oxazoline rings, connected through a central structure **X** (spacer) that could contain other heteroatoms, thus generating tri- or tetradentate ligands (Figure 26).
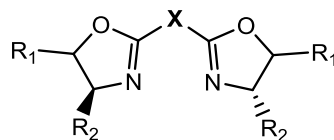
Figure 26

In these ligands coordination to the metal center occurs through the oxazoline nitrogen atoms, and potentially through another heteroatom present in the spacer. The degree of substitution of the oxazoline rings and the metal employed in the catalyst construction are crucial factors governing the efficiency and the applicability of these ligands in asymmetric catalysis.

[256] A. Pfaltz, *Acc. Chem. Res.,* **1993**, 26, 339.
[257] P. von Matt, A. Pfaltz, *Tetrahedron Asymmetry,* **1991**, 2, 691.
[258] G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.,* **2006**, 106, 3561.

Bis(oxazolines) with a carbon spacer between the two oxazolinic rings are the most commonly used, affording high selectivity in a wide range of metal-catalyzed reactions. In 2006, Sibi[259] reported the application of a bis(oxazoline) bearing phenyl substituents in enantioselective Diels-Alder reaction, achieving excellent enantiomeric excesses, up to 95% (Scheme 86).
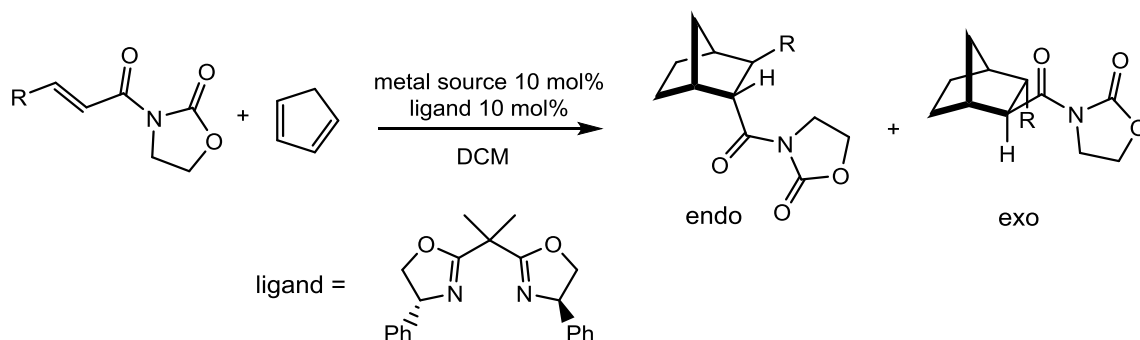
Scheme 86

The same ligand was reported to complex with copper salts like Cu(OTf)$_2$, and then successfully applied by Yamazaki[260] in the Friedel-Crafts reaction of a range of ethenetricarboxylate with various indoles in both high yields and enantiomeric excesses. Isopropyl-substituted bis(oxazolines) were reported to be effective for enantioselective Mannich-type reaction of imines in the presence of Lewis acids.[261]

In an attempt to increase the selectivity of bis(oxazolines), more bulky substituents were introduced in 4,4'-positions of the oxazolines. One of the first bulky oxazoline was reported in 1998 by Desimoni, that developed a ligand bearing 2-naphtyl groups in 4,4'-positions on the oxazoline rings. The ligand was employed in a Diels-Alder reaction between cyclopentadiene and N-alkenoyl-oxazolidin-2-ones, obtaining the desired product with higher ee's% as compared to the same bis(oxazoline) bearing a benzyl substituent.[262] Ligand bearing a 1-naphtyl substituent was compared to the benzyl substituted in Mukayama aldol reactions as copper(II)-complexes. The naphtyl-substituted ligand achieved higher enantioselectivities, although significantly lower than with the tert-butyl-substituted ligand.[263] Reiser studied the synthesis of bis(oxazoline) ligands which possess hydroxy groups at the stereogenic 4,4'-positions of the oxazoline rings, then applied in copper and zinc coordination. The ligands were tested in copper(II)-catalyzed conjugate addition of diethylzinc to

[259] M. P. Sibi, S. Manyem, H. Palencia, *J. Am. Chem. Soc.,* **2006**, 128, 13660.

[260] S. Yamazaki, Y. Iwata, *J. Org. Chem.,* **2006**, 71, 739.

[261] S. Nakamura, H. Sano, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Tetrahedron Lett.,* **2007**, 48, 5565.

[262] S. Crosignani, G. Desimoni, G. Faita, P. Righetti, *Tetrahedron,* **1998**, 54, 15721.

[263] H. L. van Lingen, J. K. W. van de Mortel, K. F. W. Hekking, F. L. van Delf, T. Sonke, F. P. J. T. Rutjes, *Eur J. Org. Chem.,* **2003**, 317.

cyclic enones with good results.[264] In a later work, Reiser et al. developed a copper(I) complex by using the same ligand as before. This ligand was then tested in a cyclopropanation reaction,[265] and the authors proposed that the hydroxy group in 4,4'-position on the oxazoline rings are able to form hydrogen bonds with the substrate, so controlling the direction of the attack.

Bis(oxazoline) ligands with a range of heteroatom-containing bridges linking the chiral oxazoline rings have been developed and applied as metal-complexes in asymmetric transformations. A peculiarity of this kind of ligands is that they can be neutral or ionic, depending on the heteroatoms. In Figure 27 are reported some examples of nitrogen-containing bridged oxazolines, so generically called aza-bis(oxazolines).

R = *i*Pr, Ph, *t*Bu
R$_1$ = H, Me
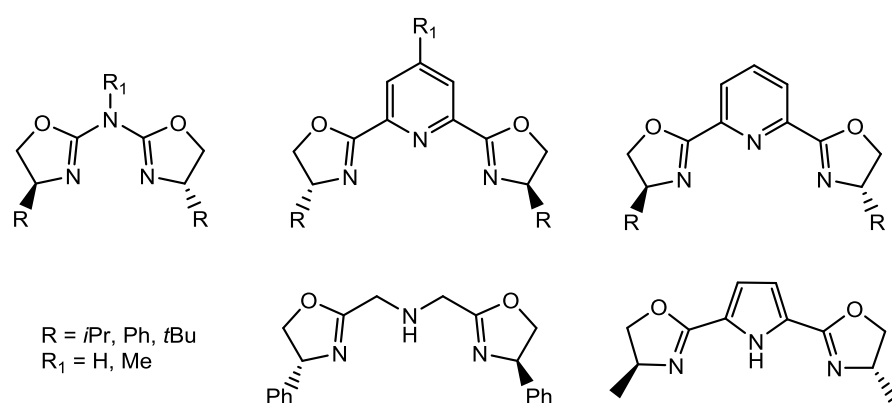
Figure 27

Ligands with a bridging NH or NMe were tested in palladium-catalyzed allylic alkylations and copper-catalyzed cyclopropanations with good results.[266] This kind of ligand was also reported to be immobilized on insoluble polymers, showing interesting activity.[267] Ligands bearing a pyridine ring between the two oxazolidines are defined as PyBOX, and have been successfully applied in different works by Nishiyama[268] and Shibasaki[269] to enantioselective aldol reductions and Diels-Alder reactions affording the desired products in high yields and enantiomeric excesses. Gimeno et al. reported the synthesis of a PyBOX-Rh(II) complex, then tested in the hydrosilylation of acetophenone.[270] Carrying out the reaction for 24 hours at room temperature resulted in high conversion rate and high

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[264] M. Schinneri, M. Seitz, A. Kaiser, O. Reiser, *Org. Lett.,* **2001**, 3, 4259.
[265] M. Schinneri, C. Bohm, M. Seitz, O. Reiser, *Tetrahedron: Asymmetry,* **2003**, 14, 765.
[266] M. Glos, O. Reiser, *Org. Lett.,* **2000**, 2, 2045.
[267] H. Werner, C. I. Hierras, M. Glos, A. Gissibl, J. M. Fraile, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.,* **2006**, 348, 125.
[268] T. Shiomi, J. Ito, Y. Yamamoto H. Nishiyama, *Eur. J. Org. Chem.,* **2006**, 5594.
[269] H. Usuda, A. Kuramochi, M. Kanai, M. Shibasaki, *Org. Lett.,* **2004**, 6, 4287.
[270] D. Cuervo, M. P. Gamasa, J. Gimeno, *J. Mol. Catal. A: Chem.,* **2006**, 249, 60.

enantioselectivity. Zhang[271] used a ligand with a CH_2NHCH_2 spacer between the two oxazoline rings in the Ru(II)-catalyzed hydrogenation of aromatic ketones, demonstrating the importance of the central NH, by comparing the excellent results achieved with the worse selectivity obtained with the use of a N-metylated analog. Gade proposed the synthesis of a monoanionic tridentate ligand, similar to the well-established family of PyBOX ligands but with a pyrrole ring instead of a pyridine as the spacer.[272] The main differences in comparison to PyBOXs are the monoanionic charge of the deprotonated molecule, and the more open structure deriving from the presence of the pyrrole ring. A palladium(II) complex with this ligand was found effective for Suzuki-type carbon-carbon cross coupling, with good yields both on activated and nonactivated substrates.

