UNIVERSITÀ DEGLI STUDI DI MILANO

DOCTORATE SCHOOL IN CHEMICAL SCIENCES AND TECHNOLOGIES

DIPARTIMENTO DI SCIENZE FARMACEUTICHE

SEZIONE DI CHIMICA GENERALE E ORGANICA "A. MARCHESINI"

DOCTORATE COURSE IN PHARMACEUTICAL SCIENCES - CYCLE XXV

AREA 03 SCIENZE CHIMICHE SSD-CHIM/06

TRANSITION METALS CATALYZED REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC SYSTEMS

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ACADEMIC YEAR 2011/2012

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Chapter 1

Introduction

In the field of palladium chemistry and catalysis, a particular focus on intramolecular C-N bond formation systems is here elucidated as a suitable method for the synthesis of heterocycles.

1.1 Palladium in organic synthesis

1.1.1 Introduction

Palladium (Pd), the 46th element on the periodic table uncovered by Wollaston in 1803, is arguably the most versatile and ubiquitous metal in modern organic synthesis.[1,2]

Palladium-mediated processes have become essential tools, spanning countless applications in the syntheses of natural products, polymers, agrochemicals, and pharmaceuticals.

The wide utility of this transition metal is due to palladium scarcely toxicity and to the ability of its complexes to be effective under mild reaction conditions, to tolerate a variety of common functional groups and to participate in catalytic transformations yielding high chemo-, regio- and stereoselecivity processes. Moreover Pd reagents and catalysts are not very sensitive to oxygen and moisture, and even to acids in many reactions catalyzed by Pd–phosphine complexes.

Nearly every area of organic synthesis has been impacted by this versatile transition metal. Palladium can be used to conduct myriad of transformations with organic molecules.

In fact, there are a number of well-known named reactions that feature this metal, just for instance, the Heck,[3] Suzuki,[4] and Buchwald-Hartwig cross-couplings,[5] the Wacker process;[6] and the Tsuji-Trost allylation.[1,2]

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[1] (a) Muzart, J. *J. Mol. Catal. A: Chem.* **2007**, *276*, 62. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Muzart, J. *Tetrahedron* **2005**, *61*, 5955. (e) Muzart, J. *Tetrahedron* **2005**, *61*, 9423. (f) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (g) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (h) Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979. (i) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435. (j) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (k) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (l) Tsuji, J. *Synthesis* **1990**, 739 and references within this chapter.

[2] (a) Tsuji, J.; *Palladium Reagents and Catalysts: new perspectives for the 21st century*; Wiley & Sons: New York, **2003**. (b) Negishi, E. I.; *Handbook of organopalladium chemistry for organic synthesis*; Wiley & Sons: New York, **2002**. (c) Tsuji, J.; *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley and Sons: New York, **1995**. (d) Tsuji, J.; *Palladium in Organic Synthesis*; Ed.; Springer: Berlin, **2005**. (e) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, **2000**.

[3] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320. (c) Oestreich, M. *The Mizoroki-Heck Reaction*, Wiley and Sons: Chichester, U.K., **2009**.

[4] Miyaura, N.;. Suzuki A. *Chem. Rev.*, **1995**, *95*, 2457.

[5] (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.***2006**, *348*, 23. (b) Hartwig, J. F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

In addition, Pd also enables hydrogenation, hydrogenolysis, carbonylation, the formation of C–C, C–O, C–N, and C–S bonds, cycloisomerizations and even pericyclic reactions.[1,2] Domino catalysis, where multiple Pd-catalyzed transformations are carried out in a single operation, is also a powerful extension of this chemistry.[7]

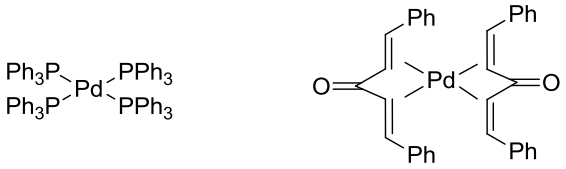
1.1.2 Palladium (0) and Palladium (II)

Oxidation states of Palladium

Although palladium can exist in a number of different oxidation states, useful organic methods are dominated by the use of Pd(0) and Pd(II),[1,2] and the utility of Pd(IV)[8] has been steadily emerging in its own right. The remaining oxidation states have not found practical applications yet and their observation remains rare. The increased stability of the even-numbered oxidation states (e.g., 0, +2, +4) can be rationalized by the low tendency of palladium to undergo one-electron or radical processes; conversely, it readily participates in two-electron oxidation or reduction.[2]

With its 10 electrons in the valence shell, palladium can form stable and isolable complexes both with 18 and 16 electrons. Catalytic species can even have 14 electrons (Figure 1)

Figure 1



$Pd(PPh_3)_4$ 18 e$^-$ $Pd(dba)_2$ 18 e$^-$

Palladium ability to undergo facile and reversible two-electron operations has contributed to its widespread use as a catalyst, since each oxidation state can yield different chemistry. Reactions such as cross-couplings and olefin hydrogenation are common to the Pd(0)

[6] Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.***2005**, *105*, 2329 and references therein.

[7] Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959.

[8] For examples of Pd(IV) transformations, see the following references and references therein: (a) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. (b) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (c) Daugulis, O.; Zaitsev, V. G.; Shabasov, D.; Pham, O.-N.; Lazareva, A. *Synlett* **2006**, 3382. (d) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148.

platform, while transformations such as alcohol oxidation and cycloisomerization can be achieved using Pd(II).

The bulk of the organopalladium literature is centered on the use of Pd(0) and Pd(II), although many reports do not clearly delineate the active catalyst (since Pd(II) precatalysts can be used to generate Pd(0) in situ).

Pd(0) can undergo either oxidation or oxidative addition, which affords a Pd(II) complex.

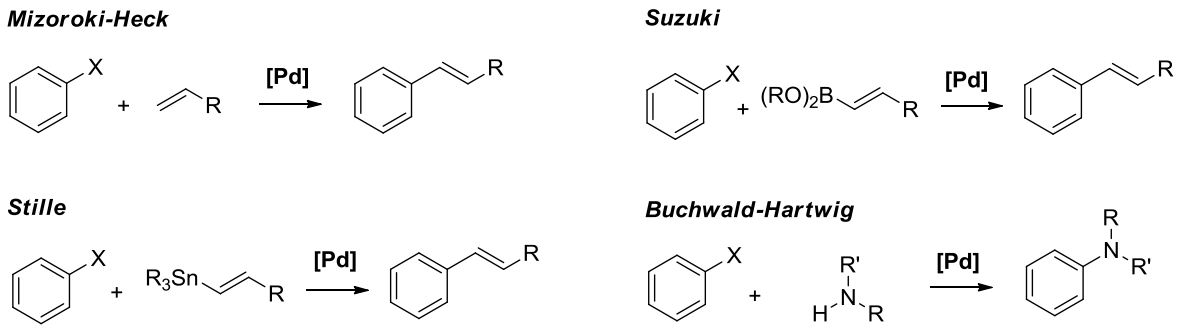
Pd(II) complexes can generate new Pd(II) complexes via processes such as β-hydride elimination, transmetallation, ligand substitution, insertion, or palladation. Finally, reductive elimination converts the Pd(II) complex back to Pd(0). This mechanistic understanding, combined with the ability of ligands and reaction parameters to modulate the reactivity of palladium, has allowed for a substantial amount of rational design in this field.

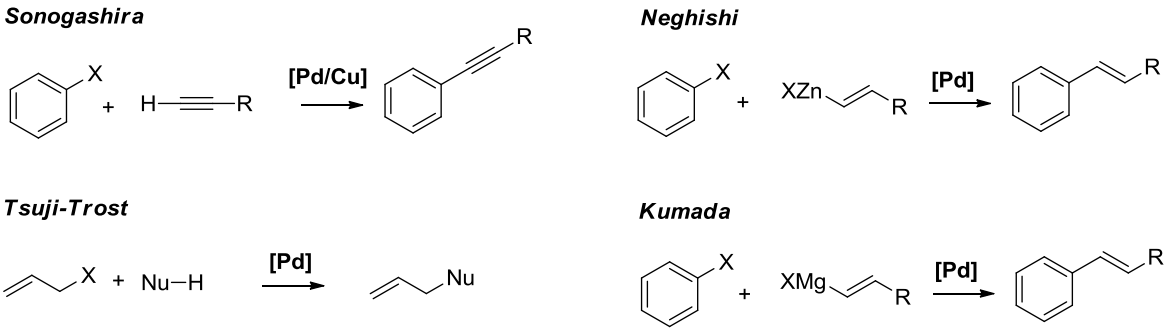
Pd (0) reactivity

Palladium(0) catalysis has been the focal point of palladium research over the past several decades, although the stabilization of the metal in this oxidation state is not easy to accomplish. A popular method of preparing Pd(0) complexes is *via* an in situ reduction of air stable Pd(II) species by reagents such as alkenes, CO, alcohols, amines, phosphines, or metal hydrides.

The principal Pd(0) catalyzed reactions are summarized in Figure 2.

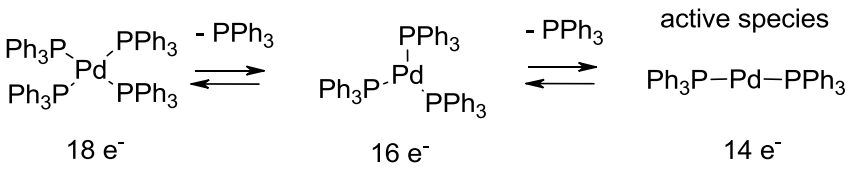
Figure 2





In all these reactions the formation of a C-C or C-heteroatom bond is promoted by a 14 electrons Pd(0) complex, which is easily oxidized to the Pd(II) state.

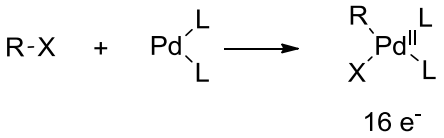
Figure 3



Most of the catalytic processes using Pd(0) generally begin with oxidative addition of palladium(0) to aryl and vinyl halides and triflates leading to a 16 electrons Pd(II) species characterized by a σ-carbon-palladium bond. (Figure 4)

In general, increasing the electron density on palladium promotes oxidative addition.

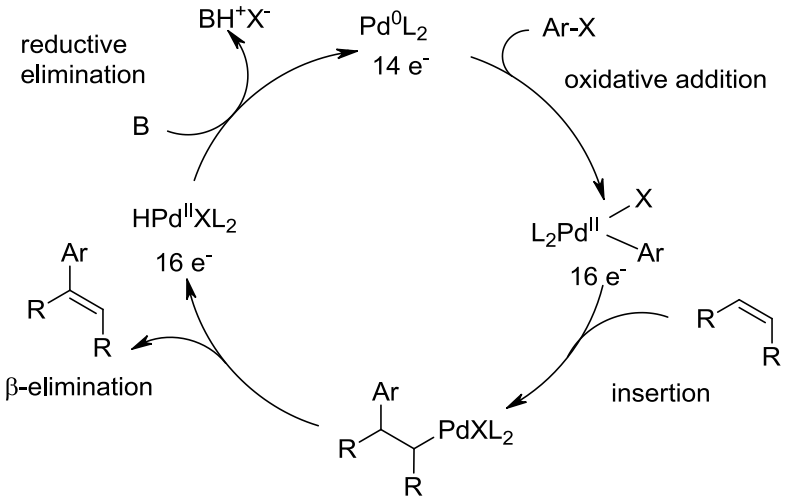
Figure 4



L= R_3P, RCN X= I, Br, Cl, OTf R= aryl, alkenyl, alkynyl, benzyl

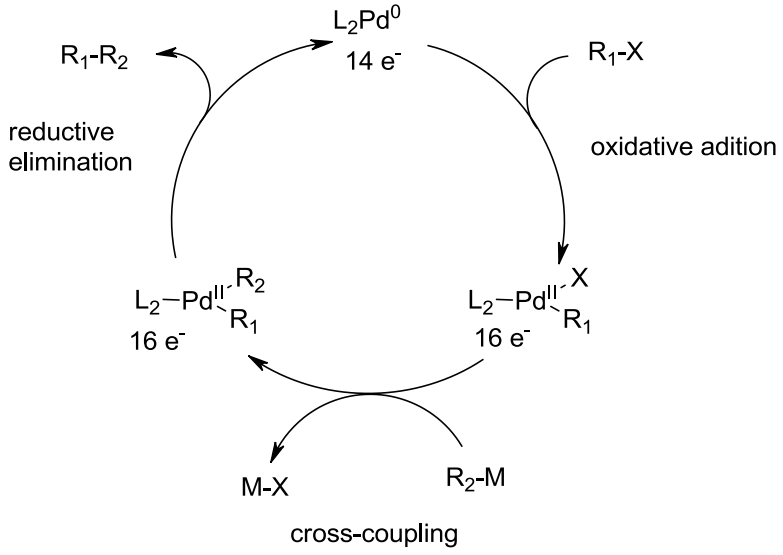
The Pd-complex thus formed can then evolve in different ways depending on the reaction conditions: for example in the presence of an olefin it can undergo coordination and insertion followed by *β-elimination* such as in the Heck reaction.(Scheme 1)

