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Transition metal catalyzed reactions on allenic substrates for heterocyclic synthesis

Ph. D. dissertation of

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“If you put your mind on it, you can accomplish everything”.
(Martie McFly, citing Emmett Lathrop “Doc” Brown, *Back to the Future Part I*)

“Quid est tempus? Si nemo a me quaerat, scio; si quaerenti explicare velim, nescio!”
(S. Agostino, *Confessioni*, XI, 14)

Ero giunto sulle soglie dell' adolescenza e ancora mi nascondevo tra le radici dei grandi alberi del bosco a raccontarmi storie. Un ago di pino poteva rappresentare per me un cavaliere, o una dama, o un buffone; io lo facevo muovere dinanzi ai miei occhi e m’esaltavo in racconti interminabili. Poi mi prendeva la vergogna di queste fantasticherie e scappavo.
E venne il giorno in cui anche il dottor Trelawney m'abbandonò. Un mattino nel nostro golfo entrò una flotta di navi impavesate, che battevano bandiera inglese, e si mise alla rada. (...). Io non avevo visto nulla. Ero nascosto nel bosco a raccontarmi storie.
Lo seppi troppo tardi e presi a correre verso la marina, gridando: - Dottore! Dottor Trelawney! Mi prenda con sè! Non può lasciarmi qui, dottore!
Ma già le navi stavano scomparendo all' orizzonte e io rimasi qui, in questo nostro mondo pieno di responsabilita e di fuochi fatui.
(Italo Calvino, *Il visconte dimezzato*)

“Bravu nin, stüdia; perché se ta stüdiat, ta podat fa ul magütt; ma se ta stüdiat mia, ta gh’et da fall, e basta.”
(Giuseppe “*Pin*” Rigamonti. Ul me nonu. Magütt.)

Ai miei Maestri, tutti, dalle suore che avevo all’asilo fino a quelli che ancora devo conoscere. Ai miei Amici straordinari, che continuano a insegnarmi qualcosa ogni giorno. A Bizzarone, che è il posto più bello del mondo.

Alla mia Mamma e al mio Papà.

Grazie.

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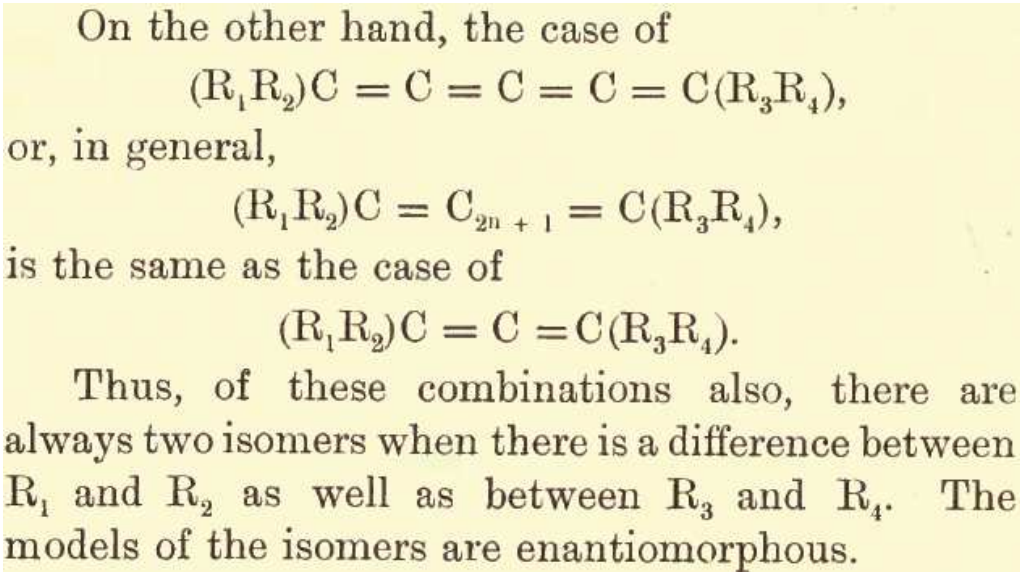
Contents

Introduction

Allenes: a bit of history

The history of allenes in chemistry has relatively recent roots. While chemical theories lose the traces of their genesis in ancient Greek's time[1], chemical compounds later known as allenes kept nearly sleeping regardless of any scientific or historic event till 1874. At that time, Jacobus van 't Hoff, a Ph. D. student in Utrecht University, accounted for the phenomenon of optical activity by assuming that the chemical bonds between carbon atoms and their neighbors were directed towards the corners of a regular tetrahedron. This three-dimensional structure perfectly accounted for the isomers found in nature, and van 't Hoff published his work on the geometry of science in his book *La chimie dans l'espace* in 1874.[2] Although initially strongly criticized by the scientific community,[3] this work was revolutionary, and later became indispensable in Science. However, van 't Hoff decided to leave the field of pure organic chemistry, going on with researches on chemical equilibrium and thermodynamics that would have brought to him the first Nobel Prize in Chemistry.[4] But some lines of his book were already waking up a new field in organic chemistry.



On the other hand, the case of

$$(R_1R_2)C = C = C = C = C(R_3R_4),$$

or, in general,

$$(R_1R_2)C = C_{2n+1} = C(R_3R_4),$$

is the same as the case of

$$(R_1R_2)C = C = C(R_3R_4).$$

Thus, of these combinations also, there are always two isomers when there is a difference between R_1 and R_2 as well as between R_3 and R_4. The models of the isomers are enantiomorphous.

Extract from *Arrangements of Atoms in Space*, 2nd ed. (1898), Longmans, Greene & Co.; English translation of *La chimie dans l'éspace*

[1] G. Lloyd, *Early Greek Science: Thales to Aristotle*, **1970**, London; Chatto and Windus, 45.
[2] J. H. van 't Hoff, *La chimie dans l'espace*, **1875**, Rotterdam; P. M. Bazendijk, 29.
[3] One such critic was the editor of the *Journal für praktische Chemie*, A. Kolbe, who stated: "*A Dr. H. van 't Hoff (…) has no liking, apparently, for exact chemical investigation. He has considered it more comfortable to mount Pegasus (…) and to proclaim in his 'La chimie dans l'espace' how the atoms appear to him to be arranged in space, when he is on the chemical Mt. Parnassus which he has reached by bold flight.*" (www.wikipedia.com)
[4] Nobel Lectures, *Chemistry 1901-1921*, Elsevier Publishing Company, Amsterdam.

These lines were entirely predictive, van 't Hoff lacking any experimental evidence. Indeed, he was the first to predict the correct core structure of a cumulated diene moiety, as well as their axial chirality. Such a particular atomic arrangement was immediately thought by the scientific community to be too extreme to be real, and it is quite interesting to note that the first synthesis of an allene (pentadienoic acid) was conducted to prove the nonexistence of this class of compounds.[5] Its failure, or in other words its success, didn't help spreading the chemical interest towards allenes; mainly due to the tedious methods of preparation and the mistaken belief that the cumulate double-bond system would prove to be relatively unstable, allenes kept being regarded as chemical curiosities for some decades. Moreover, at that time, with the analytical tools available, it was almost impossible to distinguish between allenes and the corresponding alkynes. Only when IR and Raman spectroscopy were introduced as tools for structural investigation it was possible to prove, by its characteristic allenic C-C vibration at about 1950 cm^{-1}, that Burton and von Pechmann had indeed synthesized an allenic molecule.[5b]

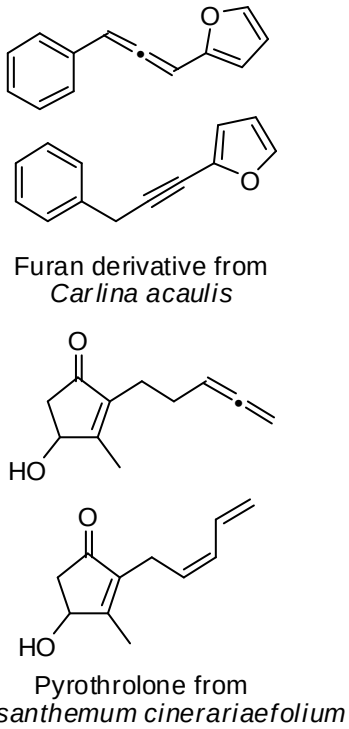


Figure 1. Compounds misbelieved as allenes. Proposed (above) and correct (below) structures.

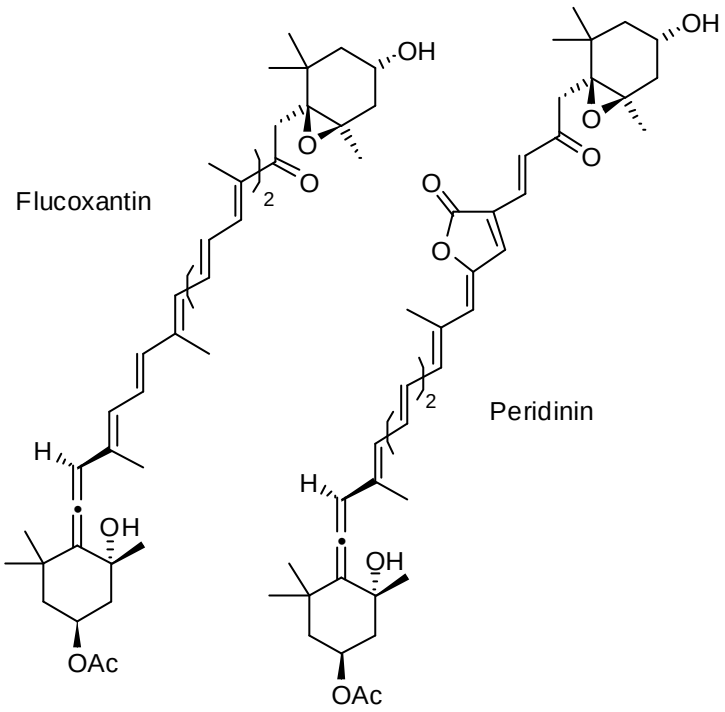


Figure 2. Allenic compounds whose structure was correctly assigned more than 50 years after their discovery.

The new techniques permitted to turn out as incorrect many assignments of allenic structures, revealing them as alkynes or conjugated dienes (Semmler's[6] and Staudinger's[7] works, Figure 1);

[5] (a) S. B. Burton, H. von Pechmann, *Chem. Ber.* **1887***, 20*, 145. (b) E. R. H. Jones, G. H. Mansfield, M. L. H. Whiting, *J. Chem. Soc.* **1954**, 3208.

[6] (a) F. W. Semmler, *Ber. Dtsch. Chem. Ges.* **1906***, 39,* 726. (b) H. Gilman, P. R. van Ess, R. R. Burtner, *J. Am. Chem. Soc.* **1933***, 55*, 3461. (c) A. St. Pfau, J. Pictet, P. Plattner, B. Susz, *Helv. Chim. Acta* **1935***, 18*, 935.

however, they were also able to confirm the allenic structures for previously discovered compounds in natural products (Figure 2)[8], thus triggering the researches aimed at developing synthetic routes to allenes.

The subsequent set up of more convenient methodologies to their obtention together with the proof that natural organisms produce "authentic" allenic compounds (the first one to be identified was mycocmyicin, a fungal metabolite with a high antibiotic activity; Figure 3)[9] eventually brought allenes to light, making them reach the high importance they had claimed for years and they definitively gained during the past four decades in organic synthesis.

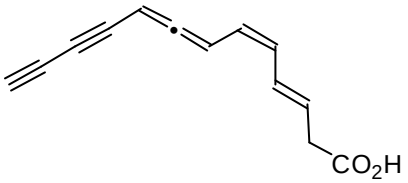


Figure 3. Mycomycin

Allene properties

Before explaining the general behavior of allenes, some words again have to be spent onto their peculiar geometry. Molecular orbital analysis of the allene molecule correctly state that the most stable bonding arrangement involves two mutually perpendicular π bonds, with the central carbon atom (sp-hybridized) joined in a straight line to the two terminal carbon atoms (sp^2-hybridized). As a consequence, only one end of the system projects its substituents above and below the plane which the rest of the molecule is comprised in (Figure 4, part a), and the two bonds don't show any conjugation effect because they are not coplanar. Conversely, in a hypothetical coplanar arrangement, the stabilization by the bonding would be around 2.4 eV lower,[10] and in such a molecule there would be two unpaired electrons (Figure 4, part b). From this point of view, allenes represent the simplest class of odd-carbon *cumulenes* compounds, which reflect this tetrahedral geometry (Figure 4, part c), while even-carbon cumulenes adopt a planar configuration.

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[7] (a) H. Staudinger, L. Ruzicka, *Helv. Chim. Acta* **1924***, 7*, 212. (b) L. Crombie, S. H. Harper, D. Thompson, *J. Chem. Soc.* **1951***,* 2906*.*

[8] (a) R. Bonnett, A. A. Spark, J. L. Tee, B. C. L. Weedon, *Proc. Chem. Soc. London* **1964***,* 419. (b) H. H. Strain, W. A. Svec, K. Aitzetmüller, M. C. Grandolfo, J. J. Katz, H. Kjøsen, S. Norgard, S. Liaaen-Jensen, F. T. Haxo, P. Wegfahrt, H. Rapport, *J. Am. Chem. Soc.* **1971***, 93*, 1823.

[9] (a) E. A. Johnson, K. L. Burdon, *J. Bacteriol.* **1947**, *54*, 281. (b) W. D. Celmer, I. A. Solomons, *J. Am. Chem. Soc*. **1952**, *74*, 1870. (c) W. D. Celmer, I. A. Solomons, *J. Am. Chem. Soc.* **1952**, *74*, 2245. (d) W. D. Celmer, I. A. Solomons, *J. Am.Chem. Soc.* **1952**, *74*, 3838.

[10] H. Fischer, *The Chemistry of Allenes*, **1964**, London, S. Patai Ed., Interscience Publishers Inc., 1025.

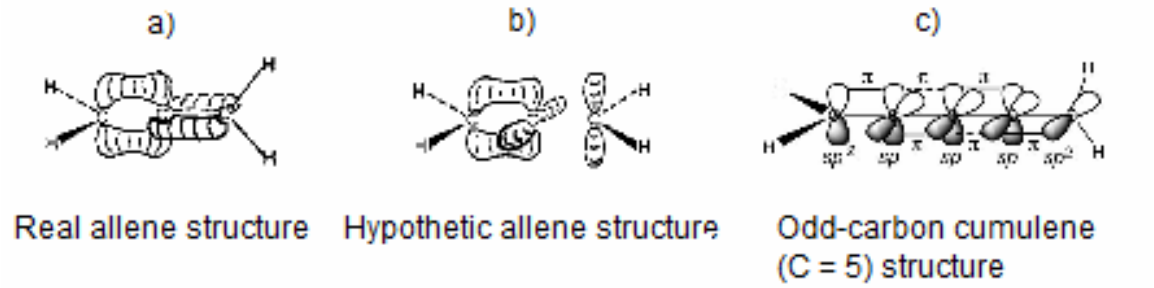

Figure 4. Bonding in allenes and cumulenes

Indeed, further geometrical and thermodynamic studies have been focused much more on cumulenes as a class than on simple allene compounds, although confirming some general features already emerged from the earlier studies onto allenes, such as the decrease of the C-C bond length toward the asymptotic limit while the number of bonds in the cumulene chains increases.[11] Exact dimensions for the allene molecule (C=C = bond angle = 116-118°) were in fact determined long ago from spectral studies and by electron diffraction,[12] showing a contraction of the double bond, relative to that in ethylene (1.33 A), which has been considered to indicate the occurrence of hyperconjugation (σ-π overlap) suggesting a partial triple-bond character (Figure 5).[13]

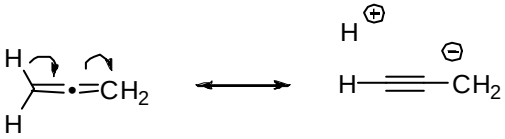

Figure 5. Hyperconjugation in allenes

As underlined in the previous chapter, the stereochemical consequences of the bonding in allenes were predicted by van 't Hoff, who foresaw that molecular symmetry droops if the terminal carbon atoms bear two different substituents, leading to optical isomerism. Thus, the mirror images in Figure 6 differ even if X = X' and Y = Y'; they become identical only if X = Y (or X' = Y').

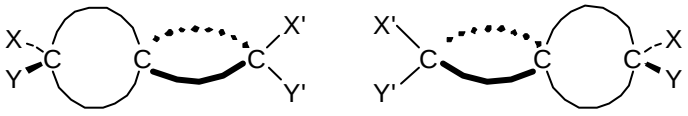

Figure 6. Existence of allenes in enantiomeric forms

Nevertheless, since an experimental proof of this prediction lacked, as recently as 1930 the suggestion that allenes adopted planar configurations was still being made,[14] witnessing the widespread idiosyncrasy toward van 't Hoff studies. Since then, however, his conclusions have been amply verified in a clear cut way by the identification and resolution of many asymmetric allenes.

[11] U. Mölder, P. Burk, I. A. Koppel *J. Mol. Structure: TEOCHEM*, **2004***, 712*, 81-89
[12] (a) B. P. Stoicheff, *Can. J. Phys.* **1955***, 33*, 811. (b) A. Almenningen, O. Bastianen, M. Traetterberg, *Acta Chem. Scand.* **1959***, 13*, 1699.
[13] (a) H. O. Pritchard, F. H. Sumner, *Proc. Roy. Soc.* **1956***, A235,* 136. (b) E. L. Allred, D. M. Grant, W. Goodlett, *J. Am. Chem. Soc.* **1965**, *87*, 673.
[14] F. Faltis, J. Pirsch, L. Bermann, *Chem. Ber.* **1930,** *63B*, 691.

Actually, two general approaches have been adopted in the isolation of enantiomers of optically active allenes. The synthesis of racemic mixtures, followed by resolution by standard procedures as reaction with optically active acids or bases, is the most obvious and ancient one. However, a more direct approach is that of stereoselective synthesis, pioneered by Maitland and Mills in a dehydration of an unsaturated alcohol with (+)- or (-)-camphor-10-sulfonic acid, whereby they obtained in each case a predominance of one stereoisomer of the tetraarylallene (Figure 7).[15]

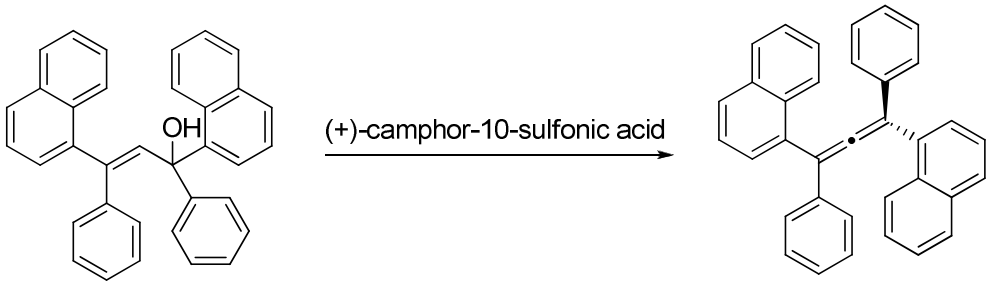

Figure 7. Maitland and Mill's first stereoselective allene synthesis.

This second choice has obviously attracted much more attention, and nowadays stereoselective synthesis are conveniently able to afford many allenic natural products and pharmaceuticals; chirality transfer from propargylic compounds, elimination reactions of allylic compounds and synthesis using chiral reagents or auxiliaries are the most developed methods (for a more detailed discussion of synthetic methods, see subchapter.[16] Some recent examples are shown in Figure 8.[17]

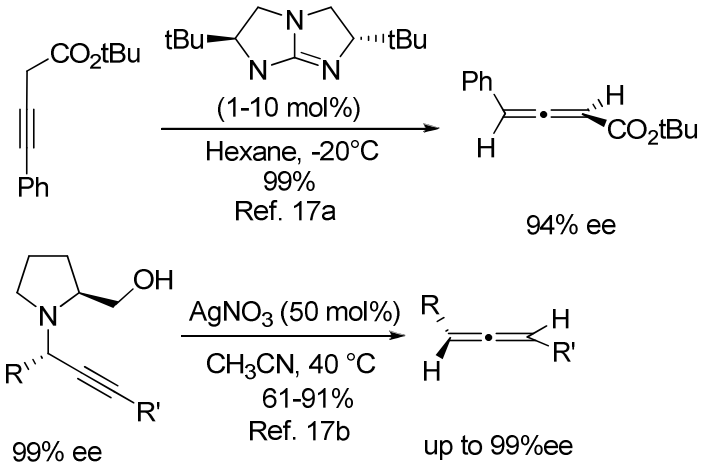

Figure 8. Recent examples of stereoselective synthesis of allenes

[15] (a) P. Maitland, W. H. Mills, *Nature* **1935***, 135*, 994. (b) P. Maitland, W. H. Mills, *J. Chem. Soc.* **1936**, 987.
[16] (a) A. Höffmann-Roder, N. Krause, *Angew. Chem., Int. Ed.* **2004***, 43*, 1196. (b) H. Ohno, Y. Nagaoka, K. Tomioka, *Enantioselective Synthesis of Allenes*, in *Modern Allene Chemistry*, **2004**, Vol. 1., N. Krause, S. Hashmi, Weinheim, Wiley-VCH.
[17] (a) H. Liu, D. Leow, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2009***, 131*, 7212. (b) V. Kar-Yan Lo, C.-Y. Zhou, M.-K. Wong, C.-M. Che, *Chem. Commun.* **2010**, *46*, 213.

Even so, resolution of mixtures is still a valuable method, in the forms of fractional crystallization, chiral columns chromatography and kinetic resolution, although this latter has been overcome by dynamic methods which can avoid consumption of half of the allene material.[16b]

Allene synthesis

As anticipated, many synthetic pathways can lead to obtain allene functionalities. Some examples of such a great variety are depicted in Figure 9.

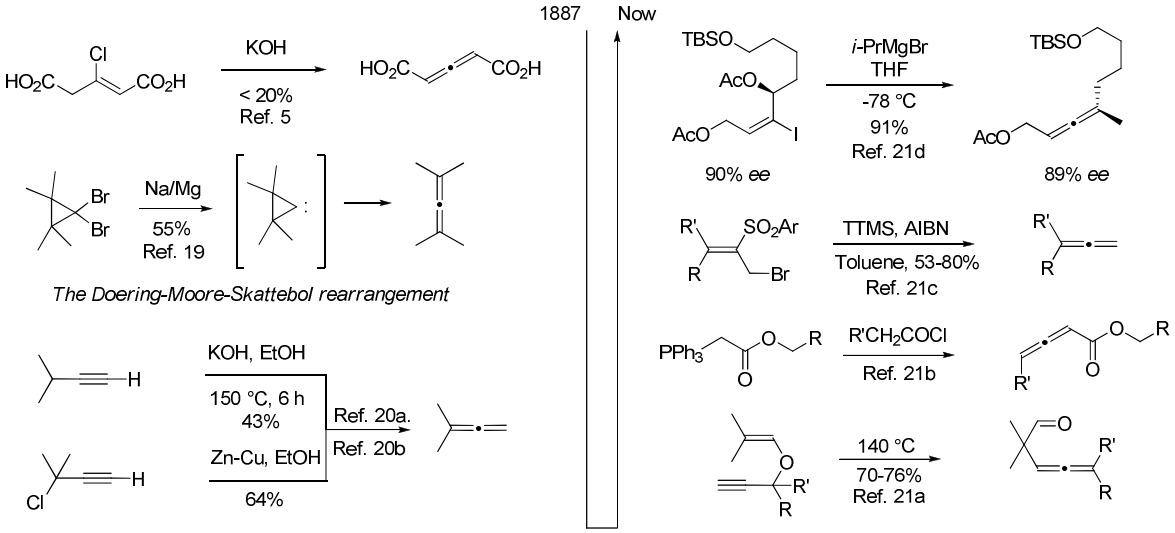

Figure 9. Allene synthesis - selected examples

Already at a first glance, it is inferable that the earliest preparations involved harsh conditions (large excesses of strong bases, hazardous reagents, high temperatures…) and were mainly based on the well established methods for introducing a carbon carbon double bond into an organic compound that already possessed a bond of this kind.[5,18] However, as time went on, newer techniques became available which were specific to the synthesis of allenes, notably the first seemingly general method being the dehalogenation of gem-dihalocyclopropanes (later known as the Doering-Moore-Skattebøl rearrangement),[19] developed together with the 1,4 additions to vinylacetylenes and the rearrangement of acetylenes [20]. Then several other protocols were found,

[18] D. R. Taylor, *Chem. Rev.* **1967**, *67*, 317.
[19] L. K. Sydnes, *Chem. Rev.* **2003**, *103*, 1133.
[20] For selected examples: (a) A. E. Favorsky, *J. Prakt. Chem. [2]* **1888**,382. (b) Y. I. Ginzburg, *Zh. Obshch. Khim.* **1940**, *10*, 513.

such as Claisen and sigmatropics rearrangements, homologation reactions inspired by the Wittig reaction or procedures involving β-elimination of suitable leaving groups.[21]
Nowadays, an enormously wide plethora of methods is available to the synthetic chemist;[22] primarily, further improvements were eventually brought after the 70s by the upcoming age of metal promoted reaction. At first, they were applied to allene synthesis with stoichiometric quantities of metal, where copper, mainly involved in Gilman reagents, is the metal of choice for what concerns generating allenes by C-C bond forming addition and substitutions reactions of multiply unsaturated substrates.[23] Later on, the new ability to use metals in catalytic amounts, the most used being palladium, opened the route to new interesting processes, where the latest results so far have been published by Ma.[24] Transition metal catalysis seems particularly attractive due to the possibility to obtain axially chiral allenes from achiral precursors by simply using catalytic amounts of chiral metal complexes.[25] We will focus now on the three methods most developed to synthesize allenes, namely a propargylic rearrangement, a Crabbé homologation reaction and a hydride transfer with $LiAlH_4$.

Allenes from propargyl electrophiles via $LiAlH_4$

A wide area in allene synthesis is covered by the use of aluminum reagents. The use of aluminum-based Lewis acids for C–C bond formation processes represents the smaller part in this field; much more developed is the formation of C–H bonds with aluminum hydrides. Various propargylic electrophiles such as alcohols, ethers, halides and oxiranes can give rise to the corresponding allenes with the aid of lithium aluminum hydride, diisobutylaluminium hydride (DIBAL-H) and other aluminum hydrides. The general mechanism of this reaction claims for a initial coordination of the aluminum atom to an oxygen atom, eventually via deprotonation; then, a hydride delivery from the aluminum species to the electrophile via an S_N2' intramolecular reaction permits the expulsion of the leaving group and results in the formation of a new carbon-hydrogen bond and a new carbon-carbon double bond (Figure 10).[26]

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[21] For selected examples: (a) D. K. Black, S. R. Landor, *J. Chem. Soc.* **1965**, 5225. (b) W. Oppolzer, C. Chapuis, *Tetrahedron Lett.* **1983***, 24*, 4665. (c) V. Mouriès, B. Delouvrié, E. Lacôte, L. Fensterbank, M. Malacria, *Eur. J. Org. Chem.* **2002**, 1776. (d) Y. Zhang, H.-D. Hao, Y. Wu, *Synlett* **2010,** 905.
[22] (a) L. Brandsma, *Synthesis of acetylenes, allenes and cumulenes: methods and techniques*, **2004**, Oxford, Elsevier. (b) K. M. Brummond, J. E. DeForrest, *Synthesis* **2007***,* 795.
[23] A. Höffmann-Roder, N. Krause, *Metal Mediated synthesis of Allenes*, in *Modern Allene Chemistry*, **2004**, Vol. 1., N. Krause, S. Hashmi, Weinheim, Wiley-VCH.
[24] J. Kuang, S. Ma, *J. Am. Chem. Soc*. **2010**, *132*, 1786.
[25] M. Ogasawara, *Tetrahedron: Asymmetry* **2009**, *20*, 259.
[26] S. Saito, in *Science of Synthesis***, 2004,** Vol. 7, H. Yamamoto, Stuttgart, Ed. Thieme.

This transformation can proceed with either *syn*- or *anti*- stereoselectivity depending on the nature of the substrate, reducing agent, and reaction temperature.[27]

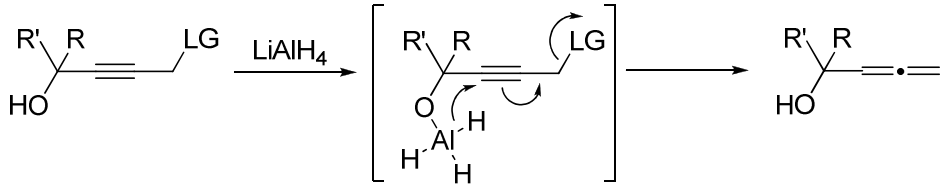

Figure 10. Mechanism of aluminum hydride-mediated reduction

Hydroxyl-directed hydride delivery with $LiAlH_4$, since its development in 1973 by Landor and co-workers,[28] has proven to be a reliable method of allene construction from propargylic moieties bearing an ether as leaving group, and this methodology is still widely used today to prepare a-hydroxyallenes. Indeed, Yoshida and coworkers recently choose this way as a step toward the total synthesis of enokipodin A to transform their tetrahydropyranyl propargyl ether into the corresponding-hydroxyallene in 83% yield (Figure 11).[29]

However, this protocol is not limited to THP-protected substrates, but on the contrary it can be applied to other kind of ethers (silyl and methyl substituted[30]) and oxygenated leaving groups, including acetals;[31] neither has oxygen necessarily to accomplish this function, since these reactions number propargyl chlorides as excellent substrates too. For example, propargyl chlorides can successfully be transformed into their allenyl counterparts with $LiAlH_4$ in high yield (Figure 12).[32]

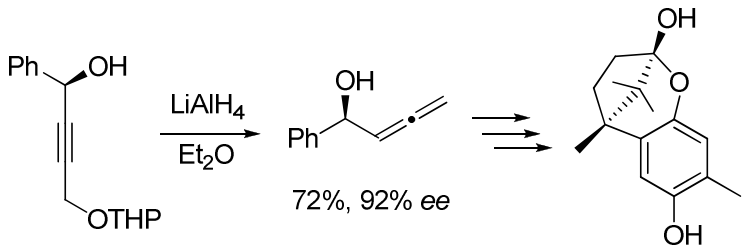

Figure 11. Yoshida's reduction

[27] A. Claesson, L.-L. Olsson, *J. Am. Chem. Soc.* **1979**, *101*, 7302.
[28] J. S. Cowie, P. D. Landor, S. R. Landor, *J. Chem. Soc., Perkin Trans. 1* **1973**, 720.
[29] M. Yoshida, Y.Shoji, K. Shishido, *Org. Lett.* **2009**, *11*, 1441.
[30] (a) M. Lautens, P. Delanghe, *J. Am. Chem. Soc.* **1994**, *116*, 8526. (b) M. P. VanBrunt, R. F. Standaert, *Org. Lett.* **2000**, *2*, 705.
[31] R. L. Snowden, S. Linder, *Helv. Chim. Acta* **2005**, *88*, 3055.
[32] C. J. Bungard, J. Morris, *J. Org. Chem.* **2002**, *62*, 2361.

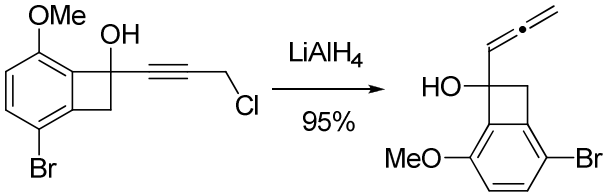

Figure 12. Transformation of propargyl chlorides

More recent applications of this chemistry include the employment of hydroxyls not only as a directing group, but also as a suitable leaving group, provided their removal as an aluminum oxide thanks to an alane species[33] as in the example described in Figure 13.[33a]

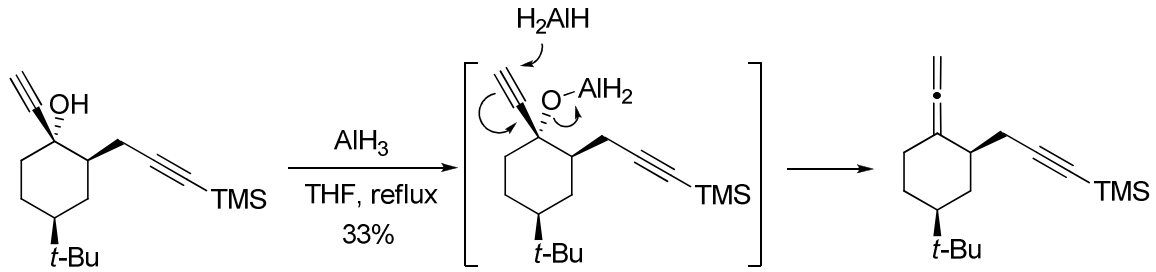

Figure 13. Hydroxyl as a leaving group.

This method has frequently been applied in natural product synthesis. Thus, reducing propargyl oxiranes with DIBAL-H allowed obtaining allenic carotinoids and terpenoids as the grasshopper ketone (Figure 14),[34] a synthesis recently adapted by Katsumura.[35] Thanks to the precoordination of the hydride to the oxygen, these reductions proceed with high *syn*-diastereoselectivity.

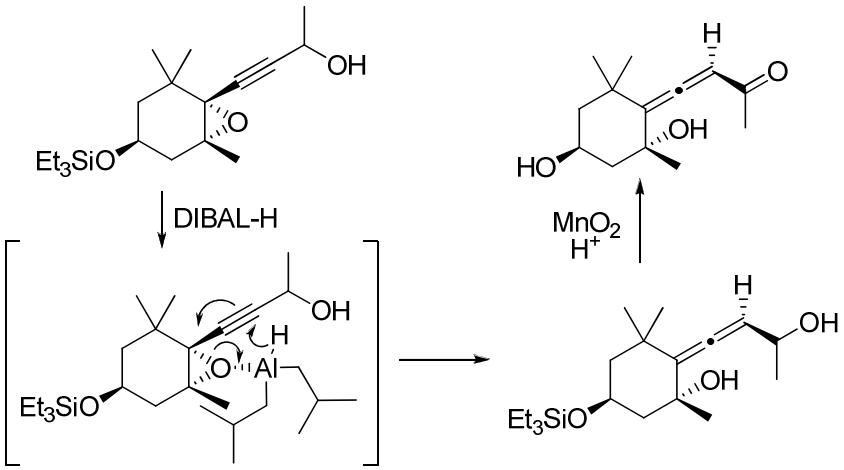

Figure 14. Eugster's synthesis of grasshopper ketone.

[33] (a) K. M. Brummond, M. M. Davis, C. Huang, *J. Org. Chem.* **2009**, *74*, 8314. (b) M. A. Daniel, C. J. Puglisi, D. L. Capone, G. M. Elsey, M. A. Sefton, *J. Agric. Food Chem.* **2008**, *56*, 9183. (c) S.-C. Hung, Y.-F. Wen, J.-W. Chang, C.-C. Liao, B.-J. Uang, *J. Org. Chem.* **2002**, *67*, 1308.

[34] A. Baumeler, W. Brade, A. Haag, C. H. Eugster, *Helv. Chim. Acta* **1990**, *73*, 700.

[35] N. Furuichi, H. Hara, T. Osaki, M. Nakano, H. Mori, S. Katsumura, *J. Org. Chem.* **2004**, *69*, 7949.

Crabbé Homologation Reaction

One of the most popular methods for the synthesis of allenes is the S_N2' reaction of propargylic derivatives with organocopper reagents.[23] Most probably a study published in 1968–69 by Rona and Crabbé represents the first example of the Cu(I)-mediated S_N2' reaction of propargylic electrophiles giving allenic products.[36] Since then, many researchers have used modified organocopper reagents with stoichiometric or catalytic amounts of Cu(I) salt, and it was again Crabbé to discover a homologation reaction that would have become one of the most useful methods for the construction of monosubstituted allenes from terminal acetylenic precursors.[37] Its mechanism consists of a copper-catalyzed addition of a propargylic substrate onto an iminium ion formed in situ from a Mannich-type reaction between paraformaldehyde and diisopropylamine. Complexation of a cuprous halide to the acetylenic triple bond results in formation of a π-complex. Subsequent intramolecular hydrogen transfer from the amine moiety to the copper species occurs to afford a hydridocopper(I) complex. The hydride is then delivered to the carbon-carbon triple bond in an S_N2' fashion (Figure 15).[38]

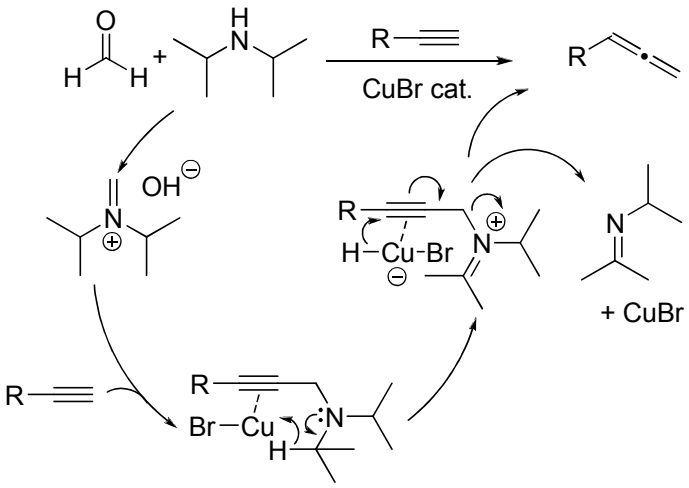

Figure 15. Mechanism of Crabbe's homologation reaction.

This homologation reaction is still investigated, mainly to develop efficient stereoselective syntheses and to improve yields and tolerance of various functional groups. Indeed, it allowed the preparation of a wide variety of functionalized monosubstituted allenes, such as allene-substituted alcohols, amides, carbamates and lactams. Crews and co-workers,[39] for example,

[36] (a) P. Rona, P. Crabbé, *J. Am. Chem. Soc*. **1968**, *90*, 4733; (b) P. Rona, P. Crabbé, *J. Am. Chem. Soc*. **1969**, *91*, 3289.
[37] (a) P. Crabbé, D. André, H. Fillion, *Tetrahedron Lett.* **1979**, *20*, 893. (b) P. Crabbé, H. Fillion, D. André, J.-L. Luche, *J. Chem. Soc., Chem. Commun.* **1979**, 859.
[38] S. Searles, Y. Li, B. Nassim, M.-T. R. Lopes, P. T. Tran, P. Crabbé, *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.
[39] A. K. Mandal, J. S. Schneekloth, C. M. Crews, *Org. Lett.* **2005**, *7*, 3645.

recently applied this method to the synthesis of the α-allenyl alcohol in Figure 16. Similarly, several groups have screened in the last years different conditions (employing different amines, cuprous salts or even utilizing microwaves) that in some cases gave much better yields than the original procedure.[40]

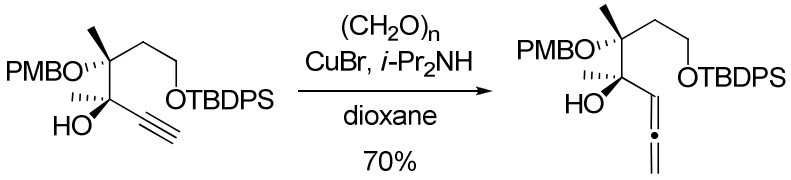

Figure 16. Crew's application of Crabbé's reaction

Prototropic rearrangement

A full, atom economic way to obtain the 1,2-diene substructure features migration of a π-bond from a non-cumulated π-bond (Figure 17). The non-cumulated bond can either be an alkyne or a conjugated or isolated diene. Thus, if group X is a hydrogen atom, a 1,3-proton shift occurs through deprotonation and protonation sequence, that is what is called a prototropic rearrangement (different X substituents could lead to sigmatropic rearrangements). Despite being known from the earliest days in allene chemistry,[20a] this still remains the most important isomerization reaction leading to such products, and quite surprisingly, debates on its mechanism have not yet come to an end.[41] Strictly speaking, equilibrium between the two forms should favor the alkyne,[42] and indeed the opposite reaction has been fruitfully applied.[43]However, several factors can drive the reaction in both directions, such as a reaction under kinetic control, a stoichiometric deprotonation followed by kinetic protonation, or a change of the relative thermodynamic stability brought, for example, by substituents. This is what happens for allenyl ethers and allenylamines, which are thermodynamically more stable than their propargylic counterparts; consequently, a prototropic rearrangement seemed a useful way too to obtain our nitrogen containing allenes.

Figure 17. Prototropic rearrangement (X = H)

[40] (a) B. M. Trost, A. McClory, *Org.Lett.* **2006**, *8*, 3627. (b) J. Kuang, S. Ma, *J. Org. Chem.* **2009**, *74*, 1763. (c) H. Nakamura, T. Sugiishi, Y. Tanaka, *Tetrahedron Lett.*, **2008**, *49*, 7230. (d) V. Kumar, A. Chipeleme, K. Chibale, *Eur. J. Org. Chem*. **2008** 43.
[41] V. B. Kobychev, N. M. Vitkovskaya, N. S. Klyba, B. A. Trofimov, *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 774.
[42] R. Kakkar, R. Garg, P. Chadha, *J. Mol. Structure: THEOCHEM* **2002**, *617*, 141.
[43] J. D. Spence, J. K. Wyatt, D. M. Bender, D. K. Moss, M. H. Nantz, *J. Org. Chem.* **1996**, *61*, 4014.

In the case of propargyl substrates substituted with a nitrogen atom, most of the examples use potassium *tert*-butoxide or *n*-butyllithium as base, exploiting the acidity of the hydrogen at the propargyl position. A number of alkyl- and aryl-substituted propargylic amines and amides have been in fact obtained in that way,[44] occasionally also providing alkynylamines as side products. In some cases, such as for the compound in Figure 18, potassium hydroxide and a phase transfer catalyst are sufficient.[45]

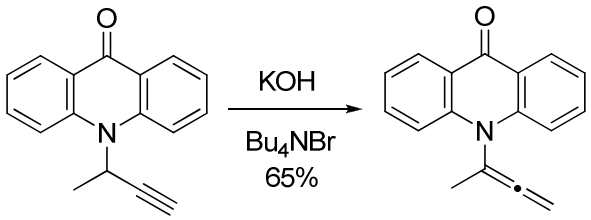

Figure 18. Prototropic rearrangement in PTC

The presence of other base-labile group, such as free hydroxyl, has been evidenced as a problem, although in some cases good yields have been obtained with selective deprotection (the same happened for competition between amides and amines). On the other hand, rare examples are propargylated hydrazines, N-propargylated imines, isonitriles, ammonium salts and azides.