Willis recently reported a type of heterotridentate bis(oxazoline) (Figure 28), in which the two oxazoline rings are linked by a dibenzofuran moiety. The ligand was employed in the Mannich reaction[273] as well as in the addition of nitrenes to cyclopropanes[274] with excellent enantioselectivities in both cases.
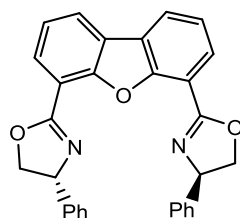
Figure 28

Pfaltz reported the use of a class of bis(oxazolines) called boraBOX, that have a BR_2 group as the spacer, in the enantioselective cyclopropanation of styrene.[275] The boraBOX complexes with copper showed similar reactivity of the corresponding BOX complexes, and bulkier substituents on the boron atom induced higher enantioselectivities.

As a further proof of the synthetic importance of bis(oxazoline) ligands, many other examples of their use as metal complexes were reported and extensively employed in different reactions. Worth of mention are bis(oxazolines) separated by a stereoaxis or by a stereoplane. Examples of the first type include ligands with biphenyl and binaphthyl backbone, or linked by a spiro moiety. These ligands are reported to form complexes with different metals, and among them copper(I) and palladium(II) were found to be particularly effective in cyclopropanations, Wacker-type reactions and

[271] Y. Jiang, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.,* **1998**, 120, 3817.

[272] C. Mazet, L. H Gade, *Organometallics,* **2001**, 20, 4144.

[273] G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociek-Kohn, M. C. Willis, *J. Am. Chem. Soc.,* **2007**, 129, 10632.

[274] M. P. Sibi, Z. Ma, C. P. Jasperse, *J. Am. Chem. Soc.,* **2005**, 127, 5764.

[275] C. Mazet, S. Roseblade, V. Koehler, A. Pfaltz, *Org. Lett.,* **2006**, 8, 1879.

more in general in a wide range of asymmetric reactions.[276] Bis(oxazolines) separated by a stereoplane include mainly ferrocenyl derivatives. In these ligands, a stereoplane replaces the usual stereocenters, in order to enhance the enantioselectivity of the tested reactions.

In 1998 Pfaltz and coworkers[277] reported the synthesis of heterotri- or polydentate bis(oxazolines) with a bridging phenolic or heterocyclic unit (Figure 29).

38
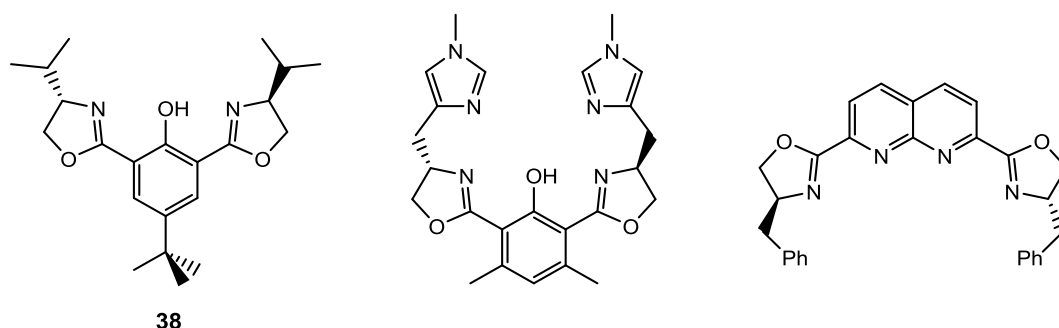
Figure 29

The phenol-derived ligands can be efficiently synthesized following different methodologies for the formation of the oxazoline rings, starting from amino alcohols and carboxylic acids.[278] The most efficient route was found to be the Vorbruggen and Krolikiewicz procedure, that involves the triphenylphosphine/CCl$_4$-mediated one-step conversion of carboxylic acids to oxazolines (Scheme 87).
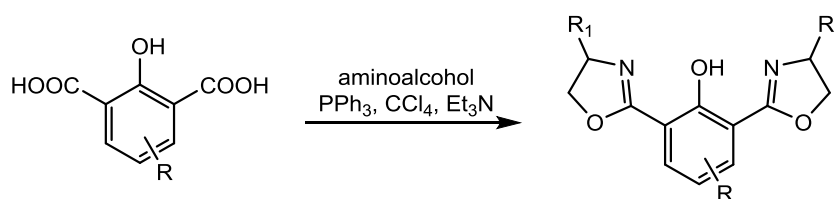
Scheme 87

This procedure usually used a large excess of triphenylphosphine, that made the isolation and purification of the products difficult. Therefore, introduction of t-butyl or methyl substituents on the phenol ring facilitated chromatographic separation and enhanced the solubility of the ligands.

[276] Y. Uozomi, H. Kyota, K. Kato, M. Ogarasawa, T. Hayashi, *J. Org. Chem.,* **1999**, 64, 1620; T. Kato, K. Marubayashi, S. Takizawa, H. Sasai, *Tetrahedron: Asymmetry,* **2004**, 15, 3693; M. B. Andrus, D. Asgari, J. A. Sclafani, *J. Og. Chem.,* **1997**, 62, 9365.

[277] C. J. Fahrni, A. Pfaltz, *Helv. Chim. Acta,* **1998**, 81, 491.

[278] H. Vorbruggen, H. Krolikiewicz, *Tetrahedron Lett.,* **1993**, 49, 9353; H. Nishiyama, M. Kondo, T. Nakamura, K. Itoh, *Organometallics,* **1991**, 10, 500; D. A. Evans, K. A- Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.,* **1991**, 113, 726.

The coordination behaviour of these ligands was investigated by Pfaltz,[279] leading to the formation of copper, nickel and zinc complexes, and detailed structural informations were reported through X-ray crystal-structure analysis. In the case of Zn(II) and Ni(II) complexes, formation of a dimeric species was observed.

We focused our attention on ligand **38** (Figure 29), that shows a suitable structure for acting as a tridentate monoanionic ligand when complexed to Rh(III). As previously said, tridentate monoanionic ligand can mimic the coordination mode typical of the cyclopentadienyl anion.

Following the five-steps procedure reported by Pfaltz and coworkers, we synthesized ligand **38**. The required dicarboxylic acid was synthesized in four steps starting from commercially available 4-(*tert*-butyl)phenol. The first step of the synthetic route involves introduction of two -CH_2OH fragments in both *ortho* positions of phenol, by reaction with formaldehyde in the presence of a strong base such as NaOH. As reported by the authors, this step proceed with a quite low yield (34%), significantly lowering the overall process yield. Slightly changing reaction conditions, we managed to greatly enhance reaction yield up to 92% (Scheme 88, path A and B).
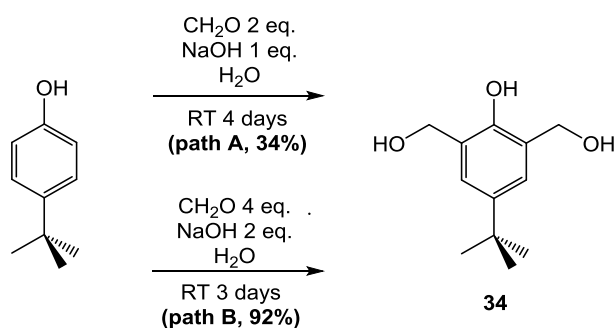
Scheme 88

Following steps were performed accordingly to Pfaltz's procedure. Synthetic pathway proceed with the selective protection of the phenol hydroxy group as a methylester, followed by oxidation of the benzylic hydroxy group to carboxylic acids. Deprotection of the phenol hydroxy group afforded the dicarboxylic acid. Reaction with (+)-valinol in the Vorbruggen conditions lead to the formation of ligand **38** in a moderate overall yield (26%)(Scheme 89).