Scheme 1



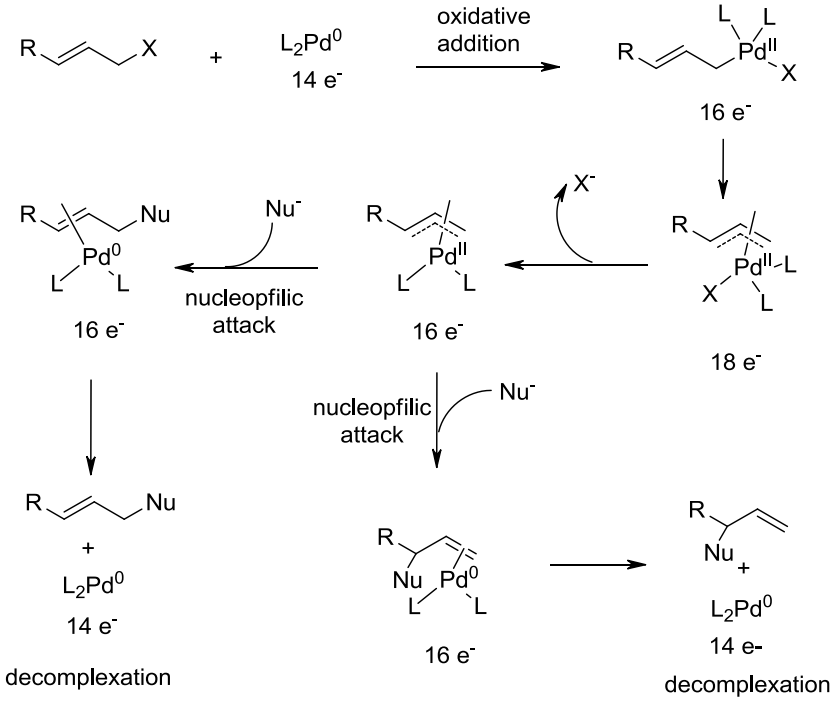
Another common reaction pathway is transmetallation followed by reductive elimination as in the cross coupling reactions.(Scheme 2)

Scheme 2



Another frequent mode of reactivity characteristic of Pd(0) involves the complexation of an olefin bearing an allylic leaving group, and the subsequent oxidative addition to generate a Pd(II) π-allyl complex (Scheme 3). Subsequent nucleophilic attack, which occurs predominately at the less-hindered carbon of the palladium π-allyl complex, affords the product and regenerates the Pd(0) catalyst.

Scheme 3



Pd (II) reactivity

Palladium(II) catalysis, in contrast to palladium(0), has received significantly less attention from the synthetic community in the past, although there has been a revitalized interest within the last several years.[9]

While Pd(0) complexes are good nucleophiles, Pd(II) complexes are typically electrophilic and air stable, and thus usually interact with electron-rich functionalities such as olefins,

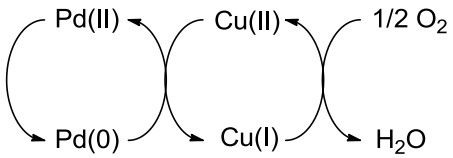
[9] (a) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem*. **2004**, *2*, 2551. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362. (c) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev*. **2004**, *104*, 3453.

alkynes, and arenes promoting the formation of new C-C, C-N and C-O bonds by C-H functionalization.[10]

However, one of the main complications that has been problematic in the development of Pd(II) methodology is the difficulty of reoxidizing Pd(0) to Pd(II). The completion of the catalytic cycle to regenerate Pd(II) requires the presence of a stoichiometric oxidant, such as $CuCl_2$, $Cu(OAc)_2$, benzoquinone, *tert*-butyl hydroperoxide (TBHP), MnO_2, HNO_3, and most recently O_2, found to be the most desirable for its environmental friendliness.[11] However, not unexpectedly, the addition of these oxidants to a reaction has often interfered with the catalyst/ligand system (or the substrates themselves), and has led to complications in maintaining chemo- or stereoselective processes.

To this aim, the catalytic use of copper salts in the presence of molecular oxygen is becoming of great success. (Figure 5) [12]

Figure 5



A typical reaction with electrophilic Pd(II) commences with the complexation of an olefin by Pd(II) (Scheme 4). An intermolecular or intramolecular nucleophilic attack on the resulting olefin complex can then occur, generally at the more substituted position of the olefin (Wacker-type mechanism). At last, the final product typically results from β-hydride elimination. The resultant palladium hydride, HPdX, then undergoes a reductive elimination–oxidation sequence to regenerate the active Pd(II) catalyst. Alternatively, a pathway involving direct attack of the $Pd(II)X_2$ complex by a nucleophile (e.g, an arene) is

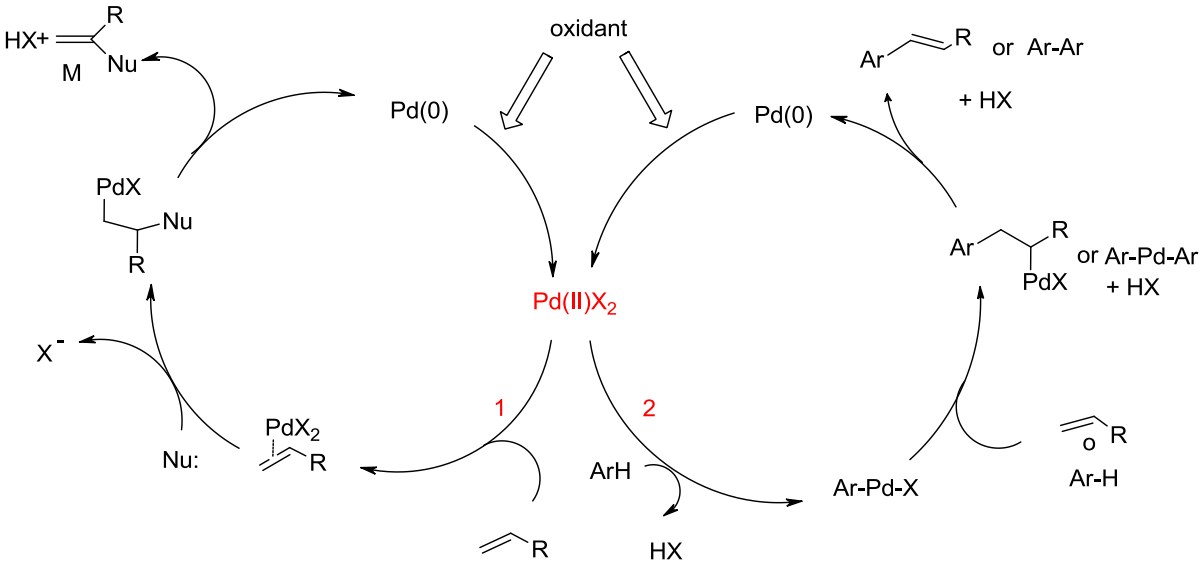
[10] (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (c) Jensen, T.; Fristrup, P. *Chem. Eur. J.* **2009**, *15*¸ 9632.

[11] (a) Stahl, S. S. *Angew. Chem., Int. Ed.*, **2004**, *43*, 3400. (b) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.*, **2006**, *45*, 6612. (c) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.*, **2008**, *47*, 3506. (d) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.*, **2009**, 3854.

[12] Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851.

also possible. Although different processes may be observed, β-hydride elimination and reductive elimination sequences are likely to be the final steps in the cycle prior to reoxidation of palladium.

Scheme 4



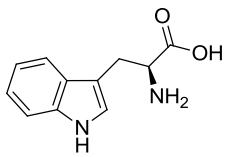
1.2 Palladium in Heterocycles synthesis

1.2.1 Nitrogen containing heterocycles

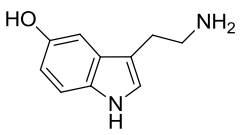
The synthesis of nitrogen-containing heterocycles continues to attract attention by synthetic chemists, as these structures are found in the cores of thousands of medicinally interesting natural and unnatural products, risulting useful in developing new therapeutics. The vast majority of these compounds are five or six-membered heterocycles with one or two oxygen or nitrogen atoms.

For example, the indole nucleus represents a basic motif with broad occurrence in biologically or synthetically relevant molecules endowed with pharmacological and agrochemical activities.[13]

Examples of indole containing molecules of biological interest are the aminoacid Tryptophan and the neurotransmitter Serotonin. More complex structures, as natural alkaloids usually presenting polyheterocyclic structures, contain the indole nucleus. Among them we can find the Yohimbine family of natural products, led by Reserpin[14] that is largely used for its sedative and ipotensive effects. Vincamine[15] is important for its anticancer activity, while the indole moiety can also be found in several psychedelic drugs derived from lysergic acid[16] and in neurotoxins derived from *Strychnos nux-vomica* such as Strychnine.[17]



TRYPTOPHAN



SEROTONIN

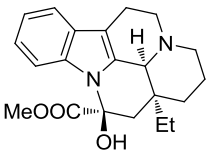
[13] (a) Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th edn., Thieme, New York, 2001; (b) Karapetyan, G.; Chakrabarty, K.; Hein, M.; Langer, P. *ChemMedChem* **2011**, *6*, 25; (c) Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630; (d) Gilchrist, T. L.; *J. Chem. Soc. Perkin Trans. 1*, **1999**, 2849.

[14] (a) Ooki, Y.; Kanedo, S.; Maeyama, K. *J. Pharmacol. Sci.*, **2008**, *106*, 197. (b) Gibbons, S.; Udo, E. E. *Phytother. Res.*, **2000**, *14*, 139.

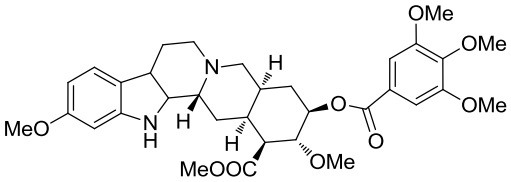
[15] Erdö, S. L.; Molnár, P.; Lakis, V.; Bence, J. Z.; Tömösköozi, Z. *Euro. J. Pharmacol.*, **1996**, *314*, 69.

[16] Fusar-Poli, P.; Borgwardt, S. *Neuropsychobiol.*, **2008**, *58*, 53

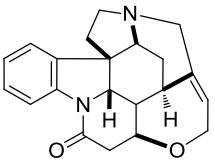
[17] Zona, S. *Economic Botany*, **2008**, *62*, 192.



VINCAMINE



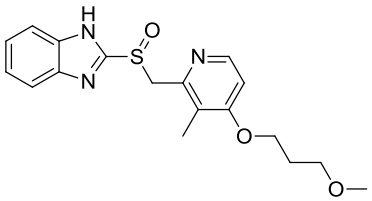
RESERPINE



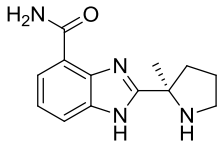
STRYCHNINE

For this reasons great efforts have been devoted to improve the preparation of indole derivatives employing innovative synthetic methodologies.[18]

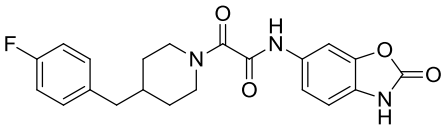
In the same way benzoimidazole- and benzoxazoles-based compounds can be found in several drug and natural compounds.



GASTRAZOLE



ABT-888



RADIPRODIL

Although they are not so widely distributed as indoles, there are examples of compounds containing these structures employed against Alzheimer and cancer, as reported in recent publications[19] and patents.[20]

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[18] (a) Gribble, G. W.; *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045; (b) Bandini, M.; Eichholzer, A. *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; (c) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449; (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 41.

[19] (a) McKee, M. L.; Kerwin, S. M. *Bioorg. Med. Chem.* **2008**, *16*, 1775 (anticancer); (b) Kusumi, T.; Ooi, T.; Walchli, M. R.; Kakisawa, H. *J. Am. Chem. Soc.* **1988**, *110*, 2954 (antibacterial); (c) Rodríguez-Rodríguez, C.; Sánchez de Groot, N.; Rimola, A.; Álvarez-Larena, A.; Lloveras, V.; Vidal-Gancedo, J.; Ventura, S.; Vendrell, J.; Sodupe, M.; González-Duarte, P. *J. Am. Chem. Soc.* **2009**, *131*, 1436. (d) Takahashi, M. ; Muta, S.; Nakazato, H. *Journal of Heterocyclic Chemistry* **1997**, *34*, 1395.

[20] (a) Sasmal, P. K.; Chintakunta, V. K.; Potluri, V.; Khanna, I. K.; Tehim, A.; Jaleel, M.; Hogberg, T.; Rist, O.; Elster, L.; Frimurer, T. M.; Gerlach,L.-O.; *PCT Int. Appl.* **2012**, WO 2012012410 A2 20120126. (b) Leblond, B.; Taverne, T.; Beausoleil, E.; Chauvignac, C.; Casagrande, A.-S.; Desire, L.; *PCT Int. Appl.* **2011**, WO 2011151423 A1 20111208.(c) Gage, A.; *PCT Int. Appl.* **2010**, WO 2010022300 A1 20100225. (d) Kuroita, T.; Oda, T.; Asano, Y.; Taya, N.; Iwanaga, K.; Tokuhara, H.; Fukase, Y.; *U.S. Pat. Appl. Publ.*

For example Gastrazole is used as a lead drug for treatment of pancreatic cancer,[21] 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide (ABT-888) is currently undergoing clinical trials on humans for treatment of a variety of cancer[22] and Radiprodil is an agent in treatment of neuropathic pain and other cronic pain conditions.[8c]

1.2.2 Intramolecular C-N bond formation

The easiest way to synthesize an heterocyclic system is through the intramolecular formation of a C-C or a C-heteroatom bond on suitable substrates.