Allenamides

Since our research line lies in a long lasting interest toward heterocycles, we focused our efforts towards allenes that could bear a heteroatom in order to afford the desired products.
In spite of the already described synthetic potential of allenes, heteroatom-substituted allenes, and in particular allenamines, have received relatively little attention. Conceptually, allenamines are synthetically useful because the nitrogen atom can donate its lone pair toward the allenic moiety to render them electron-rich and readily activated in the presence of an electrophile. However, the same high reactivity also makes them sensitive to hydrolysis, polymerization and isomerization even at low temperatures, thereby creating serious difficulties in preparation and handling. Conversely, electron-deficient allenamines, such as allenamides, have a diminished donating ability. Consequently they are less reactive, but represent a more stable allenic system

[44] For some recent examples: (a) A. G. Lohse, R. P. Hsung, *Org. Lett.* **2009**, *11*, 3430. (b) E. Skucas, J. R. Zbieg, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 5054. (c) Á. González-Gómez, L. Añorbe, A. Poblador, G. Domínguez, J. Pérez-Castells, *Eur. J. Org. Chem.* **2008**, 1370.
[45] J. Reisch, R. A. Salehi-Artimani, *J. Heterocycl. Chem.* **1989**, 1803.

and have the potential to function as an allenamine-equivalent. For these reasons, allenamides have been chosen as appropriate substrates for our studies.

In particular, since we had no specific necessity to have the nitrogen atom directly substituted onto the allenic moiety, we envisaged that the synthesis of not only α- but also β-allenamides could be useful to lead to starting materials able to undergo cyclization reactions catalyzed by transition-metal complexes.

The available ways to synthesize α- and β- allenamides are basically the same previously described for allene synthesis, and it seems unnecessary to report here specific applications to allenamides. It is just worth to mention the historical value of the first examples, since both involve the same reactivity brought by base-induced isomerization that we adopted in some of our protocols, thus reasserting its efficiency unchanged through years. In fact, to repeat an earlier preparation of a propargyl amide en route to oxotremorine, a potent muscarinic agent, Dickinson reported in 1967 the first preparation of allenamide from lactam under basic conditions (MeONa or NaH, Figure 19).[46] The first acyclic allenamide, closer to our substrates, is instead due to Corbel, who in 1976 reported the first example of its obtention via the isomerization of N-propargyl phosphoramides (Figure 20).[47]

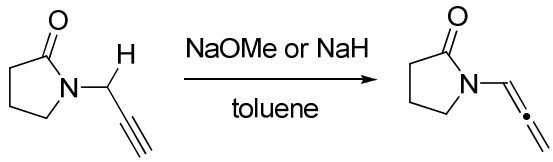

Figure 19. Dickinson's first allenamide synthesis

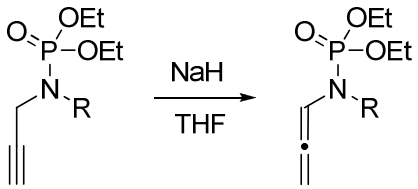

Figure 20. Corbel's acyclic allenamide

Allene reactivity

Allenic compounds are able to react in so many different ways and a complete analysis would be beyond the scopes of this manuscript. Moreover, in most of cases allenes behave as a double alkene system, thus undergoing the wide panorama of reactions typically available to functionalize olefinic substrates (Diels-Alder reactions, dipolar cycloadditions, electrophilic

[46] W. B. Dickinson, P. C. Lang, *Tetrahedron Lett.* **1967**, *8*, 3035.
[47] B. Corbel, J.-P. Paugam, M. Dreux, P. Savignac, *Tetrahedron Lett.* **1976**, *17*, 835.

attacks, nucleophilic attacks when properly substituted…). An overview, though inexhaustive, of recent reactivities of alkenes is depicted in Figure 21.[48,49]

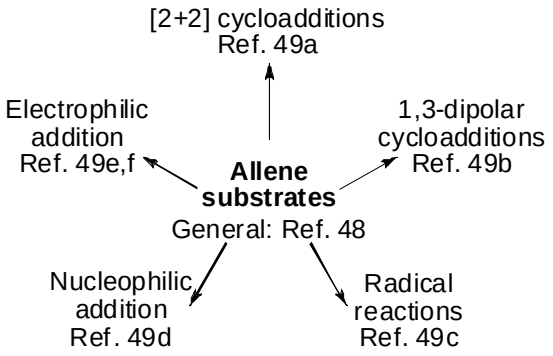

Figure 21. Recent overviews of allene reactivity.

However, since our interest deals mainly with transition metal catalyzed cyclization of allenes with nucleophiles,[49d] we will focus directly on that subclass, evidencing the behavior of the metals we used to investigate such reactivity, *i.e.* palladium, gold and ruthenium.

Transition-metal catalyzed cyclization of allenes with heteroatomic nucleophiles

For this kind of reactions, three main and hardly distinguishable mechanisms have been put forward. The first one is represented in Figure 22. In the presence of an electrophilic metal complex, such as palladium(II), an η^2-complex might form with one of the allene double bonds.

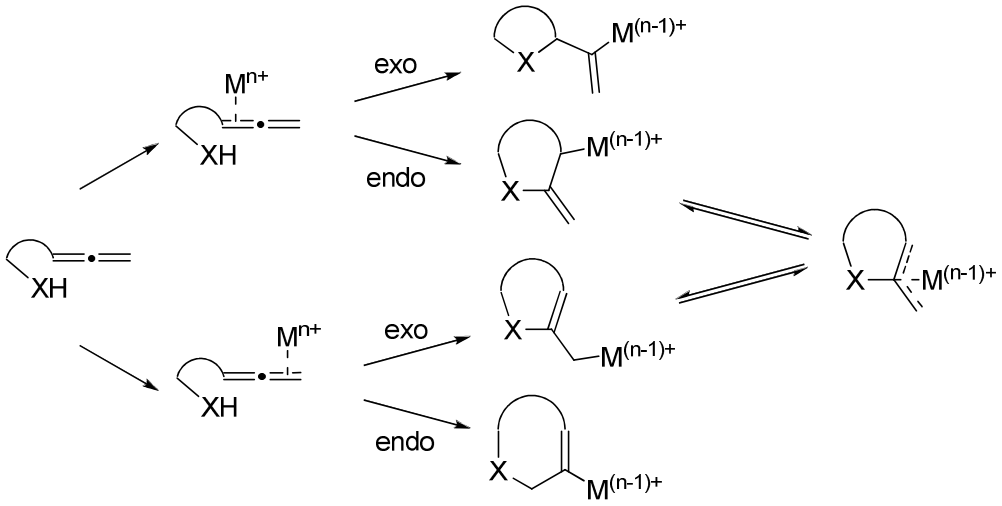

Figure 22. First mechanistic possibility for the interaction between nucleophile-bearing allenes and transition metals

The metal-coordinated double bond is thus activated toward intramolecular nucleophilic attack by a nucleophile at either coordinated carbon atom. This reactivity is analogous to that observed in the Wacker reaction. Thus four possible σ-complexes, two vinyl and two allyl, could be formed,

[48] (a) H. Kim, L. J. Williams, *Curr. Opin. Drug Discov. Devel.* **2008**, *11*, 870. (b) S. Ma, *Aldrichim. Acta* **2007**, *40*, 91. (c) H. H. A. M. Hassan, *Curr. Org. Synth.* **2007**, *4*, 413. (d) S. Ma, *Chem. Rev*. **2005**, *105*, 2829.

[49] (a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Soc. Rev.* **2010**, *39,* 783. (b) T. M. V. D. Pinho e Melo, *Curr. Org. Chem.* **2009**, *13*, 1406. (c) F. Pan, C.-L. Fu, S. Ma, *Chin. J. Org. Chem.* **2004**, *24*, 1168. (d) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701. (e) S. Ma, *Acc. Chem. Res.* **2009***, 42*, 1679. (f) S. Ma, *Pure App. Chem.* **2007**, *79*, 261. (g) S. Ma, *Pure App. Chem.* **2006**, *78*, 197.

depending on the double bond attacked, the latter couple being in equilibrium with the same η^3-complex. It is also possible that the η^2-complex would react with ligands (such as halides) on the metal, leading to other intermediates and pathways. The final reaction products would then come from an evolution of the above intermediates, such as reductive elimination (if the metal has a σ-bonded ligand), β-elimination, protonolysis or CO insertion.

A second alternative foresees that the insertion of the allene might then generate an η^3-allyl complex. This could cyclize by nucleophilic attack on either terminus. In many cases either a η^2- or a η^3- mechanism can be drawn leading to the same product (Figure 23).

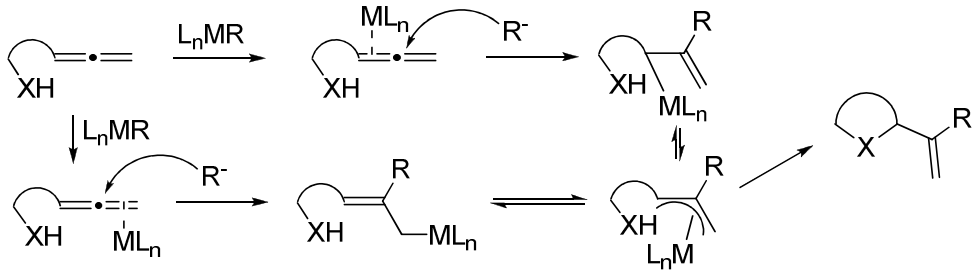

Figure 23. Second mechanistic possibility for the interaction between nucleophile-bearing allenes and transition metals

The third alternative is that the metal complex initially interacts with the "nucleophilic" group; this is followed by insertion and reductive elimination. Insertion may involve either of the allene double bonds to generate different ring sizes (Figure 24).

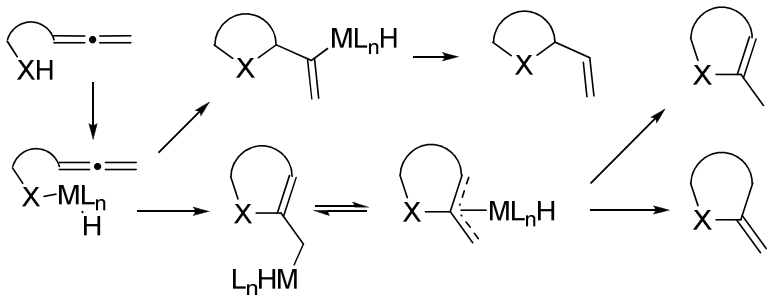

Figure 24. Third mechanistic possibility for the interaction between nucleophile-bearing allenes and transition metals

Palladium

The use of palladium can enable the synthesis of a variety of heterocyclic compounds starting from allenyl derivatives. In all known examples, heterocyclic synthesis can be accomplished when allene substrates interact with a palladium(II) complex, which can be directly employed in the reaction environment or derive from an *in situ* Pd(0)-oxidation process. The former protocols can furthermore be divided in two subclasses: in the first case, palladium can interact with the allene

moiety by forming a π-allyl complex, which is then intramolecularly trapped by nitrogen, as in reactions developed by Bäckvall and Alcaide,[50] thus giving rise to halopalladation/nucleophilic attack sequences (Figure 25). An oxidant is needed to bring the metal to palladium(II) oxidation state again. Evidence has been given by isolation of some intermediate π-allyl complexes.

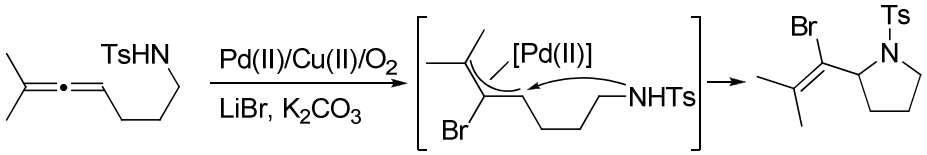

Figure 25. Backvall's Pd(II)-catalyzed bromoamidation reaction

Alternatively, nitrogen may attack one or the other Pd(II)-activated unsaturations of the allene moiety, which behave as isolated double bonds. These reactions historically developed before other allene-involving processes, and hydroamination or carbonylation processes are usually encountered in this subclass.[51] A graphical synopsis of these reactions is given in Figure 26.

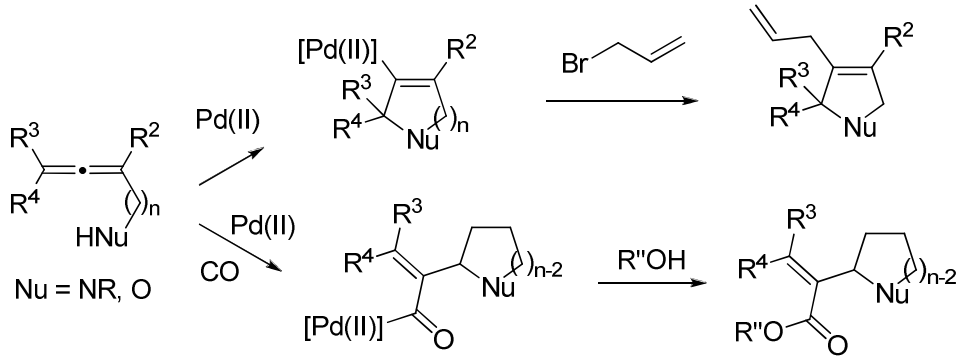

Figure 26. Olefin-like behaviour of allenes in Pd(II)-catalyzed reactions

Walkup and Gallagher[52] reported a palladium-catalyzed 5-exo regioselective cyclization of allenes bearing a nucleophile in γ-position in the presence of iodobenzene. This kind of reactivity has marked a milestone in palladium catalyzed reaction of allenes; indeed, the authors proposed a mechanism that for the first time was not the one historically set up by Cazes and Tsuji about intermolecular allenes Pd(0)-carbopalladation, that is, claiming for the formation of a π-allylic

[50] a) C. Jonasson, A. Horvath, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2000**, *122*, 9600. b) B. Alcaide, P. Almendros, R. Rodriguez-Acebes, *J. Org. Chem.* **2006**, *71*, 2346.

[51] Selected examples: a) S. Ma, F. Yu, W. Gao, *J. Org. Chem.* **2003**, *68*, 5943. b) S. Ma, W. Gao, *J. Org. Chem.* **2002**, *67*, 6104. c) M. Kimura, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1995**, *60*, 3764. d) M. Kimura, N. Saeki, S. Uchida, H. Harayama, S. Tanaka, H. Fugami, Y. Tamaru, *Tetrahedron Lett.* **1993**, *34*, 7611.

[52] R. D. Walkup, L. Guan, M. D. Mosher, S. W. Kim, Y. S. Kim, *Synlett* **1993**, 88. b) I. W. Davies, D. I. C. Scopes, T. Gallagher, *Synlett* **1993**, 85.

complex.[53] Instead, an ArPd(II) complex formed *in situ* is here supposed to coordinate one of the double bonds (namely, the internal one) and undergoes a subsequent nucleophilic attack by the heteroatom. A reductive elimination of the metal from the vinylpalladium intermediate intervenes to yield the product and release palladium in the initial oxidation state (Figure 27).

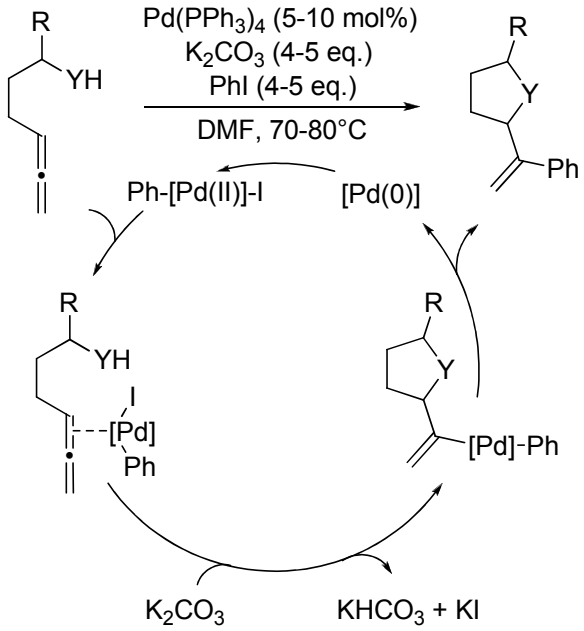

Figure 27. Nucleophilic attack / carbopalladation sequence

While in most of such reactions a clear cut evidence toward the action of a mechanism or another lacks, some cases and mostly the first interesting example by Hiemstra[54] are example of the effectiveness of this idea, because a carbopalladation-amination sequence would fail to explain the obtention of products from the allenic lactam (Figure 28).

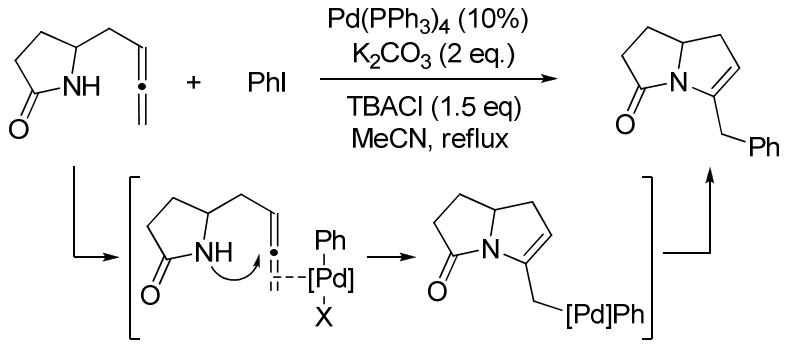

Figure 28. Hiemstra's dihydropyrroles synthesis

[53] (a) I. Shimizu, J. Tsuji, *Chem. Lett.* **1984**, 233. (b) M. Ahmar, B. Cazes, J. Goré, *Tetrahedron Lett.* **1984**, *25*, 4505. (c) B. Cazes, *Pure App. Chem.* **1990**, *62*, 1867.

[54] W. F. J. Karstens, F. P. J. T. Rutjes, H. Hiemstra, *Tetrahedron Lett.* **1997**, *38*, 6275.

Chiral allenes have also been cyclized with chirality transfer; therefore, this mechanism has been indicated as effective, since chiral information would be lost in a planar π-allyl intermediate.[55] However, while this mechanism has been the first to be proposed for the intervention of non-carbon nucleophiles, a second one analogous to Cazes and Tsuji's well established intermolecular version of allene carbopalladation has been later proposed in palladium catalyzed cyclizations onto allenes.[56] The coordination of the metal to the double bond, in fact, can also lead to a carbopalladation process, which only in a second instance is followed by a nucleophilic attack. In this case, the time order between C-C and C-X bond formation is inverted in respect to the mechanism described so far. That is the case of reactions developed first by Kang and successively mostly by Ma's group. In particular, Kang first claimed for this mechanism in a paper where he was also able to show how hypervalent iodonium salts could be used as aryl moiety deliverers leading to the key Pd(II) species (Figure 29).[56a]

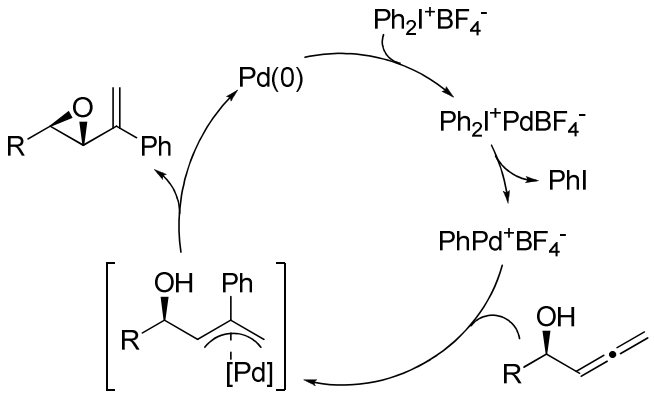

Figure 29. Kang's carbopalladation/oxygenation sequence

Following the same mechanistic sequence, that is with the palladation step prior to the nucleophile addition one, allylic halides have also been trapped *in lieu* of aryl moieties;[57] moreover, halides (*i.e.*, bromides) can be also used as suitable leaving groups to form allyl dications from bromoallenes, yielding a reactive π-allyl intermediate able to cyclize in presence or absence of a Pd(0) species.[58]

An interesting and not yet fully explored variation on this theme has been finally discovered by Liu, who described a protocol in which the palladium intermediate does not deliver neither a

[55] S. Ma, Z. Shi, *Chem. Commun.* **2002**, 540.
[56] For some examples: a) S.-K. Kang, T. Yamaguchi, S.-J. Pyun, Y.-T. Lee, T.-G. Baik, *Tetrahedron Lett.* **1998**, *39*, 2127. b) F. P. J. T. Rutjes, K. C. M. F. Tjen, L. B. Wolf, W. F. J. Karstens, H. E. Schoemaker, H. Hiemstra, *Org. Lett.* **1999**, *1*, 717. b) H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tanaka, Y. Takemoto, T. Ibuka, *J. Org. Chem.* **2001**, *66*, 4904. c) S. Ma, Z. Zheng, X. Jiang, *Org. Lett.* **2007**, *9*, 529.
[57] S. Ma, S. Zhao, *J. Am. Chem. Soc.* **1999**, *121*, 7943.
[58] H. Ohno, H. Hamaguchi, M. Ohata, T. Tanaka, *Angew. Chem., Int. Ed.* **2003**, *42*, 1749.

carbon nor a halogen atom onto the central allene carbon, but instead a protonic species, leading to a hydroamination procedure affording alkenyl substituted pyrrolidines and piperidines.[59]

Eventually, palladium can react with nucleophile bearing allenes also in a transmetalation fashion. Ma and Sha discovered in fact a curious Pd(0)-Ag(I) cocatalyzed cyclization of α-allenic acids with aryl and vinylic halides, where a primarily cyclized silver intermediate is believed to evolve into a palladium complex which eventually yields the desired product (Figure 30).[60]

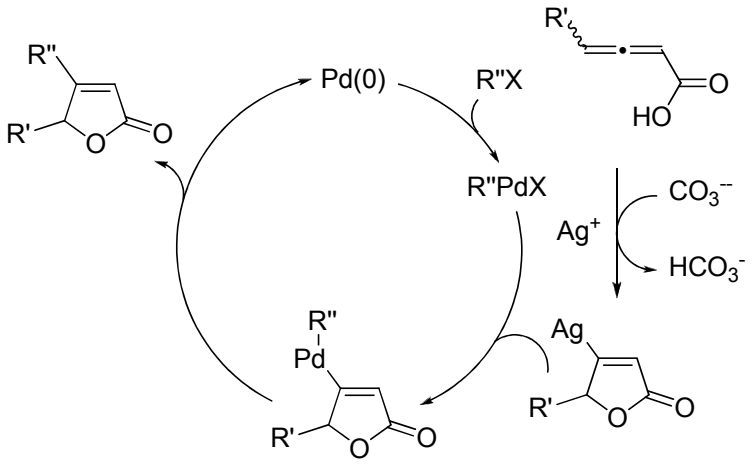

Figure 30. Cyclization of allenes through transmetalation mechanism.

Gold

Compared to palladium, the golden era of homogeneous catalysis was born much later, nearly at the end of 20th century, but could find rapidly a wide application also in allene chemistry. A series of five- and six-membered heterocycles can be constructed using the gold-catalyzed annulation of allenes with pendant nucleophiles including alcohols, esters, ketones, thiols, amines, sulfonamides, amides, and enamines formed *in situ*.

The mechanism by which these reactions usually proceed depends on the oxidation state of the metal. Some authors seem to evidence the existence of processes where Au(III) or Au(I)-complexes essentially behave in the same way, thus admitting a formal in situ conversion between the two states.[61]

However, most of all when dealing with oxygen nucleophiles, a difference between the two states can be evidenced, as Au(III) behaves in a more oxophylic way while Au(I) complexes prefer to coordinate unsaturated carbon-carbon bonds. Figure 31 depicts a gold-catalyzed

[59] S. Qiu, Y. Wei, G. Liu, *Chem. Eur. J.* **2009**, *15*, 2751**.**
[60] S. Ma, Z. Shi, *J. Org. Chem.* **1998**, *63*, 6387
[61] N. T. Patil, L. M. Lutete, N. Naoko, Y. Yamamoto, *Tetrahedron Lett.* **2006**, *47***,** 4749.

cycloisomerization of a bromoallene whose selectivity depends on the oxidation state of the catalyst used. While $AuCl_3$ favors the formation of 3-bromofuran likely initiated by the activation of the carbonyl group, the lower oxidation state catalyst Et_3PAuCl interacts with allene preferentially to trigger the carbonyl oxygen cyclization leading to an isomeric bromofuran structure.[62]

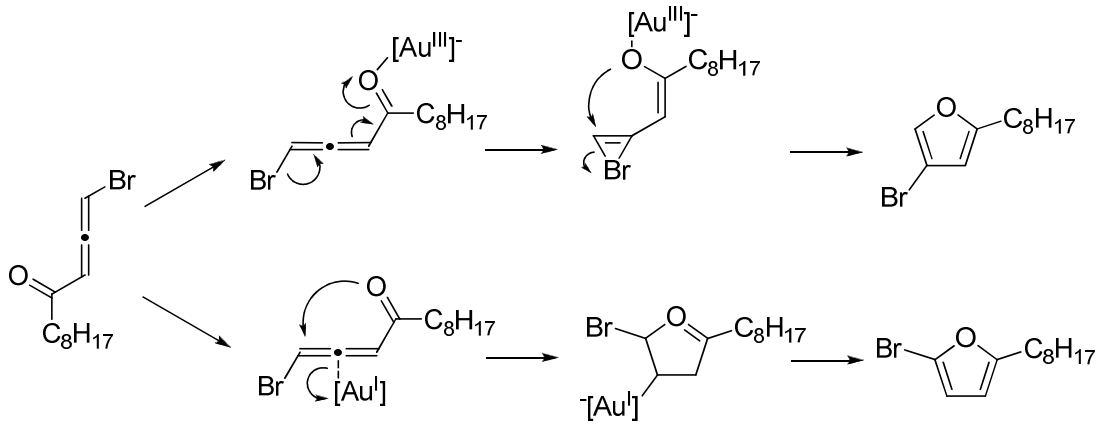

Figure 31. Regiodivergent Au(I) and Au(III)-catalyzed cycloisomerization of bromoallenes.

Toste[63a] and Widenhofer[63b] independently reported Au(I)-catalyzed intramolecular enantioselective hydroamination and hydroalkoxylation of allenes. Both groups utilized chiral dinuclear gold–phosphine complexes, which gave excellent enantioselectivities. As in previous studies, Toste demonstrated the effectiveness of chiral anionic counterions in the intramolecular hydroalkoxylation, hydroamination, and hydrocarboxylation reactions.[64] As expected, the two strategies can be combined, so as to obtain matched and mismatched pairing effects on the asymmetric induction.

Ruthenium

Despite ruthenium catalysts have been mostly used in metathesis reactions of allenes, they have recently created their own place also in nucleophilic cyclizations.

Indeed, Trost and co-workers first reported a ruthenium catalyzed cycloetherification and subsequently applied the same protocol to a cycloamination reaction.[65] For both variants, two

[62] Y. Xia, A. S. Dudnik, V. Gevorgyan, Y. Li, *J. Am. Chem. Soc.* **2008**, *130*, 6940.
[63] a) R. L. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452. b) Z. Zhang, C. F. Bender, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2007**, *119*, 287,
[64] G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496.
[65] (a) B. M. Trost, A. B. Pinkerton, *J. Am. Chem. Soc.* **1999**, *121*, 10842. (b) B. M. Trost, A. Pinkerton, D. Kremzow, *J. Am. Chem. Soc.* **2000**, *122*, 12007.

alternative pathways have been postulated. The former involves the formation of a vinlylruthenium species and its insertion into the enone, while the second accounts for the formation of a ruthenacycle which is subsequently internally trapped by the nucleophilic oxygen or nitrogen (Figure 32). The latest studies in this field by Trost's group describe a similar cyclization of allenic carboxylic acids, wherein the hydroxyl group of this function plays the role of the nucleophile.[40]

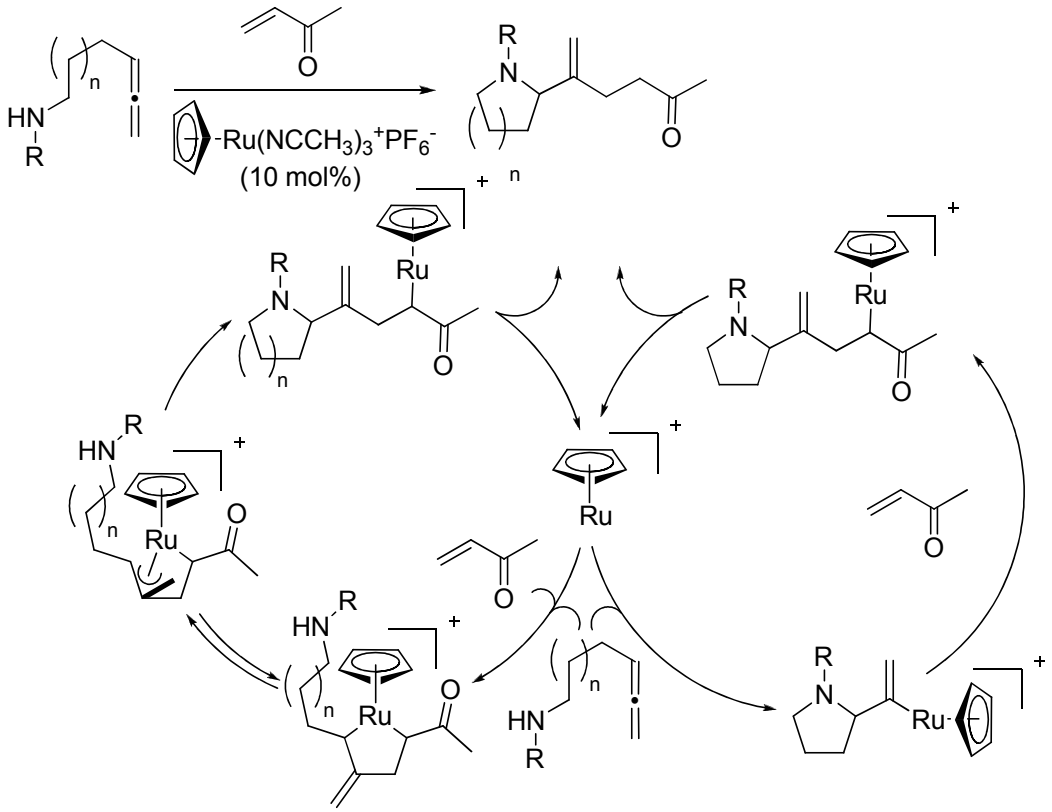

Figure 32. Trost's Ru-catalyzed pyrrolidine and piperidine formation from aminoallenes

A variation on this theme involves the use of carbon monoxide *in lieu* of enones. Indeed, it has proved possible to intercept the pro-nucleophile with CO prior to cyclization, this resulting in a series of γ– and δ-lactones and lactams.[66] The mechanism proposed in this occasion involves only an oxidative addition of ruthenium to the N-H bond, insertion of the allene followed by that of carbon monoxide and a final reductive elimination to complete the sequence (Figure 33).

[66] (a) E. Yoneda, S.-W. Zhang, K. Onitsuka, S. Takahashi, *Tetrahedron Lett.* **2001***, 42*, 5459. (b) S. K. Kang, K. J. Kim, C.-M. Yu, J.-W. Hwang, Y.-K. Do, *Org. Lett.* **2001***, 3*, 2851.

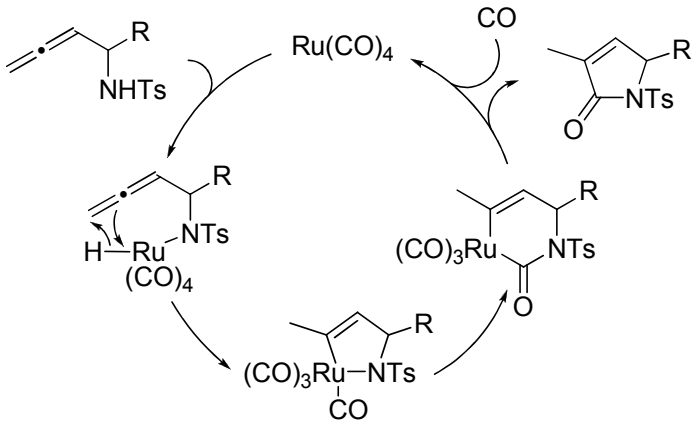

Figure 33. Ruthenium-catalyzed cyclocarbonylation

However, in contrast to palladium and gold, ruthenium has never proven able to afford any hydroamination product reacting with allenes (see Figure 34).

			Substrates			
Ru-complex and catalytic system	**Inter molecular**	**Intra molecular**	**Alkene**	**Alkyne**	**Diene**	**Allene**
$[Ru(CO)_2(PPh_3)(PPh_2C_6H_5C_2H_3)]/NH_4PF_6$	X			X		
$[Ru_3(CO)_{12}]/NH_4PF_6$		X		X		
$[Ru_3(CO)_{12}]$ or CuI		X		X		
$[Ru_3(CO)_{12}]/NH_4PF_6$	X			X		
$[Ru_3(CO)_{12}]/HBF_4OEt_2$ or $[RuH(PCy_3)_2(CO)(CH_3CN)_2]BF_4$	X			X		
$[Ru\text{-}CHCH\text{-}C(CH_3)_2(Cl)(PCy_3)_2(CO)]BF_4$	X		X		X	
$[Ru(2\text{-methylallyl})_2(P\text{-}P)]/TfOH$	X		X			
$[Ru(H)Cl(CO)(PPh_3)_3]$	X		X			
$[Ru(P\text{-}P)(2\text{-methylallyl})_2]$	X		X			
$[Ru(\eta_6\text{-cot})(dmfm)_2]$ or $[Ru_3(CO)_{12}]$		X		X		
$[RuCp(C_2H_4)(PPh_3)_2]BF_4$	X		X			
$[Ru_3(CO_{12})]/NH_4PF_6$	X			X		
$[Ru_3(CO_{12})]$	X			X		

Figure 34. Known Ruthenium-catalyzed hydroamination reactions

Heterocycles

Our interest toward nitrogen containing heterocycles brought us soon to investigate new synthetic ways toward such structures exploiting allenamides. More precisely, we chose to incorporate α-aminoacids or anthranilic acid to the allenamide substrate so as to end up with two-nitrogen containing heterocycles such as imidazoles, benzodiazepines and piperazines. A brief description of the above heterocyclic structures is reported here below.

Imidazolidinones (Figure 35) **–** Although the industrial importance of these compounds is restricted to few examples, the attractiveness they show in organic chemistry is undoubtable.

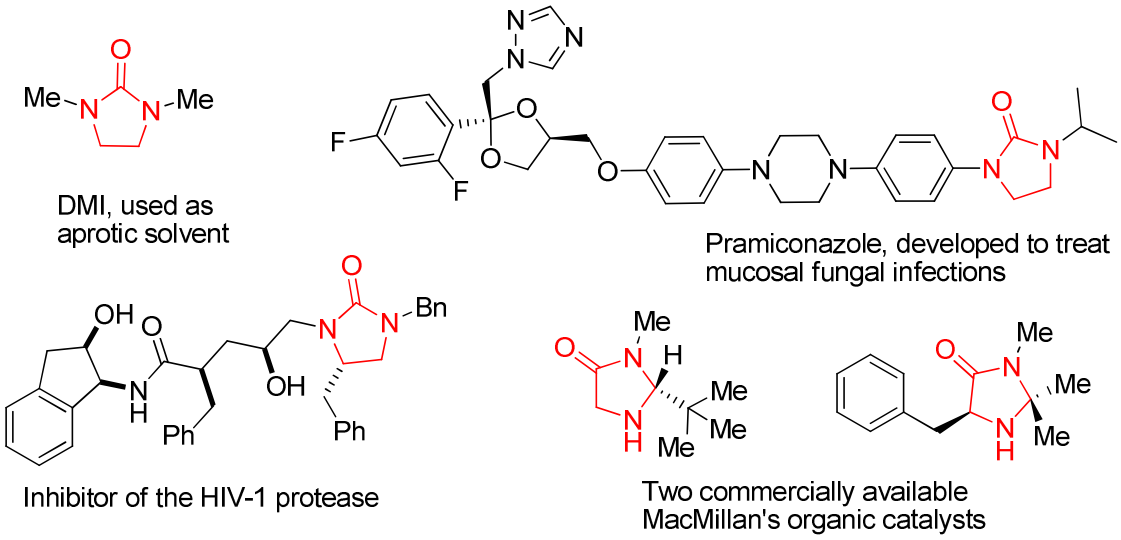

Figure 35. Some examples of the importance of the imidazolidinone nucleus

Structures of this kind are utilized for instance as structural elements in a number of molecules with potent anti-HIV or anti-fungal activity.[67] In addition, closely related to the compounds we were able to synthesize is a certain class of imidazolidinone compounds (also called MacMillan organocatalysts) which were demonstrated to be suitable catalysts for many asymmetric reactions.[68] These catalysts work by forming *in situ* an activated (low LUMO) chiral iminium ion with carbonyl groups of α,β-unsaturated aldehydes (enals) and enones able of transferring a high asymmetric induction to the final product. The catalysts have been used in Diels-Alder reactions, Michael additions, Friedel-Crafts alkylations, transfer hydrogenations and epoxidations, and they are now commercially available.

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[67] (a) N. Vale, M. S. Collins, J. Gut, R. Ferraz, P. J. Rosenthal, M. T. Cushion, R. Moreira, P. Gomes, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 485. (b) M. J. Araujo, J. Bom, R. Capela, C. Casimiro, P. Chambel, P. Gomes, J. Iley, F. Lopes, J. Morais, R. Moreira, E. De Oliveira, V. Do Rosario, N. Vale, *J. Med. Chem.* **2005**, *48*, 888. (c) D. B. Elrod, S. D. Worley, *Ind. Eng. Chem. Res.* **1999**, *38*, 4144.

[68] Seminal paper: K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

Piperazines (Figure 36) – Piperazines and their keto derivatives are amongst the most important backbones in today's drug discovery. Owing to the high number of positive hits encountered in biological screening with this heterocycle and its congeners, and the presence of this moiety in complex natural products, the piperazine template too certainly deserves the title of "privileged scaffold" in medicinal and drug chemistry.[69] Moreover, the ability of these scaffolds to impart specific conformational properties and protein-like characteristics to their derivatives, gives them also the role of basic skeleton for many peptidomimetic structures.[70] Thus, it is no wonder that there is an increasing interest in the development of new synthetic methods that allow for the fast and efficient assembly of these heterocyclic systems.

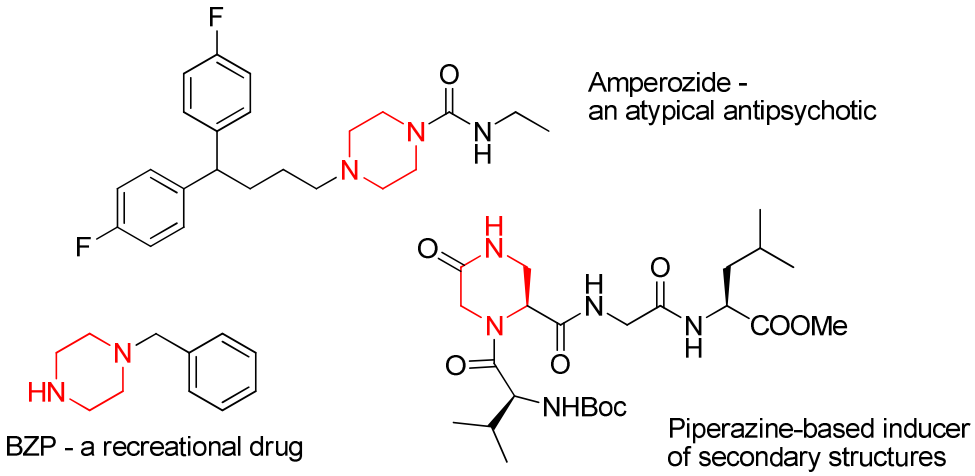


Figure 36 - Application of some piperazine-based molecules

Unfortunately, public opinion has been recently interested on piperazines as they emerged as a new 'family" of drugs for non-medical recreational purposes. BZP (Benzylpiperazine, A2, *a.k.a*. Frenzy or Nemesis), TFMPP (1-[3-(trifluoro-methyl)phenyl]piperazine) and mCPP (meta-chlorophenylpiperazine, 1-(3-Chlorophenyl)- piperazine) are psychoactive drugs with stimulant effects comparable to amphetamines but with a lower potency and differential global scheduling

[69] For some examples: a) A. A. Patchett, R. P. Nargund, *Annu. Rep. Med. Chem.* **2000**, *35*, 289. (b) S. Kitamura, H. Fukushi, T. Miyawaki, M. Kawamura, N. Konishi, Z. Terashita, T. Naka, *J. Med. Chem.* **2001**, *44*, 2438. (c) S. Herrero, M. T. Garcia-Lopez, M. Latorre, E. Cenarruzabeitia, J. Del Rio, R. Herranz, *J. Org. Chem.* **2002**, *67*, 3866.