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[279] C. J. Fahrni, A. Pfaltz, M. Neuberger, M. Zehnder, *Helv. Chim. Acta,* **1998**, 81, 507.
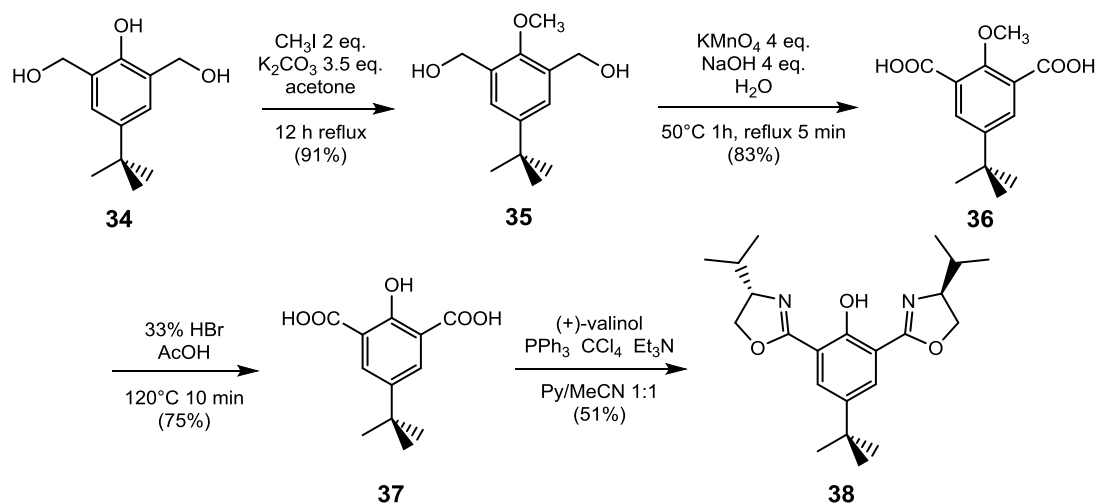
Scheme 89

With the ligand in our hand, we tried to synthesize a rhodium(III) complex through reaction with RhCl$_3$ x H$_2$O. First attempt was performed reacting the ligand **38** and RhCl$_3$ with triethylamine in dichloromethane at room temperature, but after 36 hours we recovered the unreacted ligand (Scheme 90, path A). Then we decided to utilize the same conditions successfully applied in the synthesis of the Tm^{Me2}RhCl$_3$ complex, refluxing the rhodium(III) salt and the ligand in ethanol. With this procedure we recovered the Rh(III) complex **39** in 49% yield (Scheme 90, path B). An improvement in the reaction yield up to 58% was achieved submitting the ligand to a previous treatment with NaH in tetrahydrofuran (Scheme 90, path C).
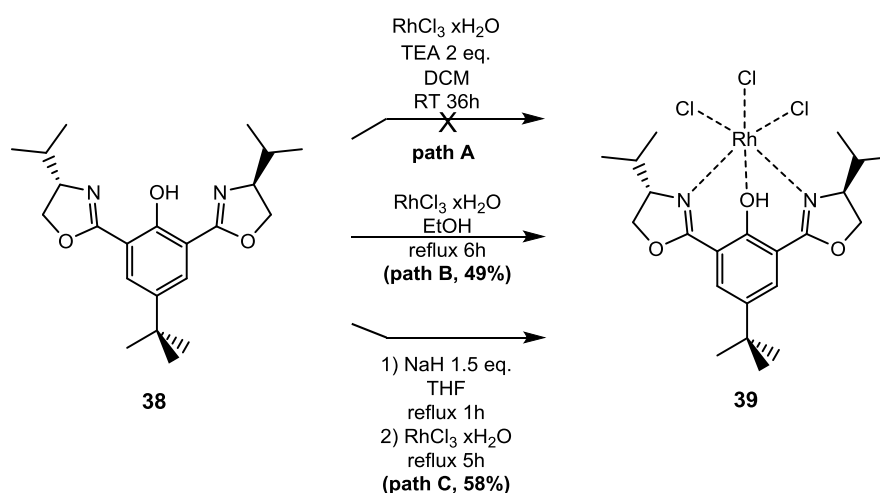
Scheme 90

Structure of complex **39** was confirmed by NMR spectra and mass analysis.

As we previously did for all the synthesized complexes, also the behaviour of complex **39** was investigated in the usual benchmark reactions. The complex showed a quite good reactivity, leading in both cases to reaction yields comparable to those achieved when $[RhCp*Cl_2]_2$ was used as the catalyst, and in the formation of the dihydroisoquinolone derivative we were also able to observe a small enantiomeric excess (Scheme 91).
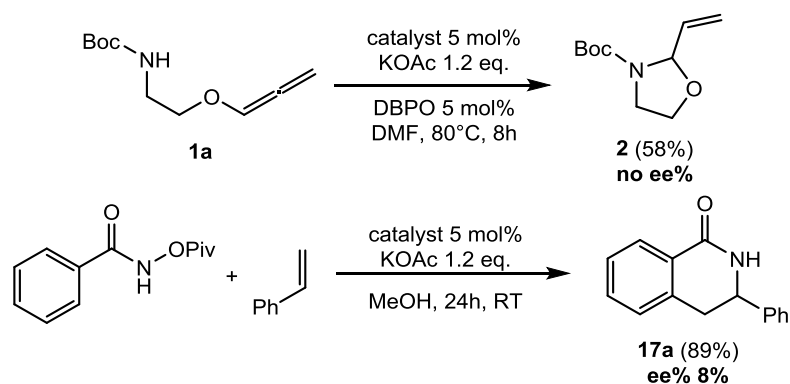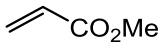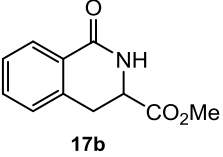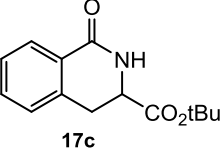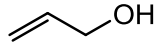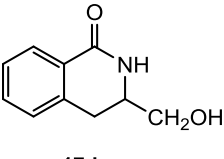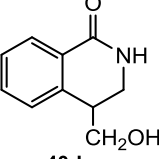
Scheme 91

We further investigate the formation of 3,4-dihydroisoquinolones testing different olefins in the same conditions as above. Lowering the load of the complex from 5 mol% to 2.5 mol% did not affect reaction yields. The products obtained were typically a mixture of regioisomers, but only in the case when allyl alcohol was employed they can be separated by flash column chromatography (Table 5, entry 4). Different sterically hindered olefins were tested, and better results in terms of enantiomeric excess were obtained with the bulky *tert*-butyl acrylate, although the ee% was still very low (Table 5, entry 3). Use of allyl alcohol and methyl acrylate lead to very poor enantiomeric excesses (entries 2 and 4).
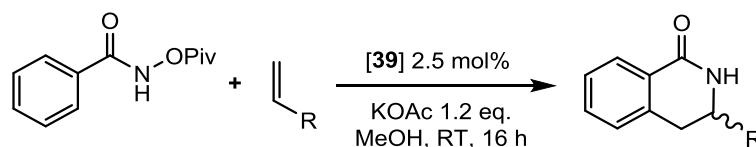
Entry	Alkene	Product	Yield	Ee%	Regioselectivity
1	⟋Ph	**17a**	89%	8%	>20:1

				Yield	ee	ratio
2	(CH2=CH)CO2Me	17b (isoquinolinone, CO2Me)		85%	4%	>20:1
3	(CH2=CH)CO2tBu	17c (isoquinolinone, CO2tBu)		94%	12%	4.5:1[a]
4	(CH2=CH)CH2OH	17d (CH2OH)	40d (CH2OH)	83%[b]	4%	1.2:1

[a] inseparable mixture of regioisomers
[b] isolated yield of both regioisomers

Table 5

Since using different olefins did not lead to a significant improvement in the enantiomeric excess, future development of this work will concern the use of different aminoalcohols with bulkier branched substituents, like for example *tert*-butyl, phenyl and naphthyl, in the synthesis of tridentate bis(oxazolines)-containing complexes. These aminoalcohols can introduce greater hindrance near the coordination sphere of the complex, thus maybe inducing an enhanced stereoselectivity, without affecting the reaction yields (Figure 30).
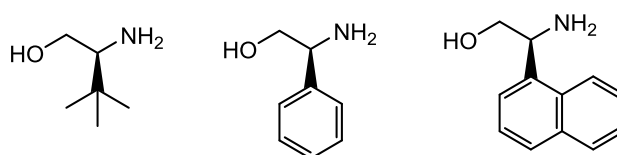
Figure 30

3.3. Conclusions

In this chapter we discussed the formation of new rhodium complexes from bidentate or polydentate ligands and the investigation of their behaviour in intramolecular hydroamination and intermolecular amination reactions.