Figure 6

Ring formation is most commonly achieved through intramolecular S_N2 reactions, halocyclizations, reductive aminations, cycloadditions, or ring closing alkene metathesis reactions.

Among the several methods to build such rings, transition-metal-promoted reactions have become one of the most versatile tool a chemist can dispose in his quest,[23] since a transition-metal catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions.

2009, US 20090227560 A1 20090910. (e) Hauel, N.; Himmelsbach, F.; Langkopf, E.; Eckhardt, M.; Maier, R.; Mark, M.; Tadayyon, M.; Kauffmann-Hefner, I.; *PCT Int. Appl.* **2004**, WO 2004050658 A1 20040617.

[21] Ormerod, D.; Willemsens, B.; Mermans, R.; Langens, J.; Winderickx, G.; Kalindjian, S. B.; Buck, I. M.; McDonald, I. M. *Org. Process Res. Dev.* **2005**, *9*, 499.

[22] Penning, T. D.; Zhu, G.-D.; Gandhi, V. B.; Gong, J.; Liu, X.; Shi, Y.; Klinghofer, V.; Johnson, E. F.; Donawho, C. K.; Frost, D. J.; Bontcheva-Diaz, V.; J. Bouska, J. J.; Osterling, D. J.; Olson, A. M.; Marsh, K. C.; Luo, Y.; Vincent L. Giranda, V. L. *J. Med. Chem.* **2009**, *52*, 514.

[23] (a) Nakamura, I.; Yamamoto,Y. *Chem. Rev.* **2004**, *104*, 2127; (b) Chemler, S. R.; Fuller, P.H. *Chem. Soc. Rev.* **2007**, *36*, 1153; (c) Shen, H.C. *Tetrahedron* **2008**, *64*, 3885; (d) Patil, N.T.; Yamamoto Y. *Chem. Rev.* **2008**, *108*, 3395; (e) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817; (f) Majumdar, K. C.; Chattopadhyay, B.; Maji, P. K.; Chattopadhyay, S. K.; Samanta, S. *Heterocycles* **2010**, *81*, 795.

The cyclization of alkenes, allenes, and alkynes bearing a pro-nucleophile heteroatom at an appropriate position of the carbon chain is therefore a useful methodology for the synthesis of four-, five-, six- or seven-membered heterocycles.

Moreover, the approach to C-N bond formation by late-transition-metal complexes is appealing as they often display good functional group compatibility and low air and moisture sensitivity, desirable features for potential synthetic applications.

In this concern, palladium has undoubtedly found a wide utility, since it is effective in mild conditions and tolerates a variety of common functional groups, thus avoiding protection group chemistry.[23e,f]

In the last years the general interest in Pd-catalyzed reactions has been shifted towards new and more challenging direct C-H functionalization studies on unactivated substrates. [24,25]

The non-functionalized carbon–carbon multiple bond systems can be recognized as latent functional groups, however, they are generally unreactive towards nucleophiles due to their electron rich π-orbitals. The development of alternative methodologies for the additions of nucleophiles towards such multiple bonds involving transition metal activation can be achieved by the complexation of the metal to the alkenes or alkynes, which makes the C–C multiple bonds susceptible towards the addition of different nucleophiles.

In particular the formation of new bonds resulting from the coupling of C-H/N-H bonds, with a nitrogen atom acting as nucleophile, is an attractive target, since the only formal by-product would be hydrogen or water in an oxidative system. Compared to conventional cross-coupling reactions of halogenated or metalated reagents, the direct coupling reactions of unactivated substrates through C-H bond cleavage have attracted significant attention as atom- and step-economical synthetic methods.

Thus the formal replacing of a C-H bond by a C-N bond through a Pd-catalyzed intramolecular processes is of great interest in the formation of a heterocyclic core.

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[24] (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285; (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318; (c) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910; (d) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142; (e) Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2009**, *15*, 5874; (f) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009; (g) Collet, F.; Dodd, R.H.; Dauban, P. *Chem. Commun.* **2009**, 5061; (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

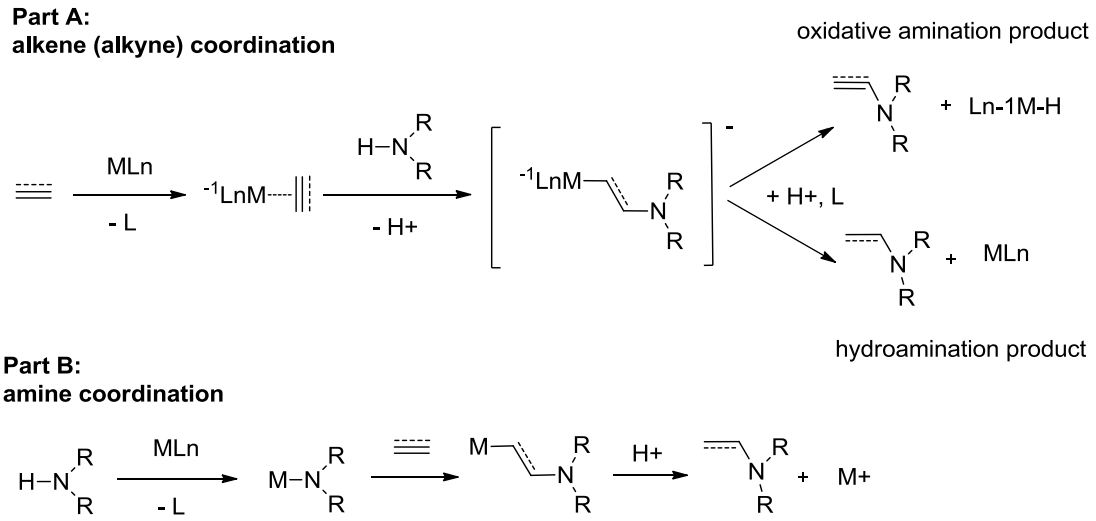
[25] Yamamoto, Y.; Radhakrishnan, U.; *Chem. Soc. Rev.*, **1999**, *28*, 199

Usually the addition of an amine to substituted alkene or alkynes lead to the β-addition when the unsaturated system is substituted with an electron-withdrawing group, following an anti-Markovnikov addition, while the reaction an aryl or alkyl substituted substrate gives Markovnikov type additions.

In the presence of a suitable metal, the electron rich unsaturated bond is activated to nucleophilic attack by an umpolung of reactivity due to the coordination of the metal. (Figure 7, part A). Then the sigma complex can either undergo a β–elimination, leading to the oxidative amination product, or reductive elimination resulting in the hydroamination process.

A different type of coordination involves the formation of hydride-amido complexes H-[M]-NR_2, olefin insertion and reductive elimination leading to the hydroamination product. (Figure 7, Part B)

Figure 7



In this vein, we decided to perform amination reactions such as hydroamination and carboamination of different substrates containing allenyl, alkynyl and alkene moieties tethered to a nitrogen atom, so as to end up with the formation of new two-heteroatom-containing cyclic systems.

Chapter 2

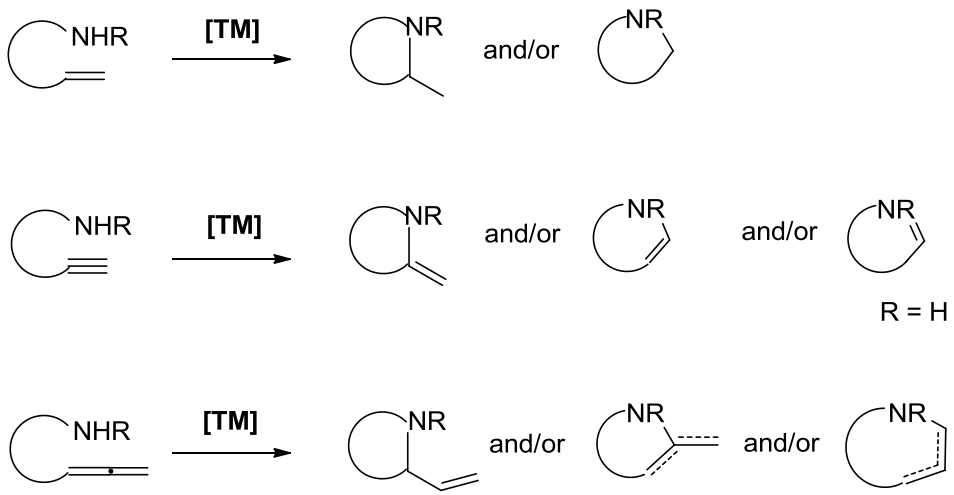
Hydroamination reactions

In this chapter palladium catalyzed hydroamination reactions are exploited on different unsaturated systems in order to obtain new polyheterocyclic systems through a C-N bond formation. One of the main feature of this reaction is its environmental friendliness since it proceeds following the atom economy principles.

2.1 Hydroamination reactions

Among the different synthetic methods to achieve nitrogen-containing heterocycles, hydroamination reactions have gained a relevant role since this formal addition of an NH group to a C-C multiple bond proceeds in an atom-economical manner.[26]
Unsaturated moieties (alkenes, alkynes and allenes) tethered to a nucleophilic atom are suitable substrates to obtain products arising from exo- or endocyclization depending on the length and rigidity of the linking alkyl chain through amination and hydroamination reactions. (Figure 1)

Figure 1



In particular using allenes the hydroamination can follow different regioselective pathways with the addition on position α, β or γ.

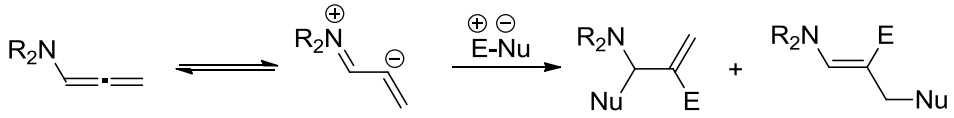
2.1.1 Hydroamination on allenes

Allenes are three-carbon functional group possessing a 1,2-diene moiety and they represent versatile precursors that can be utilized as a useful building block in a variety of synthetic transformations, leading to complex structures that are useful for constructing natural and

[26] Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.*, **2008**, *108*, 3795

unnatural products.[27] Subgroups of allenes are those substituted at the terminal carbon with a heteroatom such as oxygen, sulfur or nitrogen. Despite the synthetic potential of allenes, heteroatom-substituted allenes and in particular allenamines, have received relatively little attention.[27a]

Conceptually, allenamines should be synthetically useful because they are electron-rich and can be readily activated in the presence of an electrophile. More significantly, the nitrogen atom can donate its lone pair toward the allenic moiety to make transformations involving additions of electrophiles and nucleophiles with high regioselectivity, which is a general challenge with reactions involving allenes.



However allenamines are known to be sensitive to hydrolysis, polymerization and isomerization even at low temperatures, thereby creating serious difficulties in their preparation and handling.

Electron-deficient allenamines, such as allenamides, have the potential to function as an allenamine-equivalent. The electron-withdrawing group on the nitrogen atom should decrease its donating ability and lead to improved stability.

Moreover, since coordination of free amine to the metals is usually irreversible giving stabilized complexes which deactivate the aminopalladation catalytic effect, amines bearing electron-withdrawing groups are more suitable substrates for palladium-catalyzed reactions.

While among the different transition metals gold and silver were large applied on allene substrates, few examples of the Pd-catalyzed hydroamination processes onto allenes are reported in the literature remain.[28]

In particular only two works reported the Pd-catalyzed intramolecular reaction on allenes tethered to a pronucleophilic nitrogen.[28c,d]

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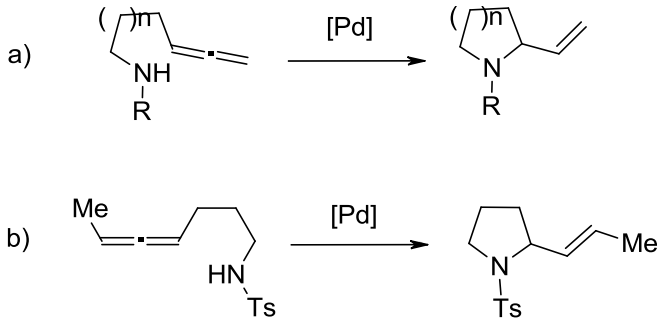
[27] (a) Saalfrank, R. W.; Lurz, C. J. *Heterosubstituierte Allene and Polyallene. In Methoden Der Organischen Chemie (Houben- Weyl)*, Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag, Stuttgart, **1993**, 3093-3102. (b) Schuster, H.E.; Coppola, G. M., *Allenes in Organic Synthesis*, John Wiley and Sons, New York, **1984**. (c) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*, Wiley-VCH: Weinheim, **2004**.