[70] For some recent examples: (a) P. Maity, B. Konig, *Org. Lett.* **2008**, *10*, 1473. (b) P. Restorp, J. Rebek, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5909. (c) K. Guitot, S. Carboni, O. Reiser, U. Piarulli, *J. Org. Chem.* **2009**, *74*, 8433. (d) P. Toovsk, P. S. Arora, *Org. Lett.* **2010**, *12*, 1588.

status. Much attention is being deserved to piperazines in Bulgaria, where they are not controlled by law neither banned, and they have been sold as a supposed legal alternative to ecstasy.[71]

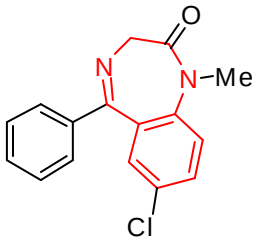


Figure 37 - *Diazepam*, world's most famous benzodiazepine

Benzodiazepines – The first benzodiazepine, chlordiazepoxide, was synthesized in 1955 by Leo Sternbach while working at Hoffmann–La Roche on the development of tranquilizers.[72] The pharmacological properties of the compounds prepared initially were disappointing, and Sternbach abandoned the project. Two years later, in April 1957, co-worker Earl Reeder noticed a "nicely crystalline" compound left over from the discontinued project while spring cleaning in the lab. This compound, later named chlordiazepoxide, had not been tested in 1955 because of Sternbach's focus on other issues. Expecting the pharmacology results to be negative and hoping to publish the chemistry-related findings, researchers submitted it for a standard battery of animal tests. Unexpectedly, the compound showed very strong sedative, anticonvulsant and muscle relaxant effects. These impressive clinical findings led to its speedy introduction throughout the world in 1960 under the brand name *Librium*. Following chlordiazepoxide, diazepam was marketed by Hoffmann–La Roche under the brand name *Valium* in 1963, and for a while these two “mother little helpers”[73] were the most commercially successful drugs. The new group of drugs was initially greeted with optimism by the medical profession, but gradually concerns arose; in particular, the risk of dependence became evident in the 1980s. However, although other antidepressants with anxiolytic properties have been introduced, and there is increasing awareness of the adverse effects of benzodiazepines, prescriptions for short term anxiety relief have not significantly dropped. Only for treatment of insomnia benzodiazepines are now less popular than nonbenzodiazepines, which include zolpidem, zaleplon and eszopiclone. In spite of the molecular difference between the two classes, they work on the same receptors. The main effect of benzodiazepines is to enhance the activity of the neurotransmitter γ-aminobutyric acid, which results in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant and amnesic action. These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. Benzodiazepines are categorized as either short-, intermediate- or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of

[71] I. Nikolova, N. Danchev, *Biotechnol. & Biotechnol. Eq.*, **2008**, *22*, 652.
[72] E. Shorter, "*Benzodiazepines*", in *A Historical Dictionary of Psychiatry,* **2005**, Oxford, Oxford University Press, 41.
[73] M. Jagger, K. Richards, *Aftermath*, **1966**, London.

insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety. Benzodiazepines work by increasing the efficiency of a natural brain chemical, GABA, to decrease the excitability of certain types of brain cells called neurons. This reduces the communication between neurons and therefore has a calming effect on many of the functions of the brain.

Quinazolinones (Figure 38) - The name quinazoline was first proposed for this compound by Weddige,[74] on observing that this was isomeric with the compounds cinnoline and quinoxaline. Of the many derivatives of quinazoline system known so far, keto-quinazolines also called as quinazolinones, are the most important compounds. The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including antibacterial, antimalarial, CNS depressant, antiparkinsonism, antiviral and anticancer activities.[75] Little number of quinazolinones was also reported as potent chemotherapeutic agents in the treatment of tuberculosis.[76]

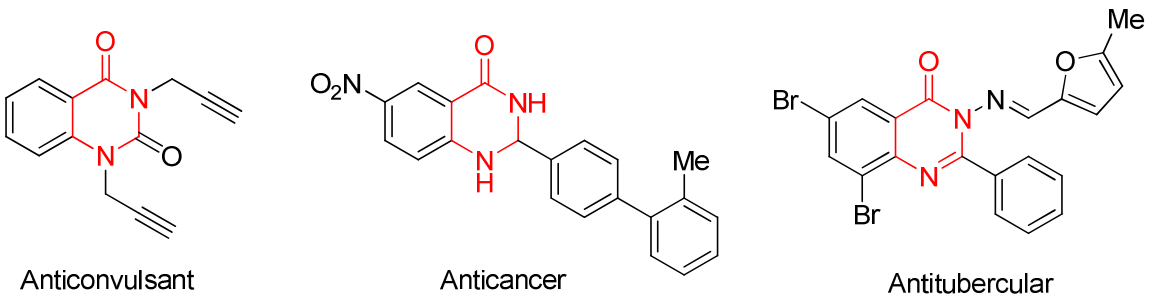


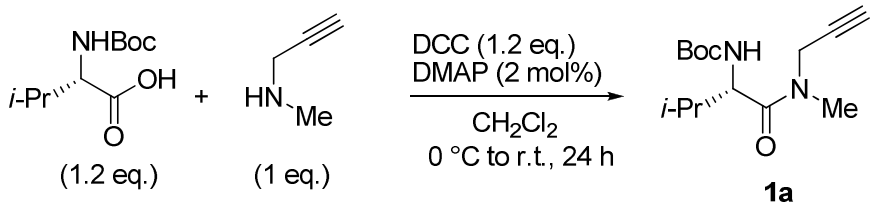
Figure 38. Some quinazolinone structures showing biological activity

[74] A. Weddige, *J. Prakt Chem.* **1887**, *2*, 141.
[75] (a) R. O. Dempcy, E. B. Skibo, *Bioorg. Med Chem Lett.* **1993**, *1*, 39. (b) C. O. Usifoha, G. K. E. Scribab, *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 261. (c) K. Waisser, G. Jii, H. Dostal, K. Jioi, L. Kubicova, V. Klimesova, J. Kaustova, *Il Farmaco* **2001**, *56*, 803. (d) N. M. Nulgulmnalli, M. Raghavendra, P. Thampi, P. M. Gurubasavarajaswamy, D. Sriram, *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 635. (e) S. H. Hwang, A. Rait, K. F. Pirollo, Q. Zhou, V. M. Yenugonda, G. M. Chinigo, M. L. Brown, E. H. Chang, *Mol. Cancer Ther.* **2008**, *7*, 559.
[76] J. Kuneš, J. Bazan, M. Pour, K. Waisserl, M. Šlosárek, J. Janota, *Il Farmaco* **2000**, *55*, 725.

Results

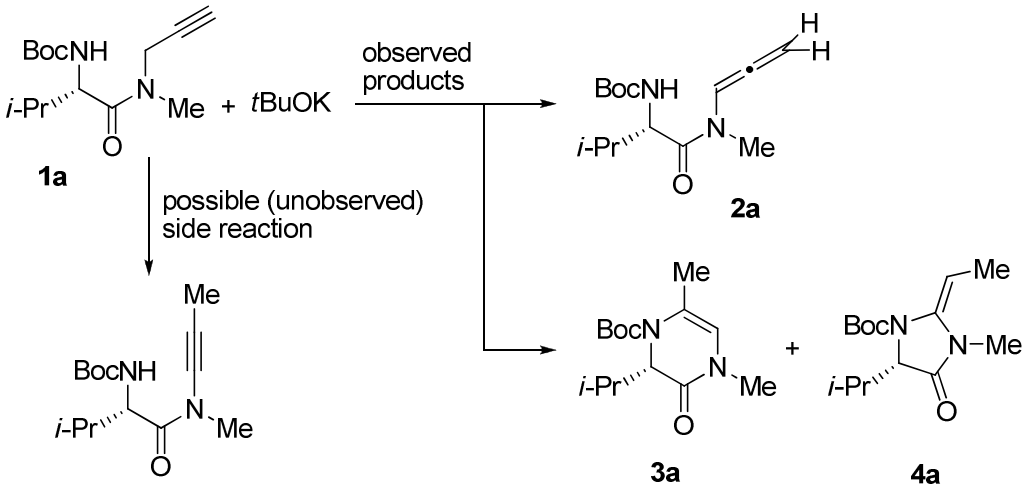
1) First cyclization: behavior of aminoallenes under metal-free conditions

At first, we decided to investigate the feasibility of cyclization processes onto allenes that could have been built starting from α-aminoacids, that is, with a pre-introduced chiral information in the starting materials able to be kept till the obtention of the final enantiopure products. The easiness of the conversion of a carboxylic acid into an amide, and the commercial availability of many suitable propargyl amines apt to insert a triple bond further convertible into an allene group, supported the choice of these building blocks. We consequently synthesized a series of propargylamides **1a-d** starting from N-Boc-protected commercially available L-aminoacids and methylpropargylamine by treatment with DCC (1.2 equiv.) and 4-(dimethylamino)pyridine (0.02 equiv.) in dichloromethane at room temperature (Scheme 1).



Scheme 1. Synthesis of propargylamide **1a**

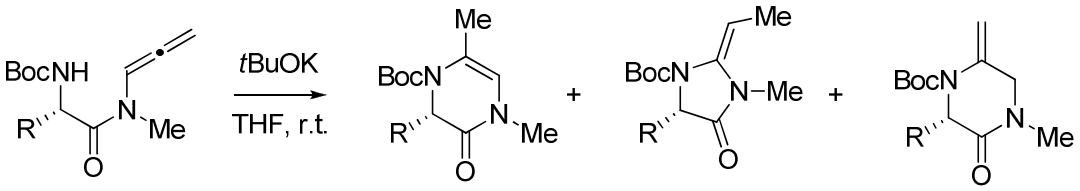
Then, chosen propargylamide **1a** as the model skeleton for our study, we envisioned a prototropic rearrangement as a convenient way to access the desired allene **2a**. The outcome of these isomerizations is normally strongly dependent on the reaction time. Indeed, basic conditions are reported to give rise to an allene intermediate which can either regenerate the starting alkyne or evolve to the internal propargylic homologue, thus realizing the so-called “acetylene zipper” reaction. Therefore, we initially submitted **1a** to different bases and reaction times in order to identify the best conditions to favor equilibration to the allene products. In our case, however, a further interesting behavior was observed. Indeed, while the formation of allene **2a** effectively took place, a prolonged exposure to the base afforded this latter along with complex mixtures of five- or six-membered heterocyclic products arising from intramolecular attack of the amino group on one of the carbon atoms of the internal unsaturation of the allene.



Scheme 2. Behaviour of propargylamide **1a** under basic conditions

With this evidence in hand, we focused our attention on this particular reactivity trying to identify efficient conditions to attain a synthetically useful heterocyclization procedure, and we isolated allene **2a** for this purpose. The cleanest reaction, with limited formation of tarry products, was accomplished in the presence of *t*-BuOK (2.5 equiv. in THF at r. t. for 4 h). We obtained in this way the 5-methyl-3,4-dihydro-pyrazin-2-one **3a** and 2-ethylydenimidazolidin-4-one **4a** in 29% and 32% yield, respectively (Table 1, entry 1).

Table 1. Nitrogen-containing heterocycles obtained by cyclization of amides **2a-c** under basic conditions.



2a-c **3a-c** **4a-c** **5b,c**

Entry	Substrate	R	Conditions	Yields (%)		
				3	**4**	**5**
1	**2a**	i-Pr	r.t., 4h	29	32	-
2	***2a***	*i-Pr*	*MW irradiation, 30 min*	*95*	-	-
3	**2b**	i-Bu	r.t., 4h	28	9	25
4	***2b***	*i-Bu*	*MW irradiation, 30 min*	*89*	-	-
5	**2c**	Bn	r.t., 4h	36	8	27
6	***2c***	*Bn*	*MW irradiation, 30 min*	*72*	-	-

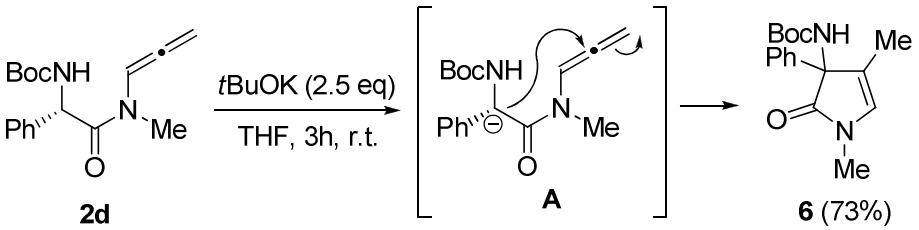
The Z-configuration of compound **4a** is consistent with the observed mutual NOE enhancements between the N-methyl group and the vinyl hydrogen atom (3.3% and 5.8%). HPLC analysis with chiral column of **3a** and **4a**, achieved in comparison to a sample of racemic mixture, proved an

enantiomeric purity better than 99.5%. Heterocyclization also occurred with allenes **2b,c** deriving from L-Leucine and L-phenylalanine according to a more regioselective process.

However, despite their structures strictly related to **2a**, different ratios of five- and six-membered products were obtained. In fact, only small amounts of imidazolidinones **4b,c** (9% and 8%, respectively) were obtained, while pyrazinones **3b,c** were the major products besides their isomers **5b,c**, so indicating preference for the β-C attack by the nucleophilic nitrogen (Table 1, entries 3 and 5).

These reactions, carried out at room temperature, furnished the heterocyclic products in moderate yields, as a high amount of tarry material was also produced. Improved yields could not be achieved by refluxing the solution due to the thermal decomposition of the substrates. The heterocyclization process was also tested in a microwave reactor.[77] Under these conditions, the reactions occurred cleanly in shorter times and higher yields giving exclusively the six-membered ring products **3** (Table 1, entries 2-4-6).

Interestingly, whilst extending the scope of the cyclization, a different behavior was observed for allenamide **2d**, arising from basic treatment of L-phenylglycine. In this case, treatment with *t*-BuOK at room temperature gave rise to the formation of the racemic γ-lactam **6** as the sole product (Scheme 3). The observed outcome can be due to the higher acidity of the benzylic α-aminoacidic hydrogen of **2d** with respect to **2a–c**. Consequently, in the presence of *t*-BuOK, the deprotonation of carbon atom instead of that of the Boc-protected amino group is operative, followed by nucleophilic attack of the carbanion species **A** on the *sp*-carbon. Such a mechanism well justifies the formation of the pyrrolidone derivative in racemic form.

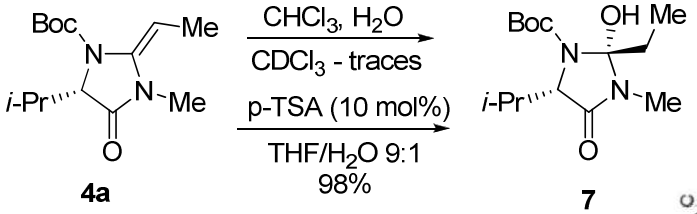


Scheme 3. Base-promoted cyclization of substrate **2d**

Eventually, serendipity, as often occurs, drove us toward a further interesting result. Compound **4a**, left in an NMR-tube for some days after the requested analysis were accomplished, was found to be transformed to some extent into a different structure which lacked the double bond. Assuming this was due to the only other elements present in a deuterated chloroform solution, *i.e.* the residual acidity and traces of water, we made the hypothesis of an acid catalyzed

[77] O. Kappe, *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

hydration of the double bond. Indeed, treatment of **4a** with catalytic amounts of *p*-TSA in THF/H_2O gave smoothly and quantitatively the same compound, which was shown to be the 2-ethyl-2-hydroxy-imidazolidin-4-one **6** (Scheme 4). This process was totally diastereoselective involving generation of the R-configurated new stereocenter in 2-position of the imidazolidinone ring, as identified by X-ray diffractometric analysis (Image 1).



Scheme 4. Acid-catalyzed hydration of the double bond of **4a**

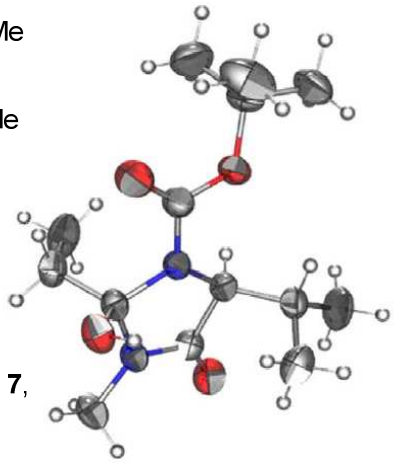


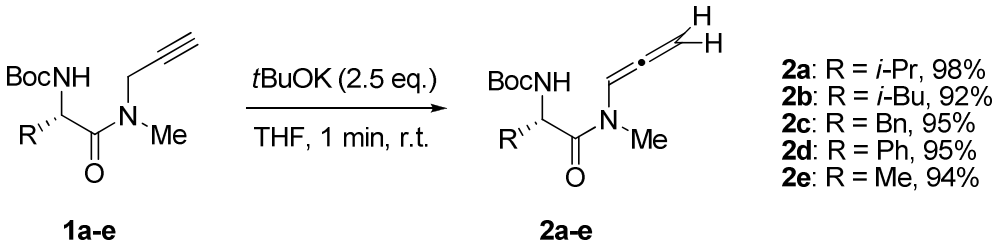
Image 1. Ortep drawing (at 30% probability level) of the molecular structure of compound **7**, highlighting the 2*R*,5*S* absolute configuration. C, gray; H, light gray; N, blue; O, red.

In conclusion, we have developed a simple procedure for building monocyclic five- and six-membered nitrogen containing heterocycles from new allenamides of L-α-aminoacids under basic conditions. The moderate yields of the reactions performed at ambient temperature could be significantly increased by applying microwave activation. Further investigations, mainly based on the use of transition metals, will be described in order to achieve more selective reactions and differently substituted products.

2) Second cyclization: a 5-*exo*-trig reaction through a carbopalladation/allylic amination sequence

Although the above results deserve attention as allow a mild and metal-free way to obtain these cyclic structures, literature shows that transition metal-catalyzed protocols often allow cleaner and efficient reactions. Therefore, we went back onto our initial goal, which consisted in the isolation of the allenamides and test of their behavior in presence of a palladium catalyst with the aim of obtaining enantiopure imidazolidinone products.

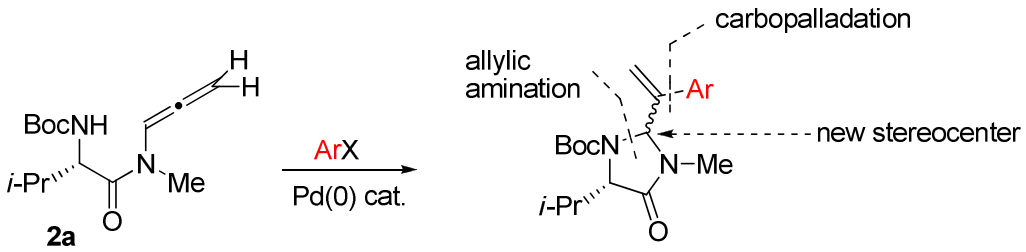
After a thorough screening we found that the propargyl-to-allene conversion was best effected with reaction times as short as 1 minute. Indeed, exceeding this short time led to a mixture of the allenamides along with the aforementioned heterocyclic structures and other tarry products. The collection of substrates **1a-e**[78], were consequently submitted to this fast prototropic shift, yielding the desired allenamides in nearly quantitative yields (Scheme 5).



1a-e **2a-e**

Scheme 5. Prototropic rearrangement leading to allenamides **2a-e**

We next decided to study the palladium-catalyzed nitrogen addition onto the α-carbon of the allene in order to obtain imidazolidinones. As described in the introduction chapter, these heterocycles are the object of great interest for organic chemists. Although the TM-catalyzed generation of heterocyclic compounds via reactions between allene bearing a nucleophilic functionality and organic halides is well established, such a strategy has never been applied to allenamides such as **2a-e**. Thus, we envisaged to obtain imidazolidinone structures through the set up of suitable conditions able to give rise to a pure domino[79] carbopalladation-amination sequence (Scheme 6).

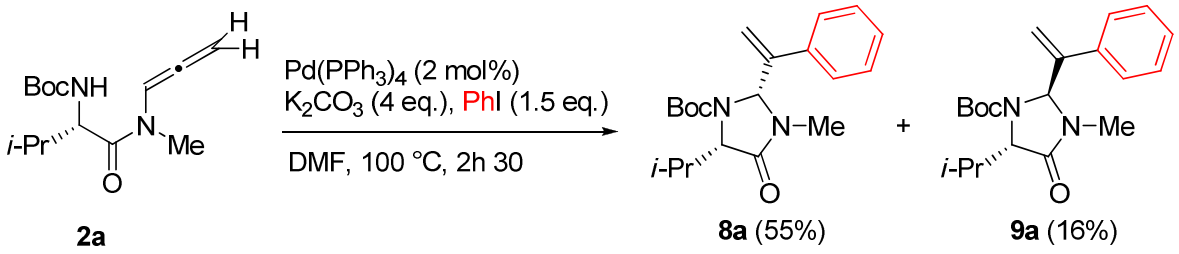


Scheme 6. Planned synthesis of imidazolidinones

After a careful screening using **2a** as the starting substrate, we found that a combination of $Pd(PPh_3)_4$ (2 mol%), potassium carbonate (4.0 equiv.) and iodobenzene (1.5 equiv.) in DMF, as reported by Kang,[80] was the ideal system to promote the desired transformation.[81] These

[78] **1e** was obtained through the same condensation depicted in Scheme 1 in 94% yield.
[79] As opposed to a pseudo-domino process: a) G. Prestat, G. Poli, *Chemtracts: Org. Chem.* **2004**, *17*, 97.
[80] S. K. Kang, K. J. Kim, *Org. Lett.* **2001**, *3*, 511.

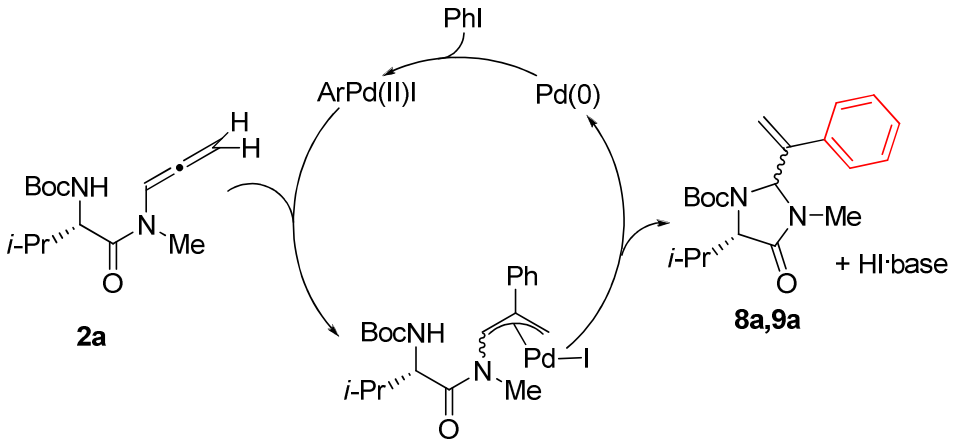
conditions were totally regioselective leading to imidazolidinones **8a** and **9a** respectively in 55% and 16% yield (Scheme 7).



Scheme 7. Pd(0)-catalyzed cyclization of compound **2a**

The heterocyclization process occurred also with PhBr as arylating agent, although in lower yields, and with a Pd(II) source such as $Pd(OAc)_2$, plausibly reduced in situ to Pd(0). The mechanism by which we suppose that this reaction occurs is analogous to the one depicted in Figure 29 with an aryl halide instead of an iodonium salt (Scheme 8).

Once again, optimized conditions were applied to all the different allenamides **2b-e** previously prepared, permitting to obtain a wide panel of imidazolidinone structures (Table 2).



Scheme 8. Plausible mechanism for the Pd(0)-catalyzed cyclization of compound **2a**

Entry	R	8 (Yield %)	9 (Yield %)
2b	Me	65	12
2c	i-Bu	54	17
2d	Bn	50	19
2e	Ph	52	20

Table 2. Scope of the carbopalladation/amination reaction on allenamides **2b-e**

[81] On the other hand, although other bases (Et_3N, Cs_2CO_3, *t*-BuOK) and solvents (acetonitrile, DMSO) also worked, the obtained products were contaminated by traces of byproducts possibly deriving from a 7-*endo*-trig reaction.

The absolute configuration of the major and minor diastereoisomer was assigned after an X-ray crystal structure analysis of the minor product **9a** (Image 2), which revealed a *trans* relationship between the hydrogen atoms in the stereogenic positions and indirectly proved a *cis* disposition for its diastereoisomer **8a**. Analogy of the ^{1}H NMR spectra of compounds **8a** and **9a** with those of **8b**-**d** and **9b**-**d**, respectively, allowed the assignment of their absolute configuration. The constant presence of two rotamers in the ^{1}H and ^{13}C NMR spectra of the *trans* diastereoisomers **9a**-**e** exclusively is the most peculiar feature allowing differentiation of the two diastereoisomers.

Moreover, HPLC comparison (Chiralcel ODH column) of a sample of **8b** with that of a racemic sample obtained starting from (±)-valine proved an enantiomeric purity better than 99.0%. The same analytical procedure on compound **8e** revealed an *ee* of 94%.

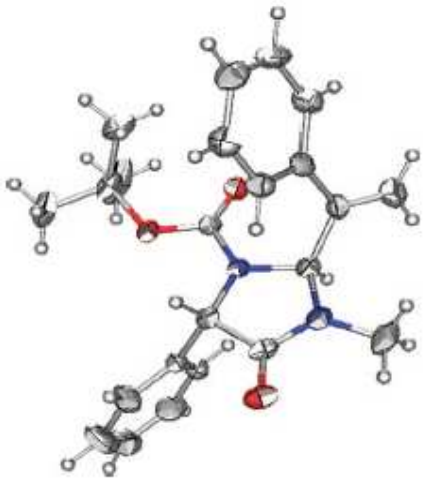


Image 2. ORTEP drawing of compound **9a** at 60% probability level

At this point, we felt that the allene structures we got in hand, combined with phenyl iodide, were also suitable substrates to undergo cyclization through insertion of carbon monoxide, permitting to achieve new different heterocycles.

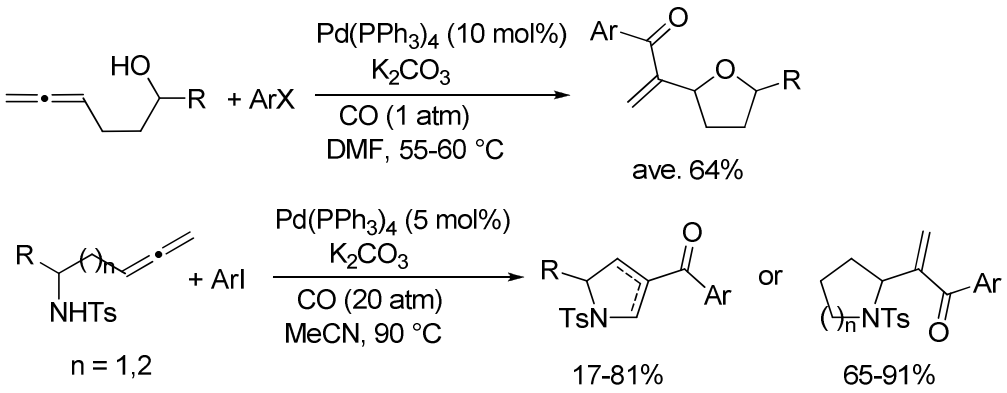
Palladium catalyzed carbonylative transformations involving allenes[82] and halides[83] are a useful tool for the preparation of several heterocycles and aromatic carbonyl compounds.

However, much less attention has been paid to three-component reactions involving N- or O-substituted allenes, carbon monoxide and aromatic halides (Scheme 9).[84]

[82] Recent examples: (a) K. Kato, T. Mochida, H. Takayama, M. Kimura, H. Moriyama, A. Takeshita, Y. Kanno, Y. Inouye, H. Akita, *Tetrahedron Lett.* **2009**, *50*, 4744. (b) P. Szolcsanyi, T. Gracza, I. Spanik, *Tetrahedron Lett.* **2008**, *49*, 1357. (c) S. Kodama, E. Nishinaka, A. Nomoto, M. Sonoda, A. Ogawa, *Tetrahedron Lett.* **2007**, *48*, 6312. (d) S. Tang, Q.-F. Yu, P. Peng, J.-H. Li, P. Zhong, R.-Y. Tang, *Org. Lett.* **2007**, *9*, 3413. (e) B. Gabriele, P. Plastina, G. Salerno, R. Mancuso, M. Costa, *Org. Lett.* **2007**, *9*, 3319. (f) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki, M. Tokuda, *J. Org. Chem.* **2006**, *71*, 5951.

[83] a) L. Kollár, *Modern Carbonylation Methods*, **2008**, Weinheim, Wiley-VCH. b) R. Skoda-Földes, R., L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097.

[84] a) R. D. Walkup, L. Guan, Y. Soo Kim, S. W. Kim, *Tetrahedron Lett.* **1995**, *36*, 3805. b) See ref. 80



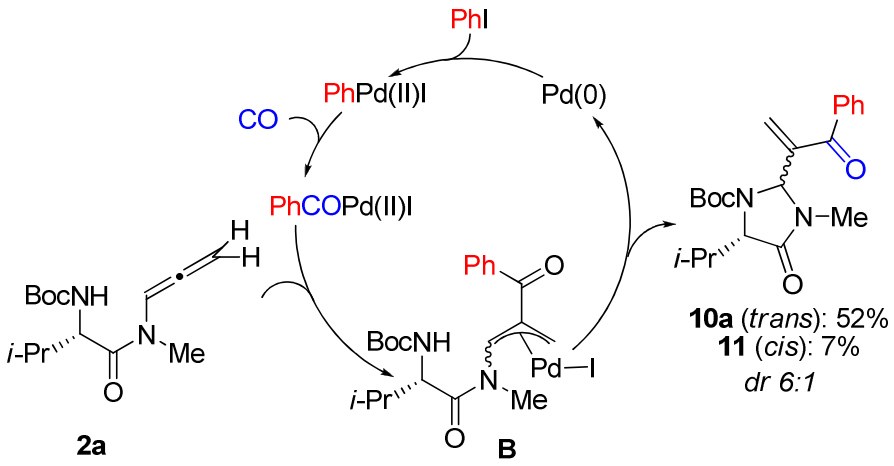
Scheme 9. Walkup's and Kang's carbonylative cyclizations

As a first example, it has been reported that the carbonylation of aryl iodides or bromides in the presence of γ-hydroxyallenes and a palladium(0) catalyst affords aryl (tetrahydrofuran-2-yl)-vinyl ketones.[81a] This reaction was supposed to occur by addition of an initially formed aroylpalladium intermediate to the allenyl unit of the γ-hydroxyallene to produce a π-allylpalladium species, which then undergoes nucleophilic attack by the hydroxyl group to give the product.
A similar mechanism has been claimed in an analogous reaction starting from allene substituted amines, previously restricted to exhibit their nucleophilicity in alkoxycarbonylation procedures.[85]
A novel three component carbonylation/N-heterocyclization undergoing onto sulfonylamides structures was in fact reported by Kang and coworkers.[81b]
However, in that case the tether between the reacting centers did not involve the presence of any functional group nor any further heteroatom. On the other hand, the presence of the amide group into our substrates represented a highly valuable goal.

Accordingly, submission of **2a-c** to the above optimized reaction conditions as described in Scheme 8 and running the reactions under CO at atmospheric pressure gave the corresponding enoyl imidazolidinones **10a**-**e**. Such a result indicated, as expected, that the initially generated PhPd(II)I complex inserted carbon monoxide prior to undergo carbopalladation, to give the new π-allyl complex **B**. Again, intramolecular allylic amination gave the final products (Scheme 10). The *trans*-configuration of **10a**-**e** was assigned by comparing their NMR spectra with those of compounds **8a**-**e** and is probably due to the bulky effect of CO group in intermediate **B**. The heterocyclization of the isopropyl-substituted substrate **2b** took place giving two diastereoisomers

[85] The Pd(II)-catalyzed methoxycarbonylation of allene-substituted amines to form pyrrolidine or piperidine carboxylic esters was known by Gallagher *et al*. See: (a) T. Gallagher, I. W. Davies, S. W. Jones, D. Lathbury, M. F. Mahon, K. C. Molloy, R. W. Shaw, P. Vernon, *J. Chem. Soc., Perkin Trans. 1* **1992**, 433. (b) D. N. A. Fox, T. Gallagher, *Tetrahedron* **1990** *46*, 4697. (c) D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy, T. Gallagher, *J. Am. Chem. Soc.* **1991**, *113*, 2652. (e) D. Lathbury, P. Vernon, T. Gallagher, *Tetrahedron Lett.* **1986**, *27*, 6009.

in a 6:1 ratio, making possible the isolation the *cis*-product **11** (7%). To optimize this procedure, the reaction was carried out under CO pressure (20 atm), but no improvements in diastereoisomeric ratio or time of the reaction were observed.



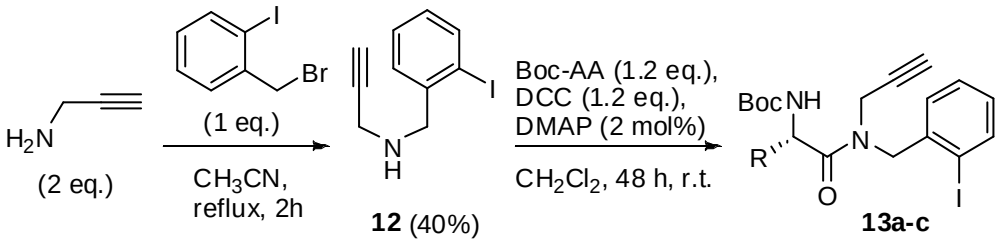
Scheme 10. Mechanism of the Pd(0) catalyzed carbonylation reaction

Entry	R	10 (%)
2b	Me	42
2c	i-Bu	38
2d	Bn	40
2e	Ph	67

Table 3. Scope of the carbonylation reaction on allenamides **2b-e**

Finally, we envisaged to incorporate all the reacting partners into the same reaction step, so as to realize a fully intramolecular carbopalladation/amination sequence. Such type of sequence is still rare in the literature[86] and however limited to build fused-ring systems having six or more atoms in the formed cycles. The amination step being already intramolecular, the key point was to realize an intramolecular carbopalladation, which could be attained tethering the aryl iodide to the allenamide substrate. This was obtained by alkylation of propargylamine with *o*-iodobenzylbromide to give the secondary amine **12** (more careful and efficient protocols to avoid the formation of overalkylated products seemed unnecessary due to the easiness and rapidity of this protocol as well as to the extremely low cost of the reactants). Subsequent treatment with the appropriate aminoacids under standard DCC conditions afforded the propargyl amides **13a-c**, which were isomerized to the corresponding allenamides **14a-c** (Scheme 11).

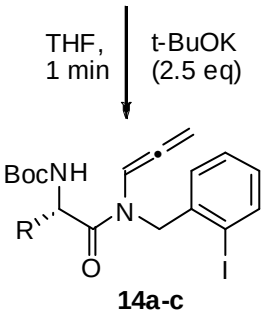
[86] (a) R. Grigg, I. Koppen, M. Rasparini, V. Sridharan, *Chem. Commun.* **2001**, 964. (b) K. Hiroi, Y. Hiratsuka, K. Watanabe, I. Abe, F. Kato, M. Hiroi, *Synlett* **2001**, 263. (c) K. Hiroi, Y. Hiratsuka, K. Watanabe, I. Abe, F. Kato, M. Hiroi, *Tetrahedron: Asymmetry* **2002**, *13*, 1351. (d) S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 5239.



Scheme 11. Synthetic way to access allenamides **14**

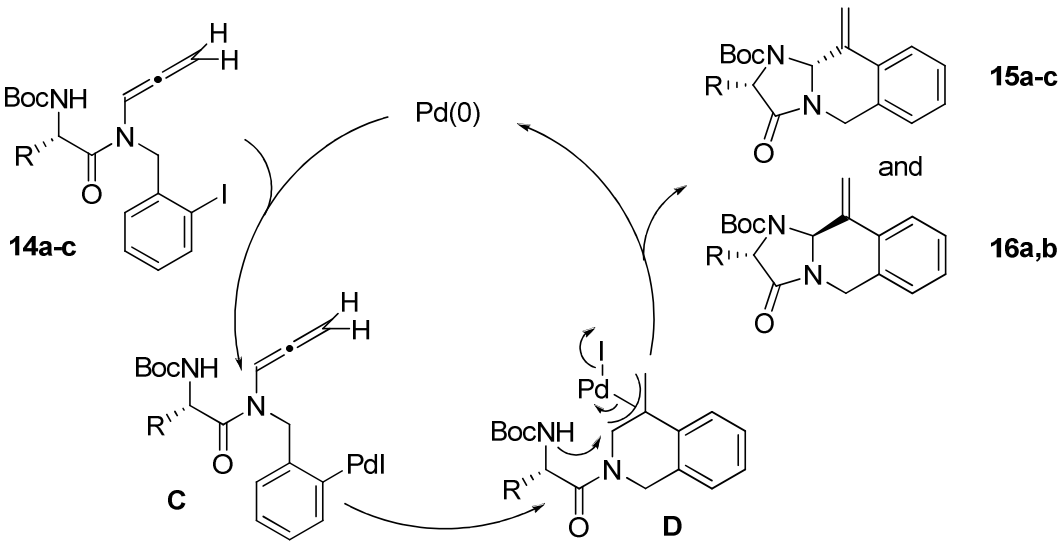
Boc-AA	R	Yields (%)	
Val	i-Pr	**13a** (90%)	**14a** (95%)
Leu	i-Bu	**13b** (81%)	**14b** (93%)
Ala	Me	**13c** (79%)	**14c** (93%)

Table 4. Yields of the condensation and of the propargylic rearrangement for the different aminoacids.



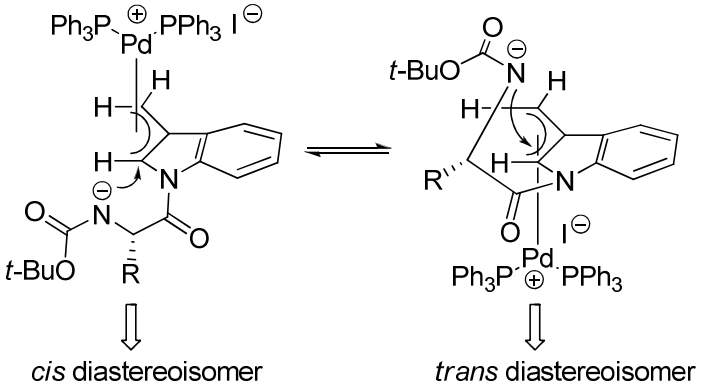
Subsequent carbopalladation/amination of the latter using $Pd(PPh_3)_4$ catalyst and K_2CO_3 as base gave the expected tricyclic products **15a**-**c** (respectively in 54%, 59% and 51% yield) and **16a,b** (8% and 6% yield) in a 6.5:1 diastereomeric ratio. Comparison of the ^{1}H NMR spectra of these products with those of **8a**-**e** allowed assignment of a *cis* configuration to the former set of major isomers and a *trans* one to the minor ones, which could be isolated only in the case of substrates arising from valine and leucine (**16a,b**).

The generation of the 1,5,10,10a-tetrahydro-2*H*-imidazo[1,2-*b*]isoquinolin-3-ones **15** and **16** can be rationalized as depicted in Scheme 12.



Scheme 12. Plausible mechanism for the Pd(0)-catalyzed cyclization of compounds **14**

The initial generation of ArPd(II)I complex **C** by oxidative addition of the iodobenzene moiety to a Pd(0) species is followed by intramolecular carbopalladation of the central carbon of the allyl group to give the π-allyl intermediate **D**. At this point, the intramolecular nucleophilic attack of the nitrogen on the inside position of the Pd-complex generates the imidazolidinone products with concomitant expulsion of the Pd(0) species, able to restart the catalytic cycle.
Inspection of molecular models of the likely equilibrating diastereomeric η^3-allyl Pd complexes $\mathbf{D_1}$ and $\mathbf{D_2}$ shows that nitrogen attack from the former one ($\mathbf{D_1}$) is relatively easy, whereas that from the latter one ($\mathbf{D_2}$) experiences a sever steric clash between the aminoacid residue and the allyl moiety. As a consequence, the higher reactivity of complex $\mathbf{D_1}$ over $\mathbf{D_2}$ well accounts for the observed stereoselectivity favoring the *cis* diastereoisomers (Scheme 13).



Scheme 13. Speculation on the selectivity of the fully intramolecular cyclization

In summary, we have developed a new and original approach to enantiopure imidazolidin-4-ones and imidazoisoquinolinones by means of a domino carbopalladation/allylic amination process, starting from α-amino allenamides of amino acid derivation. In all three protocols developed, the vinyl group present in the final products may allow further improvement of the known organocatalytic properties of such compounds. Moreover, the results have established the feasibility of the above heterocyclization process having an amide group in the tether, without any interference of the carbonyl oxygen. Work is now in progress to investigate the ability of the newly obtained imidazolidin-4-ones as building blocks for more complex structures[87] and as organocatalysts in reactions involving R-unsaturated aldehydes.[88]

[87] L. Basolo, E. M. Beccalli, E. Borsini, G. Broggini, M. Khansaa, M. Rigamonti, *Eur. J. Org. Chem.* **2010**, 1694.
[88] G. Broggini, A. Casoni, F. Clerici, M. Khansaa, "Diastero- ed enantioselezione nelle reazioni di cicloaddizione: una nuova classe di organocatalizzatori", XIII Convegno Nazionale sulle Reazioni Pericicliche – Pavia 17-18 settembre 2009.

3) Shifting towards the obtention of 7-membered heterocycles

This part of my thesis has been spent in the laboratories of professor Poli's group at Université Pierre et Marie Curie, in Paris, in the frame of a cooperation agreement. The main goal we intended to achieve was a palladium-catalyzed synthesis of benzodiazepines using allene substrates. In particular, our interest was devoted to 1,4-benzodiazepin-5-ones, a subset of many biologically and pharmacologically active compounds.[89] Thus, synthesis of new analogues of this structure is highly desirable as it might allow obtaining new compounds showing better pharmaceutical activity. Interestingly, the synthesis of simple bicyclic skeletons, which have captivated interest as simplified forerunners of active tricyclic systems,[90] has not been extensively reported as compared to that of other 1,4-benzodiazepinone derivatives.