Rhodium complexes with bidentate P,P and O,O ligands, tridentate N_3 and N,O,N ligands and a tetradentate N_2O_2 ligand were synthesized in quite satisfactory yields. Some complexes showed

excellent activity in the selected reactions, compared to the commercially available [RhCp*Cl$_2$]$_2$, while only the tridentate bis(oxazoline)-containing complex showed an enantiomeric excess in the amination reaction, although with very low values.

Further experiments will be made to modify the ligand structures and achieve conversion and enantiomeric excess.

3.4. Experimental section

General remarks

Air sensitive liquids and solutions were transferred via a gas-tight syringe or cannula. Removal of solvents was accomplished by evaporation on a Buchi rotary evaporator (water bath 40°C) or directly from the Schlenk using an oil pump.

The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution or a nynhidrine solution. Flash column chromatography was performed using silica gel (60 Å, particle size 40-64 μm) as stationary phase. ^{1}H- and ^{13}C-NMR spectra were recorded measured on a Bruker DRX 400MHz. Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl$_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded with a 400 MHz spectrometer operating at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard (CDCl$_3$, δ = 77.23 ppm).

Mass spectra (MS) were acquired on a HPLC-MS LCQ-Advantage Thermo Finnigan instrument mass spectrometer (ESI ion source). Chiral HPLC analysis were performed with a Shimadzu instrument equipped with a Diode Array detector. Elemental analyses were performed on a Perkin Elmer Series II CHNS/O Analyzer 2000. Infrared spectra were recorded on a standard FT-IR 550 Nicolet instrument. Melting point were determined on a Büchi B-540 instrument. Commercially available reagents were used as received, unless indicated otherwise.

Synthesis of the [((R)-BINAP)RhCp*Cl]BF$_4$ complex 18
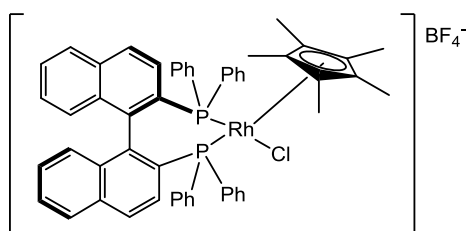
[Cp*RhCl$_2$]$_2$ (60 mg, 0.096 mmol) was added to a solution of (R)-BINAP (120 mg, 0.197 mmol) in DCM (5 mL). The solution was left to stir 10 minutes, then AgBF$_4$ (81 mg, 0.42 mmol) was added. Solution was left to stir overnight at room temperature in the absence of light. The crude was filtered on a

celite pad and washed twice with DCM. Solvent was removed under vacuum, then the crude was washed two times with hexane. Removal of solvent under vacuum afforded the complex in 52% yield as a purple solid.

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ = 1.42 (s, 15 H), 6.76-6.81 (m, 3H), 7.03-7.08 (m, 3H), 7.15 (t, *J* = 7.5 Hz, 3H), 7.32-7.35, (m, 3H), 7.46-7.51 (m, 5H), 7.56-7.59 (m, 4H), 7.64 (t, *J* = 7.4 Hz, 2H), 7.73-7.82 (m, 5H), 8.15 (d, *J* = 8.3 Hz, 2H), 8.37 (d, *J* = 8.5 Hz, 2H); MS[((R)-BINAP)RhCp*Cl]: *m/z* 895 (M$^+$)

Synthesis of the [((R)-BINOL)RhCp*] complex 19
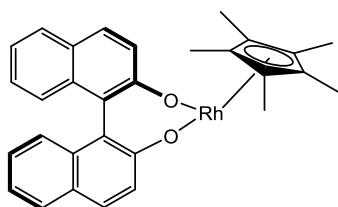
TEA (70 µL, 0.516 mmol) was added dropwise to a solution of (R)-BINOL (80 mg, 0.258 mmol) in DCM (6 mL). The solution was left to stir 30 minutes, then [Cp*RhCl$_2$]$_2$ (80 mg, 0.129 mmol) was added. Solution was left to stir 48 hours at room temperature. The crude was filtered on a silica pad and washed twice with a mixture DCM/EtOH 4:1. Solvent was removed under vacuum, then the crude was titritated with cold DCM/hexane. Filtration on buchner afforded the complex in 64% yield as an orange solid.

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ = 1.58 (s, 15H), 7.14 (d, *J* = 1.2 Hz, 2H), 7.32 (t, *J* = 1.4 Hz, 2H), 7.37-7.43 (m, 4H), 7.93 (d, *J* = 8.0 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H); ^{13}C-NMR (100 MHz, CD$_2$Cl$_2$): δ = 9.1 (q), 117.8 (d), 123.7 (d), 124.1 (d), 127.1 (d), 128.3 (d), 129.4 (s), 129.6 (s), 131.0 (d), 132.7 (s), 134.0 (s), 152.8 (s). MS: *m/z* 522 (M$^+$).

Synthesis of (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl 20
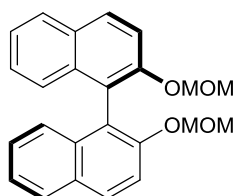
NaH (6.50 g, 60% in oil, 162.5 mmol) was suspended in dry THF (300 ml) in a round bottom flask at 0 °C under nitrogen atmosphere. A solution of (*R*)-BINOL (20.2 g, 70.5 mmol) in THF (100 mL) was added dropwise from a dropping funnel. After the addition, the mixture was stirred at 0 °C for 1 h, then allowed to warm up to room temperature in 15 min. After the mixture was re-cooled to 0 °C,

chloromethyl methyl ether (12.5 mL, 162.5 mmol) was slowly added from the dropping funnel. After the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous NH_4Cl (100 mL) was added to the flask, then the THF was removed *in vacuo*. The residue was extracted with CH_2Cl_2 (150 mL x 3). The organic layers were combined, washed with brine (250 mL), dried over Na_2SO_4, and concentrated in a 500 ml round bottom flask. Hexane (60 ml) was added and the flask was stirred at rotavapor (50°C, 330 mbar) for 3 minutes. Hexane was decanted off into e flask, and treatment (addition of hexane, rotavapor, decantation) was repeated two more times. Evaporation of hexane from the "mother liquors" gave 4.4 g of mineral oil from NaH. The decantation solid residue was dissolved in a minimal amount of DCM. A small amount of hexane was added and the mixture was cooled to 0 °C, until formation of a crystalline precipitate. Crystals were washed with hexane and a few mL of ice cold 1/1 hex/Et_2O mixture. The mother liquors were evaporated and crystallized again as described above. Compound **20** was recovered in 82 % yield as a white solid.

^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 3.18 (s, 6H), 5.03 (d, *J* = 6.6 Hz, 2H), 5.09 (d, *J* = 6.6 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 8.3 Hz, 2H), 7.36 (t, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H). MS: *m/z* 374 (M$^+$) Spectroscopic data of the product were in good agreement with the literature.[280]

Synthesis of (R)-3,3'-dihydroxy-2,2'bis(methoxymethoxy)-1,1'-binaphthyl 21
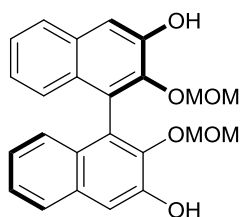
In a schlenk at -78 °C under nitrogen atmosphere, to a solution of **20** (18.92 g, 50.5 mmol) in THF (150 mL), a 1.6 M hexane solution of n-BuLi (76 mL, 122.0 mmol) was added dropwise by a dropping funnel. The color of the mixture changed from light yellow into brown. This mixture was allowed to warm to 0 °C and stirred for 1 h then cooled back to -78 °C. Trimethoxyborane (17.0 mL, 152.0 mmol) was added dropwise by syringe and the resulting mixture was allowed to warm to room temperature and stirred overnight. Removal of THF under high vacuum afforded the crude borate which was suspended in benzene (175 mL), and hydrogen peroxide (30% aqueous solution, 15.5 mL) was added dropwise at 0 °C. After putting a condenser with N_2 inlet on the schlenk's neck, the mixture was heated and refluxed for 2 h. After cooling to 10 °C, the resulting mixture was poured into 100 ml ice-

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[280] F. Romanov, M. Romanova-Michaelides, M. Pupier, A. Alexakis, *Chem. Eur. J.*, **2015**, 21, 5561.

cooled saturated Na_2SO_3 and extracted with ethyl acetate. The organic extracts were washed with brine and dried over Na_2SO_4. After removing solvents *in vacuo*, a pale orange foam was obtained in a 75% yield. The crude is pure enough to be used in the next step without further purification.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 3.40 (s, 6H), 4.64 (d, *J* = 6.3 Hz, 2H), 4.72 (d, *J* = 6.3 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.12 (dd, *J* = 1.2, 6.9 Hz, 2H), 7.34 (dd, *J* = 1.2, 6.9 Hz, 2H), 7.45 (br s, 2H), 7.51 (s, 2H), 7.78 (s, 2H). MS: *m/z* 406 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[281]