[28] (a) Besson, L.; Gorè, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857; (b) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett*. **1997**, *38*, 6071; (c) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421; (d) S. Qiu, Y. Wei, G. Liu *Chem. Eur. J.* **2009**, *15*, 2751.



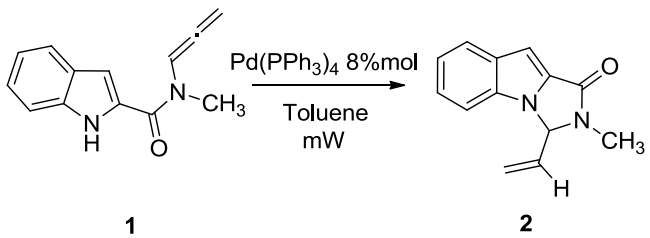
2.2 Pd-Catalyzed hydroamination on allenes under microwave irradiation

As a part of the study directed to the reactivity of indole derivatives, we decided to focus our attention on the reactivity of *N*-allenyl 2-indolecarboxamides. The interest of these substrates is due to the presence of the allenyl group linked to the indole moiety which nitrogen atom can act as nucleophile to give intramolecular cyclization.

Searching conditions to explore the protocols of cyclization, we investigated the behavior of the indolyl allenamide **1** under microwave irradiation.

Using $Pd(PPh_3)_4$ 8% mol as catalyst in toluene as the best solvent, a 5-*exo*-allylic hydroamination process took place, affording the vinyl derivative **2**.

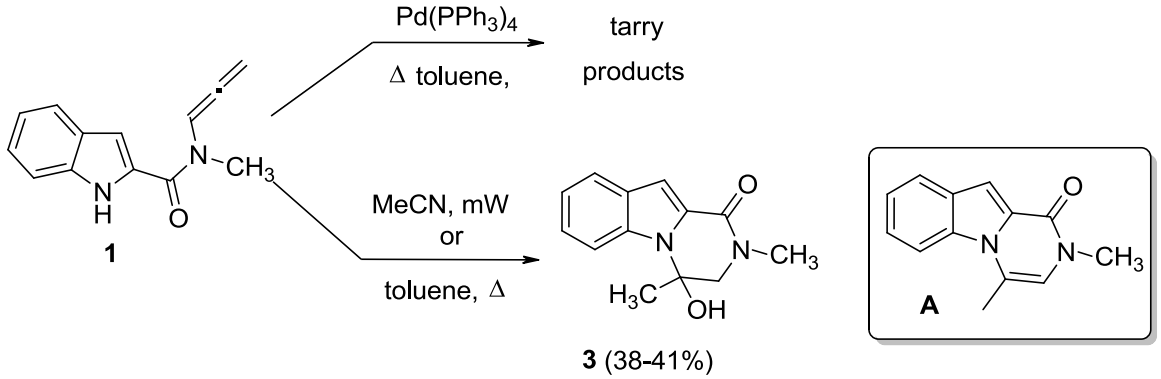
Scheme 1



To reach a better insight about the hydroamination process, we found that the presence of both palladium catalyst and microwave irradiation are necessary for the formation of **2**. In fact, working in the absence of microwave activation only a tarry mixture of degradation products was obtained. Conversely, the lack of the palladium catalyst afforded the

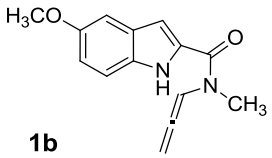
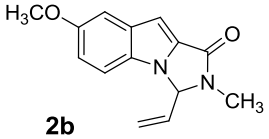
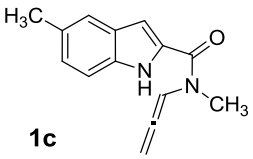
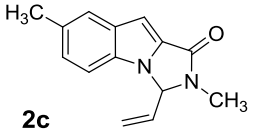
formation of the hydroxy-substituted pyrazino[1,2-*a*]indole **3** (41%). This latter arises from **A** by a formal addition of water and the use of microwave activation is not essential, being achievable in 38% yield also by conventional heating of a solution of **1** in toluene.

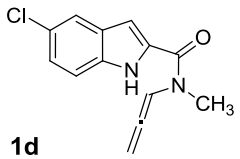
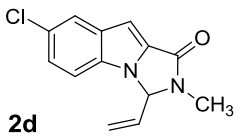
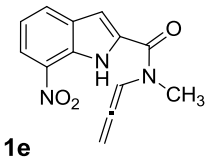
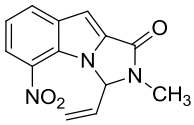
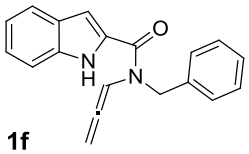
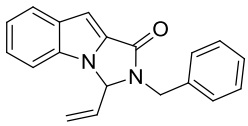
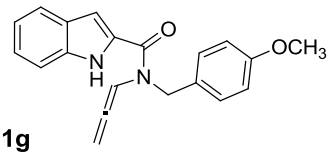
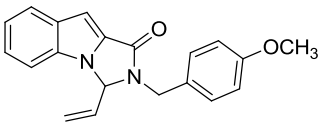
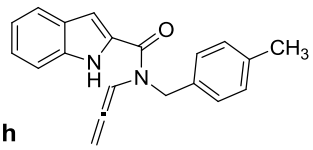
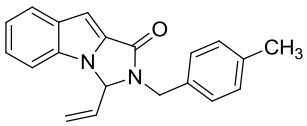
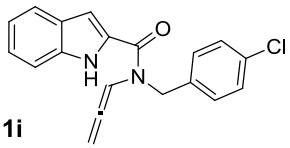
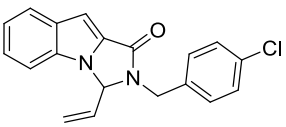
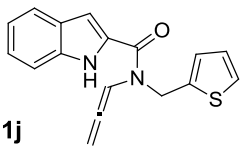
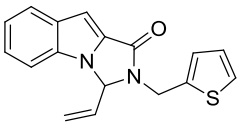
Scheme 2



A similar trend of reactivity was observed when the reaction was carried out on different indole allenamides variously substituted on the phenyl ring as well as on the amide nitrogen. Thus, the substrates **1b-j** afforded the imidazo [1,5-*a*]indoles **2b-j** bearing a useful vinyl group in position 2 that allows further functionalizations, in satisfactory to high yields (Table 1).

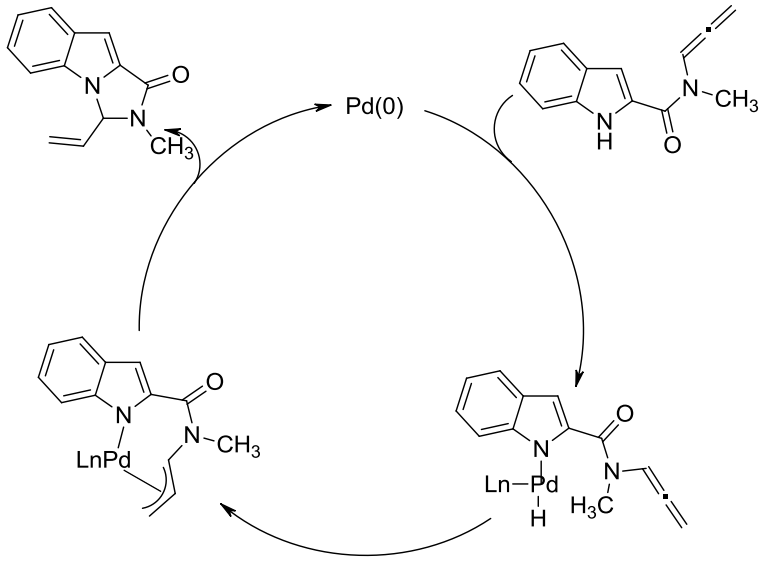
Table 1

	Substrate	Product	Yield (%)
1	 **1b**	 **2b**	67
2	 **1c**	 **2c**	78

3	 **1d**	 **2d**	85
4	 **1e**	 **2e**	58
5	 **1f**	 **2f**	63
6	 **1g**	 **2g**	89
7	 **1h**	 **2h**	69
8	 **1i**	 **2i**	85
9j	 **1j**	 **2j**	72

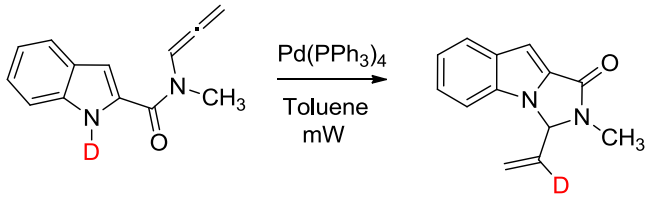
In view of its novelty, the observed hydroamination reaction of the allenamides **1a-j** deserves a mechanistic picture. Similarly to what was previously reported for different NH groups (i.e., amines, amides, and pyrrole), an initial coordination of the Pd(0) catalyst with the indole nitrogen can give the Pd(II)-hydride complex (Scheme 3). Such an intermediate would be susceptible to insertion of the allene group into the Pd-H bond to generate the π-allyl-Pd(II) complex, which in turn would undergo the intramolecular formation of the new carbon-nitrogen bond and the subsequent reductive elimination of a Pd(0) species.

Scheme 3



As a support for the proposed mechanism, we found that the deuterated hydroamination product **2k** was formed in the cyclization of the deuterium-substituted allene **1k**, prepared by treatment of a solution of **1a** in $CDCl_3$ with D_2O (Scheme 4).

Scheme 4

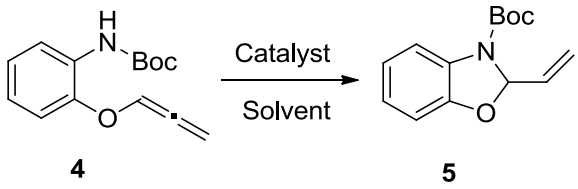


1k **2k** (68%)

We then decided to prove the new hydroamination protocol on other allenes bearing a nitrogen acting as nucleophile.

To this purpose the *O*-allenylether of the 2-aminophenol (**4**) was chosen as suitable substrate and several reaction conditions were screened starting with the best found on indole derivatives (Table 2, entry 1). By changing different parameters as solvent, catalyst and heating source the reaction was optimized finding that the use of $PdCl_2(CH_3CN)_2$ as catalyst in CH_3CN as solvent, under microwave activation, achieved the desired vinyl derivative **5** in high yield, providing a 5-*exo*-allylic hydroamination. (Table 2, entry 5)

Scheme 5



4 **5**

Table 2

	Catalyst	Additive	Solvent	T (°C)	Time	Yield (%)
1	$Pd(PPh_3)_4$ 8% mol	---	Toluene	120 °C (MW)	40’	20
2	$Pd(PPh_3)_4$ 8% mol	---	CH_3CN	120 °C (MW)	40’	30
3	$Pd(PPh_3)_4$ 8% mol	---	THF	120 °C (MW)	40’	50
4	$Pd(PPh_3)_4$ 8% mol	---	DMF	120 °C (MW)	40’	50
5	$PdCl_2(CH_3CN)_2$ 5% mol	---	CH_3CN	120 °C (MW)	40’	70
6	$Pd_2(dba)_3$ 5% mol	---	THF	120 °C (MW)	40’	0
7	$Pd(PPh_3)_4$ 15% mol	PPh_3 10%mol	Toluene	110°C	120’	68
8	$Pd(PPh_3)_4$ 15% mol	PPh_3 10%mol	Toluene	90°C (MW)	40’	60
9	$Pd(PPh_3)_4$ 8% mol	PPh_3 10%mol	Toluene	90°C (MW)	40’	62
10	$Pd(PPh_3)_4$ 5% mol	PPh_3 5%mol	Toluene	90°C (MW)	40’	30

Good results were obtained also under thermal heating, using 15% mol of $Pd(PPh_3)_4$ as catalyst in the presence of 10% mol of PPh_3. (Table 2, entry 7) However the use of the same catalytic system under microwave heating gave comparable results. Since a higher catalyst loading was employed, we decided to explore whether the catalytic system reactivity could be improved: by performing the reaction under microwave heating a lower catalyst loading was permitted (entry 9). It has to be pointed out that the presence of 10% of PPh_3 resulted to be crucial to obtain the product in good yield. (entry 1, 10 vs 9).

The approach to hydroamination by other late-transition-metal complexes is appealing and well established. Gold complexes, for example, have been employed as catalysts for a number of selective organic transformations and applied to good effect as catalysts for the

hydroamination of alkynes, alkenes, allenes, and conjugated dienes.[29] Though also examples of platinum[30] and nickel[31] catalyzed hydroamination reactions are reported in the literature, we decided to compare our catalytic system to different reaction conditions employing other transition metals that were found to be effective in the literature.

The results of this screening is reported in the table below and in particular the hydroamination product **5** was formed in slightly comparable yields by only a silver-gold couple and ruthenium (entry 1 and 5), while in the presence of nickel no product was formed at all.