In fact, known methods to access these compounds start from substrates such as benzamides[91] or anilines,[92] and require appropriate pre-functionalizations or harsh conditions, or lack in atom economy. Aryne nucleophilic substitutions[93] also hide limited diversity as a drawback. Better results are obtained with supported and solid synthesis.[94] More appealing transition-metal catalyzed processes have also been developed. However, although some of these reactions have been reported to form tricyclic 1,4-benzodiazepin-5-ones,[95] just one Pd(II)-catalyzed intramolecular route to bicyclic structures is known.[96]

To widen this research area, we envisioned allenes as suitable substrates, and herein we developed the first synthesis of bicyclic 1,4-benzodiazepin-5-ones via a pure domino Pd(0) catalyzed carbopalladation/allylic amination process involving allenes. To the best of our

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[89] For some examples: a) Q. Zhou, W. Duan, D. Simmons, Y. Shayo, M. A. Raymond, R. T. Dorr, L. H. Hurley, *J. Am. Chem. Soc.* **2001**, *123*, 4865. i) I. A. O'Neil, S. Thompson, S. B. Kalindjian, T. C. Jenkins, *Tetrahedron Lett.* **2003**, *44*, 7809. d) R. F. Anton, H. Myrick, A. M. Baros, P. K. Latham, P. K. Randall, T. M. Wright, S. H. Stewart, R. Waid, R. Malcolm, *J. Clin. Psycopharm.* **2009**, *29*, 334. e) M. Wallner, R. W. Olsen, *Brit. J. Pharmacology* **2008**, *154*, 288.

[90] a) A. Walser, R. I. Fryer, in *Chemistry of heterocyclic compounds. Bicyclic diazepines;* **1991**, Chichester, UK, Eds.: E. C. Taylor, A. Weissberger, Wiley, 431. b) A. N. Osman, A. A. El-Gendy, R. H. Omar, L. Wagdy, A. H. Omar, *Ind. J. Chem. (B)* **2002**, *41B*, 871.

[91] a) K. Hemming, C. Loucou, *Tetrahedron* **2004**, *60*, 3349. b) D. Ferraris, R. P. Ficco, D. Dain, M. Ginski, S. Lautar, K. Lee-Wisdom, S. Liang, Q. Lin, M. X.-C. Lu, L. Morgan, B. Thomas, *Bioorg. Med. Chem. Lett.* **2003**, *11*, 3695. c) P. Tempest, V. Ma, M. G. Kelly, W. Jones, C. Hulme, *Tetrahedron Lett.* **2001**, *42*, 4963.

[92] a) R. A. Tapia, C. Cesar, *Synth. Commun.* **2004**, *34*, 2757. b) D. J. Skalitzky, J. T. Marakovits, K. A. Maegley, A. E. Ekker, X.-H. Yu, Z. Hostomsky, S. E. Webber, B. W. Eastman, R. Almassay, J. Li, N. J. Curtin, D. R. Newell, A. H. Calvert, R. J. Griffin, B. T. Golding, *J. Med. Chem.* **2003**, *46*, 210. c) G. L. Grunewald, V. H. Dahanukar, P. Ching, K. R. Criscione, *J. Med. Chem.* **1996**, *39*, 3539. d) C. Bagolini, P. De Witt, L. Pacifici, M. T. Ramacci, *J. Med. Chem.* **1978**, *21*, 476. e) C. Corral, R. Madronero, S. Vega, *J. Heterocycl. Chem.* **1977**, *14*, 99.

[93] H. Yoshida, E. Shirakawa, Y. Honda, T. Hiyama, *Angew. Chem,. Int. Ed*. **2002**, *41*, 3247.

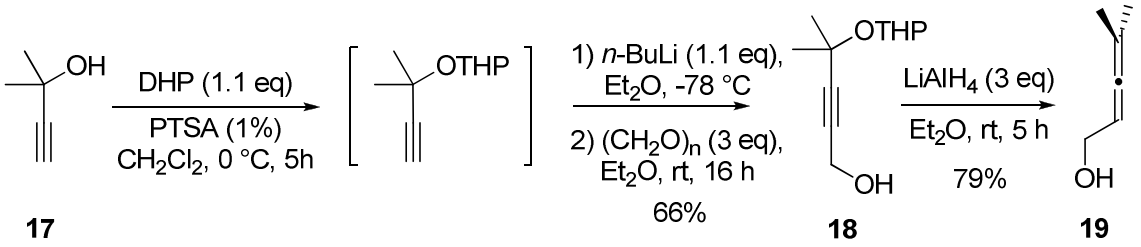
[94] a) S.-C. Lee, S. B. Park, *Chem. Commun.* **2007**, 3714. b) S. Braese, C. Gil, *Chem. Eur. J.* **2005**, *11*, 2680

[95] a) E. M. Beccalli, G. Broggini, G. Paladino, C. Zoni, *Tetrahedron* **2005**, *61*, 61. b) L. P. Tardibono, M. J. Miller, *Org. Lett.* **2009**, *11*, 1575.

[96] E. M. Beccalli, G. Broggini, G. Paladino, A. Penoni, C. Zoni, *J. Org. Chem*. **2004**, *69*, 5627.

knowledge, such reactivity has never been explored in reactions leading to 7-membered nitrogen containing cycles. To obtain such a goal, we forcedly needed an interatomic distance of 6 atoms between the two reacting centers, since the new bond we wanted to build would have represented the seventh bond of the azepinic ring. The ideal substrate to fruitfully accomplish this condition was identified with compound **23a**, whose synthesis was projected to undergo in seven steps starting from the propargylic alcohol **17**.

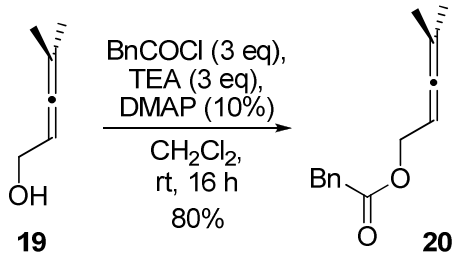
Part of the synthesis followed a way already developed into professor Poli's laboratory for a different work on a carbopalladation/alkylation protocol on allenes.[97] Namely, the motivation leading to the three steps toward compound **19** are completely described into doctor Kammerer's thesis work (Scheme 14).[95b]



Scheme 14. Synthesis of the allenyl alcohol **19**

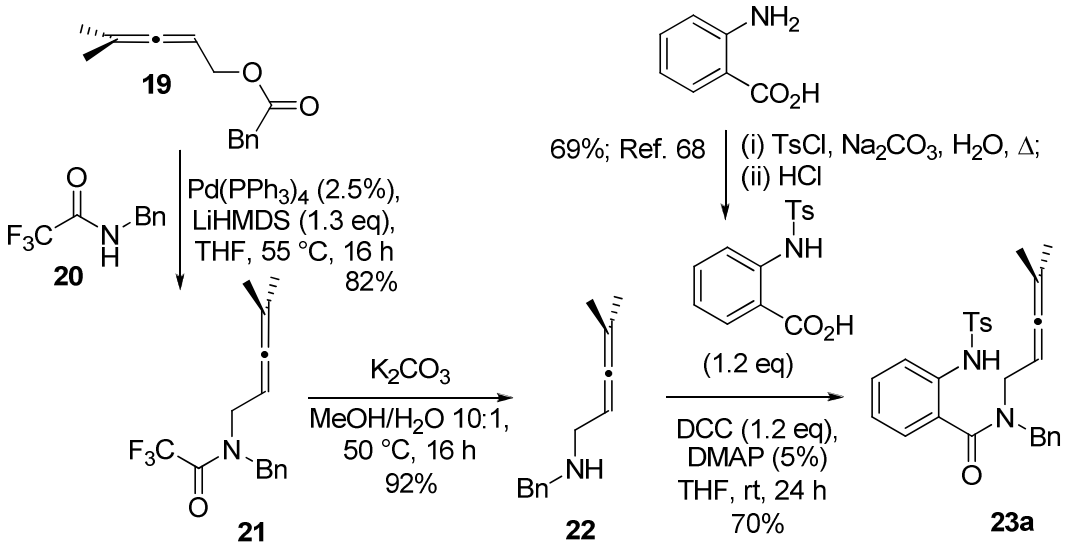
A significant change was brought in the transformation of **19**. Previously adopted protections (i.e., benzyl carbonate, benzoate and acetate) all showed some limitations in yield (carbonate) or handling (very low volatility of the two ester groups). Since the yields obtained with the two ester groups were however higher than what observed with the carbonate protection, we consequently chose a different and heavier residue on the ester protection in order to avoid the volatility issue. To our delight, the ester **20** resulting from condensation between phenacetyl chloride and allene **19** was obtained in high yields and did not evaporate to any observable extent at atmospheric pressure (Scheme 15).

[97] a) C. Kammerer, G. Prestat, D. Madec, G. Poli, *Chem. Eur. J.* **2009**, *15*, 4224. b) "Formation de liaisons c-c par enchaînements domino et cycloisomérisations catalysés par des complexes de palladium, ruthénium et or", Ph.D. thesis of Dr. Claire Kammerer, Paris, June 2009.



Scheme 15. Protection of allenyl alcohol **19** as phenylacetate.

The last reaction was a palladium-catalyzed nucleophilic substitution. Amine **21**, previously identified as the best partner, efficiently reacted with compound **20** to yield amide **22.** After deprotection we obtained the desired allenamine **22**. Eventually, a simple condensation reaction with tosyl-protected anthranilic acid[98] afforded the allenyl anthranilic amide **23a** with an overall yield of 17% after 7 steps (Scheme 16). This latter and 4-iodotoluene (1.2 equiv.) were chosen as model coupling partners to test the carbopalladation/amination sequence (Table 5).



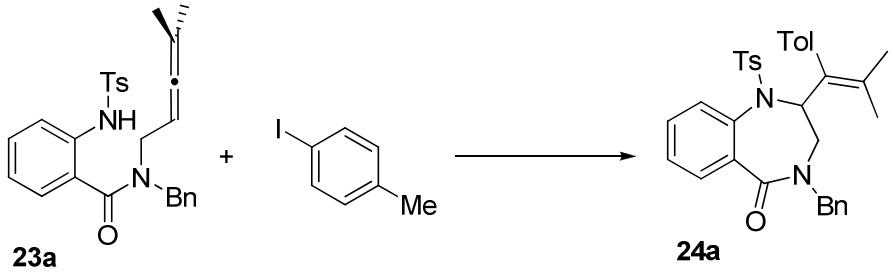
Scheme 16. Final synthetic steps towards the cyclization precursor.

The system $Pd(OAc)_2$/NaH gave a modest conversion (Table 5, entry 1). On the other hand, the use of phosphine-free conditions as previously reported by us[95] was more successful (Table 5, entry 2). The active species was generated dissolving $Pd(CH_3CN)_2Cl_2$ (5 mol%) as precatalyst in DMSO in the presence of BuLi (10%), 4-iodotoluene (1.2 equiv.) and TBAB (20%); then a solution of sodium amidate (obtained through deprotonation of amide **23a** by NaH) in DMSO was added.

[98] M. D. Surman, M. J. Mulvihill, M. J. Miller, *Org. Lett.* **2002**, *4*, 139.

When the same experiment was repeated at 90 °C, the yield of **24a** could be raised to 82% (Table 5, entry 3). On the other hand, switching to a carbonate as the base (entries 4, 5 and 6) or omitting the base (entry 7) gave no product.

Table 5. Optimization of the carbopalladation/amination reaction

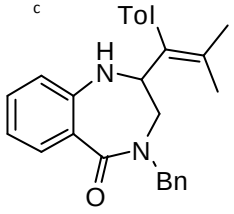


23a **24a**

Entry	Catalytic system	Base	T (°C)	Additive	Solvent	Conversion (%)	Yield (%)
1	$Pd(OAc)_2$ (5%)	NaH (1.2 eq)	50	-	CH_3CN	75	27
2	$Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%)	NaH (1.2 eq)	r.t.->50	TBAB (20%)	DMSO	84	46
3	$Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%)	NaH (1.2 eq)	50 ->90	TBAB (20%)	DMSO	100	82
4	$Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%)	Cs_2CO_3 (2 eq)	50	TBAB (20%)	DMSO	6	n.i.
5	$Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%)	K_2CO_3 (2 eq)	50	TBAB (20%)	DMSO	20	n.i.
6	$Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%)	K_2CO_3 (2 eq)	90	TBAB (20%)	DMSO	20	n.i.
7	$Pd(CH_3CN)_2Cl_2$ (5%), BuLi (10%)	-	90	TBAB (20%)	DMSO	0	-

Chosen the best conditions for the reaction, we then investigated the reactivity of different protecting group on the nucleophilic nitrogen. This was aimed to obtain unprotected benzodiazepinones, in order to identify another site on the vinyl-substituted products that could lead to further functionalizations. Results are summarized in Table 6.

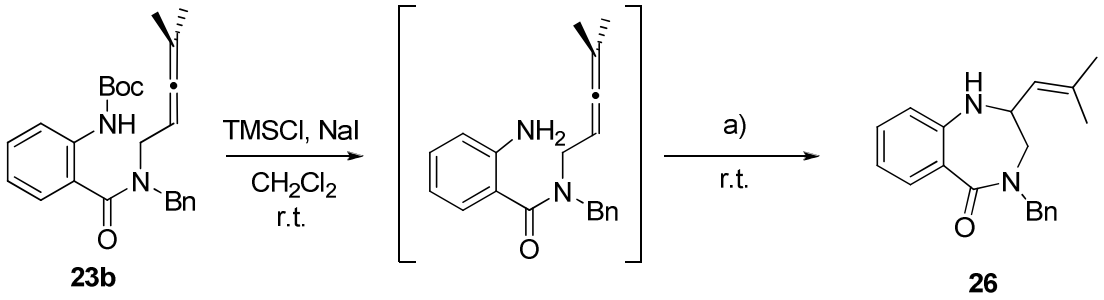
Table 6. Evaluation of different nitrogen protecting groups.

Entry	PG	Acylation yield[a]	Cyclization yield[a]	Deprotection yield	
1	SES	-	-	-	-
2	BOC	58% (**23b**)	48% (**24b**)	-	
3	Nosyl	62% (**23c**)	80% (**24c**)	traces[b]	[c]  **25** (13%)
4	Tosyl	70% (**23a**)	82% (**24a**)	n.r[d,f]	degradation[e]
5	H	Obtained product **26**. See discussion in the text and notes below Scheme 16			

a) Isolated yield. Deprotection conditions: b) PhSH (1 eq), K_2CO_3 (1 eq), DMF, r.t., 4h; c) PhSH (1 eq), K_2CO_3 (1 eq), DMF, 50°C, 24h; d) TBAF, THF, (reflux[a]e) Mg, MeOH, reflux, 2h f) HCl, microwaves, EtOH/AcOH/H_2O.

While N-SES protection of anthranilic acid failed (entry 1), the N-Boc protected analogues were discarded due to the low cyclization yield (entry 2). Other sulfonyl groups gave better results, due to their higher nucleophilicity (entries 3, 4), and they were subsequently studied in the deprotection reaction. However, deprotection of the tosyl group failed and that of the nosyl gave product **25** only in 13% yield (entry 3). This result was considered far from satisfactory.

Finally, we decided to remove BOC group from allenylamide **23b** to test the cyclization on an unprotected substrate. ^{1}H-NMR of the crude product obtained from treatment of **23b** with TMSCl/NaI revealed the presence of the desired NH_2 group. Much to our surprise, purification over a silica gel column (entry 5) gave a spontaneous intramolecular hydroamination affording product **26**. Although literature reports intramolecular hydroamination of allenes promoted by bases or metals, such a behavior is unprecedented. As we suspected that the hydroamination reaction was triggered by the acidity of silica gel, other acidic conditions were tested. After a few trials we found that treatment of the crude product from **23b** with p-TSA (1 equiv.) in DMF at r.t. gave the hydroaminated product 25 in 92% yield (Scheme 17).



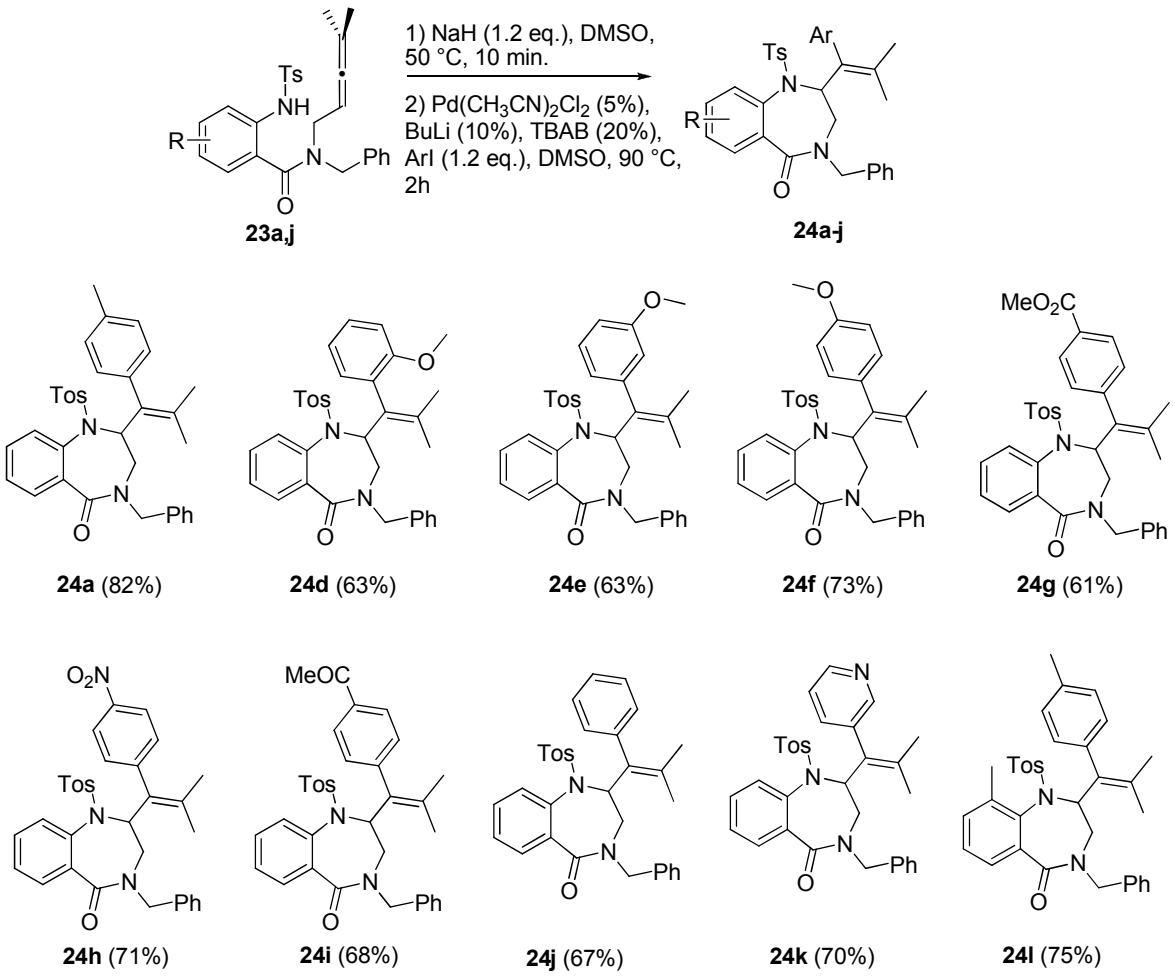
Conditions a:
1) purification over silica gel column (75%).
2) A (1 eq.), PTSA (1 eq.), DMF (92%)
3) A (1 eq,), PTSA (10%) DMF (80%)
4) A (1 eq.), PTSA (10%), CH_2Cl_2 (55%).
Yields are calculated over the 2 steps.

Scheme 17. Acid-catalyzed cyclization of substrate **23b** after deprotection

The above results indicated that the tosyl group was the protecting group of choice to extend our protocol (Scheme 18). Thus, using the optimized phosphine-free conditions, the scope of the domino sequence was next examined on a 0.1 mmol scale with various aryl iodides.

Electron-rich 4-, 3- and 2-iodoanisoles all reacted smoothly, affording the expected corresponding benzodiazepinones **24d-f** in 63%, 63% and 73% respectively. The effect of electron-withdrawing substituents was next investigated. Reactions of 4-methoxycarbonyl, 4-nitro and 4-acetyl iodobenzene gave satisfactory yields of 61%, 71% and 68% (**24g-i**).

The use of simple iodobenzene led to the benzodiazepinone **24j**, which was isolated in 67% yield. Heteroaromatic iodides also gave good yields, as 3-iodopyridine afforded the expected product **24k** in 70% yield. The same protocol was also shown to be able to sustain substitutions onto the aromatic ring, since the 3-methyl anthranilic allenylamide **23l** afforded the corresponding benzodiazepinone **24l** in good yield (75%).



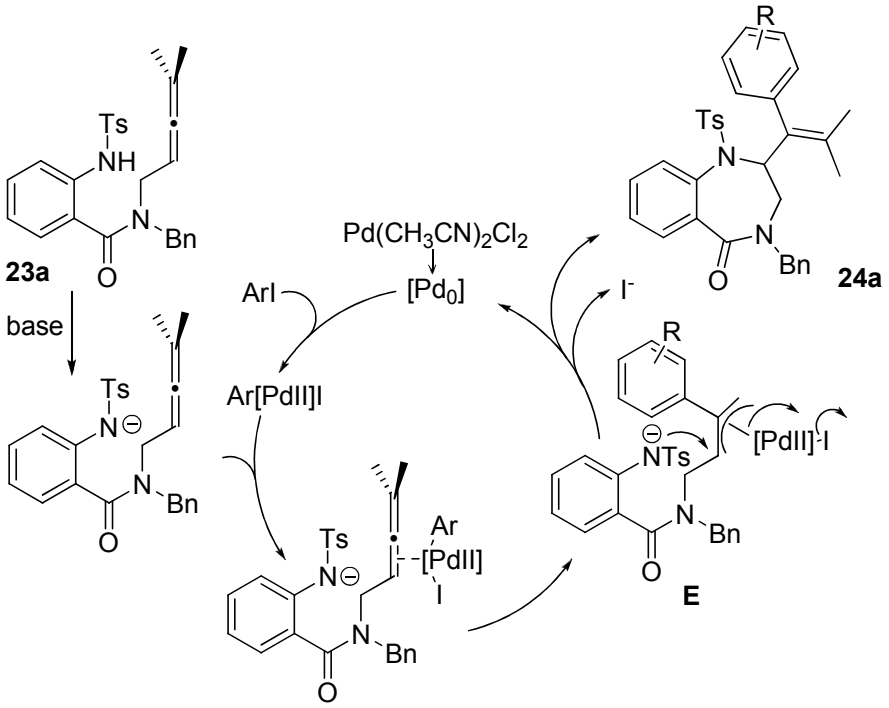
Scheme 18. Scope of the carbopalladation/amination sequence leading to benzodiazepinones

The formation of 1,4-benzodiazepin-5-ones can be rationalized according to the mechanistic proposal depicted in Scheme 19. At first, a Pd(0) complex is generated in DMSO from $Pd(CH_3CN)_2Cl_2$, by using BuLi as an in situ reducing agent.[99] The generation of PhPd(II)I by oxidative addition of iodobenzene to Pd(0)-species follows, involving a carbopalladation of the central carbon of the allyl moiety that gives π-allyl complex **E**. The nucleophilic attack of the

[99] a) E. Negishi, T. Takahashi, K. Akiyoshi, *J. Chem. Soc., Chem. Commun.* **1986**, 1338. b) M. Bottex, M. Cavicchioli, B. Hartmann, N. Monteiro, G. Balme, *J. Org. Chem.* **2001**, *66*, 175.

nitrogen atom on the internal carbon atom closes the pure domino sequence, with generation of the benzodiazepinone products and Pd(0)-species, able to restart the catalytic cycle.

In all the cases studied, the carbopalladation/amination sequence was totally regioselective, yielding the desired 1,4-benzodiazepin-5-ones as the sole products. Such an outcome is probably due to the major stability of the diazepinic heterocyclic ring with respect to the alternative 9-membered product.



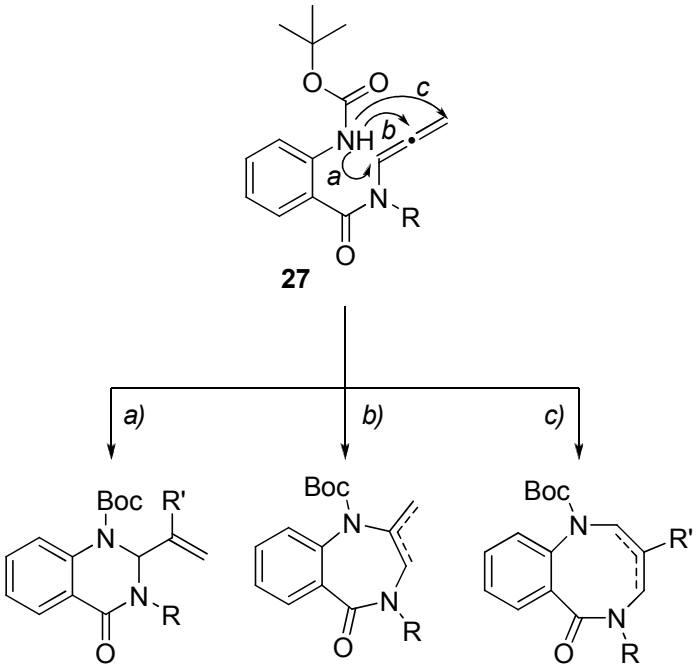
Scheme 19. Mechanistic pathway toward 1,4-benzodiazepin-5-one **24a**

We have in this way developed a new and original approach to 1,4-benzodiazepin-5-ones via a pure domino carbopalladation/allylic amination process starting from allenylamides of anthranilic acid. These results represent the first example of synthesis of 7-membered heterocycles starting from allene *via* carbopalladation. Besides their intrinsic pharmacological interest, the obtained scaffolds are an interesting DOS-compatible platform,[100] amenable to modular synthesis (via the use of differently substituted anthranilic acids), orthogonal protections and easy modifications of the vinylic moiety (use of different iodides), still susceptible of further functionalizations. Furthermore, this study reports the first example of Brønsted-acid catalyzed intramolecular hydroamination of allenes.

[100] DOS: Diversity oriented Organic Synthesis: S. L. Schreiber, *Science* **2000**, *287*, 1964.

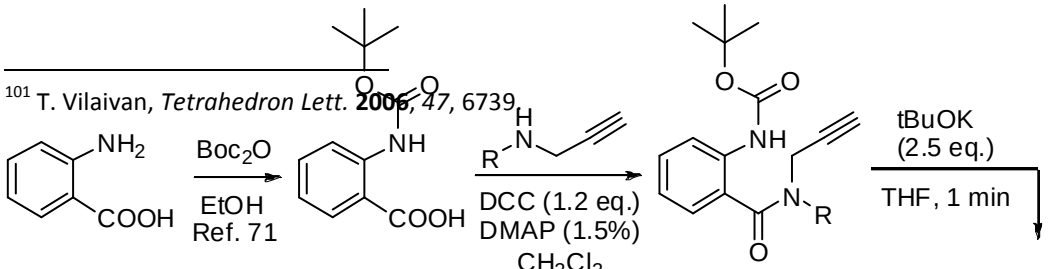
4) Exploiting the anthranilic scaffold, back to allenamides – A) a 6-exo trig carbopalladation/amination reaction

In view of our previous studies using allenamides **2** and using the anthranilic acid fragment as the nucleophilic partner for our cyclizations, we logically thought to combine these two moieties so as to study the cyclization behavior of anthranilic enamides of type **27**. In this case, a 6-exo-dig, a 7-exo or endo-dig or an 8-endo-dig process would generate quinazolinones, benzodiazepinones or benzodiazocinones, respectively (Scheme 20).

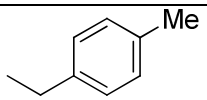
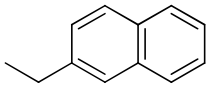
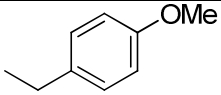
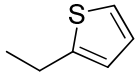


Scheme 20. Possible cyclization outcomes deriving from **27**

Accordingly, anthranilic acid was N-Boc protected,[101] then transformed into propargyl amide **28a**. Subsequent base-promoted prototropic rearrangement gave the corresponding desired allenamide **27a** (Scheme 21). Following a similar protocol, a series of additional 6 anthranilic acid enamide precursors was also synthesized (**27b-g**, Table 7).

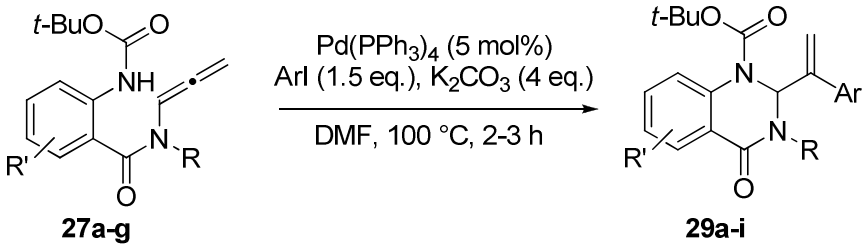


[101] T. Vilaivan, *Tetrahedron Lett.* **2006**, *47*, 6739.

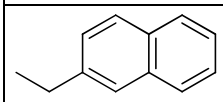
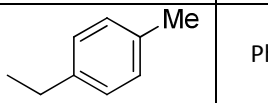
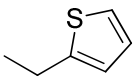
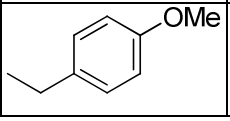
R	Yields (%)		R	Yields (%)	
Me	**28a** (76%)	**27a** (97%)		**28e** (45%)	**27e** (98%)
	**28b** (54%)	**27b** (72%)		**28f** (62%)	**27f** (60%)
	**28c** (28%)	**27c** (36%)	Me (R'= 5-Cl)	**28g** (73%)	**27g** (80%)
Benzyl	**28d** (50%)	**27d** (47%)			

With these precursors in hand, their submission to the previously mentioned optimized conditions ($Pd(PPh_3)_4$ (5 mol%), aryl iodide (1.5 equiv.), potassium carbonate (4 equiv.), DMF, 100 °C) gave the expected styrylquinazolinones **29** in good yields (Table 8).

Table 8. Carbopalladation/amination process results on enamides **27**



27a-g **29a-i**

R	Ar	Yield	R	Ar	Yield	R	Ar	Yield
Me	Ph	**29a** (73%)	Benzyl	Ph	**29d** (62%)	Me (R'=5-Cl)	Ph	**29g** (40%)
	Ph	**29b** (44%)		Ph	**29e** (43%)	Me	4-CO_2Et-C_6H_4	**29h** (60%)
	Ph	**29c** (66%)		Ph	**29f** (50%)	Me	4-COMe	**29i** (56%)

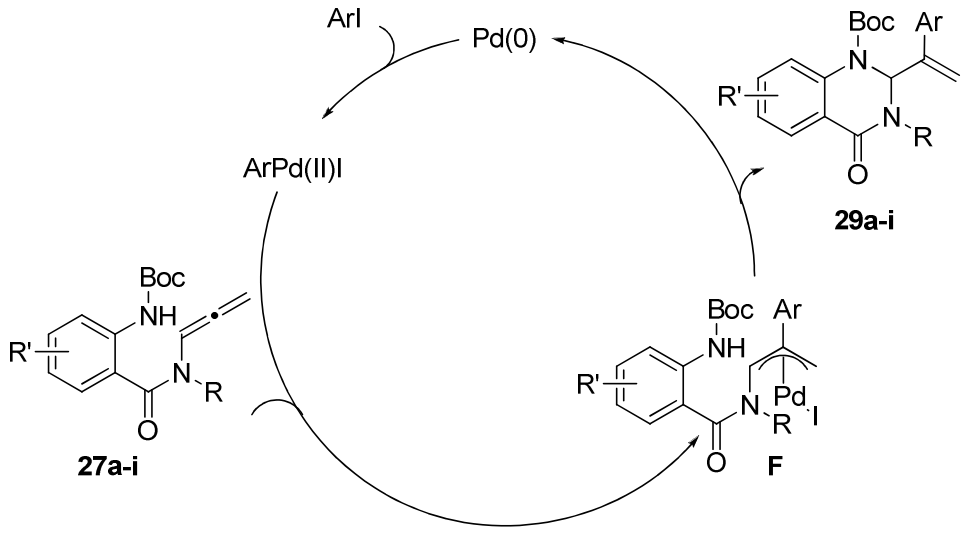
As depicted, we obtained a large variety of quinazolinonic products, arising from a 6-exo-dig cyclization process. This was achieved by using:

i) differently substituted aryl iodides;

ii) substrates bearing different substitutions on the amidic nitrogen;

iii) substrates bearing different substitutions on the aromatic ring.

Conversely to what observed in the cyclization of **2**, the nature of the halogen atom is crucial to attain the formation of styrylquinazolinones, as the replacement of iodine for a less reactive bromine atom led only to the recovery of unreacted starting material. The mechanism is expected to follow the aforementioned carbopalladation/amination sequence (Scheme 22).



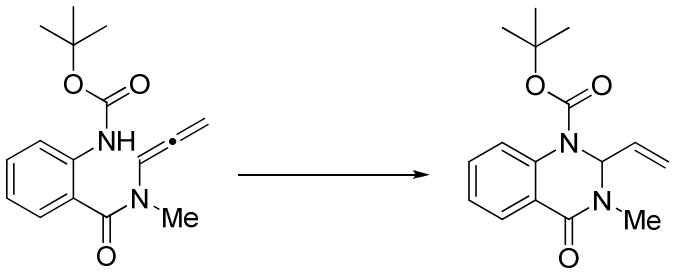
Scheme 22. Mechanistic pathway leading to styril-1,2-dhyidroquinazolin-4-ones **29a-i**

4) Exploiting the anthranilic scaffold, back to allenamides – B) a 6-exo trig hydroamination reaction

All the cyclized products presented so far show an interesting double bond susceptible of further functionalizations. However, the constant presence of a phenyl ring into the vinyl appendage somewhat reduces the possibility of obtaining highly differentiated compounds. As a consequence, we turned our attention toward variations of this cyclization that allow the formation of a vinyl appendage as opposed to a less interesting styryl moiety.

The first envisaged strategy, inspired from recent results of our group,[102] was based on a Pd(0)-catalyzed hydroamination process. However, a preliminary test using allenamide **27a** indicated that such a process was not satisfactory (Table 9).

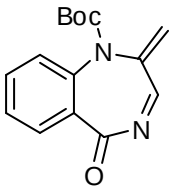
Table 9. Cyclization trials for Pd(0)-catalyzed hydroamination



27a **30a**

Entry	Conditions	Solvent	T (°C)	Time	Outcome
1	$Pd(PPh_3)_4$ (5 mol%), MW	Toluene	25-150 °C	2h	**30a** (10%)
2	$Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv.), MW	Toluene	25-120 °C	25 min	n. r. + degradation
3	$Pd(PPh_3)_4$ (5 mol%), MW	CH_3CN	25-100 °C	45 min	n. r. + degradation
4	$Pd(PPh_3)_4$ (5 mol%), MW	Toluene	25-150 °C	2h 40 min	**30a** (traces)

Alternatively, a hydroamination reaction of allenes can also be accomplished under a palladium(II) catalysis in presence of an oxidant system, as recently demonstrated in studies by Liu and coworkers.[59] However, also in this case we did not obtain clear cut results, as allenes **27** reacted to some extent, but unfortunately were only transformed into a compound whose structure is supposed to be **31**, although in too low yields to be isolated and characterized.[103] Therefore, we abandoned palladium catalysis shifting to other transition metals.

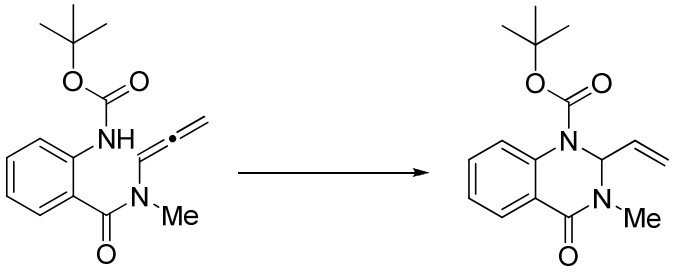


31

Platinum was soon discarded after few trials in light of the unsatisfactory ratio observed between the not enthusiastic yields and the cost of the catalyst; on the other hand, prompted by the good results obtained by another branch of our group onto gold-catalyzed allene hydroamination reactions, [104] we submitted allene **27a** to some gold-catalyzed protocols obtaining results described in Table 10.

[102] E. M. Beccalli, A. Bernasconi, E. Borsini, G. Broggini, M. Rigamonti, G. Zecchi, *J. Org. Chem.* **2010***, 75*, 6923.
[103] Allenes **2** were also unable to give any cyclization product when submitted to Pd(II)-catalyzed reactions.
[104] A. M. Manzo, A. D. Perboni, G. Broggini, M. Rigamonti, *Tetrahedron Lett*. **2009**, *50*, 4696.

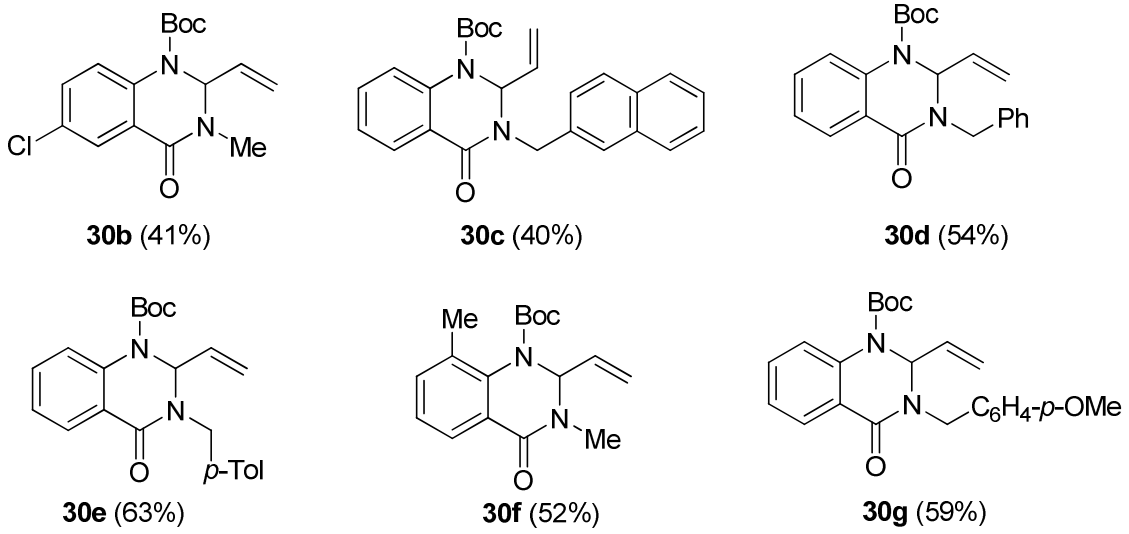
Table 10. Cyclization trials for Au-catalyzed hydroamination



27a **30a**

Entry	Reagents	Solvent	T (°C)	Time	Outcome
1	$AuCl_3$ (5 mol%)	MeCN	Reflux	12h	Starting material
2	$AuCl_3$ (5 mol%), $AgOSO_2CF_3$ (10 mol%)	CH_2Cl_2	r.t.	12h	Starting material
3	$Au(PPh_3)Cl$ (5 mol%), K_2CO_3 (1.5 equiv.)	MeCN	Reflux	12h	Starting material
4	$AuCl_3$ (10 mol%), MW	toluene	25 to 110	2 h	Starting material
4	$AuCl_3$ (5 mol%)	MeCN	Reflux	12h	**30a** (45%)
5	$Au(PPh_3)Cl$ (7.5 mol%), K_2CO_3 (1.5 equiv.)	MeCN	Reflux	12 h	Starting material
5	$AuCl_3$(5 mol%), $CaCO_3$ (1 equiv.)	CH_2Cl_2/MeCN 12:1	r.t. to reflux	20 h	Starting material
6	$AuCl(PPh_3)$ (7.5 mol%), AgOAc (22.5 mol%), $CuCl_2$ (5 equiv.)	CH_2Cl_2	r.t.	24 h	Degradation products

No cyclized product was obtained either in the presence of gold(I) catalyst or in combination with an oxidant. The reaction proceeded only in presence of an Au(III) catalyst (entry 4) and in moderate yields. Acetonitrile at reflux was necessary for the cyclization. Once identified the best protocol, we applied it to a number of different compound, obtaining the cyclized products depicted in Scheme 23.



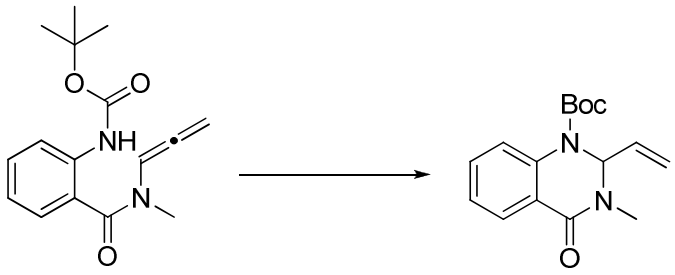
30b (41%) **30c** (40%) **30d** (54%)

30e (63%) **30f** (52%) **30g** (59%)

Scheme 23. Cyclization compounds obtained from the gold-catalyzed hydroamination reaction

Despite the promising results obtained under gold catalysis, we decided to continue our study switching to Ru catalysis. This choice was motivated by the low cost of $RuCl_3$ and by the fact that Ru-catalyzed hydroaminations of allenes is, to the best of our knowledge, still unknown. Our results are shown in Table 11.