Synthesis of (R)-3,3'-dimethoxy-2,2'bis(methoxymethyl)-1,1'-binaphthyl 22
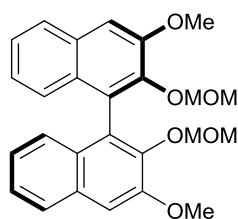
To a 1-necked flask containing crude **21** (20.9 g, 50 mmol), K_2CO_3 (31.1 g, 225 mmol) and acetone (450 ml) were added. Methyl iodide (15.6 mL, 250 mmol) was added and a condenser with a nitrogen inlet was placed at the flask neck. The mixture was heated and refluxed overnight. Acetone was evaporated off at rotavapor, and the mixture was dissolved in 250 ml of AcOEt. Then it was washed with water and the aqueous phase was extracted 2 more times with AcOEt. The organic extracts were washed with brine (200 mL) and dried over Na_2SO_4. Evaporation gave the crude **22** in 60% yield, that was directly used in the next step without further purification.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 2.57 (s, 6H), 4.03 (s, 6H), 4.83 (d, *J* = 6.0 Hz, 2H), 4.97 (d, *J* = 6.0 Hz, 2H), 7.10-7.18 (m, 4H), 7.30 (s, 2H), 7.36 (dd, *J* = 2.1, 6.0 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H). MS: *m/z* 434 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[281]

## Synthesis of (R)-3,3'-dimethoxy-BINOL 23
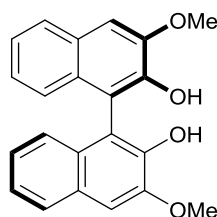
[281] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.*, **2003**, 125, 5139.

Crude **22** (12 g) was dissolved in dioxane (110 mL) and 37% concentrated aqueous HCl (3 mL) was added and the mixture was heated to 45 °C for 3.5 h. Dioxane was evaporated off, and ethyl acetate (100 ml) was added. The mixture was washed with water (100 mL) the aqueous phase was extracted 2 more times with AcOEt. The organic extracts were washed with brine (200 mL) and dried over Na_2SO_4. Evaporation of solvents gave **23** as a white solid in 84% yield.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 4.10 (s, 6H), 5.86 (br s, 2H), 7.13-7.22 (m, 4H), 7.30-7.36 (m, 4H), 7.78 (d, *J* = 8.2 Hz, 2H). MS: *m/z* 346 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[281]

Synthesis of the [((R)-3,3'-dimethoxy-BINOL)RhCp*] complex 24
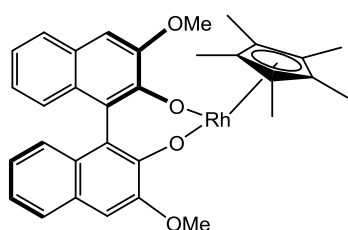
TEA (60 μL, 0.402 mmol) was added dropwise to a solution of product **23** (70 mg, 0.200 mmol) in DCM (6 mL). The solution was left to stir 30 minutes, then [Cp*RhCl$_2$]$_2$ (60 mg, 0.100 mmol) was added. Solution was left to stir 48 hours at room temperature. The crude was filtered on a silica pad and washed twice with a mixture DCM/EtOH 4:1. Solvent was removed under vacuum, then the crude was titritated with cold DCM/hexane. Filtration on buchner afforded the complex in 69% yield as a brown solid.

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ = 1.58 (s, 15H), 3.27 (s, 6H), 7.07-7.09 (m, 2H), 7.14-7.18 (m, 2H), 7.32-7.35 (m, 4H), 7.81-7.83 (m, 2H); ^{13}C-NMR (100 MHz, CD$_2$Cl$_2$): δ = 9.4 (q), 56.3 (q), 103.2 (d), 123.6 (d), 124.4 (d), 125.4 (s), 127.3 (d), 128.1 (d), 129.4 (s), 130.5 (s), 132.7 (s), 145.3 (s), 151.8 (s). MS: *m/z* 582 (M$^+$).

Synthesis of tris(pyrazol-1-yl)methanes 27 a-b
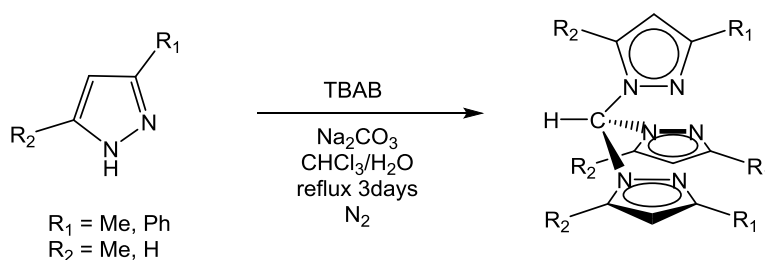
Na$_2$CO$_3$ (127 mg, 1.2 mmol) was carefully added under stirring to a solution of the proper pyrazole (0.2 mmol) and TBAB (3.2 mg, 0.01 mmol) in distilled and degassed water (0.4 mL). Solution was cooled to room temperature, and CHCl$_3$ (0.1 mL) was added. Solution was left to stir under reflux (70°C) for three days, then cooled to room temperature and filtered. Organic and aqueous layers were separated. Organic layer was washed three times with distilled water, dried on Na$_2$SO$_4$ and the solvent removed under vacuum. The crude was purified on cold finger, and the recovered solid filtered on a silica pad with DCM. Removal of the solvent under vacuum afforded the desired tris(pyrazol-1-yl)methane.

Tris(3,5-dimethyl-1*H*-pyrazol-1-yl)methane 27a
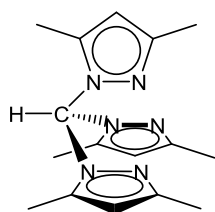
Yield 35%. White solid. M. p. 153-155°C. ^{1}H-NMR (400 MHz, acetone-*d*$_6$): δ = 2.03 (s, 9H), 2.06 (s, 9H), 5.91 (s, 3H), 8.20 (s, 1H). Spectroscopic data of the product were in good agreement with the literature.[282]

Tris(3-phenyl-1*H*-pyrazol-1-yl)methane 27b
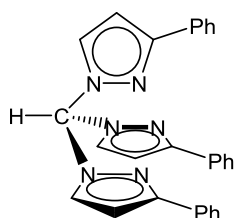
Yield 37%. White solid. M. p. 175°C. ^{1}H-NMR (400 MHz, acetone-*d*$_6$): δ = 6.90 (d, 3H, *J* = 2.4 Hz), 7.35 (tt, 3H, *J* = 1.2, 2.8 Hz), 7.38-7.44 (m, 6H), 7.88-7.92 (m, 6H), 8.10 (d, 3H, *J* = 2.4 Hz), 8.86 (s, 1H). Spectroscopic data of the product were in good agreement with the literature.[282]

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[282] D. L. Reger, T. C. Grattan, K. J. Brown, C. A. Little, J. J.S. Lamba, A. L. Rheingold, R. D. Sommer, *J. Organomet. Chem.* **2000**, 607, 120.

Synthesis of potassium tris(3,5-dimethyl-1*H*-pyrazol-1-yl)hydroborate 25
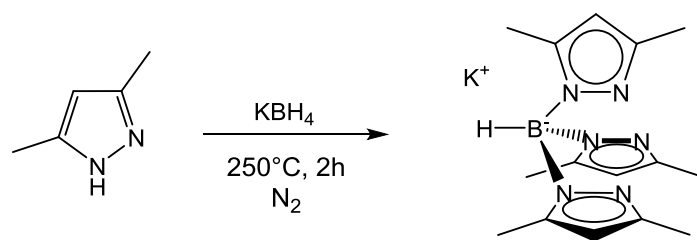
KBH$_4$ (44.2 mg, 0.82 mmol) and 3,5-dimethyl-pyrazole (300 mg, 3.12 mmol) were heated in sand bath to 250°C for 1 hour. The reaction mixture was cooled down to 90°C, and toluene (1 mL) was added. After precipitation of a sediment, the liquid fraction is recovered. Solid phase was washed with toluene (1 mL) and the two liquid fractions added together. The solvent was removed under vacuum affording the desired tris(pyrazol-1-yl)hydroborate.