Table 3

	Catalytic system	Solvent	T (°C)	Time (h)	Yield (%)
1	$AuCl_3$ 5% mol; Ag(OTf) 5% mol	Dioxane	50 °C	4	60
2	Ag(OTf) 5% mol	Dioxane	50 °C	4	25
3	$PtCl_2(CH_3CN)_2$ 5% mol; PPh_3 10% mol	Dioxane	80 °C	6	40
4	$Ni(acac)_2$ 10% mol BINAP 40% mol	THF	60 °C	6	0
5	$RuCl_3$ 1% mol; dppe 1% mol K_2CO_3 $CuCl_2$	CH_3CN	60 °C	2	62

However, since our catalytic system proved good reactivity and hydroamination reactions promoted by palladium catalyst are not widely explored, the scope of the reaction was then widened to a range of allenes synthesized starting from different 2-aminophenols (**4b-d**) and to 2-aminoaniline (**6**), along with *O*-allenyl-ethanolamine and *N*-allenyl-ethylendiamine derivatives (**7**, **8**). Using the best reaction conditions found: $PdCl_2(CH_3CN)_2$ 5%, THF, 120°C (MW) (Table 4, conditions I), good results were obtained with non aromatic systems. However when aminophenols and aminoaniline

[29] (a) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610. (b) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661. (c) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443; (d) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron Asymm.* **2001**, *12*, 2715. (e) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (f) Han, X.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1747. (g) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121; (h) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (i) Nishina, N.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3314.

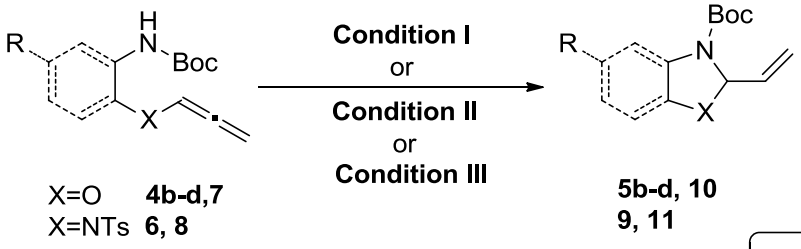
[30] Bender, C. F.; Widenhoefer, R. A.; *J. Am. Chem. Soc.* **2005**, *127*, 1070.

[31] Yoshida, Y.; Kurahashi, T.; Matsubara, S. *Chem. Lett*., **2011**, *40*, 1067-1068

derivatives were submitted to these reaction conditions a lower amount of the desired products were recovered and the formation of the dealkylated side products **B** was detected.

By using $Pd(PPh_3)_4$ in the presence of PPh_3 10% mol in toluene at 90 °C (MW or conventional heating) (conditions II and III) we found that better results were obtained on the substituted aryl derivatives **4b-d, 6**. Moreover the presence of additional PPh_3 was found to be crucial, probably acting as a stabilizing agent for the intermediate thus avoiding the dealkylation process (Scheme 6 and Table 4).

Scheme 6

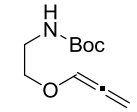
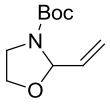
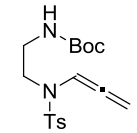
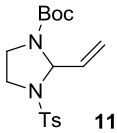
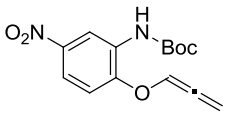
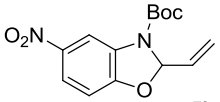


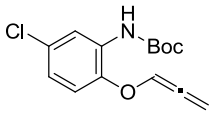
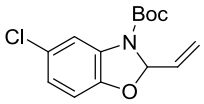
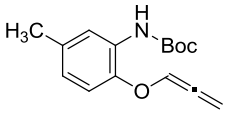
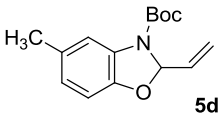
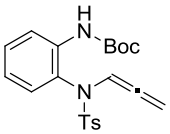
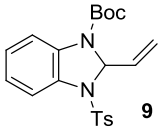
Condition I: $PdCl_2(CH_3CN)_2$ 5%mol, CH_3CN, 120 °C, MW

Condition II: $Pd(PPh_3)_4$ 8%mol, PPh_3 10%mol, toluene, 90 °C, MW

Condition III: $Pd(PPh_3)_4$ 15%mol, PPh_3 10%mol,toluene, 90 °C

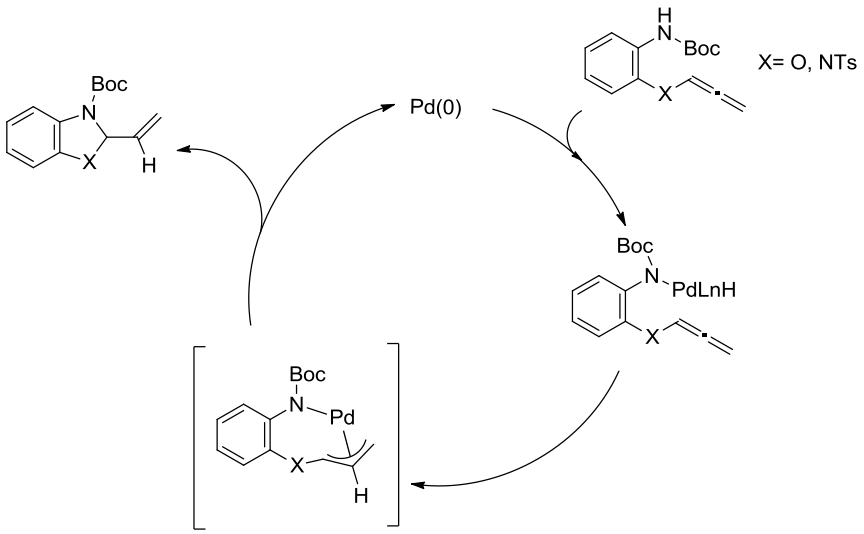
Table 4

	Substrate	Product	Condition I (%)	Condition II (%)	Condition III (%)
1	 **7**	 **10**	76	n.a.	n.a.
2	 **8**	 **11**	61	n.a.	n.a.
3	 **4b**	 **5b**	Traces	40	35

4	 **4c**	 **5c**	16	65	91
5	 **4d**	 **5d**	22	42	71
6	 **6**	 **9**	16	67	79

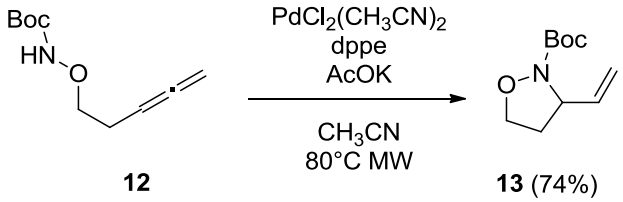
The mechanistic pathway is similar to the one described for the indolyl allenylamide derivatives. An initial coordination of the Pd(0) catalyst to the nitrogen atom can give the Pd(II)-hydride complex able to generate the π-allyl-Pd(II) complex. (Scheme 7) This species undergoes the nucleophilic attack of the nitrogen to the inner carbon of the allenyl system giving the formation of the new C-N bond with the concomitant reductive elimination of a Pd(0) species.

Scheme 7



At last, the hydroamination process was applied also to the hydroxylamine derivative **12** to confirm the effectiveness of the procedure and the vinyl isoxazolidine **13** was obtained in good yield. (Scheme 8)

Scheme 8



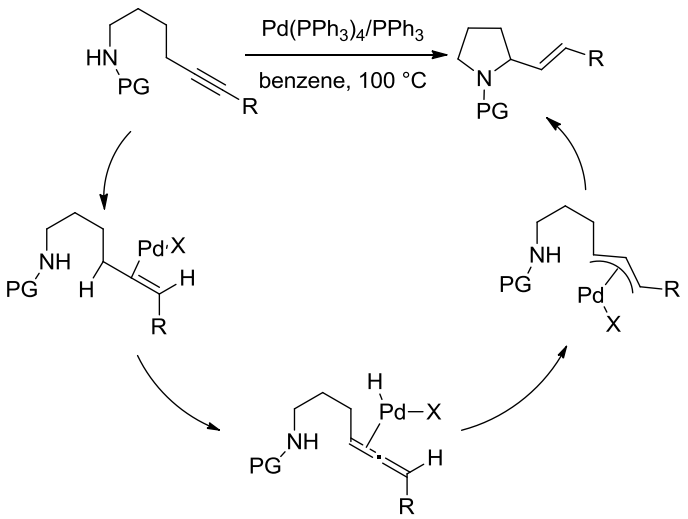
12 **13** (74%)

2.3 Palladium and Platinum catalyzed hydroamination on terminal alkynes

The hydroamination reaction of alkynes is another attractive route to reach N-containing compounds. The literature data reports different hydroamination reactions of alkynes by using transition-metal based catalytic systems to promote the hydroamination of carbon-carbon multiple bonds.
Since the allenyl moiety arises from the alkynyl group we decided to explore the reactivity of palladim catalysis towards these substrates.

Yamamoto reported the intramolecular hydroamination and hydroalkoxylation of alkynes in the presence of palladium/benzoic acid or palladium/PPh_3 catalysts, producing the five-membered heterocycles in good yields (Scheme 9).[32] The described mechanism involves a first Pd-mediated formation of the corresponding allene and a second hydropalladation leading to a π-allyl-palladium intermediate; the intramolecular nucleophilic attack of NH to the π-allyl-palladium complex and subsequent reductive elimination of Pd(0) forms the allylic substituted heterocyclic system.

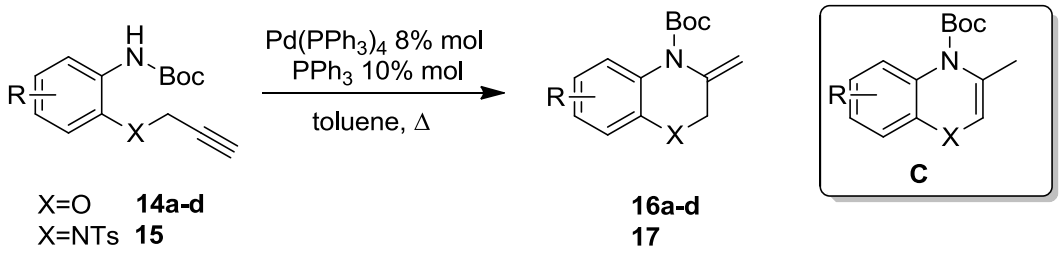
Scheme 9

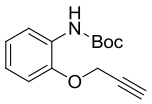
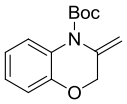
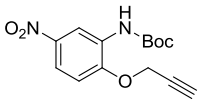
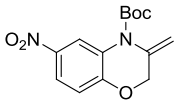
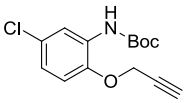
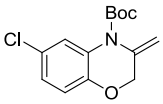
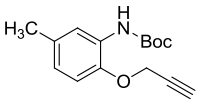
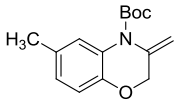
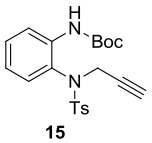
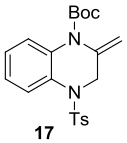


[32] (a) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570. (b) Lutete, L. M.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347. (c) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207.

However, when we tested the same reaction conditions on our substrates **14a-d, 15** the 3-methylene-dihydrobenzoxazines **16a-d** and 2-methylenedihydroquinoxaline **17** were obtained instead of the usual dihydrobenzoxazole (imidazole) ring system, then not confirming the hypothesis that the propargyl derivative reacts via allene intermediate. (Scheme 9)

Scheme 10



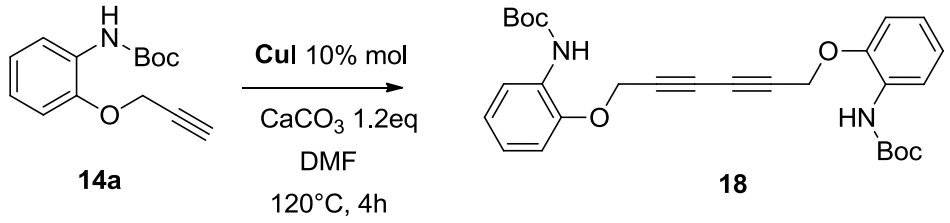
	Substrate	Product	Yields (%) [1]
1	 **14a**	 **16a**	95 (58)
2	 **14b**	 **16b**	82 (76)
3	 **14c**	 **16c**	87 (45)
4	 **14d**	 **16d**	88 (70)
5	 **15**	 **17**	90 (83)

[1.] Yields determined by ^{1}H-NMR on the crude reaction mixture; in parenthesis yields calculated after chromatography on silica gel column. In some cases the SiO_2 column resulted in a mixture with the isomerized product C, thus yield can be drastically lower.

In searching for new reaction conditions we tested the same propargyl precursor **14a** with different transition metals (gold, silver, ruthenium, rhodium) which resulted to be unreactive.

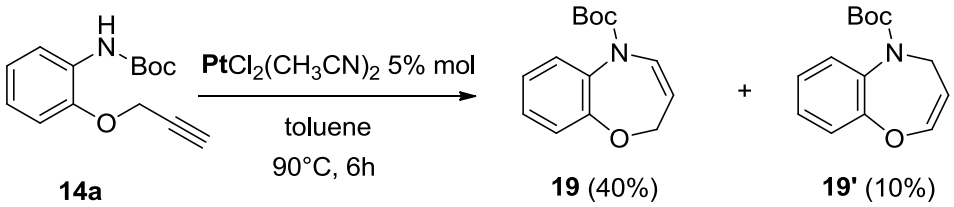
On the other hand, in the presence of a copper salt as CuI a Ulmann type reaction took place yielding to the alkynyl dimer **18**.