Table 11. Cyclization trials for Ru-catalyzed hydroamination



27a **30a**

Entry	Catalytic System	Solvent	T (°C)	Time	Products
1	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppp (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	MeCN	80 °C	20 h	**30a** (26%) + starting material
2	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppp (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	dioxane	90 °C 50 °C	5 h 24 h	**30a** (5%) + starting material
3	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppp (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	N-Me-morpholine	100 °C	24 h	Degradation products
4	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppp (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.),	MeCN	80 °C	48 h	**30a** (40%) + starting material
5	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppe (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	MeCN	60 °C	2 h	**30a** (80%)
6	dppe (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	MeCN	60 °C	24 h	Starting material
7	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	MeCN	60 °C	24 h	**30a** (tracce)
8	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), Bu_4NCl (1 mol%), K_2CO_3 (2 equiv.), allylacetate (4 equiv.)	MeCN	60 °C	24 h	Starting material
9	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppe (1 mol%), K_2CO_3 (2 equiv.)	MeCN	60 °C	24 h	Starting material
10	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppe (1 mol%), K_2CO_3 (2 equiv.), BQ (4 equiv.)	MeCN	60 °C	24 h	Starting material
11	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppe (1 mol%), K_2CO_3 (2 equiv.), O_2	MeCN	60 °C	24 h	**30a** (20%)
12	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppe (1 mol%), K_2CO_3 (2 equiv.), $CuCl_2$ (5 mol% equiv.), O_2	MeCN	60 °C	24 h	**30a** (5%)
13	$RuCl_3 \cdot 2.4H_2O$ (1 mol%), dppe (1 mol%), K_2CO_3 (2 equiv.), $CuCl_2$ (1 equiv)	MeCN	60 °C	2 h	**30a** (90%)

The conditions reported by Kondo for intramolecular amination reactions on olefins[105] furnished the hint for undergoing the investigation on our allene substrates We initially screened the influence of different solvents (entries 1-3). While dioxane and N-Me-morpholine didn't give satisfactory results, acetonitrile brought to the desired product in a 26% yield. This was consequently chosen as the ideal solvent. Prolonging reaction the yield increased (entry 4), although conversion was not total yet. This latter condition was accomplished by using a different phosphine ligand, which afforded the vinyl quinazolinone **29a** in 80% yield. Substitution of allyl acetate with copper chloride as oxidant (entries 12 and 13) slightly improved the yield up to 90%; the use of several ligands able to stabilize in a different way the ruthenium complex or to intervene somehow in the reaction mechanism has not brought so far to better results than the ones obtained with entry 5. These results prompt us to look for better conditions; indeed, the reaction is still under investigation, as well as its mechanistic pathway, still unclear. However, it is possible to infer some key features of this reaction from experimental evidences, that is: a) an oxidant is surely needed, as its absence inhibits the cyclization process (entry 9), and b) critical for the reaction success are phosphines as ligands for whatever may be the ruthenium species involved in the reaction.

[105] T. Kondo, T. Okada, T.-a. Mitsudo, *J. Am. Chem. Soc.* **2002**, *124*, 186.

Conclusions

We have developed six strategies resulting in the synthesis of novel diheteroatomic nitrogen containing heterocyclic scaffolds, exploiting the reactivity of allene compounds.

The first strategy provided useful piperazinonic structures through a metal-free base-catalyzed cyclization reaction. The use of a metal, namely palladium, was instead investigated in three different protocols which led to the obtention of imidazolidinones, benzodiazepinones and styryl-substituted quinazolinones. Finally, gold and ruthenium were able to promote an intramolecular hydroamination process able to yield vinyl-substituted quinazolinones.

The main reaction which we focused our attention on has been the carbopalladation/allylic amination sequence, which has been extensively exploited and applied under different conditions (carbonylative conditions, fully intramolecular protocols, phosphine-free catalytic systems). On the other hand, the ruthenium catalyzed cyclization, which is still under investigation, is worth of interest as it represents the first hydroamination protocol on allenes employing this metal.

Abbreviations and Glossary

AA: aminoacid

Ac.: acetyl

Bn: benzyl

Boc: *tert*-butoxycarbonyl

i-Bu: *iso*-butyl

t-Bu: *tert*-butyl

Cat.: catalytic

Cy: cyclohexyle

DCC: dicyclohexylcarbodiimide

DCM: dichloromethane

DMAP: 4,4'-dimethylaminopyridine

DMF: *N*,*N*-dimethylformamide

dppb: 1,4-bis(diphenylphosphino)butane

dppe: 1,2-bis(diphenylphosphino)ethane

dppf: 1,1'-bis(diphenylphosphino)ferrocene

d.r.: diastereomeric ratio

e.e.: enantiomeric excess

equiv.: equivalent

Et: ethyl

EWG: electron withdrawing group

h: hour

HPLC: High liquid pressure chromatography

I.R.: Infra-Red

L: ligand

LG: leaving group

Me: methyl

min: minute

m.p.: melting point

nOe: nuclear Overhauser effect

NMP: N-methylpyrrolidinone

NMR: Nucelar Magnetic Resonance

Ns: Nosyl

Nu: nucleophile

PG: protecting group

Ph: phenyl

PTSA: para-toluenesulfonic acid

i-Pr: *iso*-propyl

r.t.: room temperature

SES: trimethylsilylethanesulfonyl

TBAB: tetrabutyl ammonium bromide

TBDMS: *tert*-butyldimetylsilyl

THF: tetrahydrofuran

TLC: thin layer chromatography

Ts: tosyl

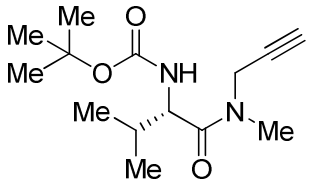
Experimental Section

1) First cyclization: behavior of aminoallenes under metal-free conditions

General procedure for the preparation of propargylamides 1a-e

DCC (10 mmol), N-methyl-propargyl amine (8.3 mmol) and DMAP (0.125 mmol) in anhydrous CH_2Cl_2 (60 mL), cooled at 0 °C, were slowly added to a solution of the appropriate Boc-protected α-aminoacid (10 mmol). The resulting solution was stirred at r.t. for 48 h, then filtered on a path of silica gel. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (light petroleum / AcOEt 7:3).

(S)-2-(t-Butoxycarbonylamino)-3-methyl-N-methyl-N-propargylbutanamide (**1a**)



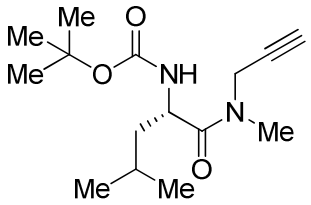
Yield: 95%.
Colorless oil.
IR (nujol): 3304, 3298, 2119, 1703, 1651 cm^{-1};
$[\alpha]^{23}_D$ = +29.5 (c = 0.80, $CHCl_3$);
Rotamers ratio 2.5:1

^1H NMR (400 MHz, $CDCl_3$)
δ: 0.92 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.45 (9H, s), 1.90-2.05 (1H, m), 2.24 (1H, d, J = 2.3 Hz), 2.93 (3H, s), 3.75-3.85 (1H, m), 4.15-4.30 (2H, m), 5.33 (1H, d, J = 8.9 Hz) (major rotamer); 0.66 (3H, d, J = 6.7 Hz), 0.72 (3H, d, J = 6.7 Hz), 1.18 (9H, s), 1.70-1.80 (1H, m), 2.22 (1H, d, J = 2.3 Hz), 2.76 (3H, s), 3.75-3.85 (1H, m), 4.15-4.30 (2H, m), 5.33 (1H, d, J = 8.9 Hz) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$)
δ:17.6 (q), 19.5 (q), 28.5 (q), 31.5 (d), 34.7 (q), 36.7 (t), 55.2 (d), 72.6 (d), 78.5 (s), 79.3 (s), 156.0 (s), 172.3 (s) (major rotamer);
17.7 (q), 19.8 (q), 28.5 (q), 31.4 (d), 34.7 (q), 39.5 (t), 55.4 (d), 73.6 (d), 78.5 (s), 79.4 (s), 155.9 (s), 172.4 (s) (minor rotamer).

MS: m/z 268 (M^+). Anal. calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found C, 62.41; H, 9.18; N, 10.60.

(*S*)-2-(t-Butoxycarbonylamino)-4-methyl-N-methyl-N-propargylpentanamide (**1b**)



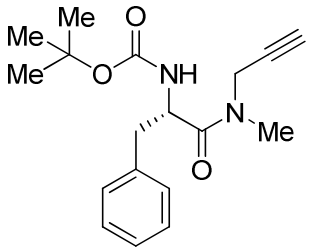
Yield: 96%.
Colorless oil.
IR: 3310, 3282, 2112, 1708, 1649 cm^{-1}.
$[\alpha]^{23}_{D}$ = +17.5 (c = 0.69, $CHCl_3$)
Rotamers ratio 2.5:1.

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.95 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.34-1.51, (11H, m), 1.70-1.80 (1H, m), 2.24 (1H, d, J = 2.5 Hz), 3.16 (3H, s), 4.16 (1H, d, J = 17.2 Hz), 4.26, (1H, d, J = 17.2 Hz), 4.60-4.68 (1H, m), 5.29 (1H, d, J = 8.0 Hz) (major rotamer);
0.95 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz), 1.34-1.51 (11H, m), 1.70-1.80 (1H, m), 2.34 (1H, d, J = 2.5 Hz), 3.03 (3H, s), 3.99 (1H, d, J = 17.2 Hz), 4.46 (1H, d, J = 17.2 Hz), 4.60-4.68 (1H, m), 5.23 (1H, d, J = 8.0 Hz) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 22.1 (q), 23.8 (q), 25.0 (d), 28.7 (q), 34.5 (q), 37.0 (t), 42.8 (t), 49.1 (d), 72.6 (d), 78.6 (s), 79.8 (s), 156.0 (s), 173.1 (s) (major rotamer);
22.1 (q), 23.8 (q), 25.0 (d), 28.7 (q), 33.9 (q), 39.6 (t), 42.4 (t), 49.0 (d), 73.6 (d), 78.2 (s), 80.6 (s), 156.0 (s), 173.1 (s)(minor rotamer).

MS: m/z 282 (M^+). Anal. calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.92. Found C, 63.51; H, 9.38; N, 10.10.

(S)-2-(t-Butoxycarbonylamino)-N-methyl-3-phenyl-N-propargylpropanamide (1c)



Yield: 94%.
Colorless oil.
IR: 3306, 3295, 2121, 1705, 1650 cm^{-1}
$[\alpha]^{23}_{D}$ = +38.8 (c = 0.40, $CHCl_3$)
Rotamers ratio 3:1

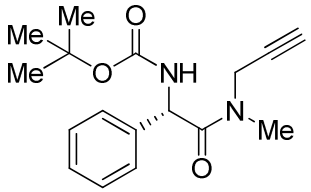
^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.43 (9H, s), 2.22 (1H, d, J = 2.4 Hz), 2.73 (3H, s), 2.80-3.20 (2H, m), 4.02 (1H, d, J = 17.2 Hz), 4.21 (1H, d, J = 17.2 Hz), 4.80-4.85 (1H, m), 5.41 (1H, d, J = 7.9 Hz), 7.19-7.30 (5H, m) (major rotamer);

1.41 (9H, s), 2.27 (1H, d, J = 2.4 Hz), 2.80-3.20 (5H, m), 3.82 (1H, d, J = 17.2 Hz), 3.97 (1H, d, J = 17.2 Hz), 4.80-4.85 (1H, m), 5.30-5.40 (1H, m), 7.19-7.30 (5H, m) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.7 (q), 34.4 (q), 36.9 (t), 40.4 (t), 51.9 (d), 72.6 (d), 78.4 (s), 80.0 (s), 127.3 (d), 128.8 (d), 129.9 (d), 136.6 (s), 155.4 (s), 171.8 (s) (major rotamer);
28.7 (q), 33.8 (q), 39.4 (t), 40.0 (t), 51.9 (d), 73.7 (d), 78.4 (s), 80.2 (s), 127.3 (d), 129.0 (d), 129.6 (d), 136.9 (s), 155.4 (s), 171.8 (s) (minor rotamer).

MS: m/z 316 (M^+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.42; H, 7.50; N, 8.89.

(S)-2-(t-Butoxycarbonylamino)-N-methyl-2-phenyl-N-propargylacetamide (**1d**)



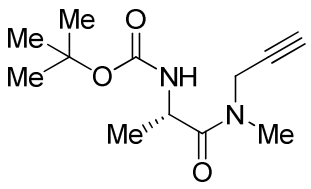
Yield: 97%.
White solid.
M. p. 78-80 °C.
IR: 3306, 3289, 2115, 1710, 1648 cm^{-1}
$[\alpha]^{23}_D$ = +152.2 (c = 0.94, $CHCl_3$)
Rotamers ratio 2.7:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.43 (9H, s), 2.22 (1H, d, J = 2.5 Hz), 2.95 (3H, s), 4.15-4.40 (2H, m), 5.58 (1H, d, J = 7.9 Hz), 5.97 (1H, d, J = 7.9 Hz), 7.30-7.40 (5H, m) (major rotamer);
1.42 (9H, s), 2.22 (1H, d, J = 2.5 Hz), 3.05 (3H, s), 3.82 (1H, d, J = 17.5 Hz), 4.12 (1H, d, J = 17.5 Hz), 5.60-5.65 (1H, m), 6.00-6.05 (1H, m), 7.30-7.40 (5H, m) (minor rotamer).

^{13}C NMR (100 MHz, CDCl3) δ: 28.7 (q), 34.6 (q), 37.4 (t), 55.7 (d), 72.7 (d), 78.3 (s), 80.1 (s), 128.1 (d), 128.7 (d), 129.4 (d), 137.9 (s), 155.4 (s), 170.3 (s) (major rotamer);
28.7 (q), 34.0 (q), 39.3 (t), 55.d (q), 73.8 (d), 78.3 (s), 80.1 (s), 128.1 (d), 128.7 (d), 129.4 (s), 137.9 (s), 155.4 (s), 170.3 (s) (minor rotamer).

MS: m/z 302 (M^+). Anal. calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found C, 67.42; H, 7.50; N, 9.47.

(*S*)-2-(t-Butoxycarbonylamino)-N-methyl-N-propargylpropanamide (**1e**)



Yield: 96%.
Colorless oil.

IR: 3306, 3291, 2122, 1705, 1649 cm^{-1}
$[\alpha]^{23}_{D}$ = +9.7 (c = 1.13, $CHCl_3$)
Rotamers ratio 2.3:1.

^{1}H- NMR (400 MHz, $CDCl_3$)
δ: 1.33 (3H, d, J = 7.2 Hz), 1.45 (9H, s), 2.24 (1H, d, J = 2.0 Hz), 3.15 (3H, s), 4.20 (1H, d, J = 17.0 Hz), 4.37 (1H, d, J = 17.0 Hz), 4.64 (1H, dq, J = 7.2, 7.2 Hz), 5.48 (1H, d, J = 7.2 Hz) (major rotamer);
1.37 (3H, d, J = 7.2 Hz), 1.45 (9H, s), 2.34 (1H, d, J = 2.0 Hz), 3.04 (3H, s), 3.96 (1H, d, J = 17.0 Hz), 4.40 (1H, d, J = 17.0 Hz), 4.64 (1H, dq, J = 7.2, 7.2 Hz), 5.41 (1H, d, J = 7.2 Hz) (minor rotamer);

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 19.1 (q), 28.7 (q), 34.5 (d), 37.1 (t), 46.8 (q), 72.7 (d), 77.8 (s), 79.4 (s), 155.6 (s), 173.1 (s) (major rotamer);
19.5 (q), 28.7 (q), 34.5 (d), 39.5 (t), 46.8 (q), 73.6 (d), 77.8 (s), 79.4 (s), 155.6 (s), 173.1 (s) (minor rotamer).

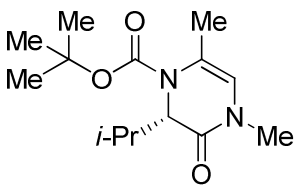
MS: m/z 240 (M+). Anal. calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found C, 60.11; H, 8.22; N, 11.43.

Procedure for the cyclization of 2a:

Thermal heating: A solution of **2a** (100 mg, 0.4 mmol) and t-BuOK (112 mg, 1.0 mmol) in THF (8 mL) was stirred for 4 h at room temperature. The solution was filtered off through a short silica gel path (hexane/AcOEt 4:1 as eluent), and the solvent was evaporated under reduced pressure affording **3a** (29 mg, 29%) and **4a** (32 mg, 32%).

Microwave irradiation: A solution of **2a** (100 mg, 0.4 mmol) and t-BuOK (112 mg, 1.0 mmol) in THF (5 mL) was heated for 30 min at 50 °C and 250 Watt in a CEM Discover microwave reactor. The solution was filtered off through a short silica gel path (hexane/AcOEt 4:1 as eluent), and the solvent was evaporated under reduced pressure affording **3a** as a colorless oil (95 mg, 95%).

(*S*)-tert-butyl 2-isopropyl-4,6-dimethyl-3-oxo-3,4-dihydropyrazine-1(2H)-carboxylate (**3a**)



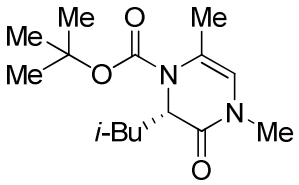
Yield: 29% (thermal), 95% (MW).
Colorless oil.
IR (Nujol): 1684, 1706 cm^{-1}.
$[\alpha]^{23}_{D}$ = +103.0 (c = 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.92 (3H, d, J = 6.7 Hz),0.98 (3H, d, J = 6.7 Hz), 1.47 (9H, s), 1.83 (1H, m), 2.06 (3H, s), 3.02 (3H, s), 4.34 (1H, m), 5.47 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 18.0 (q), 19.4 (d), 28.3 (q), 28.6 (q), 33.2 (q), 63.8 (d), 81.8 (s), 117.8 (d), 119.7 (s), 153.4 (s), 166.1 (s).

MS: m/z 268 (M+). Anal. calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found C, 62.51; H, 9.13; N, 10.40.

(*S*)-tert-butyl 2-isobutyl-4,6-dimethyl-3-oxo-3,4-dihydropyrazine-1(2H)-carboxylate (**3b**)



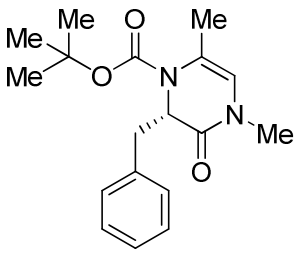
Yield: 28% (thermal), 89% (MW).
Colorless oil.
IR (CH_2Cl_2): 1681, 1705 cm^{-1}.
$[\alpha]^{23}_D$ = +203.7 (c = 0.23, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.95 (3H, d, J = 6.6 Hz),0.99 (3H, d, J = 6.6 Hz), 1.26-1.35 (2H, m) 1.47 (s, 9H), 1.60-1.65 (1H, m), 2.06 (3H, s), 3.03 (s, 3H), 4.78 (1H, s br), 5.55 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 18.0 (q), 19.4 (d), 20.0 (t), 28.3 (q), 28.6 (q), 33.2 (q), 63.8 (d), 81.8 (s), 117.8 (d), 119.7 (s), 153.4 (s), 166.1 (s).

MS: m/z 282 (M+). Anal. calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.82. Found C, 63.76; H, 9.14; N, 9.84.

(*S*)-tert-butyl 2-benzyl-4,6-dimethyl-3-oxo-3,4-dihydropyrazine-1(2H)-carboxylate (**3c**)



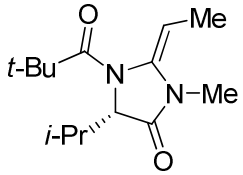
Yield: 36% (thermal), 72% (MW).
Yellow oil.
IR (CH_2Cl_2): 1680, 1708 cm^{-1}.
$[\alpha]^{23}_D$ = +123.4 (c = 0.87, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.23 (9H, s),2.12 (3H, s br), 2.78 (1H, dd, J = 13.4, 10.9 Hz) 2.93 (1H, dd, J = 13.4, 2.9 Hz), 3.07 (3H, s), 4.98-5.02 (1H, m), 5.46 (1H, s br), 7.18-7.31 (5H, m)

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 18.0 (q), 28.2 (q), 33.3 (q), 35.3 (t), 59.9 (d), 81.7 (s), 116.6 (d), 119.3 (s), 127.1 (d), 128.6 (d), 130.1 (d), 137.1 (s), 152.6 (s), 166.6 (s).

MS: m/z 316 (M+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.24; H, 7.59; N, 8.99.

(*S,E*)-2-ethylidene-5-isopropyl-3-methyl-1-pivaloylimidazolidin-4-one (**4a**)



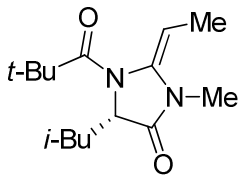
Yield: 32% (thermal)
Pale yellow oil.
IR (Nujol): 1685, 1710 cm^{-1}.
$[\alpha]^{23}_D$ = +3.7 (c 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ = 0.89 (3H, d, J = 6.9 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.51 (9H, s), 1.71 (3H, d, J = 7.1 Hz), 2.26 (1H, dqq, J = 3.5 Hz, 6.9 Hz, 6.9 Hz), 2.96 (3H, s), 4.26 (1H, d, J = 3.5 Hz), 4.44 (1H, q, J = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 13.3 (q), 17.3 (q), 19.2 (q), 26.2 (q), 28.6 (q), 32.8 (d), 66.7 (d), 82.3 (s), 89.2 (d), 138.6 (s), 152.7 (s), 170.5 (s).

MS: m/z 252 (M+). Anal. calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found C, 66.71; H, 9.62; N, 11.04.

(*S,E*)-2-ethylidene-5-isobutyl-3-methyl-1-pivaloylimidazolidin-4-one (**4b**)



Yield: 9% (thermal)
Pale yellow oil.
IR (Nujol): 1683, 1709 cm^{-1}.
$[\alpha]^{23}_D$ = +13.4 (c 0.05, $CHCl_3$).

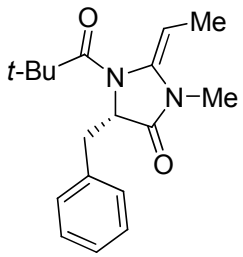
^{1}H NMR (400 MHz, $CDCl_3$)

δ = 0.97 (3H, d, J = 6.7 Hz), 1.01 (3H, d, J = 6.7 Hz), 1.26-1.35 (2H, m), 1.51 (9H, s), 1.65-1.67 (1H, m), 1.73 (3H, d, J = 7.0 Hz), 2.98 (3H, s), 4.28-4.32 (1H, m), 4.48 (1H, q, J = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 13.1 (q), 17.2 (t), 17.4 (q), 26.2 (d), 28.6 (q), 29.3 (q), 33.5 (q), 66.7 (d), 82.3 (s), 89.2 (d), 138.6 (s), 152.7 (s), 170.5 (s).

MS: m/z 266 (M+). Anal. calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found C, 67.70; H, 9.81; N, 10.46.

(*S,E*)-5-benzyl-2-ethylidene-3-methyl-1-pivaloylimidazolidin-4-one (**4c**)



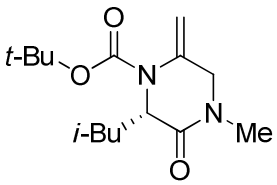
Yield: 8% (thermal)
Pale yellow oil.
IR (Nujol): 1688, 1709 cm^{-1}.
$[\alpha]^{23}_D$ = +10.6 (c 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ = 1.53 (9H, s), 1.79 (3H, d, J = 7.2 Hz), 2.65-2.81 (2H, m), 3.01 (3H, s), 4.28-4.32 (1H, m), 4.45 (1H, q, J = 7.2 Hz), 7.12-7.55 (5H, m).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 19.2 (q), 24.5 (t), 26.2 (q), 28.6 (q), 32.8 (q), 66.7 (d), 82.3 (s), 89.2 (d), 127.3 (d), 127.5 (d), 127.7 (d), 130.4 (s), 138.6 (s), 152.7 (s), 170.5 (s).

MS: m/z 300 (M+). Anal. calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found C, 72.05; H, 8.18; N, 9.31.

(*S*)-tert-butyl 2-isobutyl-4-methyl-6-methylene-3-oxopiperazine-1-carboxylate (**5b**)



Yield: 25% (thermal).
Colorless oil.
IR (CH_2Cl_2): 1680, 1703 cm^{-1}.
$[\alpha]^{23}_D$ = +153.7 (c = 0.14, $CHCl_3$).

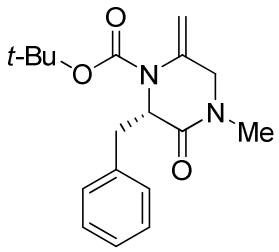
^{1}H NMR (400 MHz, $CDCl_3$)

δ: 0.91 (3H, d, J = 6.6 Hz),0.96 (3H, d, J = 6.6 Hz), 1.47 (s, 9H), 1.50-1.58 (1H, m), 1.90-1.95 (2H, m), 3.03 (s, 3H), 3.88-3.90 (2H, m), 4.43 (1H, s), 4.59 (1H, s), 4.73-4.77 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 18.0 (q), 22.4 (q), 24.8 (d), 28.3 (q), 31.1 (t), 36.2 (q), 62.9 (d), 82.8 (s), 86.8 (d), 142.7 (s), 153.5 (s), 170.1 (s).

MS: m/z 282 (M+). Anal. calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.82. Found C, 63.86; H, 9.15; N, 9.86.

(*S*)-tert-butyl 2-benzyl-4-methyl-6-methylene-3-oxopiperazine-1-carboxylate (**5c**)



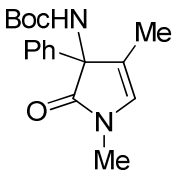
Yield: 27% (thermal).
Colorless oil.
IR (CH_2Cl_2): 1686, 1703 cm^{-1}.
$[\alpha]^{23}_D$ = +166.4 (c = 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.48 (s, 9H), 3.03 (s, 3H), 3.20-3.38 (2H, m), 3.88-3.90 (2H, m), 4.43 (1H, s), 4.60 (1H, s), 4.83-4.90 (1H, m), 7.29-7.40 (5H, m).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 28.3 (q), 35.1 (t), 36.2 (q), 62.9 (d), 82.8 (s), 86.8 (d), 127.2 (d), 127.4 (d), 127.6 (d), 130.1 (s), 142.7 (s), 153.5 (s), 170.1 (s).

MS: m/z 316 (M+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.46; H, 7.65; N, 8.86.

***tert*-butyl 1,4-dimethyl-2-oxo-3-phenyl-2,3-dihydro-1H-pyrrol-3-ylcarbamate** (**6**)



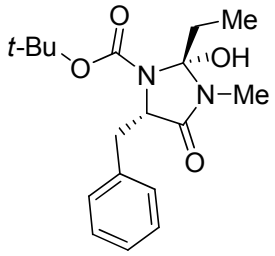
Yield: 73%.
Pale yellow oil.
IR (Nujol): 1697, 1712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.42 (9H, s), 1.74 (3H, d, J = 1.6 Hz), 3.01 (3H, s), 5.24 (1H, s br, missing after deuteration), 6.24 (1H, q, J = 1.6 Hz), 7.37 (5H, m).

^{13}C NMR (100 MHz, $CDCl_3$):
δ: 10.9 (q), 24.3 (q), 29.8 (q), 68.1 (s), 80.8 (s), 119.6 (s), 126.2 (d), 129.0 (d), 129.3 (d), 129.5 (d), 137.5 (s), 154.4 (s), 177.8 (s).

MS: m/z 302 (M+). Anal. calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found C, 67.63; H, 7.28; N, 9.34.

(2*R*,5*S*)-tert-butyl 5-benzyl-2-ethyl-2-hydroxy-3-methyl-4-oxoimidazolidine-1-carboxylate (**7**)



Yield: 98%.
White solid. M.p. 121–122 °C.
IR (Nujol): 1680, 1709, 3380 cm^{-1}.
$[\alpha]^{23}_D$ = +7.1 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.93 (3H, X part of ABX_3 system, J = 7.5 Hz), 1.00 (3H, d, J = 6.9 Hz), 1.17 (3H, d, J = 6.9 Hz), 1.52 (9H, s), 2.07 (1H, A part of ABX_3 system, J = 14.9 Hz, 7.5 Hz), 2.28 (1H, m), 2.51 (1H, B part of ABX_3 system, J = 14.9 Hz, 7.5 Hz), 2.87 (3H, s), 3.97 (1H, d, J = 4.1 Hz), 4.58 (1H, s br, missing after deuteriation).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 9.8 (q), 17.5 (q), 20.2 (d), 24.8 (q), 28.7 (q), 30.9 (t), 31.5 (d), 63.6 (d), 82.4 (s), 100.6 (s), 154.7 (s), 170.6 (s).

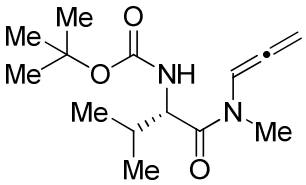
MS: m/z 302 (M+). Anal. calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.68. Found C, 64.63; H, 7.81; N, 8.74.

2) Second cyclization: a 5-*exo*-trig reaction through a carbopalladation/allylic amination sequence

General procedure for the preparation of allenamides 2a-e

t-BuOK (2.5 mmol) in THF (10 mL) was added to a solution of 3 (1 mmol). The resulting solution was stirred at r.t. for 1 min, then filtered on silica gel (AcOEt). The solvent was evaporated under reduced pressure and the residue was used without further purification for the next step.

(S)-2-(t-Butoxycarbonylamino)-3-methyl-N-methyl-N-(1,2-propadienyl)butanamide (**2a**)



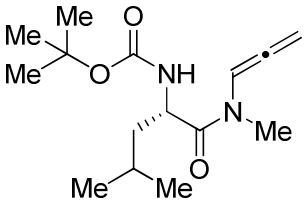
Yield: 98%.
Colorless oil.
IR: 3301, 1947, 1719, 1648 cm^{-1}
$[\alpha]^{23}_{D}$ = +55.4 (c = 0.94, $CHCl_3$)
Rotamers ratio 1.1:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.92 (3H, d, J = 6.8 Hz), 1.00 (3H, d, J = 6.8 Hz), 1.45 (9H, s), 1.90-2.10 (1H, m), 3.14 (3H, s), 4.50-4.65 (1H, m), 5.25-5.35 (1H, m), 5.43 (2H, d, J = 6.4, Hz), 7.54 (1H, dd, J = 6.4, 6.4 Hz) (major rotamer);
0.90 (3H, d, J = 6.8 Hz), 1.00 (3H, d, J = 6.8 Hz), 1.45, (9H, s), 1.90-2.10 (1H, m), 3.04 (3H, s), 4.50-4.65 (1H, m), 5.25-5.35 (1H, m), 5.43 (2H, d, J = 6.4 Hz), 6.97 (1H, dd, J = 6.4, 6.4 Hz) (minor rotamer);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.5 (q), 19.9 (q), 28.8 (q), 31.9 (q), 33.5 (d), 55.7 (d), 80.0 (s), 87.4 (t), 100.1 (d), 156.2 (s), 171.1 (s), 201.6 (s) (major rotamer);
17.6 (q), 20.0 (q), 28.8 (q), 31.9 (q), 33.5 (d), 56.1 (d), 80.0 (s), 87.8 (t), 101.3 (d), 156.2 (s), 171.1 (s), 203.0 (s) (minor rotamer).

MS: m/z 268 (M^+). Anal. calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found C, 62.37; H, 9.19; N, 10.49.

(*S*)-2-(t-Butoxycarbonylamino)-4-methyl-N-methyl-N-(1,2-propadienyl)pentanamide (**2b**)



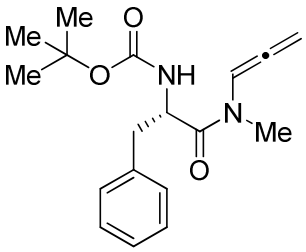
Yield: 92%.
Yellow oil.
IR: 3302, 1938, 1709, 1640 cm^{-1}
$[\alpha]^{23}_D$ = +45.8 (c = 0.72, $CHCl_3$)
Rotamers ratio 1.1:1.

^1H NMR (400 MHz, $CDCl_3$)
δ: 0.94 (3H, d, J = 6.7 Hz), 1.00 (3H, d, J = 6.7 Hz), 1.44 (9H, s), 1.45-1.55 (2H, m), 1.70-1.80 (1H, m), 3.11 (3H, s), 4.68-4.78 (1H, m), 5.24-5.26 (1H, m), 5.41 (2H, d, J = 6.4 Hz), 7.49 (1H, dd, J = 6.4, 6.4 Hz) (major rotamer);
0.94 (3H, d, J = 6.7 Hz), 1.00 (3H, d, J = 6.7 Hz), 1.44 (9H, s), 1.45-1.55 (2H, m), 1.70-1.80 (1H, m), 3.11 (3H, s), 4.68-4.78 (1H, m), 5.24-5.26 (1H, m), 5.41 (2H, d, J = 6.4 Hz), 6.93 (1H, dd, J = 6.4, 6.4 Hz) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 22.1 (q), 23.7 (q), 25.1 (d), 28.7 (q), 32.0 (q), 43.0 (t), 49.8 (d), 80.0 (s), 87.8 (t), 100.2 (d), 156.0 (s), 171.9 (s), 202.9 (s) (major rotamer);
22.1 (q), 23.7 (q), 25.9 (d), 28.7 (q), 33.0 (q), 43.0 (t), 49.4 (d), 80.0 (d), 87.3 (t), 100.9 (d), 155.9 (s), 171.9 (s), 201.7 (s) (minor rotamer).

MS: m/z 282 (M^+). Anal. calcd for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.28; N, 9.92. Found C, 64.04; H, 9.03; N, 10.07.

(*S*)-2-(t-Butoxycarbonylamino)-N-methyl-3-phenyl-N-(1,2-propadienyl)propanamide (**2c**)



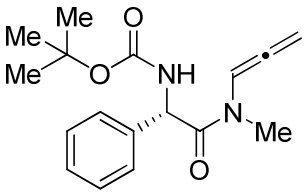
Yield: 95%.
Yellow oil.
IR: 3306, 1942, 1701, 1650 cm^{-1}
$[\alpha]^{23}_D$ = +56.7 (c = 0.63, CHCl3)
Rotamers ratio 1.4:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.36 (9H, s), 2.72 (3H, s), 2.90-3.06 (2H, m), 4.83-4.90 (1H, m), 5.30 (2H, d, J = 6.3 Hz), 5.62-5.69 (1H, m), 7.08-7.35 (5H, m), 7.44 (1H, dd, J = 6.3, 6.3 Hz) (major rotamer);
1.36 (9H, s), 2.91 (3H, s), 2.90-3.06 (2H, m), 4.90-4.97 (1H, m), 5.25 (2H, d, J = 6.3 Hz), 5.62-5.69 (1H, m), 6.79 (1H, dd, J = 6.3, 6.3 Hz), 7.08-7.35 (5H, m) (minor rotamer);

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 28.7 (q), 33.0 (q), 40.2 (t), 52.6 (d), 80.0 (s), 87.6 (t), 100.0 (d), 127.3 (d), 128.8 (d), 129.8 (d), 136.6 (s), 155.5 (s), 170.6 (s), 202.9 (s) (major rotamer);
28.7 (q), 32.0 (q), 39.8 (t), 52.2 (d), 80.0 (s), 87.0 (t), 100.9 (d), 127.1 (d), 128.7 (d), 129.8 (d), 136.6 (s), 155.5 (s), 170.4 (s), 201.7 (s) (minor rotamer).

MS: m/z 316 (M^+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.05; H, 7.82; N, 9.09.

(*S*)-2-(t-Butoxycarbonylamino)-N-methyl-2-phenyl-N-(1,2-propadienyl)acetamide (**2d**)

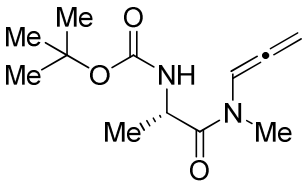


Yield: 95%.
Yellow oil.
IR: 3306, 1946, 1704, 1644 cm^{-1}
$[\alpha]^{23}_D$ = +51.3 (c = 0.89, $CHCl_3$)
Rotamers ratio 1.5:1.
^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.43 (9H, s), 2.91 (3H, s), 5.27-5.42 (2H, m), 5.64 (1H, d, J = 8.0 Hz), 5.95 (1H, d, J = 8.0 Hz), 6.77 (1H, dd, J = 6.4, 6.4 Hz), 7.25-7.75 (5H, m) (major rotamer);
1.43 (9H, s), 3.03 (3H, s), 5.27-5.42 (2H, m), 5.70 (1H, d, J = 8.0 Hz), 5.95 (1H, dd, J = 8.0, 8.0 Hz), 7.25-7.75 (6H, m) (minor rotamer);

^{13}C NMR (100 MHz, CDCl3) δ: 28.7 (q), 33.0 (q), 56.3 (d), 80.3 (s), 88.0 (t), 100.7 (d), 128.1 (d), 128.8 (d), 129.5 (d), 137.6 (s), 155.4 (s), 168.9 (s), 202.7 (s) (major rotamer);
28.7 (q), 32.2 (q), 55.8 (d), 80.3 (s), 87.3 (t), 100.2 (d), 128.1 (d), 128.8 (d), 129.5 (d), 137.9 (s), 154.3 (s), 168.9 (s), 201.6 (s) (minor rotamer).

MS: m/z 302 (M^+). Anal. calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found C, 67.49; H, 7.61; N, 9.42.

(S)-2-(t-Butoxycarbonylamino)-N-methyl-N-(1,2-propadienyl)propanamide (2e)



Yield: 94%.
Colorless oil.
IR: 3306, 1940, 1705, 1649 cm^{-1}
$[\alpha]^{23}_D$ = +54.5 (c = 1.80, $CHCl_3$)
Rotamers ratio 1.1:1.

^1H NMR (400 MHz, $CDCl_3$)
δ: 1.37 (3H, d, J = 5.7 Hz), 1.45 (9H, s), 3.11 (3H, s), 4.73 (1H, dq, J = 5.7, 5.7 Hz), 5.40-5.50 (3H, m), 7.49-7.52 (1H, m) (major rotamer);
1.35 (3H, d, J = 5.7 Hz), 1.45 (9H, s), 3.04 (3H, s), 4.73 (1H, dq, J = 5.7, 5.7 Hz), 5.40-5.50 (3H, m), 6.85-6.88 (1H, m) (minor rotamer);

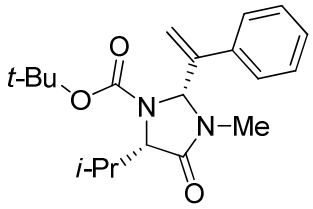
^{13}C NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 28.7 (q), 31.9 (q), 47.3 (d), 79.9 (s), 87.8 (t), 100.1 (d), 155.5 (s), 171.5 (s), 201.6 (s) (major rotamer);
19.2 (q), 28.7 (q), 33.0 (q), 46.9 (d), 79.9 (s), 87.3 (t), 100.9 (d), 155.5 (s), 171.5 (s), 202.8 (s) (minor rotamer).

MS: m/z 240 (M^+). Anal. calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found C, 60.17; H, 8.12; N, 11.50.

General procedure for the carbopalladation/amination of allenamides 2a-e: synthesis of imidazolidinones 8a-e and 9a-e

K_2CO_3 (4 mmol), iodobenzene (1.5 mmol) and $Pd(PPh_3)_4$ (2%) in DMF (10 mL) were added to a solution of **2** (1 mmol). The resulting solution was heated at 100 °C for 2 h, then was cooled, diluted with brine and extracted with AcOEt (3 x 20 mL). The resulting crude was purified by flash chromatography to afford the desired products **8** and **9.**

(2*R*,5*S*)-(t-Butoxycarbonylamino)-5-isopropyl-3-methyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (**8a**)

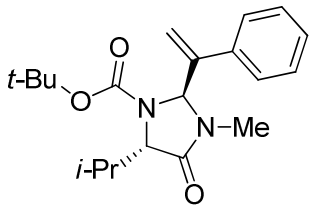


Yield: 55%.
Colorless oil.
IR: 1708, 1671 cm^{-1}
$[\alpha]^{23}_D$ = +4.9 (c = 0.35, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.72 (3H, d, J = 6.9 Hz), 0.77 (3H, d, J = 6.9 Hz), 1.43 (9H, s), 2.00-2.20 (1H, m), 2.85 (3H, s), 3.76-3.78 (1H, m), 5.37-5.51 (3H, m), 7.12-7.29 (5H, m).
^{13}C NMR (100 MHz, CDCl3) δ: 18.5 (q), 20.4 (q), 27.6 (q), 28.6 (q), 32.4 (d), 64.3 (d), 78.8 (d), 81.7 (s), 120.7 (t), 128.3 (d), 128.5 (d), 128.7 (d), 138.6 (s), 146.3 (s), 155.1 (d), 170.8 (d).

MS: m/z 344 (M^+). Anal. calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found C, 69.53; H, 8.28; N, 8.11.

(2*S*,5*S*)-(t-Butoxycarbonylamino)-5-isopropyl-3-methyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (**9a**)



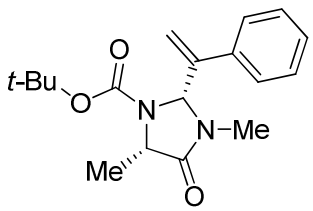
Yield: 16%.
Yellow oil.
IR: 1710, 1658 cm^{-1}
$[\alpha]^{23}_D$ = +33.7 (c = 0.81, $CHCl_3$).
Rotamers ratio 1.1:1.

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.86 (3H, d, J = 6.9 Hz), 1.14 (3H, d, J = 6.9 Hz), 1.41 (9H, s), 2.60-2.78 (1H, m), 2.90 (3H, s), 3.91-3.94 (1H, m), 5.44-5.54 (3H, m), 7.12-7.33 (5H, m) (major rotamer);
0.86 (3H, d, J = 6.9 Hz), 1.11 (3H, d, J = 6.9 Hz), 1.33 (9H, s), 2.25-2.50 (1H, m), 2.80 (3H, s), 3.64-3.68 (1H, m), 5.44-5.54 (3H, m), 7.12-7.33 (5H, m) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 16.4 (q), 18.4 (q), 26.7 (q), 28.6 (q), 28.8 (d), 63.6 (d), 79.1 (d), 81.1 (s), 120.7 (t), 121.2 (d), 127.6 (d), 128.4 (d), 137.5 (s), 145.3 (s), 152.3 (s), 169.5 (s) (major rotamer);
16.6 (q), 18.5 (q), 28.5 (q), 28.6 (q), 31.1 (d), 63.7 (d), 79.4 (d), 81.7 (s), 121.2 (t), 128.0 (d), 128.7 (d), 129.1 (d), 137.5 (s), 146.1 (s), 152.3 (s), 169.8 (s) (minor rotamer).

MS: m/z 344 (M^+). Anal. calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found C, 69.81; H, 7.93; N, 8.28.

(2*R*,5*S*)-(t-Butoxycarbonylamino)-3,5-dimethyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (**8b**)



Yield: 65%.