Yield 28%. White solid. M. p. 169°C. IR (KBr pellet): 2452 cm^{-1}. ^{1}H-NMR (400 MHz, D$_2$O): δ = 1.78 (s, 9H), 2.05 (s, 9H), 5.81 (s, 3H). Spectroscopic data of the product were in good agreement with the literature.[283]

Synthesis of the [Tm^{Ph}RhCOD]BF$_4$$^-$ complex 29
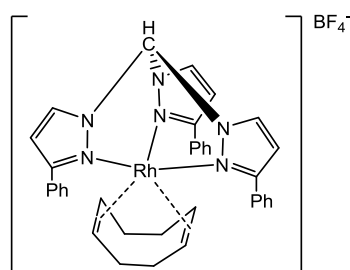
(CODRhCl)$_2$ (100 mg, 0.202 mmol) was added to a solution of Tm^{Ph} **27b** (188 mg, 0.43 mmol) in DCM (10 mL). The solution was left to stir 10 minutes, then AgBF$_4$ (81 mg, 0.42 mmol) was added. Solution was left to stir overnight at room temperature in the absence of light. The crude was filtered on a celite pad and washed twice with DCM. Solvent was removed under vacuum, then the crude was washed three times with hexane. Removal of solvent under vacuum afforded the complex in 78% yield as a green solid.

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ = 1.25-1.27 (m, 4H), 1.70-1.72 (m, 4H), 3.49 (s, 4H), 6.84 (d, *J* = 2.64 Hz, 2H), 7.55-7-63 (m, 9H), 7.97-7.99 (m, 6H), 8.31 (s, 3H), 8.87 (s, 1H). MS [Tm^{Ph}RhCOD]: *m/z* 653 (M$^+$).

[283] Kitajima N., Moro-oka Y., Kitagawa T., Tatsumi K., *J. Am. Chem. Soc.* **1992**, 114, 1277.

Synthesis of the [Tp^{Me2}RhCOD] complex 26
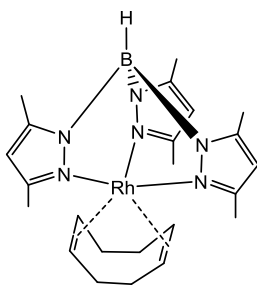
(CODRhCl)$_2$ (180 mg, 0.36 mmol) was added to a solution of Tm^{Me2} **25** (250 mg, 0.73 mmol) in DCM (7 mL). Solution was left to stir overnight at room temperature in the absence of light. The crude was filtered on a celite pad and washed twice with DCM. Solvent was removed under vacuum, then the crude was washed three times with hexane. Removal of solvent under vacuum afforded the complex in 73% yield as a yellow solid.

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ = 1.27-1.29 (m, 4H), 1.60-1.62 (m, 4H), 2.12-2.15 (m, 9H), 2.33-2.35 (m, 9H), 4.13 (s, 4H), 5.85 (s, 3H). MS [Tm^{Me2}RhCOD]: *m/z* 508 (M$^+$)

Synthesis of the [Tm^{Me2}RhCl$_3$] complex 28
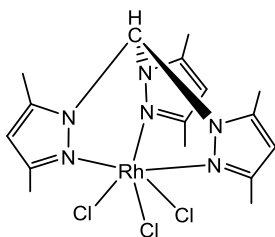
RhCl$_3$ x 3H$_2$O (100 mg, 0.38 mmol) was added to a solution of Tm^{Me2} **27a** (125 mg, 0.42 mmol) in EtOH (6 mL). Solution was left to stir 2 hours under reflux. The crude was filtered on a celite pad and washed twice with diethyl ether. Removal of solvent under vacuum afforded the complex in 81% yield as a red solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.48-2.50 (m, 9H), 2.64-2.66 (m, 9H), 6.29 (s, 3H), 7.82 (s, 1H). MS [Tm^{Me2}RhCl$_3$]: *m/z* 506 (M$^+$)

Synthesis of (R,R)-(-)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine 30
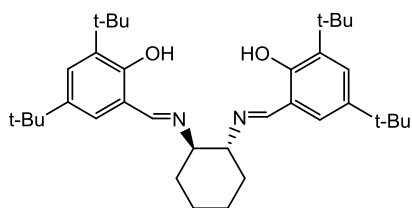
3,5-(*tert*-Butyl)salicylaldehyde (2.05 g, 8.8 mmol) and trans-1,2-diaminocyclohexane (0.5 g, 4.4 mmol) were dissolved in EtOH (15 mL) and stirred under reflux for 2 hours. The solution was cooled down in an ice bath until formation of a precipitate. Precipitate product was filtered off and dried under vacuum affording a yellow powder.

Yield: 94%. M. p.: 207°C. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.24 (s, 18H), 1.43 (s, 18H), 1.50-1.99 (m, 8H), 3.35-3.37 (m, 2H), 7.02 (s, 2H), 7.33 (s, 2H), 8.32-8.34 (m, 2H), 13.73 (br s, 2H). Spectroscopic data of the product were in good agreement with the literature.[284]

Synthesis of dichloro-1,2-cyclohexanediamino-*N*-(3,5-di-*tert*-butylsalicylidene)-*N'*-(3,5-di-*tert*-butyl-2-hydroxysalicylidene) Rh(III) 31
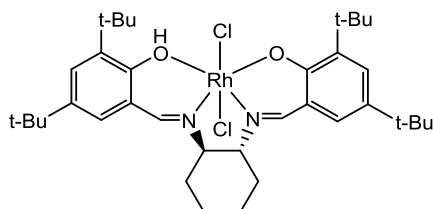
RhCl$_3$· 3H$_2$O (50 mg, 0.19 mmol)and the Schiff base ligand **30** (100 mg, 0.19 mmol) were added to a Schlenk flask with a magnetic stirrer bar. Degassed ethanol (10 mL) was transferred into the reaction flask via a cannula. The mixture was heated to reflux under N$_2$ for 6 hours and was then allowed to cool to room temperature. The solvent was removed in vacuo. The remaining solid was washed with ether (3 x 5 mL) and the insoluble material was dissolved in DCM and passed through a short column of celite. Solvent was evaporated under reduced pressure, affording a brown solid.

Yield: 48%. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.32 (s, 18H), 1.35-1.52 (m, 4H), 1.59 (s, 18H), 1.82-1.85 (m, 2H), 2.82-2.86 (m, 2H), 3.90-3.94 (m, 2H), 7.19 (d, *J* = 2.4 Hz, 2H), 7.55 (d, *J* = 2.4 Hz, 2H), 7.99 (s, 2H). Spectroscopic data of the product were in good agreement with the literature.[249]

[284] W. Xia, K. A. Salmeia, S. Vagin, B. Rieger, *Chem. Eur. J.*, **2015**, 21, 4384.

Synthesis of chloro-*trans*-1,2-cyclohexanediamino-*N-N'*-bis(3,5-di-*tert*-butylsalicylidene) Rh(III) 32
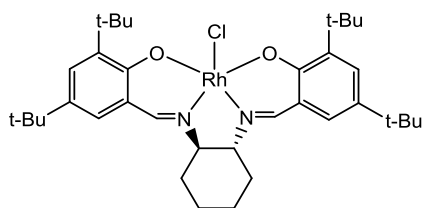
Complex **31** (130 mg, 0.18 mmol) and Ag_2CO_3 (24 mg, 0.09 mmol) were added to a Schlenk flask with a magnetic stirrer bar, in the presence of air. THF (10 mL) was added to the flask via a cannula. The flask was next covered with aluminium foil to exclude light. The mixture was then stirred at room temperature for 24 hours. The mixture was filtered through celite to remove any insoluble solids, and the solvent was evaporated under reduced pressure, affording a dark brown solid.

Yield: 91%. ^{1}H-NMR (400 MHz, THF-d_8): 1.34 (s, 18H), 1.53 (s, 18H), 1.65-1.69 (m, 2H), 1.84-1.87 (m, 2H), 1.97-2.03 (m, 2H), 2.90-2.93 (m, 1H), 3.00-3.04 (m, 1H), 3.70-3.73 (m, 2H), 7.12 (t, J = 2.6 Hz, 2H), 7.41 (t, J = 2.9 Hz, 2H), 8.11 (s, 1H), 8.25 (s, 1H). Spectroscopic data of the product were in good agreement with the literature.[249]

Synthesis of *trans*-1,2-cyclohexanediamino-*N-N'*-bis(3,5-di-*tert*-butylsalicylidene) Rh(III) hexafluoroantimonate 33
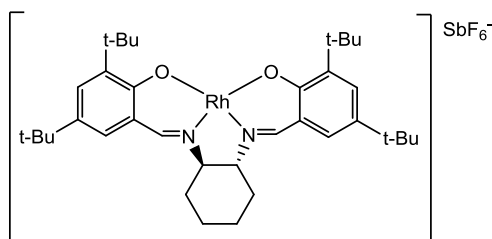
Complex **32** (200 mg, 0.29 mmol) and $AgSbF_4$ (100 mg, 0.29 mmol) were added to a Schlenk flask with a magnetic stirrer bar. THF (15 mL) was added to the flask via a cannula. The flask was next covered with aluminium foil to exclude light. The mixture was then stirred at room temperature for 24 hours. The mixture was filtered through celite to remove any insoluble solids, and the solvent was evaporated under reduced pressure, affording a dark brown solid.