Scheme 11



Platinum[33] was found to be the only effective catalyst by leading to the formation of a new product. In fact by performing the reaction with 5% mol $PtCl_2(CH_3CN)_2$ in toluene as solvent a benzoxazepine ring system was obtained in two isomeric forms. (Scheme 11)

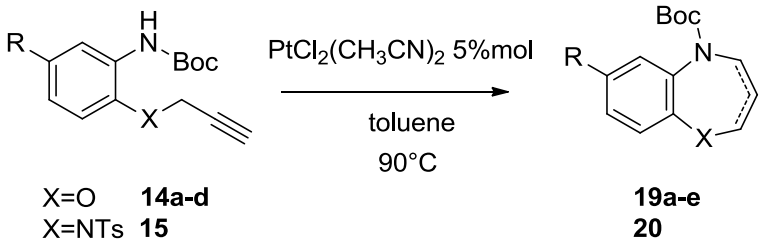
Scheme 12



The reaction was then performed on the other alkyne derivatives **14a-d** and **15** obtaining the seven membered cyclized products **19a-e** and **20** as a mixture of the two isomers in which the one carrying the double bond in α to the nitrogen always resulted to be the major product.

[33] (a) Jean-Jacques Brunet, J. J.; Chu, N. C.; Diallo, O.; Vincendeau, S.; *J. Mol. Cat.*, **2005**, *240*, 245; (b) Tsukano, C.; Yokouchi, S.; Girard, A.-L.; Kuribayashi, T.; Sakamoto, S.; Enomoto, T.; Takemoto, Y. *Org. Biomol. Chem.*, **2012**, *10*, 6074; (c) Gruit, M.; Pews-Davtyan, A.; Beller, M. *Org. Biomol. Chem.*, **2011**, *9*, 1148

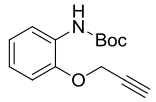
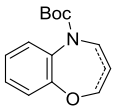
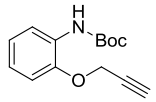
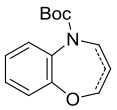
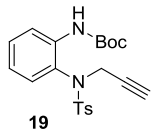
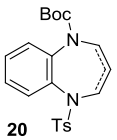
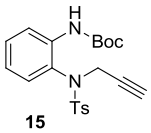
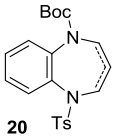
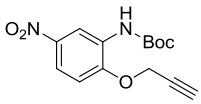
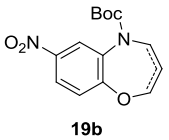
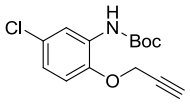
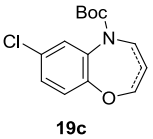
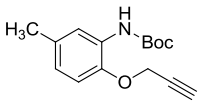
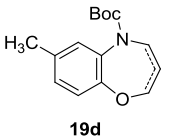
Scheme 13



X=O **14a-d**
X=NTs **15**

19a-e
20

Table 5

	Substrate	Catalytic system	Solvent	T(°C)	Time	Product	Yield (%)
1	 **14a**	$PtCl_2(CH_3CN)_2$ 5%mol	Toluene	90 °C	6 h	 **19a**	50
2	 **14a**	$PtCl_2(CH_3CN)_2$ 5%mol PPh_3 10% mol	Dioxane	90 °C	2 h 30	 **19a**	30
3	 **19**	$PtCl_2(CH_3CN)_2$ 5%mol	Toluene	90 °C	6 h	 **20**	0
4	 **15**	$PtCl_2(CH_3CN)_2$ 5%mol PPh_3 10%mol	Dioxane	90 °C	18 h	 **20**	0
5	 **14b**	$PtCl_2(CH_3CN)_2$ 5%mol	Toluene	90 °C	18 h	 **19b**	0
6	 **14c**	$PtCl_2(CH_3CN)_2$ 5%mol	Toluene	90 °C	24 h	 **19c**	20
7	 **14d**	$PtCl_2(CH_3CN)_2$ 5%mol	Toluene	90 °C	4 h	 **19d**	60

It can be noted that the presence of electron-withdrawing groups on the aryl system affects the reactivity of the catalytic system. Thus, while *p*-methyl substituted benzoxazepine

derivative **19d** is achieved in good yields, *p*-chloro-derivative **14c** resulted to be less reactive. The conversion is only partial although the longer reaction time.

At last *p*-nitro-aminophenol an *o*-aminoaniline derivatives **14b** and **15** were found completely unreactive.

Chapter 3

Domino processes

As a part of the study directed to the development of intramolecular palladium-catalyzed procedure in obtaining polyheterocyclic systems, this chapter is focused on the intramolecular palladium catalysed carboamination reactions on substrates containing an allenyl moiety.

3.1 Domino reactions

The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bond in the target molecule. However, it would be much more efficient if one could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents.[35] It is obvious that this type of reaction would allow the minimization of waste and thus making the waste management unnecessary. Compared to stepwise reactions the amount of solvents, reagents, adsorbents and energy would be dramatically decreased. Thus, these reactions would allow an ecologically and economically favorable production. We call this type of transformation a domino reaction.[36]

The usefulness of a domino reaction is correlated firstly to the number of bonds which are formed in one sequence, we call this the bond-forming efficiency (or bond-forming economy), secondly, the increase in structural complexity (structure economy) and, thirdly, to its suitability for a general application.

Domino processes such as carboaminations,[37] aminooxygenations[38] and aminohalogenations,[39] enabling easy access to (poly)functionalized acyclic and cyclic compounds as well as bicyclic ring systems, are particularly fascinating and useful in organic synthesis. As a consequence, the set-up of selective and tailored procedures based on new combinations of various kinds of bonds constitutes a challenge that justifies ongoing efforts in this field.

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[35] (a) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *105*, 137; *Angew.Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem.Ind.* **1995**, 453. Waldmann, H. "*Domino Reaction*" *in Organic Synthesis Highlight II*; Waldmann, H., Ed.; VCH: Weinheim, **1995**; pp 193-202. (c) Hall, N. *Science* **1994**, *266*, 32.

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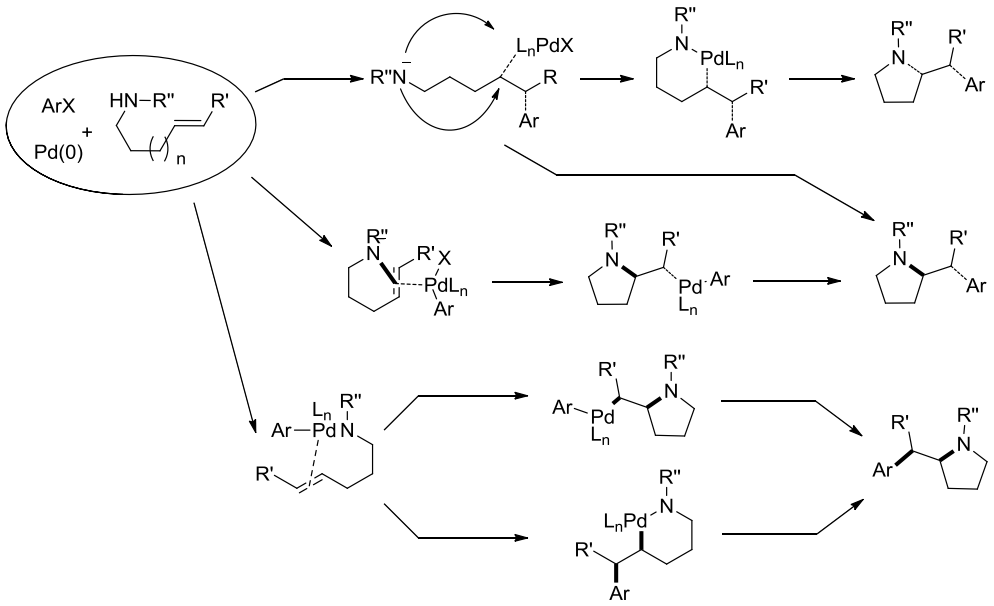
3.2 Pd-catalyzed carboamination

Among the plethora of Pd-catalyzed domino reactions, carboaminations are an efficient method for the synthesis of nitrogen heterocycles.[36a] In these reactions involving a multiple bond (alkenes, alkynes, allenes) bearing a nucleophilic substituent, a new C-N and a new C-C bond are formed.

Pd(0)-catalyzed carboaminations of alkenes tethered to a nucleophilic nitrogen have been recently reviewed.[36b,c] These protocols currently accept a mechanism starting with the intervention of an aryl halide to form a Pd(II) complex, which undergoes a nucleophilic attack of a nitrogen atom to give the cyclization products. The halide can be furnished by a different reactant or can be part of the substrate and a Pd(0) species is always released at the end of the cycle. (Figure 1).

Figure 1



Different outcome should be hypothesized widening the reaction to allene derivatives.

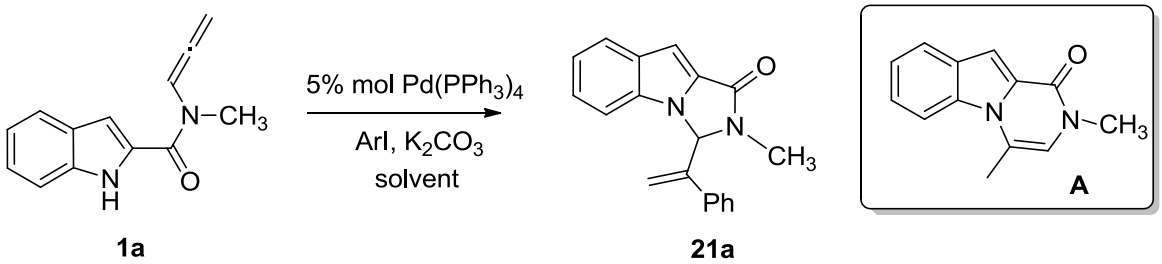
3.2.1 Carboamination of allenes tethered to a nitrogen nucleophile

Since we were interested to obtain indole-containing polyheterocyclic systems, we decided to perform carboamination reactions on the allenylamide of 2-indolecarboxylic acid.

Thus, exploiting the known reactivity of the π-allyl-palladium complex, easily generated by carbopalladation of the allene moiety, the reaction of substrate **1** with $Pd(PPh_3)_4$ in the presence of aryl iodide gave the cyclization product through an intramolecular nucleophilic attack of the indolyl nitrogen atom. In the present case, the second step of the domino process could have been accomplished by either the nitrogen atom or the C-3 of the indole ring, but the reaction proved to be regioselective to the first.

Under the best conditions typically used to promote this kind of reaction (1.5 equiv of PhI, 5 % mol of $Pd(PPh_3)_4$, 4.0 equiv of K_2CO_3 in DMF as solvent), the cyclization took place giving the α-styryl imidazo-[1,5-a]indole derivative **21a** (Scheme 1). However, the presence of the base gave also the pyrazino [1,2-*a*]indole side product **A**, afforded by the nucleophilic attack of the nitrogen atom to the central carbon of the 1,2-diene moiety.

Scheme 1



Other conditions were then tested to avoid the formation of this side product and to maximize the formation of the desired compound. Among the array of solvents explored to optimize the reaction (DMF, DMA, CH_3CN, dioxane), acetonitrile was proven as the most effective.