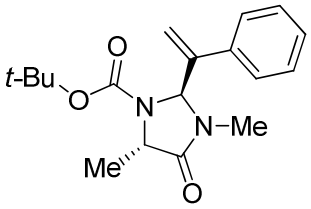
Yellow oil.
IR: 1703, 1664 cm^{-1};
$[\alpha]^{23}_{D}$ = +10.4 (c = 0.46, $CHCl_3$)

^1H NMR (400 MHz, $CDCl_3$)
δ: 0.84 (3H, d, J = 6.7 Hz), 1.47 (9H, s), 2.90 (3H, s), 3.99-4.03 (1H, m), 5.41 (1H, s), 5.49 (1H, s), 5.52 (1H, s) 7.08-7.11 (2H, m), 7.28-7.30 (3H, m)

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 17.2 (q), 27.0 (q), 28.6 (q), 55.2 (d), 79.2 (d), 81.3 (s), 120.7 (t), 128.3 (d), 128.5 (d), 128.7 (d), 138.2 (s), 146.2 (s), 153.4 (s), 171.3 (s).

MS: m/z 316 (M^+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.45; H, 7.51; N, 9.09.

(2*S*,5*S*)-(*t*-Butoxycarbonylamino)-3,5-dimethyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (**9b**)



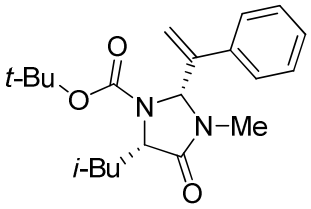
Yield: 12%.
Pale yellow oil.
IR: 1710, 1658 cm^{-1}
$[\alpha]^{23}_{D}$ = +41.1 (c = 0.25, $CHCl_3$).
Rotamers ratio: 1.2:1

^1H NMR (400 MHz, $CDCl_3$)
δ: 1.35-1.55 (12 H, m), 2.93 (3H, s), 3.50-3.60 (1H, m), 5.45-5.56 (3H, m), 7.09-7.33 (5H, m) (major rotamer);
1.35-1.55 (12H, m), 2.85 (3H, s), 3.70-3.90 (1H, m), 5.45-5.56 (3H, m), 7.09-7.33 (5H, m) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 18.3 (q), 27.1 (q), 28.7 (q), 55.0 (d), 78.8 (d), 81.2 (s), 121.3 (t), 127.8 (d), 128.5 (d), 128.8 (d), 137.8 (s), 145.1 (s), 152.6 (s), 171.6 (s) (major rotamer);
17.1 (q), 27.1 (q), 28.7 (q), 55.0 (d), 78.8 (d), 81.6 (s), 120.9 (t), 128.2 (d), 128.7 (d), 129.1 (d), 137.6 (s), 146.0 (s), 152.3 (s), 171.5 (s) (minor rotamer).

MS: m/z 316 (M^+). Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found C, 68.02; H, 7.89; N, 8.68.

(2*R*,5*S*)-(t-Butoxycarbonylamino)-5-isobutyl-3-methyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (8c)



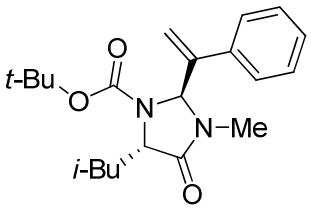
Yield: 54%.
Pale yellow oil.
IR: 1702, 1653 cm^{-1}
$[\alpha]^{23}_{D}$ = +11.3 (c = 1.13, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$)
δ: 0.70-0.95 (8H, m), 1.49 (9H, s), 1.81-1.86 (1H, m), 2.90 (3H, s), 3.95-4.05 (1H, m), 5.40 (1H, s), 5.49-5.55 (2H, m), 7.07-7.09 (2H, m), 7.31-7.33 (3H, m).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 22.3 (q), 23.4 (d), 24.6 (q), 27.2 (q), 28.7 (q), 43.2 (t), 57.0 (d), 79.2 (d), 81.5 (s), 120.9 (t), 128.4 (d), 128.5 (d), 129.0 (d), 138.1 (s), 145.9 (s), 153.8 (s), 171.4 (s).

MS: m/z 358 (M^+). Anal. calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found C, 70.51; H, 8.32; N, 8.02.

(2*S*,5*S*)-(t-Butoxycarbonylamino)-5-isobutyl-3-methyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (9c)



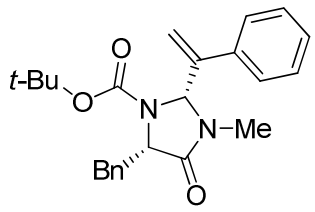
Yield: 17%.
Colorless oil.
IR: 1710, 1658 cm^{-1}
$[\alpha]^{23}_{D}$ = +50.9 (c = 0.44, $CHCl_3$).
Rotamers ratio 1.3:1

1H NMR (400 MHz, $CDCl_3$)
δ: 0.82-0.94 (6H, m), 1.05-2.03 (12H, m), 2.90 (3H, s), 3.60-3.65 (1H, m), 5.44-5.54 (3H, m), 7.09-7.16 (2H, m), 7.25-7.29 (3H, m) (major rotamer);
0.82-0.94 (6H, m), 1.05-2.03 (12H, m), 2.82 (3H, s), 3.90-3.93 (1H, m), 5.44-5.54 (3H, m), 7.09-7.16 (2H, m), 7.25-7.29 (3H, m) (minor rotamer).

^{13}C NMR (100 MHz, CDCl3) δ: 22.6 (q), 23.3 (d), 24.2 (q), 24.6 (q), 27.0 (q), 39.8 (t), 58.0 (d), 79.0 (d), 81.2 (s), 121.2 (t), 127.6 (d), 128.4 (d), 129.0 (d), 137.9 (s), 146.0 (s), 152.4 (s), 171.9 (s) (major rotamer);
23.1 (q), 23.8 (d), 24.4 (q), 25.1 (q), 27.0 (q), 38.0 (t), 57.9 (d), 79.0 (d), 81.2 (s), 120.8 (t), 128.1 (d), 128.7 (d), 129.0 (d), 137.6 (s), 145.2 (s), 152.0 (s), 171.9 (s) (minor rotamer).

MS: m/z 358 (M+). Anal. calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found C, 70.54; H, 8.20; N, 8.04.

(2*R*,5*S*)-5-Benzyl-(t-butoxycarbonylamino)-3-methyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (8d)



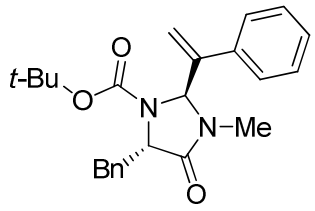
Yield: 50%.
Colorless oil.
IR: 1711, 1650 cm^{-1}
$[\alpha]^{23}_D$ = -5.2 (c = 0.85, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$)
δ: 1.38 (9H, s), 2.30-2.40 (2H, m), 2.90 (3H, s), 4.20-4.25 (1H, m), 5.00-5.50 (2H, m), 5.55 (1H, s), 7.08-7.38 (10H, m).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 27.3 (q), 28.6 (q), 38.8 (t), 60.6 (d), 78.5 (d), 81.8 (s), 120.8 (t), 126.8 (d), 128.6 (d), 130.1 (d), 138.1 (s), 138.7 (s), 145.7 (s), 153.9 (s), 170.2 (s).

MS: m/z 392 (M^+). Anal. calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found C, 73.61; H, 7.02; N, 6.86.

(2*S*,5*S*)-5-Benzyl-(t-butoxycarbonylamino)-3-methyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (9d)



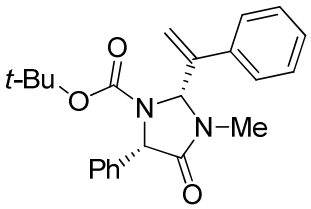
Yield: 19%.
Yellow oil.
IR: 1710, 1658 cm^{-1}
$[\alpha]^{23}_D$ = +101.6 (c = 0.42, $CHCl_3$).
Rotamers ratio 1.5:1

^1H NMR (400 MHz, $CDCl_3$)
δ: 1.47 (9H, s), 2.60 (3H, s), 3.13-3.15 (1H, m), 3.68-3.70 (1H, m), 4.22-4.24 (1H, m), 4.65 (1H, s), 5.24 (1H, d, J = 1.6 Hz) 5.43 (1H, d, J = 1.6 Hz), 7.05-7.30 (10H, m) (major rotamer);
1.45 (9H, s), 2.60 (3H, s), 3.13-3.15 (1H, m), 3.25-3.30 (1H, m), 4.00-4.04 (1H, m), 4.68 (1H, s), 5.24 (1H, d, J = 1.6 Hz) 5.43 (1H, d, J = 1.6 Hz), 7.05-7.30 (10H, m).

^{13}C NMR (100 MHz, CDCl3) δ: 26.7 (q), 28.8 (q), 34.5 (t), 60.4 (d), 79.0 (d), 81.6 (s), 120.9 (t), 127.2 (d), 127.7 (d), 128.3 (d), 128.6 (d), 129.0 (d), 130.3 (d), 136.5 (s), 137.6 (s), 145.6 (s), 152.3 (s), 169.8 (s) (major rotamer);
26.7 (q), 28.7 (q), 36.3 (t), 60.6 (d), 79.0 (d), 121.0 (t), 127.3 (d), 128.1 (d), 128.5 (d), 128.7 (d) 129.7 (d), 130.2 (s), 136.0 (s), 137.9 (s), 145.1 (s), 152.0 (s), 169.8 (s) (minor rotamer).

MS: m/z 392 (M^+). Anal. calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found C, 73.56; H, 7.36; N, 7.03.

(2R,5S)-(t-Butoxycarbonylamino)-3-methyl-5-phenyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (**8e**)



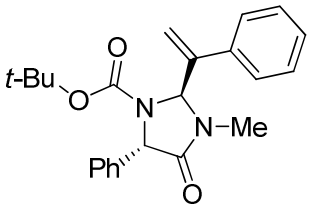
Yield: 52%.
Yellow oil.
IR: 1706, 1649 cm^{-1};
$[\alpha]^{23}_D$ = +66.5 (c = 1.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.31 (9H, br s), 2.99 (3H, s), 5.11 (1H, br s), 5.51 (1H, s), 5.52-5.66 (2H, m), 7.02-7.37 (10H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.6 (q), 28.4 (q), 62.9 (d), 79.0 (d), 81.2 (s), 121.4 (t), 127.2 (d), 127.5 (d), 128.0 (d), 128.4 (d), 128.7 (d), 129.4 (d), 136.7 (s), 138.5 (s), 146.3 (s), 154.1 (s), 168.9 (s).

MS: m/z 378 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_3$: C,72.99; H, 6.92; N, 7.40. Found C, 73.06; H, 7.07; N, 7.13.

(2*S*,5*S*)-(t-Butoxycarbonylamino)-3-methyl-5-phenyl-2-(1-phenylvinyl)-2,3-dihydroimidazolidin-4(5H)-one (**9e**)



Yield: 20%.
Yellow solid. M. p. 155-157 °C.
IR: 1703, 1646 cm^{-1}
$[\alpha]^{23}_D$ = +207.5 (c = 0.26, $CHCl_3$).
Rotamers ratio 3:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.08 (9H, s), 2.97 (3H, s), 4.53 (1H, s), 5.57 (1H, s), 5.67 (1H, s), 5.84 (1H, s), 7.20-7.37 (10H, m) (major rotamer);
1.40 (9H, s), 2.88 (3H, s), 4.86 (1H, s), 5.57 (1H, s), 5.67 (1H, s), 5.84 (1H, s), 7.20-7.37 (10H, m) (minor rotamer).

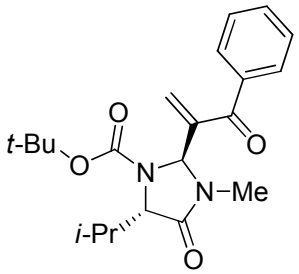
^{13}C NMR (100 MHz, $CDCl_3$)
δ: 27.4 (q), 28.2 (q), 63.5 (d), 79.4 (d), 81.2 (s), 121.9 (t), 126.6 (d), 127.0 (d), 127.8. (d), 128.4 (d), 128.6 (d), 128.9 (d), 137.8 (s), 138.9 (s), 145.1 (s), 152.3 (s), 169.3 (s) (major rotamer);
27.4 (q), 28.6 (q), 63.2 (d), 79.4 (d), 81.2 (s), 121.4 (t), 126.6 (d), 127.0 (d), 127.8 (d), 128.4 (d), 128.6 (d),128.9 (d), 137.8 (s), 138.9 (s), 145.1 (s), 152.3 (s), 169.3 (s).

MS: m/z 378 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found C, 73.18; H, 6.71; N, 7.61.

General procedure for the preparation of enones 10a-e and 11

$Pd(PPh_3)_4$ (2%), iodobenzene (1.5 mmol) and K_2CO_3 (4 mmol) were added to a solution of **2** (1 mmol) in DMF (10 mL) under CO atmosphere (balloon). The suspension was stirred at 60 °C for 4 h, then cooled, diluted with brine and extracted with AcOEt (3 x 20 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude mixture was purified by flash chromatography to afford **10a-e** and, in the case of compound **2a**, also **11**.

(2*S*,5*S*)-(t-Butoxycarbonylamino)-5-isopropyl-3-methyl-2-[(1-phenyl)-2-propen-1-on-2-yl]-2,3-dihydroimidazolidin-4(5H)-one (**10a**)



Yield: 52%.
Pale yellow solid. M. p. 130-132 °C.
IR: 1701, 1675, 1644 cm^{-1}
$[\alpha]^{23}_D$ = +113.4 (c = 0.28, $CHCl_3$).
Rotamers ratio 3:1

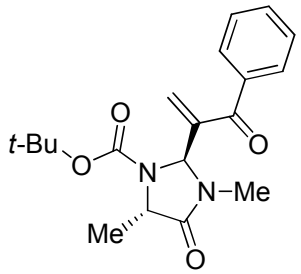
^{1}H NMR (400 MHz, CDCl3)
δ: 0.91 (3H, d, J = 7.2 Hz), 1.18 (3H, d, J = 7.2 Hz), 1.38 (9H, s), 2.40-2.50 (1H, m), 2.88 (3H, s), 4.08-4.10 (1H, m), 5.69 (1H, s), 5.85 (1H, d, J = 4.2 Hz), 6.02 (1H, d, J = 4.2 Hz), 7.42-7.85 (5H, m) (major rotamer);

0.88 (3H, d, J = 7.2 Hz), 1.21 (3H, d, J = 7.2 Hz), 1.31 (9H, s), 2.40-2.50 (1H, m), 2.82 (3H, s), 4.20-4.30 (1H, m), 5.68 (1H, s), 5.85 (1H, d, J = 4.2 Hz), 6.02 (1H, d, J = 4.2 Hz), 7.42-7.85 (5H, m) (minor rotamer).

^{13}C NMR (100 MHz, CDCl3) δ: 16.7 (q), 18.4 (d), 18.6 (q), 28.5 (q), 31.0 (q), 63.8 (d), 75.3 (d), 81.5 (s), 128.0 (t), 128.5 (d), 128.8 (d), 130.3 (d), 137.2 (s), 144.5 (s), 153.0 (s), 170.1 (s), 196.3 (s) (major rotamer);
16.1 (q), 18.4 (d), 18.6 (q), 28.5 (q), 31.0 (q), 63.5 (d), 72.5 (d), 82.2 (s), 128.0 (t), 128.5 (d), 128.8 (d), 130.3 (d), 136.6 (s), 144.4 (s), 153.2 (s), 169.7 (s), 195.2 (s) (minor rotamer).

MS: m/z 372 (M^+). Anal. calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found C, 67.74; H, 7.36; N, 7.83.

(2*S*,5S)-(t-Butoxycarbonylamino)-3,5-dimethyl-2-[(1-phenyl)-2-propen-1-on-2-yl]-2,3-dihydroimidazolidin-4(5H)-one (**10b**)



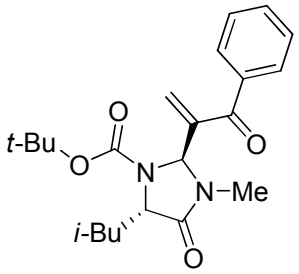
Yield: 42%.
Pale yellow oil.
IR: 1703, 1670, 1646 cm^{-1}
$[\alpha]^{23}_D$ = +153.5 (c = 0.31, $CHCl_3$).
Rotamers ratio 3:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.24 (3H, d, J = 6.3 Hz), 1.37 (9H, s), 2.83 (3H, s), 4.07-4.13 (1H, m), 5.67 (1H, s), 5.84 (1H, s), 6.06 (1H, s), 7.28-7.82 (5H, m) (major rotamer);
1.22 (3H, d, J = 6.3 Hz), 1.30 (9H, s), 2.79 (3H, s), 4.15-4.22 (1H, m), 5.67 (1H, s), 5.81 (1H, s), 6.04 (1H, s), 7.28-7.82 (5H, m) (minor rotamer).

^{13}C NMR (100 MHz, CDCl3)
δ: 18.3 (q), 26.0 (q), 27.1 (q), 55.0 (d), 75.2 (d), 81.5 (s), 128.6 (t), 128.7 (d), 130.1 (d), 133.2 (d), 137.3 (s), 143.8 (s), 153.0 (s), 171.9 (s), 196.5 (s) (major rotamer);
17.3 (q), 26.0 (q), 27.1 (q), 55.2 (d), 72.9 (d), 82.1 (s), 128.6 (t), 128.8 (d), 130.3 (d), 133.6 (d), 136.6 (s), 143.8 (s), 153.0 (s), 171.9 (s), 196.5 (s) (minor rotamer).

MS: m/z 344 (M^+). Anal. calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found C, 66.16; H, 6.76; N, 8.35.

(2*S*,5*S*)-(t-Butoxycarbonylamino)-5-isobutyl-3-methyl-2-[(1-phenyl)-2-propen-1-on-2-yl]-2,3-dihydroimidazolidin-4(5H)-one (**10c**)



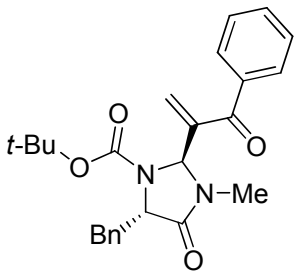
Yield: 38%. Pale yellow oil.
IR: 1700, 1673, 1648 cm^{-1}
$[\alpha]^{23}_{D}$ = +93.7 (c = 0.31, $CHCl_3$).
Rotamers ratio 3:1

^1H NMR (400 MHz, $CDCl_3$)
δ: 0.79 (3H, d, J = 5.6 Hz), 1.09 (3H, d, J = 5.6 Hz), 1.37 (9H, s), 1.81-2.03 (3H, m), 2.82 (3H, s), 4.10-4.20 (1H, m), 5.64 (1H, s), 5.84 (1H, s), 6.04 (1H, s), 7.28-7.56 (3H, m), 7.81-7.83 (2H, m) (major rotamer);
0.79 (3H, d, J = 5.6 Hz), 1.09 (3H, d, J = 5.6 Hz), 1.29 (9H, s), 2.40-2.50 (3H, m), 2.79 (3H, s), 4.27-4.30 (1H, m), 5.64 (1H, s), 5.81 (1H, s), 6.01 (1H, s), 7.28-7.56 (3H, m), 7.81-7.83 (2H, m) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.1 (q), 24.2 (q), 26.9 (d), 28.7 (q), 40.1 (t), 57.9 (d), 75.2 (d), 81.5 (s), 128.3 (t), 128.5 (d), 130.2 (d), 133.2 (d), 137.3 (s), 144.1 (s), 153.0 (s), 171.6 (s), 196.5 (s) (major rotamer);
22.6 (q), 23.9 (q), 26.9 (d), 28.6 (q), 38.1 (t), 56.9 (d), 72.8 (d), 81.8 (s), 128.0 (t), 128.5 (d), 128.8 (d), 130.3 (d), 133.6 (s), 144.4 (s), 153.0 (s), 171.6 (s), 196.5 (s) (minor rotamer).

MS: m/z 386 (M^+). Anal. calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found C, 68.56; H, 7.66; N, 7.43.

(2*S*,5*S*)-5-Benzyl-(t-butoxycarbonylamino)-3-methyl-2-[(1-phenyl)-2-propen-1-on-2-yl]-2,3-dihydroimidazolidin-4(5H)-one (**10d**)



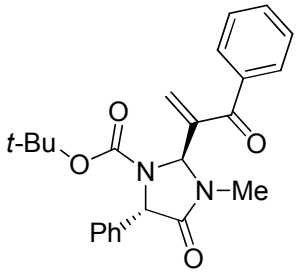
Yield: 40%.
Pale yellow oil.
IR: 1702, 1678, 1646 cm^{-1}
$[\alpha]^{23}_{D}$ = +78.7 (c = 0.46, $CHCl_3$).
Rotamers ratio 3:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.48 (9H, s), 2.58 (3H, s), 3.19-3.23 (1H, m), 3.42-3.48 (1H, m), 4.46-4.60 (1H, m), 4.85 (1H, s), 5.77-5.97 (2H, m), 7.13-7.81 (10H, m) (major rotamer);
1.34 (9H, s), 2.57 (3H, s), 3.19-3.23 (1H, m), 3.69-3.75 (1H, m), 4.46-4.60 (1H, m), 5.02 (1H, s), 5.77-5.97 (2H, m), 7.13-7.81 (10H, m) (minor rotamer).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 24.2 (q), 28.7 (q), 36.3 (t), 60.6 (d), 75.2 (d), 81.9 (s), 127.3 (t), 128.1 (d), 128.5 (d), 128.8 (d), 130.2 (d), 130.4 (d), 133.2 (d), 136.1 (s), 137.2 (s), 144.0 (s), 152.7 (s), 170.1 (s), 196.3 (s) (major rotamer);
24.2 (q), 28.5 (q), 34.6 (t), 60.4 (d), 72.9 (d), 82.2 (s), 127.3 (t), 128.1 (d), 128.6 (d), 128.7 (d), 130.1 (d), 130.3 (d), 133.6 (d), 136.2 (s), 137.2 (s), 144.0 (s), 152.0 (s), 170.0 (d), 195.1 (d) (minor rotamer).

MS: m/z 420 (M+). Anal. calcd for C25H28N2O4: C, 71.41; H, 6.71; N, 6.66. Found C, 71.56; H, 6.46; N, 6.43.

(2*S*,5*S*)-(t-Butoxycarbonylamino)-3-methyl-5-phenyl-2-[(1-phenyl)-2-propen-1-on-2-yl]-2,3-dihydroimidazolidin-4(5H)-one (**10e**)



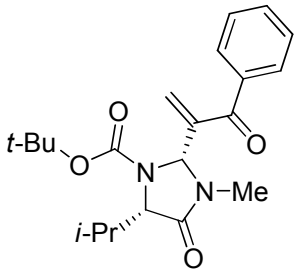
Yield: 67%.
Pale yellow solid. M. p.: 182-184 °C.
IR: 1708, 1673, 1656 cm^{-1}
$[\alpha]^{23}_{D}$ = +131.5 (c = 0.80, $CHCl_3$).
Rotamers ratio 3:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.95 (9H, s), 2.76 (3H, s), 4.89 (1H, s), 5.91 (1H, s), 6.04 (1H, s), 6.37 (1H, s), 7.28-7.80 (10H, m) (major rotamer);
1.26 (9H, s), 2.70 (3H, s), 5.02 (1H, s), 5.75 (1H, s), 6.14 (1H, s), 6.47 (1H, s), 7.28-7.80 (10H, m) (minor rotamer).

^{13}C NMR (100 MHz, CDCl3) δ: 27.3 (q), 28.3 (q), 63.7 (d), 77.1 (d), 81.6 (s), 128.4 (d), 128.7 (d), 128.9 (d), 129.2 (d), 129.6 (t) 130.3 (d), 133.4 (d), 137.5 (s), 138.9 (s), 143.4 (s), 157.8 (s), 169.8 (s), 196.7 (s) (major rotamer); too weak signals for the minor rotamer.

MS: m/z 406 (M^+). Anal. calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found C, 70.66; H, 6.66; N, 6.73.

(2*S*,5*R*)-(t-Butoxycarbonylamino)-3,5-dimethyl-2-[(1-phenyl)-2-propen-1-on-2-yl]-2,3-dihydroimidazolidin-4(5H)-one (11)



Yield: 7%.
Pale yellow oil.
IR: 1701, 1683, 1657 cm^{-1}
$[\alpha]^{23}_{D}$ = -30.4 (c = 0.28, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.10 (6H, d, J = 6.8 Hz), 1.38 (9H, s), 2.18-2.25 (1H, m), 2.86 (3H, s), 4.00-4.10 (1H, m), 5.76 (1H, s), 5.85 (1H, s), 5.91 (1H, s), 7.28-7.90 (5H, m).

^{13}C NMR (100 MHz, $CDCl_3$)
δ: 16.8 (q), 18.5 (d), 18.7 (q), 28.6 (q), 31.0 (q), 63.9 (d), 75.5 (d), 81.2 (s), 128.0 (t), 128.5 (d), 128.8 (d), 130.1 (d), 137.2 (s), 144.6 (s), 153.0 (s), 170.2 (s), 196.3 (s).

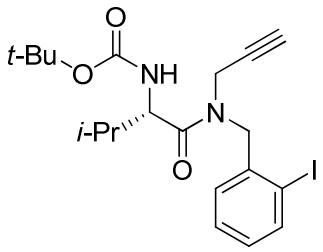
MS: m/z 372 (M^+). Anal. calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found C, 67.88; H, 7.41; N, 7.97.

General procedure for the preparation of propargylamides 13a-c

DCC (10 mmol), **12**[106] (8.3 mmol) and DMAP (0.125 mmol) were slowly added to a solution of the appropriate Boc-protected α-aminoacid (10 mmol) in anhydrous CH_2Cl_2 (60 mL) cooled at 0 °C. The resulting solution was stirred at r.t. for 48 h, then filtered on silica gel and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtPe / AcOEt 8:2).

[106] L. Shen, R. P. Hsung, *Org. Lett.* **2005**, *7*, 775.

(*S*)-2-(t-Butoxycarbonylamino)-N-(2-iodobenzyl)-3-methy-N-propargylbutanamide (**13a**)



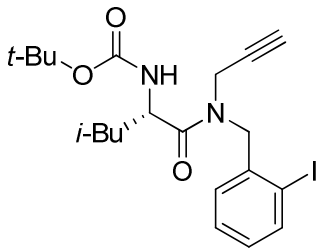
Yield: 90%.
Colorless oil.
IR: 2924, 1659 cm^{-1}
$[\alpha]^{23}_{D}$ = -3.7 (c = 0.25, $CHCl_3$).
Rotamers ratio 3:2

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.93 (3H, d, J = 6.8 Hz), 0.96 (3H, d, J = 6.8 Hz), 1.42 (9H, s), 1.92-2.01 (1H, m), 2.31 (1H, dd, J = 2.1, 2.2 Hz), 3.79-3.91 (1H, m), 4.38-4.46 (1H, m), 4.51, 4.87 (2H, AB system, J = 15.9 Hz), 4.54-4.62 (1H, m), 5.22-5.34 (1H, m), 6.92 (1H, dd, J = 7.4, 7.7 Hz), 7.06 (1H, d, J = 7.7 Hz), 7.22 (1H, dd, J = 7.4, 7.6 Hz), 7.79 (1H, d, J = 7.6 Hz) (major rotamer);
0.88 (3H, d, J = 6.8 Hz), 1.00 (3H, d, J = 6.8 Hz), 1.37 (9H, s), 2.04-2.13 (1H, m), 2.21 (1H, br s), 3.79-3.91 (1H, m), 4.38-4.46 (2H, m), 4.68, 4.71 (2H, AB system, J = 17.1 Hz), 5.22-5.34 (1H, m), 6.97 (1H, dd, J = 7.5, 7.7 Hz), 7.06 (1H, d, J = 7.7 Hz), 7.29 (1H, dd, J = 7.5 , 7.9 Hz), 7.83 (1H, d, J = 7.9 Hz) (minor rotamer).

^{13}CNMR (100 MHz, $CDCl_3$) δ: 17.8 (q), 19.8 (q), 28.3 (q), 31.2 (d), 37.2 (t), 53.7 (t), 55.6 (d), 73.3 (d), 78.3 (s), 79.8 (s), 98.7 (s), 128.0 (d), 128.5 (d), 129.1 (d), 138.2 (s), 139.6 (d), 156.0 (s), 173.0 (s) (major rotamer);
17.8 (q), 19.6 (q), 28.3 (q), 31.5 (d), 34.6 (t), 55.4 (d), 55.5 (t), 72.4 (d), 78.2 (s), 79.5 (s), 98.0 (s), 127.5 (d), 128.6 (d), 129.6 (d), 137.3 (s), 140.0 (d), 155.5 (s), 172.8 (s) (minor rotamer).

MS: m/z 470 (M^+). Anal. calcd for $C_{20}H_{27}IN_2O_3$: C, 51.07; H, 5.79; N, 5.96. Found C, 51.18; H, 5.51; N, 6.08.

(*S*)-2-(t-Butoxycarbonylamino)-N-(2-iodobenzyl)-4-methyl-N-propargylpentanamide (**13b**)



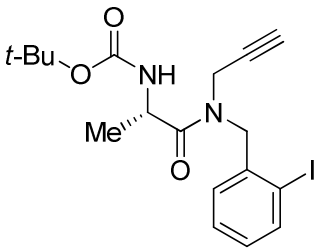
Yield: 81%.
Colorless oil.
IR: 2926, 1655 cm^{-1}
$[\alpha]^{23}_{D}$ = -3.2 (c = 0.29, $CHCl_3$).
Rotamers ratio 3:2

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.98 (3H, d, J = 6.6 Hz), 1.03 (3H, d, J = 6.6 Hz), 1.46 (9H, s), 1.55-1.86 (3H, m), 2.33 (1H, dd, J = 2.4, 2.4 Hz), 3.85-3.89 (1H, m), 4.52, 4.92 (2H, AB system, J = 15.9 Hz), 4.55-4.82 (2H, m), 5.13 (1H, d, J = 9.1 Hz), 6.97 (1H, dd, J = 7.1, 7.8 Hz), 7.12 (1H, d, J = 7.1 Hz), 7.29 (1H, dd, J = 7.8, 8.2 Hz), 7.84 (1H, d, J = 8.2 Hz) (major rotamer);
0.86 (3H, d, J = 6.9 Hz), 0.92 (3H, d, J = 6.9 Hz), 1.41 (9H, s), 1.55-1.86 (3H, m), 2.24 (1H, dd, J = 2.5, 2.5 Hz), 3.81-3.85 (1H, m), 3.99, 4.42 (2H, AB system, J = 17.3 Hz), 4.55-4.82 (2H, m), 5.17 (1H, d, J = 8.8 Hz), 7.02 (1H, dd, J = 6.9, 7.6 Hz), 7.12 (1H, d, J = 6.9 Hz), 7.35 (1H, dd, J = 7.6 , 7.7 Hz), 7.88 (1H, d, J = 7.7 Hz).

^{13}CNMR (100 MHz, $CDCl_3$)
δ: 21.8 (q), 23.5 (q), 24.7 (d), 28.3 (q), 37.0 (t), 41.9 (t), 48.9 (d), 54.0 (t),73.4 (d), 78.1 (s), 79.8 (s), 98.7 (s), 127.4 (d), 128.6 (d), 129.1 (d), 138.1 (s), 139.9 (d), 155.4 (s), 173.6 (s) (major rotamer);
21.6 (q), 23.4 (q), 24.5 (d), 30.9 (q), 35.0 (t), 42.8 (t), 49.1 (d), 55.4 (t), 72.5 (d),
78.1 (s), 79.8 (s), 97.8 (s), 127.7 (d), 128.1 (d), 129.5 (d), 138.1 (s), 139.6 (d), 154.8 (s), 173.6 (s)(minor rotamer).

MS: m/z 484 (M^+). Anal. calcd for $C_{21}H_{29}IN_2O_3$: C, 52.07; H, 6.03; N, 5.78. Found C, 51.96; H, 6.31; N, 5.52.

(*S*)-2-(t-Butoxycarbonylamino)-N-(2-iodobenzyl)-N-propargylpropanamide (**13c**)



Yield: 79%.
Colorless oil.
IR: 2927, 1651 cm^{-1}
$[\alpha]^{23}_D$ = -4.4 (c = 0.19, $CHCl_3$).
Rotamers ratio 3:2

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.30 (3H, d, J = 6.7 Hz), 1.44 (9H, s), 2.33 (1H, dd, J = 2.4, 2.4 Hz), 3.88, 4.41 (2H, AB system, J = 18.5 Hz), 4.53-4.76 (2H, m), 4.88 (1H, d, J = 15.9 Hz), 5.39 (1H, d, J = 7.9 Hz), 6.96 (1H, dd, J = 7.4 , 7.5 Hz), 7.12 (1H, d, J = 7.5 Hz), 7.28 (1H, d, J = 7.7 Hz), 7.82 (1H, d, J = 7.7 Hz) (major rotamer);
1.30 (3H, d, J = 6.7 Hz), 1.42 (9H, s), 2.23 (1H, br s), 4.04, 4.32 (2H, AB system, J = 17.3 Hz), 4.53-4.76 (3H, m), 5.43 (1H, d, J = 7.6 Hz), 7.01 (1H, dd, J = 7.5, 7.7 Hz), 7.07 (1H, d, J =7.7 Hz), 7.34 (1H, dd, J = 7.5, 7.8 Hz), 7.86 (1H, d, J = 7.8 Hz) (minor rotamer).

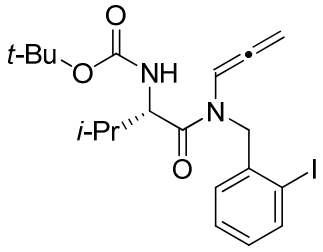
^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 18.9 (q), 28.3 (q), 37.0 (t), 46.4 (d), 53.9 (t), 73.4 (d), 78.0 (s), 79.8 (s), 98.7 (s), 128.2 (d), 128.5 (d), 129.2 (d), 138.1 (s), 139.7 (d), 155.3 (s), 173.6 (s) (major rotamer); 19.4 (q), 28.3 (q), 34.8 (t), 46.7 (d), 55.3 (t), 72.6 (d), 77.9 (s), 79.6 (s), 98.7 (s), 127.1 (d), 128.6 (d), 129.6 (d), 137.1 (s), 140.0 (d), 154.8 (s), 173.4 (s) (minor rotamer).

MS: m/z 442 (M^+). Anal. calcd for $C_{18}H_{23}IN_2O_3$: C, 48.88; H, 5.24; N, 6.33. Found C, 48.98; H, 4.99; N, 6.48.

General procedure for the preparation of allenamides 11a-c

To a solution of 10 (1 mmol) in THF (10 mL) *t*-BuOK (2.5 mmol) was added. The resulting solution was stirred at r.t. for 1 min, then filtered on silica gel (AcOEt). The solvent was evaporated under reduced pressure. The residue was used without no further purification for the next step.

(S)-2-(t-Butoxycarbonylamino)-N-(2-iodobenzyl)-3-methyl-N-(1,2-propadienyl)butanamide (**14a**)



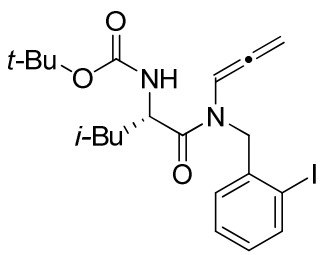
Yield: 95%.
Colorless oil.
IR: 3321, 1650 cm^{-1}
$[\alpha]^{23}_{D}$ = +30.8 (c = 0.27, $CHCl_3$).
Rotamers ratio 1:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.94 (6H, d, J = 6.7 Hz), 1.04 (6H, d, J = 6.7 Hz), 1.45 (18H, s), 2.10-2.21 (2H, m), 4.59-4.83 (6H, m), 5.05-5.45 (6H, m), 6.87-7.03 (4H, m), 7.24 (2H, dd, J = 7.5, 7.9 Hz), 7.56-7.63 (1H, m). 7.79 (2H, d, J = 7.9 Hz), 7.77-7.85 (1H, m).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 17.4 (q), 17.6 (q), 19.6 (q), 28.7 (q), 31.6 (d), 31.9 (d), 54.0 (t), 55.2 (t), 56.1 (d), 56.4 (d), 80.0 (s), 80.1 (s), 87.7 (t), 88.1 (t), 97.5 (s), 98.3 (s), 99.0 (d), 100.2 (d), 126.8 (d), 126.9 (d), 128.7 (d), 129.0 (d), 129.4 (d), 129.7 (d), 138.2 (s), 138.7 (s), 139.9 (d), 140,1 (d), 155.7 (s), 156.4 (s), 171.5 (s), 201.9 (s), 202.8 (s).

MS: m/z 470 (M^+). Anal. calcd for $C_{20}H_{27}IN_2O_3$: C, 51.07; H, 5.79; N, 5.96. Found C, 51.38; H, 5.59; N, 5.73.

(*S*)-2-(t-Butoxycarbonylamino)-N-(2-iodobenzyl)-4-methyl-N-(1,2-propadienyl)pentanamide (**14b**)



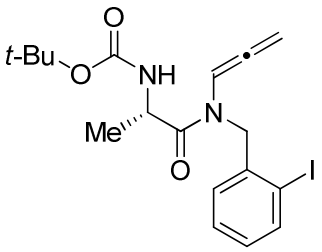
Yield: 93%.
Colorless oil.
IR: 3319, 1655 cm^{-1}
$[\alpha]^{23}_{D}$ = -6.1 (c = 0.15, $CHCl_3$).
Rotamers ratio 1:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.98 (6H, d, J = 6.6 Hz), 1.02 (6H, d, J = 6.5 Hz), 1.26 (18H, s), 1.55-1.83 (6H, m), 4.41-4.81 (4H, m), 4.51, 4.93 (2H, AB system, J =15.9 Hz), 5.12-5.21 (2H, m), 5.37 (4H, dd, J = 4.9, 4.9 Hz), 6.97 (1H, dd, J = 6.8, 7.4 Hz), 7.02 (1H, dd, J = 7.4, 7.5 Hz), 7.07-7.19 (2H, m), 7.21-7.53 (4H, m), 7.84 (1H, d, J = 7.9 Hz), 7.87 (1H, d, J = 7.8 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 21.8 (q), 23.5 (q), 24.7 (d), 28.3 (q), 35.0 (t), 37.1 (t), 48.9 (d), 54.0 (t), 55.4 (t), 79.8 (s), 87.6 (t), 98.7 (s), 100.1 (d), 128.1 (d), 128.6 (d), 129.1 (d), 129.5 (d), 129.8 (d), 130.0 (d), 137.3 (s), 138.1 (s), 139.6 (d), 140.0 (d), 155.9 (s), 173.7 (s), 206.9 (s).

MS: m/z 484 (M^+). Anal. calcd for $C_{21}H_{29}IN_2O_3$: C, 52.07; H, 6.03; N, 5.78. Found C, 52.28; H, 5.79; N, 5.56.

(S)-2-(t-Butoxycarbonylamino)-N-(2-iodobenzyl)-N-(1,2-propadienyl)propanamide (**14c**)



Yield: 93%.
Colorless oil.
IR: 3326, 1655 cm^{-1}
$[\alpha]^{23}_{D}$ = +13.6 (c = 0.30, $CHCl_3$).
Rotamers ratio 1:1

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.19-1.27 (6H, m), 1.43 (18H, s), 4.39-4.87 (6H, m), 5.13-5.22 (4H, m), 5.41 (1H, br s), 5.54 (1H, br s), 6.82-7.01 (5H, m), 7.18-7.31 (2H, m), 7.51-7.62 (1H, m), 7.76 (1H, d, J = 7.9 Hz), 7.79 (1H, d, J = 7.6 Hz).

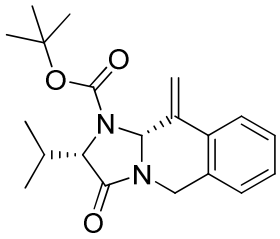
^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 18.9 (q), 28.3 (q), 46.9 (d), 47.1 (d), 53.6 (t), 54.7 (t), 79.8 (s), 87.3 (t), 98.7 (s), 99.2 (d), 126.4 (d), 128.3 (d), 128.6 (d), 129.3 (d), 129.6 (d), 137.8 (s), 138.2 (s), 139.4 (d), 139.5 (d), 155.3 (s), 172.5 (s), 201.5 (s), 202.4 (s).

MS: m/z 442 (M^+). Anal. calcd for $C_{18}H_{23}IN_2O_3$: C, 48.88; H, 5.24; N, 6.33. Found C, 48.61; H, 5.38; N, 6.56.

General procedure for the preparation of imidazolidinones 15a-c and 16b,c

K_2CO_3 (4 mmol) and $Pd(PPh_3)_4$ (2%) were added to a solution of **14** (1 mmol) in DMF (10 mL). The resulting suspension was heated at 100 °C for 2 h, then cooled, diluted with brine and extracted with AcOEt (3 x 20 mL). The resulting crude mixture was purified by flash chromatography to afford the desired products **15** and **16**.

(2*S*,10*aR*)-1-(t-Butoxycarbonyl)-2-isopropyl-10-methylene-1,5,10,10a-tetrahydro-1Himidazo[1,2-b]isoquinolin-3(2H)-one (**15a**)



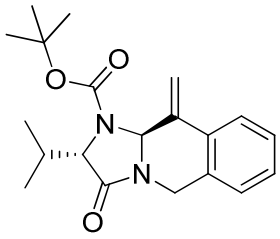
Yield: 54%.
White solid. M. p.: 112-115 °C.
IR: 1703,1648 cm^{-1}
$[\alpha]^{23}_D$ = -30.6 (c = 0.21, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.99 (3H, d, J = 6.9 Hz), 1.03 (3H, d, J = 7.0 Hz), 1.53 (9H, s), 2.10-2.27 (1H, m), 4.23-4.30 (1H, m), 4.39, 5.16 (2H, AB system, J = 17.4 Hz), 5.35 (1H, d, J = 1.5 Hz), 5.69 (1H, s), 5.77 (1H, d, J = 1.5 Hz), 7.19 (1H, d, J = 7.1 Hz), 7.25-7.40 (2H, m), 7.66 (1H, d, J = 7.3 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.9 (q), 19.6 (q), 28.7 (q), 32.2 (d), 42.2 (t), 65.3 (d), 70.7 (d), 82.0 (s), 110.1 (t), 126.1 (d), 126.8 (d), 127.8 (d), 129.1 (d), 130.7 (s), 131.7 (s), 139.4 (s), 155.6 (s), 168.8 (s).