Yield: 53%. ^{1}H-NMR (400 MHz, THF-d_8): 1.36 (s, 18H), 1.55 (s, 18H), 1.65-1.69 (m, 2H), 1.83-1.88 (m, 2H), 1.97-2.04 (m, 2H), 2.89-2.95 (m, 1H), 3.00-3.05 (m, 1H), 3.70-3.73 (m, 2H), 7.12 (t, J = 2.6 Hz, 2H), 7.41 (t, J = 2.9 Hz, 2H), 8.14 (s, 1H), 8.27 (s, 1H). MS [LRh]: *m/z* 647 (M$^+$).

Synthesis of 5-(*tert*-butyl)-2-hydroxybenzene-1,3-dimethanol 34
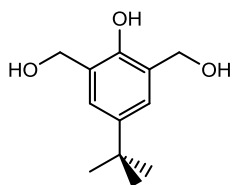
4-(*tert*-Butyl)phenol (1.5 g, 10 mmol) was dissolved in a mixture of 36% aqueous formaldehyde (3 mL, 40 mmol) and 35% aqueous NaOH solution (1.6 mL, 20 mmol) in water (20 mL). The resulting solution was allowed to stand at room temperature for 3 days. The solution was treated with HCl 2M until pH 6, then extracted with AcOEt (3 x 20 mL). Combined organic phase was dried on Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified on silica gel column (petroleum ether - AcOEt 6:4), affording **34** as a white solid.

Yield 92%. M. p. 74°C. ^{1}H-NMR (400 MHz, CDCl₃): δ = 1.25 (s, 9H), 2.10-2.50 (br s, 2H), 4.78 (d, *J* = 2.88 Hz, 4H), 7.07 (s, 2H). MS: *m/z* 210 (M[+]). Spectroscopic data of the product were in good agreement with the literature.[285]

Synthesis of 5-(*tert*-butyl)-2-methoxybenzene-1,3-dimethanol 35
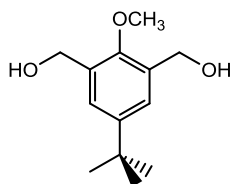
To a solution of **34** (1.8 g, 8.6 mmol) in acetone (12 mL) K_2CO_3 (4.14g, 30 mmol) and MeI (1.1 mL, 17 mmol) were added. The resulting suspension was stirred vigorously under reflux (45°C) for 12h, then cooled to room temperature. Solvent was removed under reduced pressure, then the crude was dissolved in distilled water (15 mL) and extracted with Et_2O (3 x 15 mL). Combined organic phases were dried on Na_2SO_4 and the solvent removed under reduced pressure, affording **35** as a yellow oil.

Yield 91%. ^{1}H-NMR (400 MHz, CDCl₃): δ = 1.27 (s, 9H), 2.2-2.30 (br s, 2H), 3.83 (s, 3H), 4.70 (d, *J* = 4.7 Hz, 4H), 7.33 (s, 2H). MS: *m/z* 224 (M[+]) Spectroscopic data of the product were in good agreement with the literature.[285]

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[285] C. J. Fahrni, A. Pfaltz, *Helvetica Chimica Acta*, **1998**, 81, 491.

**Synthesis of 5-(*tert*-butyl)-2-methoxyisophtalic acid 36**
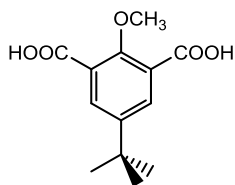
To a solution of NaOH (1.15 g, 29 mmol) in water (50 mL), **35** (1.6 g, 7.2 mmol) was added. The mixture was heated to 50°C, and under vigorous stirring KMnO$_4$ (4.5 g, 29 mmol) was added in portions. After stirring at 50°C for 1 hour, the mixture was refluxed for 5 minutes and cooled down to 60°C. Excess of KMnO$_4$ was cautiously destroyed with EtOH. The warm mixture was filtered through a pad of celite and washed with hot 5% aqueous NaOH solution. After chilling in an ice bath, the filtered solution was acidified with HCl conc. until pH 1. Solution was extracted with AcOEt (3 x 15 mL), then combined organic phases were washed with water and dried on Na$_2$SO$_4$ and the solvent removed under reduced pressure, affording **36** as a white solid.

Yield 83%. M. p. 180°C. IR: 1707, 1675, 1305 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.37 (s, 9H), 4.09 (s, 3H), 8.33 (s, 2H). MS: *m/z* 252 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[285]

**Synthesis of 5-(*tert*-butyl)-2-hydroxyisophtalic acid 37**
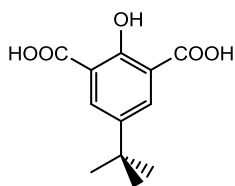
A suspension of **36** (2.1 g, 8.3 mmol) in 33% HBr/AcOH (10 mL) was heated to 120°C with vigorous stirring until the gas evolution subsided (10 min). The solution was cooled to room temperature and diluted with distilled water until the product started to precipitate. The precipitated product was filtered off, washed with water and dried in vacuo affording **37** as white solid.

Yield 75%. M. p. 256°C. IR: 2965, 1710, 1683 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-*d$_6$*): δ = 1.25 (s, 9H), 2.45-2.50 (br s, 1H), 7.94 (s, 2H), 12.17-12.43 (br s, 2H). MS: *m/z* 238 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[285]

Synthesis of 4-(*tert*-butyl)-2,6-bis[(4S)-4,5-dihydro-4-isopropyloxazol-2-yl]phenol 38
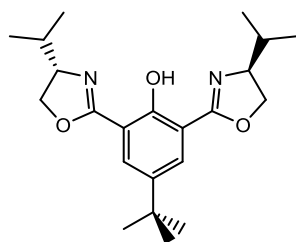
To a solution of **37** (1 g, 4.2 mmol) and (+)-L-valinol (0.95 g, 9.2 mmol) in anhydrous pyridine/MeCN 1:1 (14 mL) under N_2, Et_3N (4.2 mL) and CCl_4 (2.8 mL) were added. To the resulting homogeneous mixture, a solution of PPh_3 (6.6. g, 25 mmol) in anhydrous pyridine/MeCN 1:1 (14 mL) was gradually added within 2 hours, maintaining the temperature below 25°C. After stirring overnight at room temperature, the precipitated salt was filtered off and washed with MeCN. The filtrate was diluted with water (40 mL) and extracted with cyclohexane (3 x 20 mL). The combined organic phases was dried on Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified on silica gel chromatography (petroleum ether/AcOEt 7:3) affording **38** as a yellow solid.

Yield 51%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.9 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H), 1.31 (s, 9H), 1.82-1.96 (m, 2H), 4.12-4.15 (m, 4H), 4.40-4.43 (m, 2H), 7.84 (s, 2H). MS: *m/z* 372 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[285]

Synthesis of the complex 39
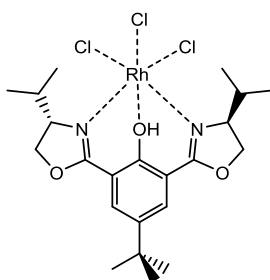
Path A: a solution of **38** (0.2 g, 0.53 mmol) and $RhCl_3$ xH_2O (0.15 g, 0.53 mmol) in degassed EtOH (15 mL) was stirred under N_2 atmosphere at reflux for 6 hours, then cooled down to room temperature. The solvent was partially removed under reduced pressure, and cold hexane was added until the formation of a precipitate. The precipitated product was filtered off, washed with cold hexane and dried in vacuo affording **39** as brownish solid in 49% yield.

Path B: to a solution of **38** (0.2 g, 0.53 mmol) in THF (12 mL), NaH (14 mg, 0.59 mmol) was added and the solution was heated to reflux. After 1 hour, $RhCl_3$ xH_2O (0.15 g, 0.53 mmol) was added, and the

temperature was maintained for 5 hours. The solution was cooled down to room temperature, and after careful addition of MeOH, solvent was removed under reduced pressure. The crude was diluted in DCM (15 mL) and washed twice with water (2 x 15 mL). The organic layer was partially evaporated under reduced pressure, then cold hexane was added until formation of a precipitate. The precipitated product was filtered off, washed with cold hexane and dried in vacuo affording **39** as brownish solid in 58% yield.