The scope of this reaction was then explored with different aryl iodides, thus providing the expected products **21 a-e**. (Scheme 2, Table1)

Scheme 2

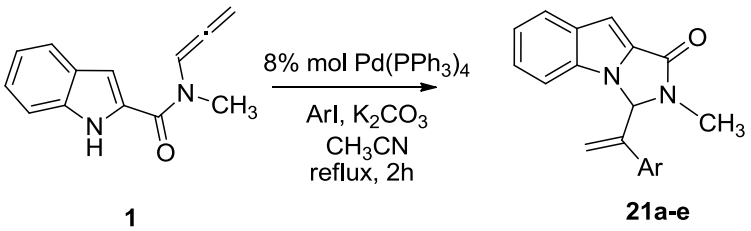
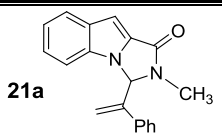
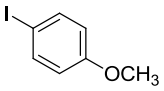
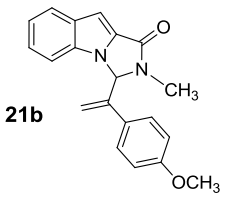
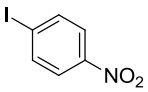
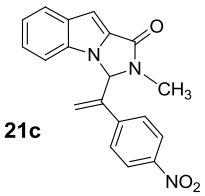
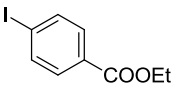
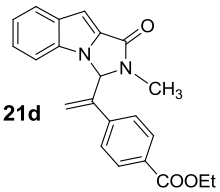
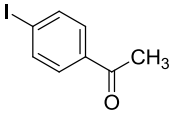
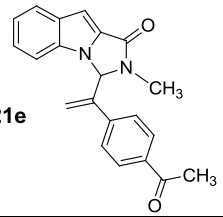


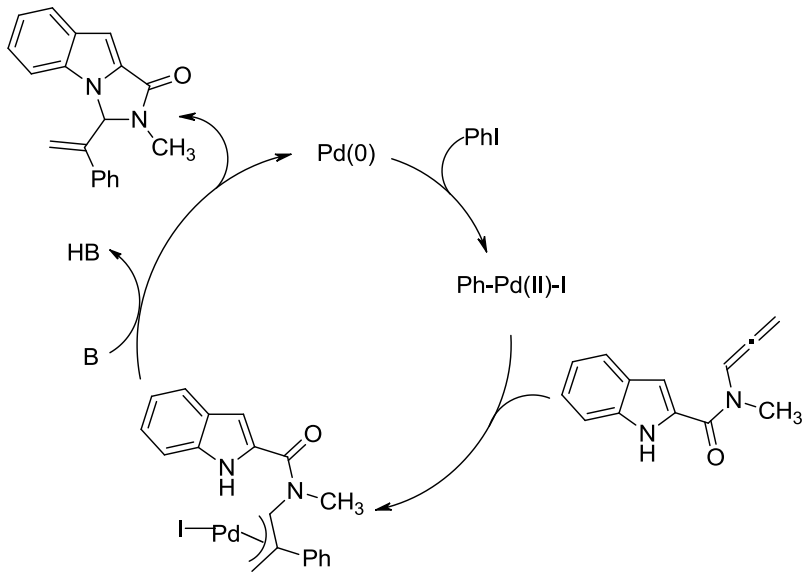
Table 1

	ArI	Products	%Yield
1		 **21a**	74
2		 **21b**	88
3		 **21c**	68
4		 **21d**	72
5		 **21e**	76

The influence of the electronic availability of the aryl iodide was limited and the expected products were afforded in good yields.

The formation of **21** constitutes an overall carbopalladation/5-exo-allylic amination process, which is doubly selective since the π-allyl-palladium complex is trapped exclusively on its internal carbon atom by the only indole nitrogen.

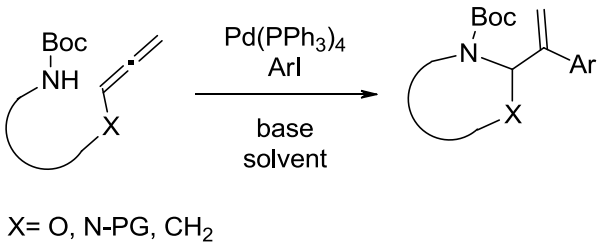
Scheme 3



The pathway proceeds with the formation of a PhPd(II)I complex by oxidative addition of Pd(0) species to the phenyl iodide, followed by carbopalladation of the allene moiety involving its central carbon, generating a π-allyl-palladium intermediate.
Subsequent nucleophilic attack of the indole nitrogen to the inner carbon of the allene and protonolysis of the carbon-metal bond would then yield the product and regenerate the catalyst. (Scheme 3)

With the aim to study these carboamination processes on different substrates obtaining heteropolycyclic systems, other allenes bearing a nitrogen able to act as nucleophile were treated with the conditions previously used on indole derivatives.

Scheme 4



Starting from commercially available *o*-amino-phenol and *o*-nitro-aniline, the formed allenyl derivatives **4a-d** and **6** were treated with aryl- or heteroaryl iodides in the presence of $Pd(PPh_3)_4$, K_2CO_3 as base and CH_3CN as solvent at reflux, to give the different substituted compounds **22a-l** and **23a-g** in good yields.(Table 2)

Scheme 5

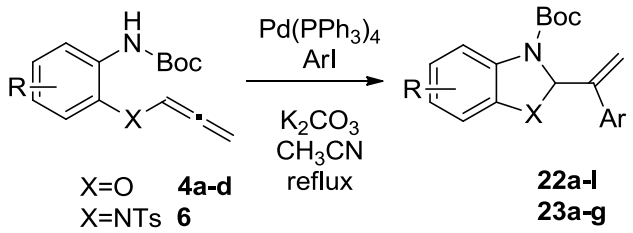
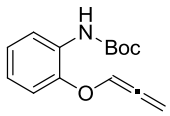
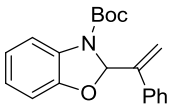
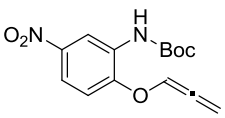
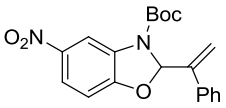
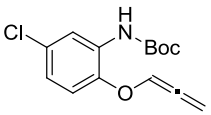
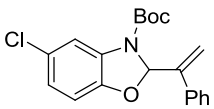
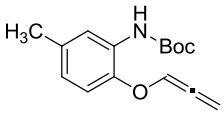
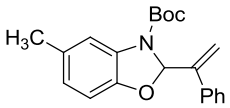
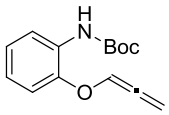
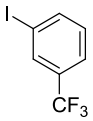
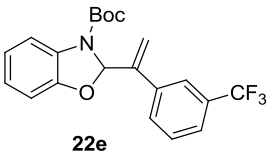
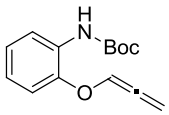
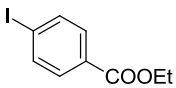
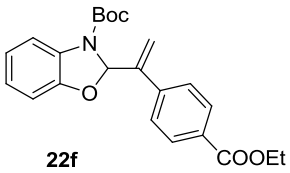
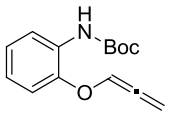
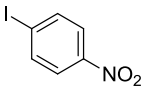
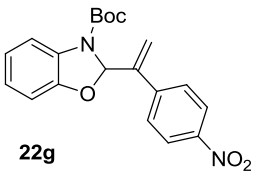
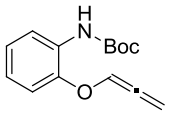
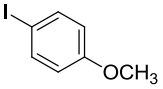
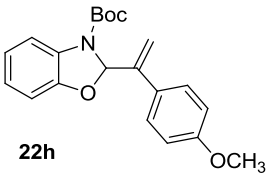
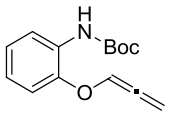
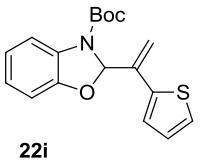
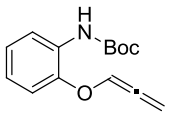
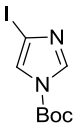
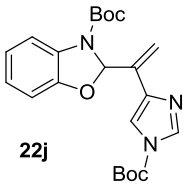
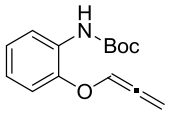
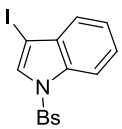
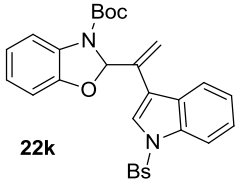
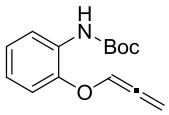
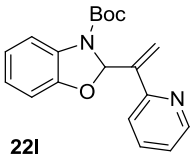
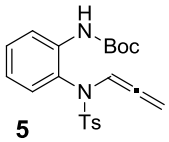
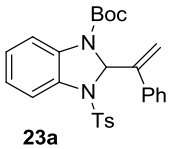
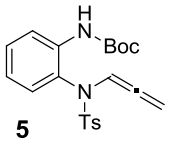
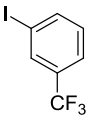
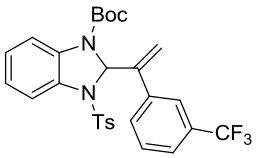
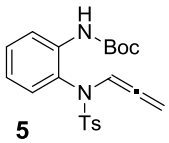
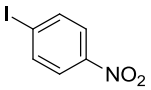
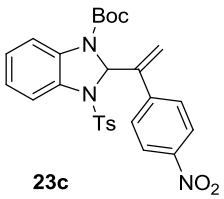
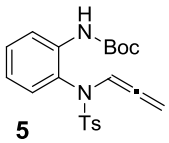
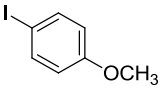
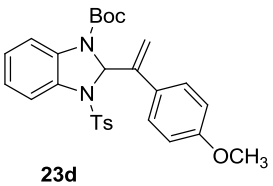
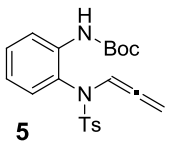
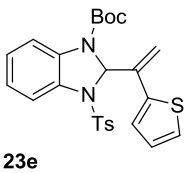
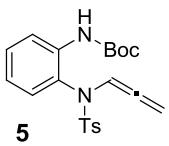
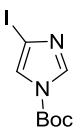
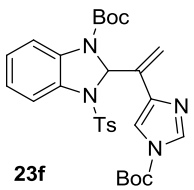
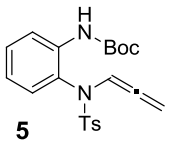
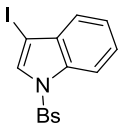
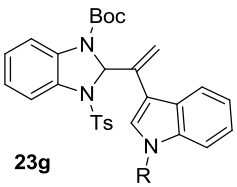


Table 2

	Substrate	ArI	Product	% Yield
1	 **4a**		 **22a**	70
2	 **4b**		 **22b**	62
3	 **4c**		 **22c**	54

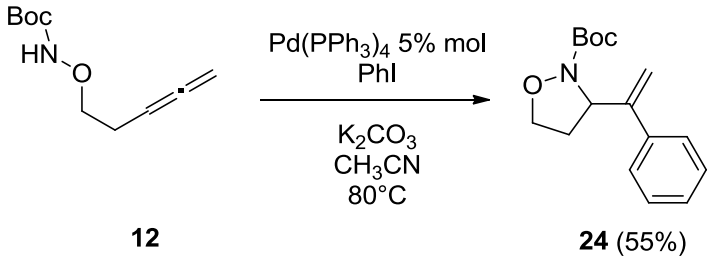
4	 **4d**		 **22d**	38
5	 **4a**		 **22e**	68
6	 **4a**		 **22f**	78
7	 **4a**		 **22g**	71
8	 **4a**		 **22h**	65
9	 **4a**		 **22i**	64
10	 **4a**		 **22j**	25
11	 **4a**		 **22k**	67

12	 **4a**		 **22l**	30
13	 **5**		 **23a**	86
14	 **5**		 **23b**	65
15	 **5**		 **23c**	86
16	 **5**		 **23d**	65
17	 **5**		 **23e**	36
18	 **5**		 **23f**	10
19	 **5**		 **23g**	7(NBs) 12(NH)

Once again, the reaction mechanism exploits the electrophilic reactivity of a π-allyl-palladium complex easily accessible by carbopalladation of the allene moiety. The second step of the domino process involves the nucleophilic addition of the nitrogen atom to the inner carbon of the π-allyl-Pd-complex to give the cyclized products, the 2-styryl dihydrobenzoxazoles **22a-l** and 2-styryl dihydrobenzoimidazoles **23a-g** in good yields.

At last the reaction was also performed on a terminal allene, tethered to an hydroxylamine moiety through an alkyl chain, in order to obtain a styryl substituted isoxazolidine. In this case the hydroxylamine nitrogen was meant to act as nucleophile, despite of its less electronic availability. The allene was submitted to the usual reaction conditions yielding the desired compound **24** in good yield. (Scheme 6)

Scheme 6



12 **24** (55%)

3.2.1 Carbonylative amination of allenes

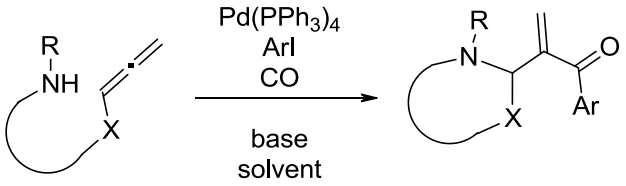
Despite the well-established palladium-catalyzed carbonylations and their applications on allene derivatives, this kind of carboamination reactions on allenes under carbonylative conditions are rarely reported in the literature.[40]

Only the Pd(II)-catalyzed cyclization of allenyl-amine derivatives by carbomethoxylation in the presence of carbon monoxide and methanol to form pyrrolidine or piperidine carboxylic esters is well known.

We thus decided to perform the domino heterocyclization of different allenes derivatives in the presence of carbon monoxide.

[40] (a) Kang, S.-K.; Kim, K-J. *Org. Lett.* **2001**, *3*, 511; (b) Beccalli, E. M.; Broggini, G.; Clerici, F.; Galli, S.; Kammerer, C.; Rigamonti, M.; Sottocornola, S. *Org. Lett.* **2009**, *11*, 1563.

Scheme 7



X= O, N-PG

By using the same catalyst, base, and solvent as in the carboamination reactions, the conversion of the indol-2-allenylamides **1** (Scheme 8, Table 3) and the allenes derived from 2-aminophenol (**4a**) and 2-aminoaniline (**6**) (Scheme 9) in the presence of different aryliodide under a CO atmosphere (1 atm) furnished the products **25a-d**, **26** and **27**, even if in modest yield due to the presence of degradation products.