MS: m/z 342 (M+). Anal. calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found C, 70.28; H, 7.39; N, 8.29.

(2S,10aS)-1-(t-Butoxycarbonyl)-2-isopropyl-10-methylene-1,5,10,10a-tetrahydro-1Himidazo[1,2-b]isoquinolin-3(2H)-one (**16a**)



Yield: 8%.

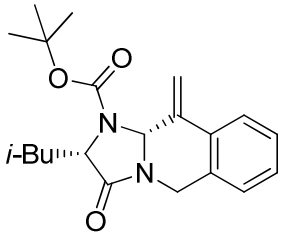
Colorless oil.
IR: 1708, 1655 cm^{-1}
$[\alpha]^{23}_{D}$ =+26.2 (c = 0.28, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.92 (3H, d, J = 6.9 Hz), 1.25 (3H, d, J = 7.1 Hz), 1.45-1.60 (9H, m), 1.98-2.30 (1H, m), 4.03-4.18 (1H, m), 4.40, 5.22 (2H, AB system, J = 17.6 Hz), 5.10 (1H, br s), 5.47 (1H, s), 5.63-5.70 (1H, m), 7.19 (1H, d, J = 7.4 Hz), 7.27-7.48 (2H, m), 7.50 (1H, d, J = 7.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 16.0 (q), 18.7 (q), 28.7 (q), 32.8 (d), 42.2 (t), 63.6 (d), 70.3 (d), 81.2 (s), 108.9 (t), 126.2 (d), 126.4 (d), 127.8 (d), 129.2 (d), 130.2 (s), 133.3 (s), 139.4 (s), 155.6 (s), 168.8 (s).

MS: m/z 342 (M^+). Anal. calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found C, 69.91; H, 7.82; N, 8.01.

(2*S*,10*aR*)-1-(t-Butoxycarbonyl)-2-isobutyl-10-methylene-1,5,10,10a-tetrahydro-1Himidazo[1,2-b]isoquinolin-3(2H)-one (**15b**)



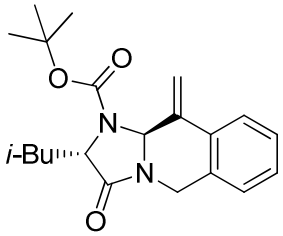
Yield: 59%.
White solid. M. p.: 108-110 °C.
IR: 1710, 1659 cm^{-1}
$[\alpha]^{23}_{D}$ = -52.2 (c = 0.56, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.95 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.50-1.70 (2H, m), 1.53 (9H, s), 1.95-2.08 (1H, m), 4.30-4.52 (1H, m), 4.40, 5.17 (2H, AB system, J = 17.4 Hz), 5.28 (1H, d, J = 1.7 Hz), 5.65 (1H, d, J = 1.7 Hz), 5.75 (1H, s), 7.18 (1H, d, J = 7.4 Hz), 7.24-7.36 (2H, m), 7.61 (1H, d, J = 7.5 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 22.6 (q), 22.8 (q), 24.3 (d), 28.4 (q), 32.8 (t), 42.0 (t), 57.8 (d), 70.0 (d), 81.6 (s), 109.0 (t), 125.8 (d), 126.3 (d), 127.3 (d), 128.8 (d), 130.4 (s), 131.3 (s), 139.6 (s), 154.6 (s), 169.9 (s).

MS: m/z 356 (M^+). Anal. calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92 N, 7.86. Found C, 70.58; H, 8.05; N, 7.69.

(2*S*,10*aS*)-1-(t-Butoxycarbonylamino)-2-isobutyl-10-methylene-1,5,10,10a-tetrahydro-1Himidazo[1,2-b]isoquinolin-3(2H)-one (**16b**)



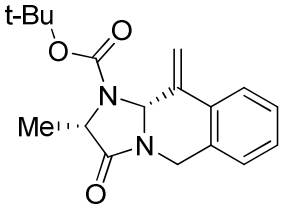
Yield: 6%.
Colorless oil.
IR: 1704, 1658 cm^{-1}
$[\alpha]^{23}_{D}$ = +33.0 (c = 0.17, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$)
δ: 0.70-2.08 (18H, m), 4.15-4.19 (1H, m), 4.38, 5.22 (2H, AB system, J = 17.4 Hz), 5.15 (1H, d, J = 1.2 Hz), 5.53 (1H, d, J = 1.2 Hz), 5.65 (1H, s), 7.12-7.65 (4H, m).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 22.4 (q), 22.5 (q), 25.5 (d), 28.0 (q), 31.0 (t), 42.8 (t), 58.2 (d), 71.2 (d), 81.6 (s), 108.0 (t), 125.7 (d), 126.5 (d), 128.3 (d), 129.4 (d), 131.5 (s), 133.0 (s), 134.7 (s), 152.0 (s), 164.0 (s).

MS: m/z 356 (M^+). Anal. calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92 N, 7.86. Found C, 70.71; H, 7.67; N, 7.63.

(2*S*,10*aR*)-1-(t-Butoxycarbonyl)-2-methyl-10-methylene-1,5,10,10a-tetrahydro-1Himidazo[1,2-b]isoquinolin-3(2H)-one (**15c**)



Yield: 51%.
Yellow oil.
IR: 1705, 1655 cm^{-1}
$[\alpha]^{23}_{D}$ = -8.8 (c = 0.40, $CHCl_3$).

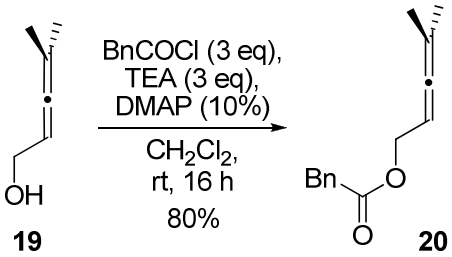
^{1}H NMR (400 MHz, $CDCl_3$)
δ: 1.15-1.25 (3H, m), 1.43 (9H, s), 4.27-4.41 (1H, m), 4.40, 5.19 (2H, AB system, J = 17.4 Hz), 5.29 (1H, d, J = 1.6 Hz), 5.61 (1H, d, J = 1.6 Hz), 5.69 (1H, s), 7.18 (1H, d, J = 7.2 Hz), 7.24-7.37 (2H, m), 7.59 (1H, d, J = 7.7 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 28.3 (q), 41.2 (t), 56.7 (d), 69.7 (d), 81.4 (s), 109.1 (t), 128.1 (d), 128.9 (d), 130.7 (d), 131.1 (s), 132.9 (s), 139.6 (d), 140.6 (s), 154.6 (s), 169.9 (s).

MS: m/z 314 (M^+). Anal. calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found C, 68.48; H, 6.91; N, 9.17.

3) Shifting towards the obtention of 7-membered heterocycles

Protection of allenyl alcohol 19 as phenylacetate 20 (modification of the synthetic steps towards amine 22[107])



19 **20**

Triethylamine (10.7 mL, 76.4 mmol, 3 equiv.) is added to a solution of 18 (2.5 g, 25.5 mmol, 1 equiv.) in dichloromethane (130 mL). Freshly distilled phenacyl chloride (10.1 mL, 76.4 mmol, 3 equiv.) is introduced dropwise at 0 °C and the resulting solution is stirred for 16h at r.t. The reaction is quenched with saturated NH_4Cl and the organic phase is extracted with CH_2Cl_2. The organic phases are washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product is purified by column chromatography (pentane/Et_2O 95:5).

Yield: 80%.
Pale yellow oil.
IR (neat): 2984, 2940, 2912, 1972, 1739, 1218 cm^{-1}

1H NMR (400 MHz, $CDCl_3$)
δ = 1.68 (6H, d, J= 3.0 Hz), 3.64 (2H s), 4.53 (d, 2H, J= 7.0 Hz), 5.08 (1H, m), 7.28-7.32 (5H, m)

^{13}C NMR (100 MHz, $CDCl_3$)
δ = 20.5 (q), 41.7 (t), 63.9 (t), 85.1 (d), 97.7 (s), 127.4 (d), 129.0 (d), 129.8 (d), 134.4 (s), 171.6 (s), 203.6 (s).

HRMS (ESI^+) Calcd. for $C_{14}H_{16}O_2Na$ ($M+Na^+$) 239.2648. Found: 239.1043.

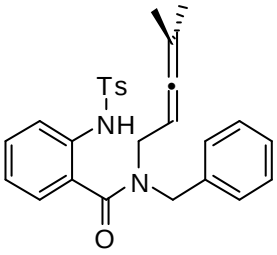
General procedure for the synthesis of N-protected allenyl amides 23

To a solution of allenyl amine (187 mg, 1 mmol, 1 equiv.) in THF (9.3 mL, 0,1 M) were rapidly added under argon atmosphere the appropriate N-protected-anthranylic acid (1.2 equiv.), DCC (248 mg, 1.2 equiv.) and DMAP (6.1 mg, 0.05 equiv.). The resulting mixture was stirred at room

[107] T. Shibata, S. Kadowaki, K. Takagi, *Heterocycles* **2002**, *57*, 2261.

temperature overnight. The completion of the reaction was verified by TLC. Cyclohexane (28 mL) was then added, the mixture was filtered over a celite pad and then concentrated in vacuo. The crude was purified by flash chromatography on silica gel eluting with cyclohexane/AcOEt 7:3.

N-benzyl-N-(4-methylpenta-2,3-dienyl)-2-(4-methylphenylsulfonamido)benzamide (**23a**)



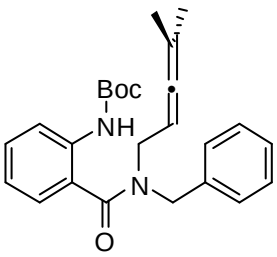
Yield: 70%.
White solid. M.p.: 107-109 °C.
IR (neat) 1620, 1597, 1337, 1164, 737 cm^{-1}.
Rotamers ratio 3.1:1.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.75 (6H, s), 2.20-2.50 (3H, m), 3.13 (2H, s br), 4.64 (2H, s br), 4.73-4.90 (1H, m), 6.70-7.80 (13H, m), 8.41 (1H, s br) (major rotamer);
1.75 (6H, s), 2.20-2.50 (3H, m), 3.96 (2H, s br), 4.17 (2H, s br), 4.85-5.10 (1H, m), 6.70-7.80 (13H, m), 8.57 (1H, s br) (minor rotamer).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 20.6 (q), 21.6 (q), 47.0 (t), 47.4 (t), 85.1 (d), 98.7 (s), 124.3 (d), 126.2 (d), 126.9 (s), 127.3 (d), 127.8 (d), 128.1 (d), 129.1 (d), 129.7 (d), 130.2 (d), 131.3 (d), 134.9 (s), 136.6 (s), 143.7 (s), 153.8 (s), 170.1 (s), 203.2 (s) (major rotamer);
20.6 (q), 21.9 (q), 47.0 (t), 47.4 (t), 85.1 (d), 98.7 (s), 123.9 (d), 126.2 (d), 126.9 (s), 127.3 (d), 127.8 (d), 128.2 (d), 129.1 (d), 129.7 (d), 130.2 (d), 131.5 (d), 134.9 (s), 136.4 (s), 144.8 (s), 153.8 (s), 167.6 (s), 203.2 (s) (minor rotamer).

HRMS (ESI $^{+}$): Calcd. for $C_{27}H_{28}N_2NaO_3S$ ($M+Na^{+}$): 483.17128, found: 483.17051.

tert-butyl 2-(benzyl(4-methylpenta-2,3-dienyl)carbamoyl)phenylcarbamate (**23b**)



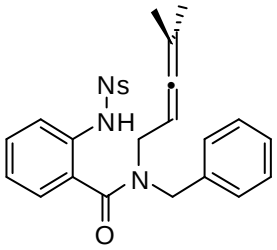
Yield: 58%.
White solid (M.p.: 98-100 °C).
IR (neat) 1728, 1626, 1516, 1157 cm-1.
Rotamers ratio: 2:1.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.52 (9H, s), 1.75 (6H, s), 3.74 (2H, s br), 4.80 (2H, s br), 4.85-5.00 (1H, m), 6.80-7.40 (8H, m), 7.70-8.25 (2H, m) (major rotamer);
1.52 (9H, s), 1.75 (6H, s), 4.04 (2H, s br), 4.57 (2H, s br), 5.00-5.20 (1H, m), 6.80-7.40 (8H, m), 7.70-8.25 (2H, m) (minor rotamer).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 20.7 (q), 28.7 (q), 47.4 (t), 48.0 (t), 80.7 (s), 85.4 (d), 98.6 (s), 121.4 (d), 122.3 (d), 124.6 (s), 126.9 (d), 127.9 (d), 128.4 (s), 129.0 (d), 130.9 (d), 137.2 (s), 153.2 (s), 170.8 (s), 203.0 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{25}H_{30}N_2NaO_3S$ ($M+Na^{+}$): 429.21486, found: 429.21436.

N-benzyl-N-(4-methylpenta-2,3-dienyl)-2-(4-nitrophenylsulfonamido)benzamide (**23c**)

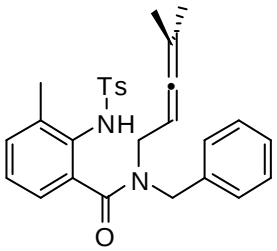


Yield: 62%.
Yellow solid. M.p.: 70-72 °C.
IR (neat) 1619, 1531, 1348, 1170 cm^{-1}.
Rogtamers ratio: 3.9:1.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.75 (6H, s br), 3.20 (2H, s br), 4.62 (2H, s br), 4.70-4.90 (1H, m), 7.00-8.40 (13H, m), 8.80 (1H, s br) (major rotamer);
1.75 (6H, s br), 3.96 (2H, s br), 4.29 (2H, s br), 4.85-5.05 (1H, m), 7.00-8.40 (13H, m), 9.0 (1H, s br) (minor rotamer).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 20.6 (q), 47.0 (t), 47.6 (t), 84.8 (d), 99.4 (s), 124.2 (d), 124.6 (d), 125.1 (d), 126.9 (s), 127.6 (d), 128.6 (d), 129.3 (d), 130.0 (d), 131.7 (d), 134.6 (d), 135.6 (s), 136.6 (s), 145.2 (s), 150.2 (s), 169.7 (s), 203.3 (s).
HRMS (ESI $^{+}$): Calcd. for $C26H_{25}N_3NaO_5S$ ($M+Na^{+}$): 514.14071, found: 514.13935

N-benzyl-3-methyl-N-(4-methylpenta-2,3-dienyl)-2-(4-methylphenylsulfonamido)benzamide (**23l**)



Yield: 60%.

White oil.
IR (neat) 1614, 1451, 1164 cm^{-1}.
Rotamers ratio 2.5:1.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.74 (6H, d, J = 2.7 Hz), 2.30 (3H, s), 2.33 (3H, s), 3.45 (2H, d, J = 4.7), 4.62 (2H, s), 4.92 (1H, dddd, J = 4.7, 4.7, 2.7, 2.7 Hz),7.00 (2H, d, J = 8.0 Hz), 7.01-7.50(m, 8H), 7.54 (2H, d, J = 8.0 Hz), 7.96 (1H, s br) (major rotamer);
1.65 (6H, d, J = 2.5 Hz), 2.29 (3H, s), 2.46 (3H, s), 3.96 (2H, d, J = 5.8 Hz), 4.38 (2H, s), 4.99-5.09 (1H, m), 7.01-7.50 (m, 10H), 7.75 (2H, d, J = 8.0 Hz), 7.86 (1H, s br) (minor rotamer).

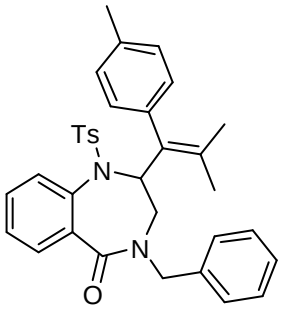
^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.6 (q), 20.9 (q), 21.7 (q), 47.9 (t), 48.3 (t), 85.5 (d), 98.2 (s), 125.4 (d), 126.6 (d),127.2 (d), 127.9 (d), 128.9 (d), 129.6 (d), 129.7 (d), 133.6 (d), 133.7 (s), 134.0 (s), 136.9 (s), 137.4 (s), 139.8 (s), 143.7 (s), 170.8 (s), 203.3 (s) (major rotamer);
19.6 (q), 20.6 (q), 21.9 (q), 45.5 (t), 52.7 (t), 84.6 (d), 96.5 (s), 124.6 (d), 126.9 (d), 127.2 (d), 127.9 (d), 129.2 (d), 129.6 (d), 129.9 (d), 133.6 (d), 133.7 (s), 134.0 (s), 136.9 (s), 137.4 (s), 139.8 (s), 144.0 (s), 171.3 (s), 203.7 (s) (minor rotamer).

HRMS (ESI $^{+}$): Calcd. for $C_{28}H_{30}N_2NaO_3S$ ($M+Na^{+}$): 497.18693, found: 497.18587.

General procedure for the Pd-catalysed domino carbopalladation/amination towards benzodiazepinones 24

NaH (4.8 mg, 0.12 mmol, 1.2 equiv., 60% dispersion in mineral oil) was added to a solution of the appropriate N-protected allenyl amide (0.1 mmol, 1 equiv.) in freshly distilled DMSO (1.6 mL) under argon atmosphere. The resulting mixture was stirred at 50°C for 10 min. In another flask, BuLi (10 mL, 0.02 mmol, 20 mol%, 2.0 M solution in hexane) was added dropwise to a solution of $PdCl_2(CH_3CN)_2$ in freshly distilled DMSO under Ar. The resulting solution, initially yellow, became dark orange. The appropriate aromatic iodide (0.12 mmol, 1.2 equiv.) and TBAB (6.4 mg, 0.02 mmol, 20 mol%) were added, and the solution containing the deprotonated amide was added via cannula. The resulting mixture was stirred at 90 °C. The completion was monitored by TLC (about 2 h) and the reaction was quenched with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with saturated NaCl, dried on $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (cyclohexane/AcOEt 8:2).

4-benzyl-2-(2-methyl-1-p-tolylprop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24a**)



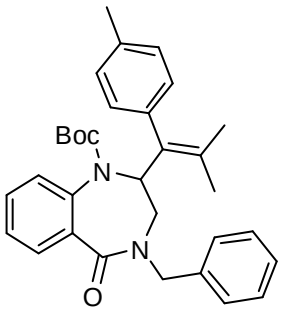
Yield: 82%.
Colorless oil.
IR (neat) 1650, 1351, 1161, 716, 660 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.41 (3H, s), 1.80 (3H, s), 2.33 (3H, s), 2.43 (3H, s), 3.06 (1H, dd, J = 15.3, 4.3), 3.33 (1H, dd, J = 15.3, 12.5), 3.74 (1H, A part of AB system, J = 14.7 Hz), 3.81 (3H, s), 4.62 (1H, B part of AB system, J = 14.7 Hz),5.38 (1H, dd, J = 12.5, 4.3), 6.33 (1H, d, J = 8.0, 0.9 Hz), 6.60-6.95 (1H, m), 7.03 (1H, ddd, J = 8.0, 7.8, 1.7 Hz), 7.10-7.17 (2H, m), 7.22 (1H, ddd, J = 7.8, 7.8, 0.9 Hz), 7.27-7.37 (7H, m), 7.42-7.47 (2H, m), 7.54 (1H, dd, J = 7.8, 1.7 Hz), 7.67-7.87 (1H, m);

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 21.4 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 64.3 (d), 127.6 (d), 128.2 (d), 128.3 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.1 (d), 131.3 (s), 133.6 (d), 133.7 (s), 134.1 (s), 134.2 (s), 136.6 (s), 136.7 (s), 137.0 (s), 143.9 (s), 168.0 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{34}H_{34}N_2NaO_3S$ ($M+H^{+}$): 551.23629, found: 551.23544

tert-butyl 4-benzyl-2-(2-methyl-1-p-tolylprop-1-enyl)-5-oxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine-1-carboxylate (**24b**)



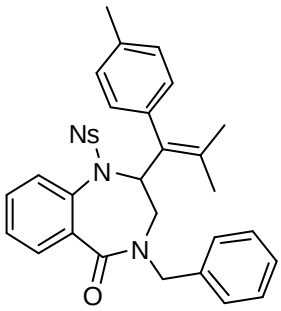
Yield: 48%.
Colorless oil.
IR (neat) 1725, 1630, 1156 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.33 (9H, s), 1.49 (3H, s), 1.69 (3H, s), 2.34 (3H, s), 3.19-3.24 (1H, m), 3.41-3.49 (1H, m), 4.70 (1H, A part of AB system, J = 14.2 Hz), 5.03 (1H, B part of AB system, J = 14.2 Hz), 5.35-5.42 (1H, m), 5.52-5.60 (1H, m), 6.30-6.40 (1H, m), 6.70-7.50 (10H, m), 7.55-7.61 (1H, m).

^{13}C-NMR: (100 MHz, $CDCl_3$)
δ: 21.4 (q), 22.7 (q), 28.5 (q), 49.5 (t), 50.4 (t), 63.1 (d), 80.8 (s), 126.6 (d), 128.2 (d), 128.6 (d), 128.7 (d), 129.1 (d), 129.2 (d), 130.0 (d), 130.6 (d), 133.4 (s), 136.7 (s), 137.5 (s), 147.5 (s), 156.1 (s), 168.0 (s).

HRMS: Calcd. For $C_{32}H_{36}N_2NaO_3$ ($M+Na^+$): 519.26181, found: 519.26114.

4-benzyl-2-(2-methtl-1-p-tolylprop-1-enyl)-1-(4-nitrophenylsulfonyl)-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24c**)



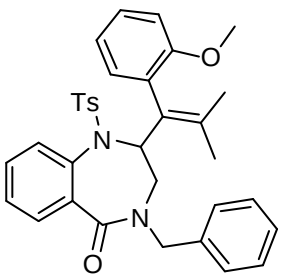
Yield: 80%.
Colorless oil.
IR (neat) 1652, 1530, 1350, 1176, 668, 616 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.44 (3H, s), 1.87 (3H, s), 2.35 (3H, s), 3.14 (1H, dd, J = 15.5, 4.4 Hz), 3.36 (1H, dd, J = 15.5, 12.3 Hz), 3.88 (1H, A part of AB system, J = 14.5 Hz), 4.64 (B part of AB system, J = 14.5 Hz), 5.48 (1H, dd, J = 12.3, 4.4 Hz), 6.31 (1H, dd, J = 8.1, 1.0 Hz), 6.25-6.50 (1H, s br), 6.60-6.90 (1H, s br), 6.56 (1H, d, J = 9.0 Hz), 7.06 (1H, ddd, J = 8.1, , 7.8, 1.7 Hz), 7.13-7.18 (2H, m), 7.23-7.41 (6H, m), 7.50 (1H, dd, J = 7.8, 1.7 Hz), 15.2 (2H, d, J = 8.9 Hz), 8.28 (2H, d, J = 8.9 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.5 (q), 21.4 (q), 22.8 (q), 49.0 (t), 49.8 (t), 65.5 (d), 124.7 (d), 128.4 (d), 128.6 (d), 128.8 (d), 129.0 (d), 129.3 (d), 129.9 (d), 131.3 (d), 132.2 (s), 132.9 (s), 133.2 (d), 134.2 (s), 136.3 (s), 136.6 (s), 136.9 (s), 144.7 (s), 150.4 (s), 167.5 (s).

HRMS (ESI $^+$): Calcd. for $C_{33}H_{31}N_3NaO_5S$ ($M+Na^+$): 604.18766, found: 604.18677.

4-benzyl-2-(1-(2-methoxyphenyl)-2-methylprop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)one (**24d**)



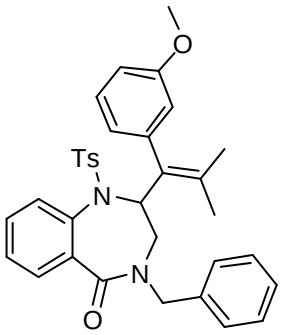
Yield: 63%.
Colorless oil.
IR (neat) 1651, 1466, 1351, 1159, 718, 658 cm^{-1}.
Rotamers ratio 1.1:1.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.43 (3H, s), 1.80 (3H, s), 2.43 (3H, s), 3.07 (1H, dd, J = 15.3, 4.0 Hz), 3.34 (1H, dd, J = 15.3, 12.5 Hz), 3.52 (3H, s br, minor rotamer) 3.70-3.85 (1H, m), 3.94 (3H, s br, major rotamer), 4.63 (1H, d, J = 14.7 Hz),5.39 (1H, dd, J = 12.5, 4.0 Hz) 5.90-6.10 (1H, m), 6.35-6.40 (1H, m), 6.78 (1H, dd, J = 7.8, 1.8 Hz), 7.00-7.25 (5H, m), 7.27-7.57 (9H, m)

^{13}C-NMR (100 MHz, $CDCl_3$):
δ: 19.3 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 55.5 (q, minor rotamer), 55.8 (q), major rotamer), 64.1 (d), 127.6 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.2 (d), 131.3 (s), 133.5 (d), 133.6 (d), 134.0 (s), 134.1 (s), 136.6 (s), 137.0 (s), 141.0 (s), 144.0 (s), 168.0 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{34}H_{34}N_2NaO_4S$ ($M+Na^{+}$): 589.21315, found: 589.21208

4-benzyl-2-(1-(3-methoxyphenyl)-2-methylprop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24e**)



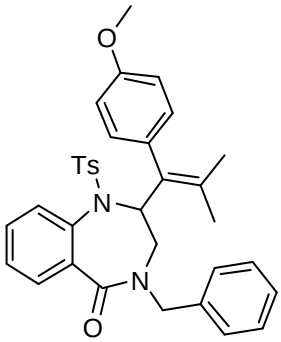
Yield: 63%.
Colorless oil.
IR (neat) 1651, 1351, 1159, 718, 658 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.40 (3H, s), 1.80 (3H, s), 2.42 (3H, s), 3.11 (1H, dd, J = 15.8, 4.5 Hz), 3.15 (3H, s), 3.49 (1H, dd, J = 15.8, 12.3 Hz), 3.66 (1H, A part of AB system, J = 14.7 Hz), 4.56 (B part of AB system, J = 14.7 Hz), 5.40 (1H, dd, J = 12.3, 4.5 Hz), 6.09 (1H, d, J = 8.1), 6.56 (1H, d, J = 9.0 Hz), 6.90-7.50 (m, 14H), 7.56 (1H, d, J = 7.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.5 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 54.8 (q), 64.6 (d), 110.6 (d), 121.4 (d), 127.6 (d), 128.1 (d), 128.3 (d), 128.5 (s), 128.7 (d), 128.9 (d), 129.1 (d), 129.7 (d), 130.1 (d), 130.5 (s), 131.1 (d), 131.3 (s), 133.7 (d), 134.1 (s), 134.6 (d), 134.7 (s), 136.9 (s), 137.2 (s), 143.8 (s), 157.3 (s), 168.2 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{34}H_{34}N_2NaO_4S$ ($M+Na^{+}$): 589.21315, found: 589.21202.

4-benzyl-2-(1-(4-methoxyphenyl)-2-methylprop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24f**)



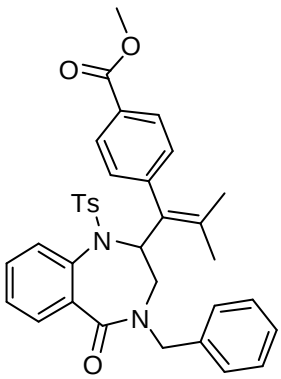
Yield: 73%.
Colorless oil.
IR (neat) 1651, 1509, 1350, 1244, 1172 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.41 (3H, s), 1.80 (3H, s), 2.43 (3H, s), 3.06 (1H, dd, J = 15.3, 4.3), 3.32 (1H, dd, J = 15.3, 12.4), 3.75 (1H, A part of AB system, J = 14.7 Hz), 3.81 (3H, s), 4.62 (1H, B part of AB system, J = 14.7 Hz),5.38 (1H, dd, J = 12.4, 4.3), 6.20-6.60 (2H, m), 6.41 (1H, dd, J = 7.9, 1.1 Hz), 6.80-7.10 (1H, m), 7.09 (1H, ddd, J = 7.9, 7.6, 1.7 Hz), 7.11-7.15 (2H, m), 7.23 (1H, ddd, J = 7.6, 7.6, 1.1 Hz), 7.27-7.37 (6H, m), 7.42-7.47 (2H, m), 7.55 (1H, dd, J = 7.6, 1.7 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 55.7 (q), 64.3 (d), 127.6 (d), 128.2 (d), 128.4 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.2 (d), 131.8 (s), 132.0 (s), 133.3 (s), 133.6 (d), 134.1 (s), 134.2 (s), 136.6 (s), 136.9 (s), 144.0 (s), 158.9 (s), 168.0 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{34}H_{34}N_2NaO_4S$ ($M+Na^{+}$): 589.21315, found: 589.21188

Methyl 4-(1-(4-benzyl-5-oxo-1-tosyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin2-yl)-2-methylprop-1-enyl)benzoate (**24g**)



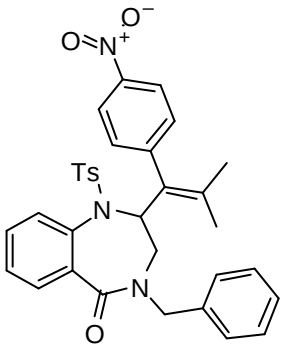
Yield: 61%.
Colorless oil.
IR (neat) 1722, 1651, 1276, 711, 659 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.38 (3H, s), 1.81 (3H, s), 2.43 (3H, s), 3.10 (1H, dd, J = 15.3, 4.2), 3.34 (1H, dd, J = 15.3, 12.5 Hz), 3.79 (1H, A part of AB system, J = 14.7 Hz), 3.94 (3H, s), 4.61 (1H, B part of AB system, J = 14.7 Hz), 5.39 (1H, dd, J = 12.5, 4.2 Hz), 6.29 (1H, d, J = 8.0 Hz), 6.52 (1H, s br), 7.02 (1H, ddd, J = 8.0, 7.6, 1.7 Hz), 7.10-7.15 (2H, m), 7.22 (1H, ddd, J = 7.7, 7.6, 1.0 Hz), 7.27-7.37 (5H, m), 7.40-7.47 (2H, m), 7.54 (1H, dd, J = 7.7, 1.7 Hz), 7.50-7.85 (2H, m), 8.05-8.35 (1H, m).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 21.9 (q), 22.7 (q), 48.9 (t), 49.5 (t), 52.4 (q), 64.0 (d), 127.6 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.0 (s), 129.2 (d), 130.1 (d), 130.2 (d), 131.4 (d), 132.1 (s), 133.1 (s), 133.2 (d), 133.8 (s), 134.0 (s), 136.3 (s), 136.8 (s), 144.2 (s), 144.9 (s), 167.4 (s), 167.9 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{35}H_{34}N_2NaO_4S$ ($M+Na^{+}$): 617.20806, found: 617.20659

4-benzyl-2-(2-methyl-1-(4-nitrophenyl)prop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24h**)



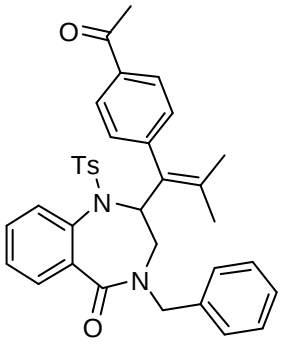
Yield: 71%.
Colorless oil.
IR (neat) 1652, 1518, 1346 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.39 (3H, s), 1.81 (3H, s), 2.44 (3H, s), 3.12 (1H, dd, J = 15.3, 4.2 Hz), 3.33 (1H, dd, J = 15.3, 12.6 Hz), 3.82 (1H, A part of AB system, J = 14.7 Hz), 4.61 (B part of AB system, J = 14.7 Hz), 5.39 (1H, dd, J = 12.6, 4.2 Hz), 6.30 (1H, dd, J = 8.0, 1.0 Hz), 6.38-6.95 (1H, m), 7.05 (1H, ddd, J =8.0, 7.6, 1.6 Hz), 7.11-7.15 (2H, m), 7.21-7.45 (6H, m), 7.40-7.45 (2H, m), 7.57 (1H, dd, J = 7.6, 1.6 Hz), 7.59-8.65 (3H, m)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.5 (q), 22.0 (q), 22.8 (q), 48.8 (t), 49.6 (t), 63.9 (d), 127.6 (d), 128.3 (d), 128.7 (d), 128.9 (d), 129.3 (d), 130.2 (d), 130.4 (d), 131.4 (d), 132.3 (s), 132.8 (d), 133.1 (s), 133.7 (s), 134.1 (s), 136.0 (s), 136.7 (s), 144.4 (s), 147.3 (s), 167.7 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{33}H_{31}N_3NaO_5S$ ($M+Na^{+}$): 604.18766, found: 604.18638.

2-(1-(4-acetylphenyl)-2-methylprop-1-enyl)-4-benzyl-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24i**)



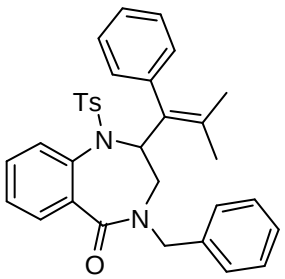
Yield: 68%.
Colorless oil.
IR (neat) 1682, 1650, 1350, 1158, 714, 660 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.39 (3H, s), 1.81 (3H, s), 2.43 (3H, s), 2.62 (3H, s), 3.11 (1H, dd, J = 15.2, 4.2 Hz), 3.34 (1H, dd, J = 15.2, 12.5 Hz), 3.79 (1H, A part of AB system, J = 14.6 Hz), 4.61 (1H, B part of AB system, J = 14.6 Hz), 5.39 (1H, dd, J = 12.5, 4.2 Hz), 6.26 (1H, dd, J = 8.1, 0.9 Hz), 6.40-6.75 (1H, br s), 6.99 (1H, ddd, J = 8.1, 7.6, 1.7 Hz), 7.13 (2H, m), 7.22 (1H, ddd, J = 7.6, 7.6, 0.9 Hz), 7.27-7.38 (5H, m), 7.41-7.46 (2H, m), 7.55 (1H, dd, J = 7.6, 1.7 Hz), 7.55-7.80 (2H, br s), 7.80-8.30 (1H, s br).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 21.9 (q), 22.7 (q), 27.0 (q), 48.9 (t), 49.5 (t), 64.0 (d), 127.6 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.2 (d), 130.1 (d), 130.2 (d), 131.2 (d), 132.1 (s), 133.1 (d), 133.8 (s), 134.1 (s), 136.0 (s), 136.3 (s), 144.2 (s), 145.2 (s), 167.8 (s), 198.2 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{35}H_{34}N_2NaO_4S$ ($M+Na^{+}$): 601.21315, found: 601.21187.

4-benzyl-2-(2-methyl-1-phenylprop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24j**)



Yield: 67%.
White oil.
IR (neat) 1651, 1351, 1160, 703, 658 cm^{-1}.

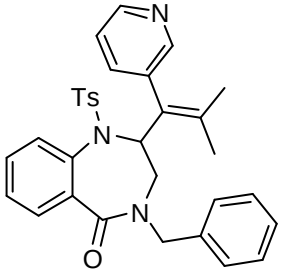
^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.40 (3H, s), 1.82 (3H, s), 2.43 (3H, s), 3.08 (1H, dd, J = 15.3, 4.2), 3.35 (1H, ddd, J = 15.3, 12.4, 0.8), 3.75 (1H, A part of AB system, J = 14.7 Hz), 4.62 (1H, B part of AB system, J = 14.7 Hz), 5.40 (1H, dd, J = 12.4, 4.2 Hz), 6.30 (2H, dd, J = 8.1, 1.1 Hz), 6.45 (1H, s br), 6.90-7.05 (1H, m), 7.03 (1H,

ddd, J = 8.1, 7.6, 1.7 Hz), 7.11-7.16 (2H, m), 7.18-1.25 (1H, m), 7.21 (1H, ddd, J = 7.6, 7.6, 1.1),7.27-7.37 (5H, m), 7.42-7.60 (4H, m), 7.54 (1H, dd, J = 7.6, 1.7 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.4 (q), 21.9 (q), 22.8 (q), 48.9 (t), 49.5 (t), 64.2 (d), 127.0 (d), 127.6 (d), 128.2 (d), 128.8 (d), 129.2 (d), 129.8 (d), 130.1 (d), 131.2 (d), 131.4 (s), 133.5 (d), 133.8 (s), 134.0 (s), 136.6 (s), 137.0 (s), 139.7 (s), 144.0. (s), 168.0 (s).

HRMS (ESI $^+$): Calcd. for $C_{33}H_{32}N_2NaO_3S$ ($M+Na^+$): 559.20258, found: 559.20159.

4-benzyl-2-(2-methyl-1-pyridin-2-yl)prop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24k**)



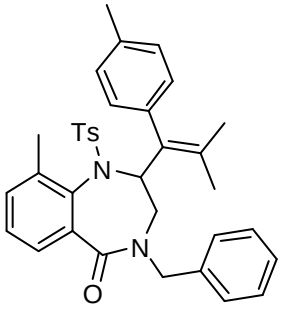
Yield: 70%.
Colorless oil.
IR (neat) 1651, 1351, 1159, 712, 658 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.40 (3H, s), 1.81 (3H, s), 2.43 (3H, s), 3.10 (1H, dd, J = 15.3, 4.2), 3.25-3.33 (1H, m), 3.86 (1H, A part of AB system, J = 14.7 Hz), 4.59 (1H, B part of AB system, J = 14.7 Hz), 5.34-5.40 (1H, m), 6.32 (1H, s br), 7.08-7.14 (3H, m), 7.17-7.40 (8H, m), 7.41-7.48 (2H, m), 7.51-7.58 (1H, m), 7.60-8.40 (1H, m), 8.52 (1H, d, J = 4.3 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.5 (q), 21.9 (q), 22.9 (q), 48.7 (t), 49.6 (t), 63.9 (d), 127.6 (d), 128.3 (d), 128.2 (d), 128.8 (d), 129.1 (s), 129.3 (d), 130.2 (d), 130.3 (d), 130.4 (d), 131.2 (s), 131.5 (d), 132.8 (s), 133.0 (s), 133.7 (d), 134.0 (s), 134.4 (s), 136.1 (s), 136.7 (s), 144.3 (s), 167.8 (s).

HRMS (ESI $^+$): Calcd. for $C_{32}H_{31}N_3NaO_3S$ ($M+Na^+$): 560.19783, found: 560.19650.

4-benzyl-9-methyl-2-(2-methyl-1-p-tolylprop-1-enyl)-1-tosyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**24l**)

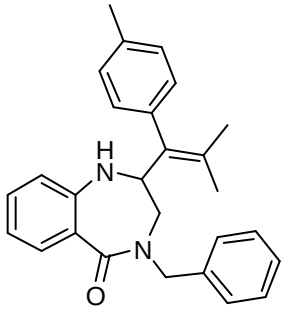


Yield: 75%.
Colorless oil.
IR (neat) 1651, 1351, 1162, 700, 658 cm^{-1}.

^{1}H-NMR: (400 MHz, $CDCl_3$)
δ: 1.48 (3H, s), 1.57 (3H, s), 1.95 (3H, s), 2.32 (3H, s), 2.46 (3H, s), 3.00 (1H, dd, J = 15.2, 3.7), 3.18 (1H, A part of AB system, J = 14.9 Hz), 3.59 (1H, dd, J = 15.2, 12.2 Hz), 4.69 (1H, A part of AB system, J = 14.9 Hz), 5.36 (1H, dd, J = 12.2, 3.6 Hz), 6.40-6.80 (1H, m), 6.90-7.05 (2H, m), 7.10-7.15 (2H, m), 7.16-7.22 (1H, m), 7.23-7.35 (6H, m), 7. 38 (2H, d, J = 8.2 Hz), 7.50-7.55 (1H, m), 7.63 (2H, d, J = 8.2 Hz)
^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 18.7 (q), 20.2 (q), 21.4 (q), 21.9 (q), 23.6 (q), 48.8 (t), 49.8 (t), 64.6 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.7 (d), 129.1 (d), 130.2 (d), 132.3 (s), 133.8 (s), 134.1 (s), 134.6 (d), 135.0 (s), 136.1 (s), 136.8 (s), 137.0 (s), 143.5 (s), 144.1 (s), 168.5 (s).

HRMS (ESI $^{+}$): Calcd. for $C_{35}H_{36}N_2NaO_3S$ ($M+Na^{+}$): 587.23388, found: 587.23221

Synthesis of 4-benzyl-2-(2-methylprop-1-enyl)-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (26)



To a solution of NH-Boc derivative XY (1 equiv.) in CH_3CN were added chlorotrimethylsilane (2 equiv.) and sodium iodide (2 equiv.) at room temperature. After complete disappearance of starting material (TLC plate, about 3 hours), methanol was added (4 equiv.). The reaction mixture was stirred for 2 hours, filtered on a celite pad and the volatile compounds were removed under reduced pressure. Purification over silica gel column (pentane/diethyl ether 6:4) or treatment of the crude product in acidic conditions (see text in the article) gave product XY in yields varying from 75% to 92%.

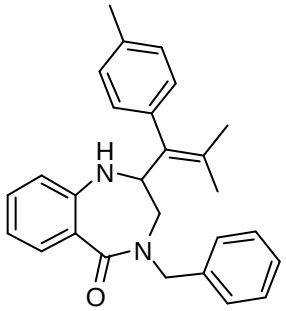
Yellow oil.
IR (neat) 3323, 1617, 1478, 749, 701 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.47 (3H, d, J = 1.3 Hz), 1.66 (3H, d, J = 1.3 Hz), 3.14 (1H, dd, J = 15.0, 3.4 Hz), 3.42 (1H, dd, J = 15.0, 9.6 Hz), 3.60 (1H, s br), 4.16 (1H, ddd, J = 9.6, 9.6, 3.4 Hz), 4.61 (1H, A part of AB system, J = 14.7 Hz), 5.03-5.08 (1H, m), 5.06 (1H, B part of AB system, J = 14.7 Hz), 5.06 (1H, m), 6.63 (1H, d, J = 8.0 Hz), 6.91 (1H, ddd, J = 8.0, 7.8, 0.8 Hz), 7.24 (1H, ddd, J = 8.0, 8.0, 1.6 Hz), 7.28-7.42 (m, 5H), 7.85 (1H, dd, J = 7.8, 1.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 18.2 (q), 26.0 (q), 50.4 (t), 51.8 (t), 58.7 (d), 120.2 (d), 120.3 (d), 123.6 (s), 123.7 (d), 127.9 (d), 128.8 (d), 129.0 (d), 132.1 (d), 132.5 (d), 136.0 (s), 137.6 (s), 143.8 (s), 170.2 (s).