^{1}H-NMR (400 MHz, CD$_2$Cl$_2$): δ = 0.76 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.35 (s, 9H), 2.27-2.35 (m, 1H), 2.69-2.77 (m, 1H), 4.53 (d, J = 7.8 Hz, 2H), 4.64 (t, J = 7.5 Hz, 1H), 4.74-4.83 (m, 1H), 4.91 (t, J = 9.7 Hz, 1H), 4.95-5.01 (m, 1H), 7.92 (d, J = 2.8 Hz, 1H), 8.13 (d, J = 3.0 Hz, 1H), 12.43 (br s, 1H). ^{13}C-NMR (100 MHz, CD$_2$Cl$_2$): δ = 13.5 (q), 16.6 (q), 18.6 (q), 28.2 (d), 30.8 (d), 33.9 (s), 63.4 (d), 67.8 (t), 69.2 (t), 72.3 (t), 110.0 (s), 114.8 (s), 132.8 (d), 136.9 (d), 137.7 (s), 160.8 (s), 169.2 (s), 169.8 (s). MS [(L$_2$Rh$_2$Cl$_4$)H$_2$OH$_3$O$^+$]: m/z 1027 (M$^+$).

Procedure for the Rh-catalyzed synthesis of 3-phenyl-3,4-dihydroisoquinolin-1(2H)-one 17a
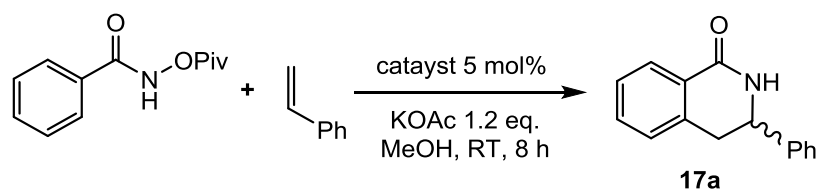
Without protective precaution from air and moisture, catalyst (0.05 mmol), eventually dibenzoylperoxide (0.05 mmol) and KOAc (1.2 mmol) were added to a solution of N-(pivaloyloxy) benzamide (1 mmol) in MeOH (5 mL). After five minutes, styrene was added. The solution was stirred at room temperature for 8 hours, then the solvent was removed under reduced pressure and the crude product was purified on a silica gel column affording **17a**. An HPLC analysis was performed for the determination of the enantiomeric excess, using a iPrOH-Hexane 10:90 mixture as eluent with a 0.5 mL/min flow.

3-Phenyl-3,4-dihydroisoquinolin-1(2H)-one 17a
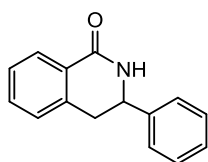
White solid. IR: 1664 cm^{-1}. M. p. 136°C. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 3.10-3.23 (m, 2H), 4.86 (m, 1H), 6.38 (br s, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.31-7.45 (m, 6H), 7.46 (m, 1H), 8.12 (dd, J = 1.2, 7.4 Hz, 1H). MS: m/z 223 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[286]

Results achieved with different complexes are reported in Table below.

| Catalyst	Yield of 17a
18	17%
19	82%
24	98%
26	-
28	-
29	-
33	27%

Table 6

Procedure for the synthesis of 3,4-dihydroisoquinolones 17b-d, 40d catalyzed by complex 39
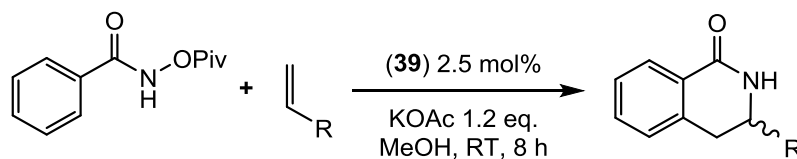
Without protective precaution from air and moisture, catalyst **39** (0.025 mmol) and KOAc (1.2 mmol) were added to a solution of N-(pivaloyloxy) benzamide (1 mmol) in MeOH (5 mL). After five minutes the desired olefin was added. The solution was stirred at room temperature for 8 hours, then the solvent was removed under reduced pressure and the crude product was purified on a silica gel column affording the products **17b-d, 40d**. An HPLC analysis was performed for the determination of the enantiomeric excess, using a iPrOH-Hexane 10:90 mixture as eluent with a 0.5 mL/min flow.
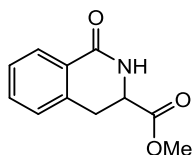
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[286] N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.*, **2011**, 133, 6449.

**3-Phenyl-3,4-dihydroisoquinolin-1(2H)-one 17a**
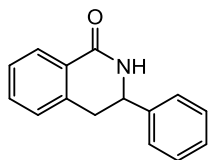
Yield 89%. Ee 8%.

**Methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate17b**

Yield 85%. Ee 4%. White solid. IR: 1659, 1704 cm^{-1}. M. p. 118°C. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 3.20 (dd, J = 9.4, 15.7 Hz, 1H), 3.31 (dd, J = 5.2, 15.7 Hz, 1H), 4.37-4.42 (m, 1H), 6.74 (br s, 1H), 7.22 (d, J = 7.5 Hz), 7.33-7.47 (m, 2H), 8.05 (d, J = 7.7 Hz). MS: m/z 205 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[286]

***Tert*-butyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 17c**
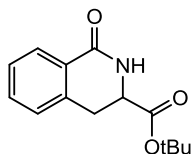
Yield 94%. Ee 12%. White solid. IR: 1660, 1698 cm^{-1}. M. p. 123°C. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.44 (s, 9H), 3.14 (dd, J = 9.6, 15.5 Hz, 1H), 3.21 (dd, J = 5.1, 15.5 Hz, 1H), 4.23-4.27 (m, 1H), 6.62 (br s, 1H), 7.21 (d, J = 7.5 Hz), 7.34-7.44 (m, 2H), 8.04 (d, J = 7.7 Hz). MS: m/z 247 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[286]

3-(Hydroxymethyl)-3,4-dihydroisoquinolin-1(2H)-one 17d
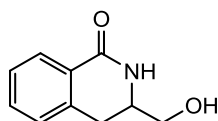
Yield 83% (with **40d**). Ee 4%. White solid. IR: 1656, 3204 cm^{-1}. M. p. 120°C. ^{1}H-NMR (400 MHz, CDCl$_3$):

δ = 2.43 (br s, 1H), 2.90-2.94 (m, 2H), 3.63-3.80 (m, 2H), 5.53 (m, 1H), 7.21-7.47 (m, 4H), 8.04 (m, 1H). MS: *m/z* 177 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[286]


4-(Hydroxymethyl)-3,4-dihydroisoquinolin-1(2*H*)-one 40d
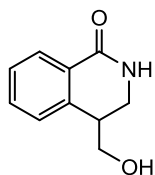
Yield 83% (with **17d**). Ee 4%. White solid. IR: 1629, 3124 cm^{-1}. M. p. 123°C. ^{1}H-NMR (400 MHz, CDCl$_3$):

δ = 2.52 (br s, 1H), 3.01-3.07 (m, 1H), 3.71-3.79 (m, 4H), 6.72 (br s, 1H), 7.26-7.29 (m, 1H), 7.38-7.49 (m, 2H), 8.06 (m, 1H). MS: *m/z* 177 (M$^+$). Spectroscopic data of the product were in good agreement with the literature.[286]

General procedure for the Rh-catalyzed synthesis of 3-(*tert*-butoxycarbonyl)-2-vinyl-oxazolidine 2
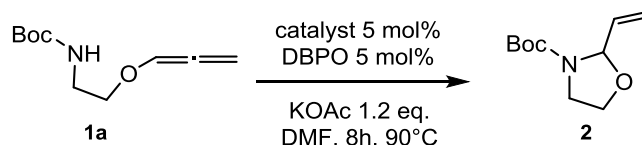
Without protective precaution from air and moisture, catalyst (0.05 mmol), dibenzoylperoxide (0.05 mmol) and KOAc (1.2 mmol) were added to a solution of *O*-allenyl *N*-Boc-2-aminoethanol (1 mmol) in DMF (5 mL). The solution was heated to 90°C and stirred for 8 hours, then the solvent was removed under reduced pressure and the crude product was purified on a silica gel column affording compound **2**. Spectroscopic data of the product were reported in the previous chapter.

Results are reported in Table below.

Catalyst	Yield of 2
18	-
19	53%
24	64%
26	-
28	-

29	-
33	-
39	58%

Table 7