HRMS: Calcd. For $C_{20}H_{23}ON_2$ ($M+H^+$): 307.18049, found: 307.17991.

Synthesis of 4-benzyl-2-(2-methyl-1-p-tolylprop-1-enyl)-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**25**)



To a solution of **23c** (1 equiv.) in DMF (0,1 M) were added PhSH (1.2 equiv.) and potassium carbonate (3 eq.) at room temperature. The reaction mixture was stirred at 40°C overnight. The mixture was treated with brine and extracted twice with ethyl acetate. It was then concentrated in vacuo and purified over silica gel column (pentane/diethyl ether 6:4).

Yield: 13%
White oil.
IR (neat) 3320, 1613, 751, 700 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.43 (3H, s), 1.63 (3H, s), 2.27-2.32 (1H, m), 2.29 (3H, s), 3.14 (1H, dd, J = 14.9, 2.6 Hz), 3.46 (1H, dd, J = 14.9, 10.3 Hz), 4.62 (1H, d, J = 10.3 Hz), 4.69 (1H, A part of AB system, J = 14.8 Hz), 4.93 (1H, B part of AB system, J = 14.8 Hz), 6.18 (1H, d, J = 7.8 Hz), 6.73-6.81 (3H, m), 7.03-7.10 (3H, m), 7.27-7.45 (5H, m), 7.77 (1H, dd, J = 7.8, 1.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 19.8 (q), 21.4 (q), 22.9 (q), 50.0 (t), 51.9 (t), 60.9 (d), 119.0 (s), 119.3 (d), 121.6 (s), 121.9 (s), 127.9 (d), 128.8 (d), 129.1 (d), 129.4 (d), 129.7 (d), 132.3 (d), 133.0 (s), 135.3 (s), 136.4 (s), 136.8 (d), 137.6 (s), 170.0 (s), 172.0 (s).

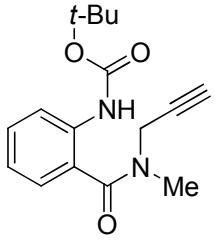
HRMS: Calcd. For $C_{27}H_{29}ON_2$ ($M+H^+$): 397.22744, found: 397.22648.

4) Exploiting the anthranilic scaffold, back to allenamides – *A) a 6-exo trig carbopalladation/amination reaction*

General procedure for the preparation of propargylamides 28a-f

DCC (10 mmol), N-propargyl amine (8.3 mmol)[108] and DMAP (0.125 mmol) were added to a solution of Boc-anthranilic acid (10 mmol) in CH_2Cl_2 (60 mL, 0 °C). The mixture reacted for 2 d at r.t., then was filtered on a silica gel path. The solvent was removed under reduced pressure and the crude purified by flash chromatography (light petroleum/AcOEt 7:3).

tert-butyl 2-(methyl(prop-2-ynyl)carbamoyl)phenylcarbamate (**28a**)



Yield: 76%.
Yellow solid. M. p. 76°C
IR: 1715, 1640 cm^{-1}

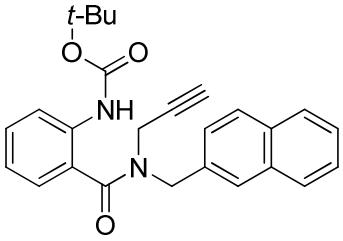
^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.50 (9H, s), 2.34 (1H, s), 3.12 (3H, s), 3.95-4.50 (2H, m), 7.03 (1H, ddd, J = 1.0, 7.2, 8.1 Hz), 7.36-7.41 (2H, m), 7.96 (1 H, b), 8.13 (1H, d, J = 8.4 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.2 (q), 33.8 (t), 54.0 (q), 75.0 (d), 78.1 (s), 80.4 (s), 120.9 (d), 121.9 (d), 122.8 (s), 127.3 (d), 130.9 (d), 137.4 (s), 152.8 (s), 170.0 (s).

MS: m/z 288 (M^+). Anal. calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found C, 66.59; H, 7.01; N, 9.75.

[108] Except for commercial N-methyl-propargyl amine, all other amines were prepared according to: E. M. Beccalli, A. Bernasconi, E. Borsini, G. Broggini, M. Rigamonti, G. Zecchi *J. Org. Chem.* **2010**, *75*, 6923.

tert-butyl 2-((naphthalen-2-ylmethyl)(prop-2-ynyl)carbamoyl)phenylcarbamate (28b)



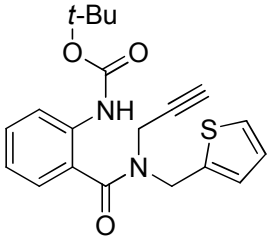
Yield:54%.
Brown oil.
IR: 1713, 1641 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.53 (9H, s), 2.01 (1H, s), 3.12 (2H, d, J = 7.2 Hz), 4.94 (2H, s), 7.03 (1H, ddd, J = 1.1, 6.5, 7.6 Hz), 7.36 – 7.41 (3H, m), 7.44 – 7.48 (2H, m), 7.74 (1H, br s), 7.79 – 7.82 (4H, m), 8.13 (1H, dd, J = 0.4, 8.2 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.3 (q), 29.7 (t), 52.4 (t), 71.9 (d), 78.3 (s), 80.6 (s), 117.0 (d), 121.5 (d), 122.4 (d), 123.6 (s), 125.5 (d), 126.2 (d), 126.4 (d), 126.9 (d), 127.7 (d), 127.8 (d), 128.8 (d), 131.1 (d), 133.0 (s), 133.3 (s), 137.2 (s), 148.0 (s), 153.0 (s), 170.4 (s).

MS: m/z 414 (M^+). Anal. calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found C, 75.49; H, 6.41; N, 6.73.

tert-butyl 2-(prop-2-ynyl(thiophen-2-ylmethyl)carbamoyl)phenylcarbamate (28c)



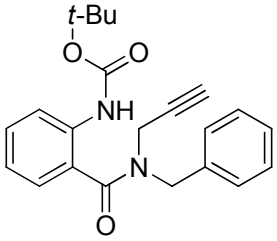
Yield: 28%
Brown oil.
IR: 1718, 1645 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.53 (9H, s), 2.37 (1H, s), 4.02 (2H, s), 4.94 (2H, s), 6.95-6.98 (1H, m), 7.04-7.08 (2H, m), 7.26-7.38 (1H, m), 7.39-7.42 (2H, m), 7.80 (1H, br s), 8.10 (1H, d, J = 8.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.3 (q), 36.9 (t), 46.6 (t), 72.0 (d), 78.3 (s), 80.4 (s), 121.4 (d), 122.3 (d), 123.6 (s), 126.1 (d), 126.7 (d), 126.9 (d), 127.5 (d), 131.1 (d), 137.2 (s), 138.3 (s), 152.9 (s), 170.0 (s).

MS: m/z 370 (M^+). Anal. calcd for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56. Found C, 64.80; H, 5.91; N, 7.70.

tert-butyl 2-(benzyl(prop-2-ynyl)carbamoyl)phenylcarbamate (**28d**)



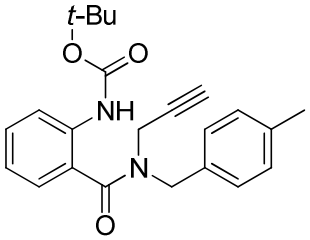
Yield: 50%.
Yellow solid (M. p. 95°C)
IR: 1720, 1640 cm^{-1}

^{1}H-NMR ($CDCl_3$)
δ: 1.53 (9H, s), 2.35 (1H, s), 3.95 (2H, s), 4.83 (2H, s), 7.05 (1H, d, J = 6.8), 7.03-7.42 (7H, m), 7.87 (1H, br s), 8.10 (1H, d, J = 8.4)

^{13}C-NMR ($CDCl_3$)
δ: 28.3 (q), 36.9 (t), 51.9 (t), 72.3 (d), 78.2 (s), 80.6 (s), 121.5 (d), 122.3 (d), 123.5 (s), 126.8 (d), 127.9 (d), 128.5 (d), 128.8 (d), 131.0 (d), 136.4 (s), 137.1 (s), 152.9 (s), 170.0 (s).

MS: m/z 364 (M^+). Anal. calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found C, 72.61; H, 6.71; N, 7.52.

tert-butyl 2-((4-methylbenzyl)(prop-2-ynyl)carbamoyl)phenylcarbamate (**28e**)



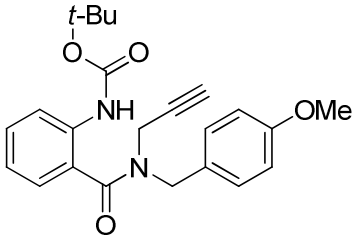
Yield: 45%.
Brown oil
IR: 1700, 1650 cm^{-1}

^{1}H-NMR ($CDCl_3$)
δ: 1.27 (1H, s), 1.52 (9H, s), 2.32 (1H, s), 4.30 (2H, s), 4.85 (2H, s), 7.00-7.04 (2H, m), 7.12-7.14 (3H, m), 7.35-7.39 (2H, m), 7.85 (1H, br s), 8.10 (1H, d, J = 8.3).

^{13}C-NMR ($CDCl_3$)
δ: 21.1 (q), 28.3 (q), 38.7 (t), 47.0 (t), 73.5 (d), 78.3 (s), 80.4 (s), 121.4 (d), 122.3 (d), 123.7 (s), 126.6 (d), 128.0 (d), 129.5 (d), 130.9 (d), 132.5 (s), 137.1 (s), 137.5 (s), 152.9 (s), 170.1 (s).

MS: m/z 378 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found C, 72.92; H, 6.96; N, 7.50.

tert-butyl 2-((4-methoxybenzyl)(prop-2-ynyl)carbamoyl)phenylcarbamate (**28f**)



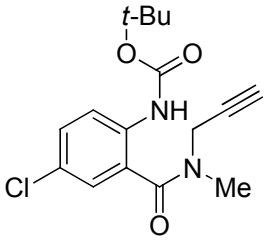
Yield: 62%.
Colorless oil
IR: 1703, 1651 cm^{-1}

^{1}H-NMR ($CDCl_3$)
δ: 1.52 (9H, s), 2.34 (1H, s), 3.59-3.72 (2H, m), 3.81 (3H, s), 4.50-4.78 (2H, br s), 6.87 (2H, d, J = 8.5 Hz), 7.03-7.42 (5H, m), 7.83 (1H, br s), 8.10 (1H, d, J = 8.4 Hz).

^{13}C-NMR ($CDCl_3$)
δ: 28.3 (q), 30.9 (t), 55.2 (q),64.4 (t), 73.5 (d), 78.3 (s), 80.5 (s), 114.2 (d), 121.4 (d), 122.3 (s), 126.9 (d), 130.9 (d), 137.1 (s), 152.9 (s), 159.3 (s), 170.1 (s).

MS: m/z 394 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found C, 69.95; H, 6.76; N, 7.12.

tert-butyl 4-chloro-2-(methyl(prop-2-ynyl)carbamoyl)phenylcarbamate (**28g**)



2-amino-5-chloro-N-methyl-N-(prop-2-ynyl)benzamide[109] (3.15 mmol) was dissolved in EtOH (15 mL). $(Boc)_2O$ (14 mmol) was added and the reactino was stirred at 50 °C for 6 d. The solvent was then evaporated under reduced pressure and the residue was purified by flash column cromatography (light petroleum/EtOAc 4:1).

Yield: 73%.
White solid. M.p. 147 °C.
IR: 1705, 1658 cm^{-1}

^{1}H-NMR ($CDCl_3$)
δ: 1.51 (9H, s), 2.37 (1H, s), 3.13 (3H, s), 3.90-4.50 (2H, m), 7.20-7.37 (2H, m), 7.85 (1H, br s), 8.11 (1H, d, J = 9.0)

[109] G. Broggini, G. Molteni, A. Terraneo, G. Zecchi, *Tetrahedron*, **1999**, *55*, 14803.

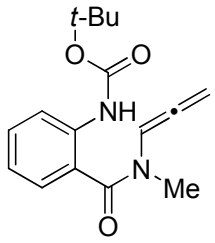
^{13}C-NMR ($CDCl_3$)
δ: 28.4 (q), 37.0 (q), 42.0 (t), 73.2 (d), 79.5 (s), 80.9 (s), 122.4 (d), 124.2 (s), 127.1 (d), 130.9 (d), 134.0 (s), 136.1 (s), 152.7 (s), 168.7 (s).

MS: m/z 322 (M^+). Anal. calcd for $C_{16}H_{19}ClN_2O_3$: C, 59.54; H, 5.93; N, 8.68. Found C, 59.66; H, 5.87; N, 8.71.

General procedure for the preparation of allenamides 27

t-BuOK (2.5 mmol) in THF (10 mL) was added to a solution of **28** (1 mmol). The resulting solution was stirred at r.t. for 1 min, then filtered on silica gel (AcOEt). The solvent was evaporated under reduced pressure and the residue was used without further purification for the next step.

tert-butyl 2-(methyl(propa-1,2-dienyl)carbamoyl)phenylcarbamate (**27a**)



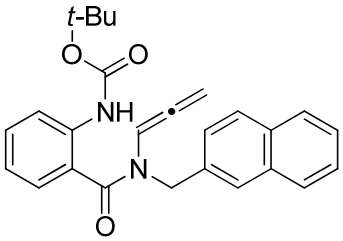
Yield: 97%
Yellow oil.
IR: 1701, 1652 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$):
δ: 1.52 (9H, s), 3.13 (3H, s), 5.40 (2H, d, J = 6.3 Hz), 6.78 (1H, br s), 7.04 (1H, ddd, J = 1.2, 6.5, 7.9 Hz), 7.28 (1H, dd, J = 1.5, 7.7 Hz), 7.39 (1H, ddd, J = 1.6, 6.2, 7.9 Hz), 7.90 (1H, br s), 8.16 (1H, dd, J = 1.0, 8.4 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$):
δ: 28.3 (q), 30.3 (q), 80.6 (s), 87.3 (t), 103.3 (d), 115.8 (s), 121.0 (d), 121.7 (d), 128.7 (d), 131.3 (d), 137.9 (s), 152.8 (s), 168.4 (s), 200.1 (s).

MS: m/z 288 (M^+). Anal. calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found C,66.71; H, 6.97; N, 9.67.

tert-butyl 2-((naphthalen-2-ylmethyl)(propa-1,2-dienyl)carbamoyl)phenylcarbamate (**27b**)



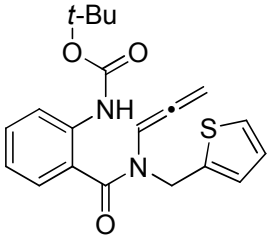
Yield: 72%.
Orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.51 (9H, s), 5.08 (2H, s), 5.30 (2H, s), 7.06 (1H, br s), 7.42 – 7.54 (5H, m), 7.77 – 7.85 (5H, m), 8.04 (1H, br s), 8.18 (1H, d, J = 8.1 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.3 (q), 48.0 (t), 80.6 (s), 87.6 (t), 102.5 (d), 117.2 (d), 121.3 (d), 122.0 (d), 125.1 (d), 125.9 (d), 126.2 (d), 127.0 (s), 127.3 (d), 127.7 (d), 127.8 (d), 128.4 (d), 129.5 (s), 131.4 (d), 132.7 (s), 133.4 (s), 134.5 (s), 152.9 (s), 168.3 (s), 200.6 (s).

MS: m/z 414 (M^+). Anal. calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found C, 75.45; H, 6.37; N, 6.70.

tert-butyl 2-(propa-1,2-dienyl(thiophen-2-ylmethyl)carbamoyl)phenylcarbamate (**27c**)



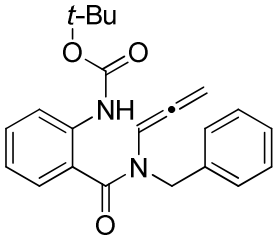
Yield: 36%
Yellow oil

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.53 (9H, s), 5.02 (2H, s), 5.45 (2H, d, J = 6.3 Hz), 6.70 (1H, br s), 6.95 – 7.05 (3H, m), 7.23 – 7.32 (2H, m), 7.39 – 7.43 (1H, m), 7.95 (1H, br s), 8.13 (1H, d, J = 8.4 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.3 (q), 42.5 (t), 80.5 (s), 88.2 (t), 101.6 (d), 121.2 (d), 121.9 (d), 125.5 (d), 126.4 (d), 127.4 (d), 128.4 (d), 129.0 (s), 131.4 (d), 137.7 (s), 139.0 (s), 152.8 (s), 168.0 (s), 200.1 (s).

MS: m/z 370 (M^+). Anal. calcd for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56. Found C, 64.96; H, 5.85; N, 7.70.

tert-butyl 2-(benzyl(propa-1,2-dienyl)carbamoyl)phenylcarbamate (**27d**)



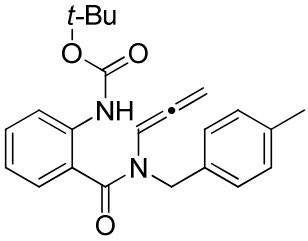
Yield: 47%.
Yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.53 (9H, s), 4.90 (2H, s), 5.29 (2H, d, J = 6.1 Hz), 6.73 (1H, br s), 7.00 – 7.42 (8H, m), 7.97 (1H, br s), 8.15 (1H, d, J = 8.2 Hz)

^{13}C-NMR ($CDCl_3$)
δ: 28.3 (q), 47.7 (t), 80.6 (s), 87.6 (t), 102.4 (d), 121.3 (d), 126.6 (d), 127.3 (s), 127.8 (d), 128.5 (d), 128.6 (d), 128.8 (d), 131.3 (d), 137.1 (s), 137.6 (s), 152.8 (s), 168.4 (s), 200.5 (s).

MS: m/z 364 (M^+). Anal. calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found C, 72.54; H, 6.67; N, 7.61.

tert-butyl 2-((4-methylbenzyl)(propa-1,2-dienyl)carbamoyl)phenylcarbamate (**27e**)



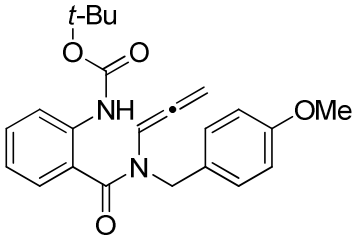
Yield: 98%
Brown oil

^{1}H-NMR ($CDCl_3$)
δ: 1.54 (9H, s), 2.34 (3H, s), 4.86 (2H, br s), 5.30 (2H, d, J = 6.0 Hz), 6.71 (1H, br s), 7.04 – 7.42 (7H, m), 7.97 (1H, br s), 8.14 (1H, d, J = 8.3 Hz)

^{13}C-NMR ($CDCl_3$)
δ: 21.1 (q), 28.3 (q), 47.7 (t), 80.5 (s), 87.5 (t), 102.4 (d), 121.2 (d), 122.0 (d), 126.8 (s), 127.8 (d), 128.5 (d), 129.0 (d), 131.3 (d), 134.1 (s), 136.9 (s), 137.7 (s), 152.8 (s), 168.3 (s), 200.5 (s).

MS: m/z 378 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 59.54; H, 5.93; N, 8.68. Found C, 59.66; H, 5.87; N, 8.71.

tert-butyl 2-((4-methoxybenzyl)(propa-1,2-dienyl)carbamoyl)phenylcarbamate (**27f**)



Yield: 60%
Yellow oil

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.51 (9H, s), 3.79 (3H, s), 4.83 (2H, br s), 5.32 (2H, d, J = 6.3 Hz), 6.55 – 7.45 (7H, m), 7.94 (1H, br s), 8.13 (1H, d, J = 8.3 Hz)

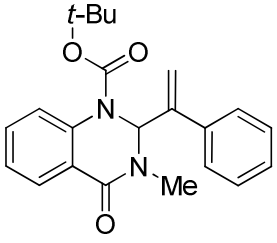
^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.3 (q), 47.1 (t), 55.2 (q), 80.5 (s), 87.5 (t), 102.3 (d), 113.9 (d), 121.2 (d), 123.0 (d), 128.5 (d), 129.4 (d), 131.3 (d), 137.6 (s), 152.8 (s), 158.8 (s), 168.3 (s), 200.5 (s).

MS: m/z 394 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found C, 70.12; H, 6.71; N, 7.21.

General procedure for the carbopalladation/amination of allenamides 26a-h: synthesis of quinazolinones 29a-h

K_2CO_3 (4 mmol), the appropriate aryl iodide (1.5 mmol) and $Pd(PPh_3)_4$ (2%) in DMF (10 mL) were added to a solution of **2** (1 mmol). The resulting solution was heated at 100 °C for 2 h, then was cooled, diluted with brine and extracted with AcOEt (3 x 20 mL). The resulting crude was purified by flash chromatography to afford the desired products **29.**

tert-butyl 3-methyl-4-oxo-2-(1-phenylvinyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**29a**)



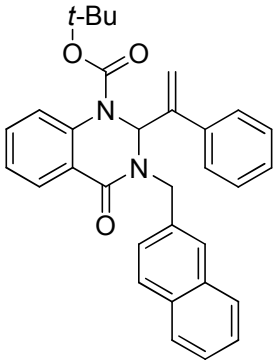
Yield: 73%.
White solid. M.p.: 165°C

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.41 (9H, s), 3.27 (3H, s), 5.03 (1H, d, J = 1.4 Hz), 5.24 (1H, d, J = 1.7 Hz), 6.67 (1H, br s), 7.16-7.22 (4H, m), 7.27-7.29 (3H, m), 7.36 (1H, ddd, J = 1.6, J = 7.2, 8.8 Hz), 8.01 (1H, dd, J = 1.1, 7.8 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 28.0 (q), 33.9 (q), 70.7 (s), 82.7 (d), 116.6 (t), 123.6 (s), 124.4 (d), 124.9 (d), 127.0 (d), 127.3 (d), 127.9 (s), 128.1 (d), 131.7 (d), 137.0 (s), 139.0 (s), 143.9 (d), 145.5 (s), 163.1 (s).

MS: m/z 364 (M^+). Anal. calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found C, 78.45; H, 6.22; N, 5.65.

tert-butyl 3-(naphthalen-2-ylmethyl)-4-oxo-2-(1-phenylvinyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**29b**)



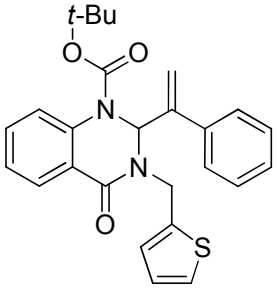
Yield: 44%.
Brown oil.

^{1}H-NMR ($CDCl_3$)
δ: 1.01 (9H, s), 4.80 (1H, br s), 5.18 (1H, d, J = 1.7 Hz), 5.24 (1H, d, J = 1.4 Hz), 5.91 (1H, br s), 6.62 (1H, br s), 7.07 – 7.09 (2H, m), 7.24 – 7.27 (4H, m), 7.40 – 7.54 (5H, m), 7.82 – 7.85 (4H, m), 8.12 (1H, d, J = 7.6 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 27.9 (q), 48.8 (t), 82.2 (s), 102.5 (d), 116.9 (t), 119.0 (d), 123.5 (s), 124.2 (d), 124.8 (d), 126.2 (d), 126.3 (d), 126.5 (d), 127.3 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.1 (d), 128.8 (d), 132.2 (d), 133.1 (s), 133.4 (s), 134.2 (s), 135.0 (d), 137.1 (s), 139.4 (s), 143.8 (s), 150.9 (s), 163.0 (s).

MS: m/z 490 (M^+). Anal. calcd for $C_{32}H_{30}N_2O_3$: C, 78.34; H, 6.16; N, 5.71. Found C, 78.45; H, 6.22; N, 5.65.

tert-butyl 4-oxo-2-(1-phenylvinyl)-3-(thiophen-2-ylmethyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**29c**)



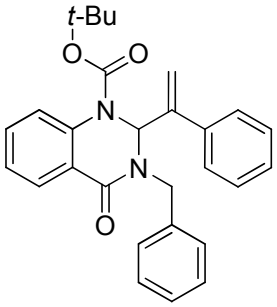
Yield: 66%.
Brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.53 (9H, s), 4.35 (1H, br s), 5.07 (1H, d, J = 1.4 Hz), 5.22 (1H, s), 5.75 (1H, br s), 6.70 (1H, br s), 6.98 – 7.07 (2H, m), 7.11 – 7.14 (3H, m), 7.22 – 7.26 (2H, m), 7.27 – 7.35 (2H, m), 7.41 – 7.47 (2H, m), 8.06 (1H, d, J = 7.2 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 27.6 (q), 44.0 (t), 68.4 (d), 82.3 (s), 116.9 (t), 120.0 (d), 121.3 (d), 124.2 (s), 124.8 (d), 126.6 (d), 127.3 (d), 127.6 (d), 127.9 (d), 128.5 (d), 136.7 (s), 137.0 (s), 138.1 (s), 143.7 (s), 151.0 (s), 162.9 (s).

MS: m/z 446 (M^+). Anal. calcd for $C_{26}H_{26}N_2O_3S$: C, 69.93; H, 5.87; N, 6.27. Found C, 69.95; H, 5.92; N, 6.34.

tert-butyl 3-benzyl-4-oxo-2-(1-phenylvinyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (**29d**)



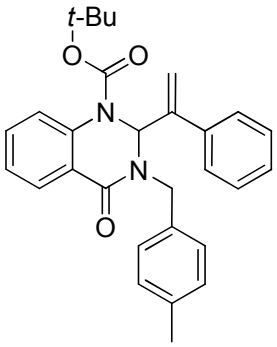
Yield: 62%
Yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.17 (9H, s), 3.94 (1H, br s), 5.13 (1H, d, J = 1.6 Hz), 5.24 (1H, s), 5.80 (1H, br s), 6.49 (1H, br s), 7.06-7.09 (2H, m), 7.22 – 7.28 (5H, m), 7.34 – 7.44 (6H, m), 8.08 (1H, d, J = 7.6 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 27.6 (q), 44.0 (t), 68.4 (d), 82.3 (s), 116.9 (t), 120.0 (d), 121.3 (d), 124.2 (s), 124.8 (d), 126.6 (d), 127.3 (d), 127.6 (d), 127.9 (d), 128.5 (d), 128.9 (d), 132.1 (d), 136.7 (s), 137.0 (s), 138.1 (s), 143.7 (s), 151.0 (s), 162.9 (s).

MS: m/z 440 (M^+). Anal. calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found C, 76.41; H, 6.51; N, 6.19.

tert-butyl 3-(4-methylbenzyl)-4-oxo-2-(1-phenylvinyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (29e)



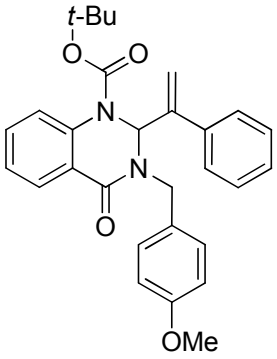
Yield: 43%.
Yellow oil.

^{1}H-NMR ($CDCl_3$)
δ: 1.47 (9H, s), 2.36 (3H, s), 3.87 (1H, br s), 5.12 (1H, d, J = 1.6 Hz), 5.23 (1H, s), 5.73 (1H, br s), 6.47 (1H, br s), 7.07-7.12 (3H,m), 7.18-7.30 (8H, m), 7.65 (1H, d, J = 2.6 Hz), 8.08 (1H, d, J = 7.7 Hz)

^{13}C-NMR ($CDCl_3$)
δ: 21.1 (q), 28.3 (q), 48.0 (t), 68.2 (d), 82.2 (s), 116.9 (t), 123.5 (s), 124.1 (d), 124.8 (d), 126.8 (s), 127.3 (d), 127.6 (d), 127.9 (d), 128.1 (d), 128.6 (d), 129.3 (s), 129.5 (d), 132.1 (s), 133.6 (s), 137.0 (s), 137.6 (d), 152.1 (s), 162.9 (s).

MS: m/z 454 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_3$: C, 76.63; H, 6.65; N, 6.16. Found C, 76.71; H, 6.72; N, 6.13.

tert-butyl 3-(4-methoxybenzyl)-4-oxo-2-(1-phenylvinyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (29f)



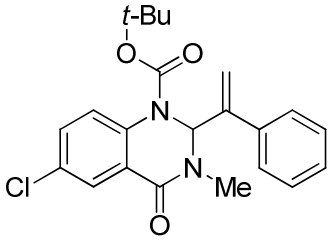
Yield: 50%.
Yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 50 °C)
δ: 1.23 (9H, s), 3.70-3.90 (2H, m), 3.81 (3H s), 5.11 (1H, d, J = 1.2 Hz), 5.20 (1H, d, J = 1.2 Hz), 6.57 (1H, br s), 6.89-7.43 (11H m), 8.05-8.09 (1H, m).

^{13}C-NMR (100 MHz, $CDCl_3$, 50 °C)
δ: 27.6 (q), 55.3 (q), 68.1 (t), 116.9 (t), 124.8 (d), 127.6 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.9 (d), 129.3 (d), 129.9 (d), 130.0 (s), 137.0 (s), 143.8 (s), 159.4 (s), 162.8 (s)

MS: m/z 470 (M^+). Anal. calcd for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found C, 74.10; H, 6.51; N, 5.88.

tert-butyl 6-chloro-3-methyl-4-oxo-2-(1-phenylvinyl)-3,4-dihydroquinazoline-1(2H)-carboxylate (29g)



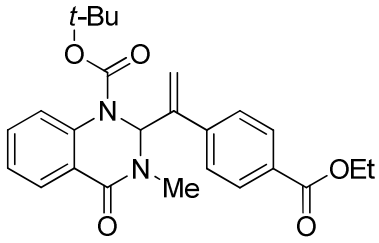
Yield: 40%.
Yellow solid. M.p.: 115°C

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.40 (9H, s), 3.28 (3H, s), 5.01 (1H, d, J = 1.8 Hz), 5.29 (1H, d, J = 1.8 Hz), 6.68 (1H, br s), 7.17-7.35 (6H, m), 7.98 (1H, d, J = 7.1 Hz), 8.01 (1H, dd, J = 1.1, J = 7.8 Hz)

^{13}C-NMR ($CDCl_3$)
δ: 28.0 (q), 34.0 (q), 70.0 (d), 83.1 (s), 116.9 (t), 124.6 (s), 125.8 (d), 126.8 (d), 126.9 (d), 128.1 (d), 128.6 (d), 130.5 (s), 131.7 (d), 135.5 (s), 138.0 (s), 143.8 (s), 152.5 (s), 162.0 (s).

MS: m/z 398 (M^+). Anal. calcd for $C_{22}H_{23}ClN_2O_3$: C, 66.24; H, 5.81; N, 7.02. Found C, 66.30; H, 5.80; N, 7.11.

tert-butyl 2-(1-(4-(ethoxycarbonyl)phenyl)vinyl)-3-methyl-4-oxo-3,4-dihydroquinazoline-1(2H)-carboxylate (29h)



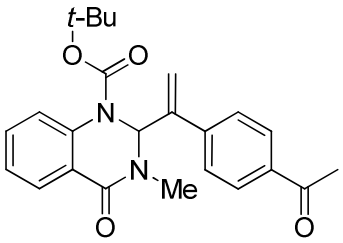
Yield: 60%.
Orange solid. M.p.: 146°C

^{1}H-NMR ($CDCl_3$)
δ: 1.40 (9H, s), 1.40 (3H, t, J = 7.1 Hz), 3.29 (3H, s), 4.39 (2H, q, J = 7.1 Hz), 5.10 (1H, s), 5.34 (1H, s), 6.67 (1H, br s), 7.22-7.28 (4H, m), 7.32-7.42 (1H, m), 7.96-8.01 (3H, m)

^{13}C-NMR ($CDCl_3$)
δ: 14.3 (q), 28.0 (q), 33.9 (q), 61.0 (t), 82.9 (s), 92.2 (d), 117.9 (t), 123.5 (s), 124.4 (d), 125.0 (d), 126.9 (d), 127.4 (d), 129.4 (d), 130.0 (s), 131.8 (d), 136.8 (s), 142.7 (s), 143.5 (s), 155.0 (s), 163.0 (s), 166.2 (s).

MS: m/z 436 (M^+). Anal. calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found C, 68.66; H, 6.42; N, 6.60.

tert-butyl 2-(1-(4-acetylphenyl)vinyl)-3-methyl-4-oxo-3,4-dihydroquinazoline-1(2H)-carboxylate (29i)



Yield: 56%.
Orange solid. M.p.: 140°C.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.41 (9H, s), 2.61 (3H, s), 3.30 (3H, s), 5.12 (1H, d, J = 1.8), 5.36 (1H, s), 6.68 (1H, br s), 7.21-7.39 (5H, m), 7.88-7.90 (2H, m), 8.01 (1H, dd, J = 1.3, 7.8 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 26.6 (q), 28.0 (q), 39.9 (q), 82.9 (s), 96.2 (d), 114.9 (s), 118.0 (t), 123.1 (s), 123.5 (d), 124.4 (d), 125.1 (d), 127.4 (d), 128.2 (d), 131.8 (d), 136.5 (s), 136.8 (s), 143.0 (s), 143.3 (s), 163.0 (s), 197.5 (s).

MS: m/z 406 (M^+). Anal. calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found C, 70.95; H, 6.42; N, 6.80.

4) Exploiting the anthranilic scaffold, back to allenamides – *B) a 6-exo trig hydroamination reaction*

General procedure for the Au-catalyzed hydroamination

To a solution of **26** (0.48 mmoli) in MeCN (8 mL) add $AuCl_3$ (0.029 mmoli). Let the mixture react under stirring for one night (60 °C).

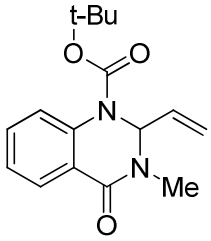
Evaporate the solvent under reduced pressure. The crude mixture is purified by silica gel flash column chromatography.

Procedure for the Ru-catalyzed hydroamination

Dissolve **26** (0.21 mmol) in MeCN (2 mL). Add $RuCl_3 \bullet 2.4\ H_2O$ (0.002 mmol), dppe (0.002 mmol), K_2CO_3 (0.42 mol) and $CuCl_2$ (0.21 mmol). Leave the mixture under stirring at 60°C for 2h.

Evaporate the solvent under reduced pressure.

tert-butyl 3-methyl-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30a**)



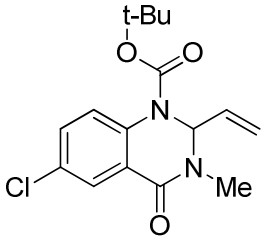
Yield: 45% (Au), 90% (Ru).
White solid (M.p.: 122 °C)

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.50 (9H, s), 3.15 (3H, s), 5.20 (2H, dd, J = 0.7, 6.8 Hz), 5.64-5.73 (1H, m), 6.11 (1H, d, J = 3.7 Hz), 7.18 (1H, ddd, J = 1.0, 6.8, 7.7 Hz), 7.43 (1H, ddd, J = 1.4, 6.8, 8.2 Hz), 7.50 (1H, d, J = 6.0 Hz), 8.01 (1H, dd, J = 1.0, 7.7 Hz)

^{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^+). Anal. calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found C, 66.70; H, 6.81; N, 9.81.

tert-butyl 6-chloro-3-methyl-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30b**)



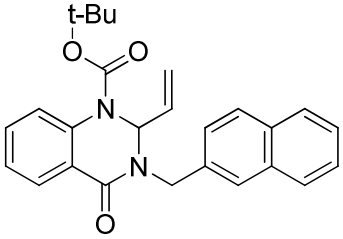
Yield: 41%.
White solid (M.p.: 120 °C)

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.53 (9H, s), 3.15 (3H, s), 5.15-5.21 (2H, m), 5.66 (1H, ddd, J = 3.6, 10.3, 15.5 Hz), 6.05 (1H, br s), 7.38 (1H, dd, J = 2.5, 8.7 Hz), 7.50 (1H, d, J = 6.3 Hz), 7.97 (1H, d, J = 2.8 Hz)

^{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^+). Anal. calcd for $C_{16}H_{19}ClN_2O_3$: C, 59.54; H, 5.93; N, 8.68. Found C, 59.62; H, 5.81; N, 8.71.

tert-butyl 3-(naphthalen-2-ylmethyl)-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30c**)



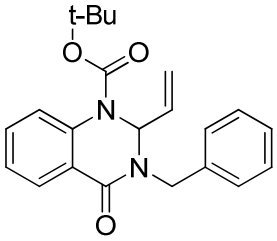
Yield: 40%.
Brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.20 (9H, s), 4.12 (1H, br s), 5.15-5.24 (2H, m), 5.68-5.76 (1H, m), 5.74 (1H, br s), 6.12 (1H, d, J = 5.3 Hz), 7.23 – 7.27 (1H, m), 7.44 – 7.49 (5H, m), 7.79 – 7.83 (4H, m), 8.11 (1H, dd, J = 1.3, 7.7 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 27.6 (q), 48.2 (t), 79.8 (s), 82.5 (d), 118.7 (t), 122.4 (d), 123.5 (s), 124.6 (d), 126.1 (d), 126.5 (d), 127.3 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.1 (d), 128.8 (d), 129.8 (d), 131.8 (d), 133.1 (s), 133.4 (s), 137.7 (s), 151.1 (s), 162.3 (s), 164.0 (s).

MS: m/z 414 (M^+). Anal. calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.26. Found C, 75.36; H, 6.41; N, 6.17.

tert-butyl 3-benzyl-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30d**)



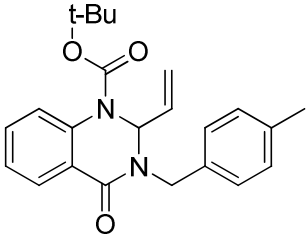
Yield: 54%.
Yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.34 (9H, s), 3.90 (1H, br s), 5.17-5.21 (2H, m), 5.59 (1H, br s), 5.70 (1H, ddd, J = 5.4, 8.9, 16.8 Hz), 6.05 (1H, br s), 7.21-7.25 (2H, m), 7.31-7.37 (4H, m), 7.47 (1H, ddd, J = 1.6, 6.0, 7.5 Hz), 7.60 (1H, br s), 8.07 (1H, dd, J = 1.5, 7.8 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 27.9 (q), 47.7 (t), 68.3 (d), 82.6 (s), 118.6 (t), 122.0 (d), 123.6 (s), 124.5 (d), 127.8 (d), 128.1 (d), 128.8 (d), 129.8 (d), 131.8 (d), 132.3 (d), 136.6 (s), 137.6 (s), 152.0 (s), 164.9 (s).

MS: m/z 364 (M^+). Anal. calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found C, 72.47; H, 6.71; N, 7.71.

tert-butyl 3-(4-methylbenzyl)-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30e**)



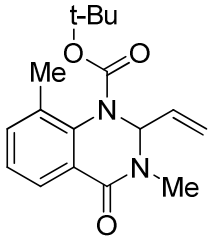
Yield: 63%.
Brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.34 (9H, s), 2.33 (3H, s), 2.41 (3H, s), 3.88 (1H, br s), 5.16-5.20 (2H, m), 5.56 (1H, br s), 5.64-5.75 (1H, m), 6.03 (1H, br s), 7.13-7.33 (4H, m), 7.45 (1H, d, J = 7.3 Hz), 7.59 (1H, br s), 8.05 (1H, d, J = 7.6 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$)
δ: 18.3 (q), 27.9 (q), 47.7 (t), 68.3 (d), 82.6 (s), 118.6 (t), 122.0 (d), 123.6 (s), 124.5 (d), 127.8 (d), 128.1 (d), 128.8 (d), 129.8 (d), 131.8 (d), 132.3 (d), 136.6 (s), 137.6 (s), 152.0 (s), 164.9 (s).

MS: m/z 378 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found C, 73.04; H, 6.81; N, 7.52.

tert-butyl 3,8-dimethyl-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30f**)



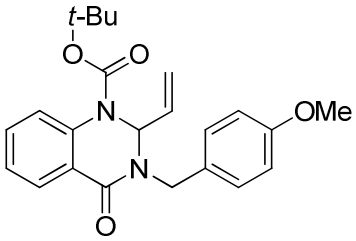
Yield: 52%
Colorless oil

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.52 (9H, s), 3.79 (3H, s), 4.54-4.62 (1H, m), 5.14-5.20 (1H, m),5.59-5.64 (1H, m), .95-6.02 (1H, m),6.85 – 7.42 (6H, m), 8.04 (1H, d, J = 1.2 Hz), 8.38-8.43 (1H, m)

^{13}C-NMR ($CDCl_3$)
δ: 27.4(q), 54.8 (q), 59.9 (t), 67.8 (d), 113.9 (d), 118.0 (t), 119.2 (d), 120.7 (d), 124.1 (d), 126.9 (d), 127.6 (d), 128.8 (d), 129.4 (d), 131.8 (d), 170.5 (s).

MS: m/z 394 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found C, 70.07; H, 6.71; N, 7.01.

tert-butyl 3-(4-methoxybenzyl)-4-oxo-2-vinyl-3,4-dihydroquinazoline-1(2H)-carboxylate (**30g**)



Yield: 59%
Colorless oil

^{1}H-NMR (400 MHz, $CDCl_3$)
δ: 1.52 (9H, s), 3.79 (3H, s), 4.54-4.62 (1H, m), 5.14-5.20 (1H, m),5.59-5.64 (1H, m), .95-6.02 (1H, m),6.85 – 7.42 (6H, m), 8.04 (1H, d, J = 1.2 Hz), 8.38-8.43 (1H, m)

^{13}C-NMR ($CDCl_3$) da verificare
δ: 27.4(q), 54.8 (q), 59.9 (t), 67.8 (d), 113.9 (d), 118.0 (t), 119.2 (d), 120.7 (d), 124.1 (d), 126.9 (d), 127.6 (d), 128.8 (d), 129.4 (d), 131.8 (d), 170.5 (s).

MS: m/z 394 (M^+). Anal. calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found C, 70.07; H, 6.71; N, 7.01.