Scheme 8

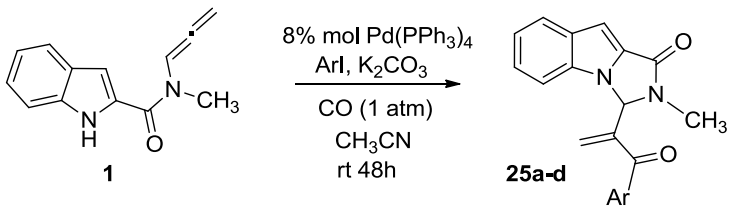
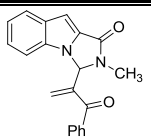
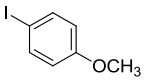
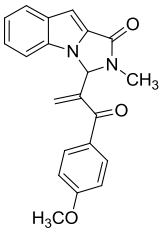
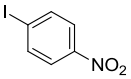
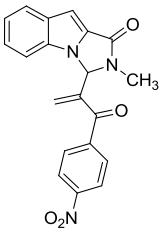
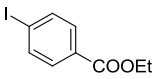
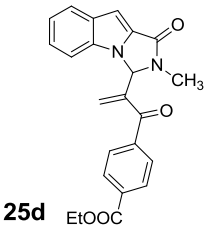
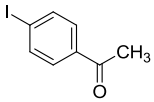
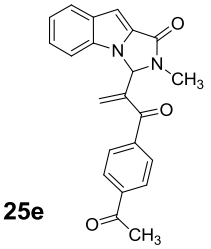
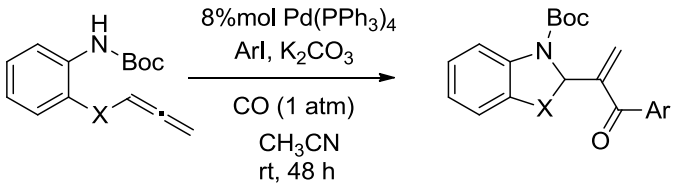


Table 3

	Ar	Product	% Yield
1		 **25a**	45
2		 **25b**	31
3		 **25c**	0

4		 **25d**	33
5		 **25e**	28

Scheme 9



This reaction gave the best results working at room temperature for a prolonged time; in fact, by refluxing the mixture for 24 h an increased amount of carboamination product was formed.

As the previous one, the mechanism of this reaction involves a π-allyl-palladium complex generated in this case by the interaction of a Ph-CO-Pd-I complex with the allene central carbon.

In particular, the first carbonylation of the PhPd(II)I species to give the PhCOPdI complex is followed by the addition of the latter to the central carbon of the 1,2-diene group to form the aroyl intermediate, which then undergoes the 5-exo-allylic cyclization to the desired compounds characterized by the new imidazole/oxazole ring system bearing an enone moiety.

3.3 Domino process on alkenes

At last our attention has been directed to the transformation of unsaturated hydrocarbons through the action of oxidative Pd(II)-catalyzed alkene functionalization in order to build carbon-carbon and carbon-heteroatom bonds.[41]

The classic pathway for this procedure typically requires the activation of the ethylenic bond induced by its coordination to the metal, which makes the bond susceptible to addition reactions, and the presence of a reoxidant agent in order to generate the suitable catalytic species.

Following the interest shown so far towards transition metal-catalyzed reactions as well as towards the synthesis of heterocyclic structures containing in particular the isoxazolidine nucleus, we decided to focus on development of domino procedures for the regioselective cyclization of hydroxylamine derivatives bearing an ethylenic moiety.

We considered the *N*-Boc *O*-but-3-enyl hydroxylamine (**28**) as a useful starting material for our studies.

As a preliminary approach, we envisioned as suitable catalytic system $PdCl_2$ (10% mol) and $CuCl_2$ (3 equiv.), typically effective in domino reactions that rely upon a first carbon-carbon or carbon-heteroatom bond forming reaction.

In agreement with this assumption, the use of this bimetallic couple in CH_3CN at room temperature allowed the conversion of the hydroxylamine **28** to the chloro derivative **29** arising from an amination/chlorination process (Scheme 10, Table 4, entry 1).

[41] a) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480–3501; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400–3420; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; c) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910–1923; d) T. Jensen, P. Fristrup, *Chem. Eur. J.* **2009**, *15*¸ 9632–9636; e) E. M. Beccalli, G. Broggini, A. Fasana, M. Rigamonti, *J. Organomet. Chem.* **2011**, 696, 277–295; f) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170–1214; g) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981–3019.

Scheme 10

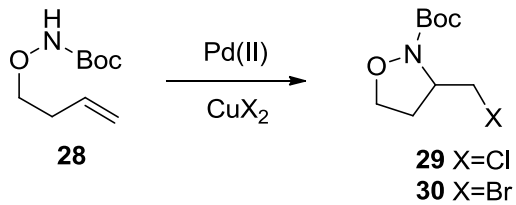


Table 4

	Catalytic system	Oxidant	Solvent	Temp	Time	Product (%yield)
1	$PdCl_2$ 10% mol	$CuCl_2$ 3eq	CH_3CN	RT	2h	**29** (30)
2	$PdCl_2(CH_3CN)_2$ 10% mol	$CuCl_2$ 3eq	THF	80°C	4h	#
3	$PdCl_2$ 10% mol	$CuCl_2$ 3eq	DMF	100°C	2h	#
4	$PdCl_2(CH_3CN)_2$ 10% mol dppp 20% mol	$CuCl_2$ 3eq	DCM	RT	1h	**29** (43)
5	$PdCl_2(CH_3CN)_2$ 10% mol	$CuCl_2$ 3eq	THF	RT	2h	**29** (48)
6	$PdCl_2(CH_3CN)_2$ 10% mol	$CuBr_2$ 3eq	THF	RT	5h	**30** (17)
7	$PdCl_2(CH_3CN)_2$ 10% mol	$CuBr_2$ 3 eq	DCM	RT	4h	**30** (43)

By increasing the temperature, only degradation products were recovered, demonstrating the instability of the starting material to harsh conditions (entries 2 and 3). Better results were obtained when $PdCl_2(CH_3CN)_2$ was used as catalyst in THF as solvent at room temperature (entry 5), while the use of 1,3-bis(diphenylphosphino)propane (dppp) as ligand did not produce great changes in the reaction outcomes. (entry 4)

Finally the replacement of $CuCl_2$ with $CuBr_2$, afforded the bromo derivative **30** (entries 6 and 7).

Conversely, we found that the use of DMF as solvent triggers a competitive reaction pathway giving the formic ester **31**, beside the chloro derivative **29**. (Scheme 11)

Scheme 11

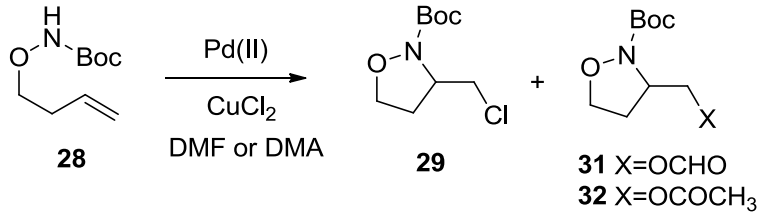


Table 5

	Catalytic system	Oxidant	Solvent	Temp	Time	29 yield%	Ester (%yield)
1	$PdCl_2$ 10% mol	$CuCl_2$ 3eq	DMF	RT	7h	20	**31**(22)
2	$PdCl_2(CH_3CN)_2$ 10% mol	$CuCl_2$ 3eq	DMF	RT	4h	31	**31**(35)
3	$PdCl_2$ 10% mol	$Cu(OAc)_2$ 3eq	DMF	RT	3h	#	#
4	$PdCl_2$ 10% mol	$CuCl_2$ 3eq	DMA	RT	18h	15	**32**(20)

This unusual domino pathway is based on an oxidative Pd(II)-catalyzed amination/esterification sequence that involves the DMF solvent.

As a confirm to this unusual pathway the reaction was carried out in DMA as solvent, achieving the acetate derivative **32** (entry 4), along with the formation of the chloro derivative **29**.

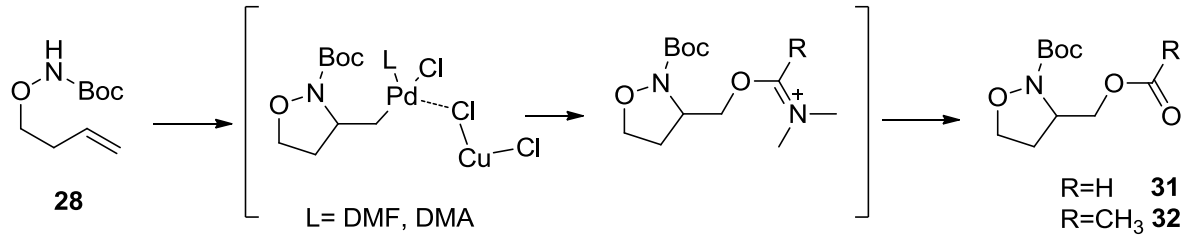
The mechanistic aspects of the above reactions can be elucidated as follow.

The formation of the chloroamination product arises from a domino process in which $CuCl_2$ donates a chlorine to the reaction intermediate. This behavior is supported by precedents in literature,[42] however, the formation of compounds **31** and **32** is quite unexpected. Only a recent example on indolyl allylamines can be found in the literature.[43] This new domino amination/esterification reaction clearly involves the amidic solvent in determining the final structure. The mechanism may involve at first the formation of a σ-alkylpalladium complex that can be stabilized by the intervention of $CuCl_2$, inhibiting palladium β-hydride elimination. (Scheme 12).

[42] (a) Jiang, H.; Ma, S.; Zhu, G.; Lu, X. *Tetrahedron* **1996**, *52*, 10945;(b) Ji, J.; Lu, X. *Synlett*, **1993**,745

[43]Broggini, G; Barbera, V.; Beccalli, E. M.; Borsini, E.; Galli, S.; Lanza, G.; Zecchi, G. *Adv. Synth. Catal.* **2012**, *354*, 159

Scheme 12



Reductive metal elimination may result in the iminium intermediate, susceptible of hydrolysis to the final product **31** or **32**.

However, we cannot exclude that the iminium species arises from a direct nucleophilic attack by the solvent oxygen on the exocyclic carbon of the σ-palladium complex.

Chapter 4

Studies towards the C1-C11 fragment of Stambomycin A

The following chapter is about the project I developed under the supervision of Dr. Edward A. Anderson during the six months term I spent at the University of Oxford.
The project was directed to the design and synthesis of a fragment of Stambomycin A, a 51 member macrolide isolated form Streptomices Ambofaciens.

4.1 Introduction

Natural products have always played a crucial role in the discovery of new and improved drugs with a broad spectrum of applications in medicine and agriculture.[1]

For this reason the recent development of genomics-guided approaches for novel natural product discovery has stimulated renewed interest in the search for natural product-based drugs.

In the past decade, numerous secondary metabolites and their biosynthetic pathways has been uncovered thanks to this new technique and several strategies have been developed to identify the metabolic products of cryptic biosynthetic pathways.[2] However, a relevant number of gene clusters appear to be expressed poorly, or even silent under laboratory growth conditions and a lot of them are not yet associated with the production of known metabolites,[3] suggesting that the reservoir of bioactive natural products is far from exhausted.

In these scenario *Streptomices ambofaciens* has revealed to be of high interest.

Recent bioinformatic analysis of *S. ambofaciens* genome led to the identification of the biosynthetic gene clusters of two well known antibiotics: the macrolide spiramycin, an antibacterial agent used for the treatment of toxoplasmosis; and the pyrrole-amide congocidine.[4] However, these analyses also revealed numerous cryptic putative secondary metabolite biosynthetic gene clusters. The metabolic products of three of these gene clusters have been identified as known antibiotics, none of which had been previously reported as product of *S. ambofaciens*,[5] but other cryptic biosynthetic gene clusters remained unknown.

In a recent work,[6] Challis and coworkers achieved the identification of a family of four polyketides, named **Stambomycins A–D**, that are metabolic products of a large cryptic type I modular polyketide synthase (PKS) gene cluster located in the right arm of the S. ambofaciens chromosome.

---

[1] a) Bérdy J *J Antibiot* **2005**, *58*, 1–26. b) Newman, D. J.; Cragg, G. M.; *J. Nat. Prod.* **2007**, *70*, 461–477

[2] Zerikly, M; Challis G. L. *ChemBioChem* **2009**, *10*, 625–633

[3] Challis G. L. *Microbiology* **2008**, *154*, 1555–1569.

[4] a) Pinnert-Sindico S. *Ann Inst Pasteur* **1954**, *87*, 702–707; b) Juguet M, et al. *Chem Biol* **2009**, *16*, 421–431; c) Karray F, et al. *Microbiology* **2007**, *153*, 4111–4122.

[5] a) Barona-Gómez F, et al. *Microbiology* **2006**, *152*, 3355–3366; b) Pang X, et al. *Antimicrob Agents Chemother* **2004**, *48*, :575–588; c) Bunet R, et al. *J Bacteriol* **2011**, *193*, 1142–1153.

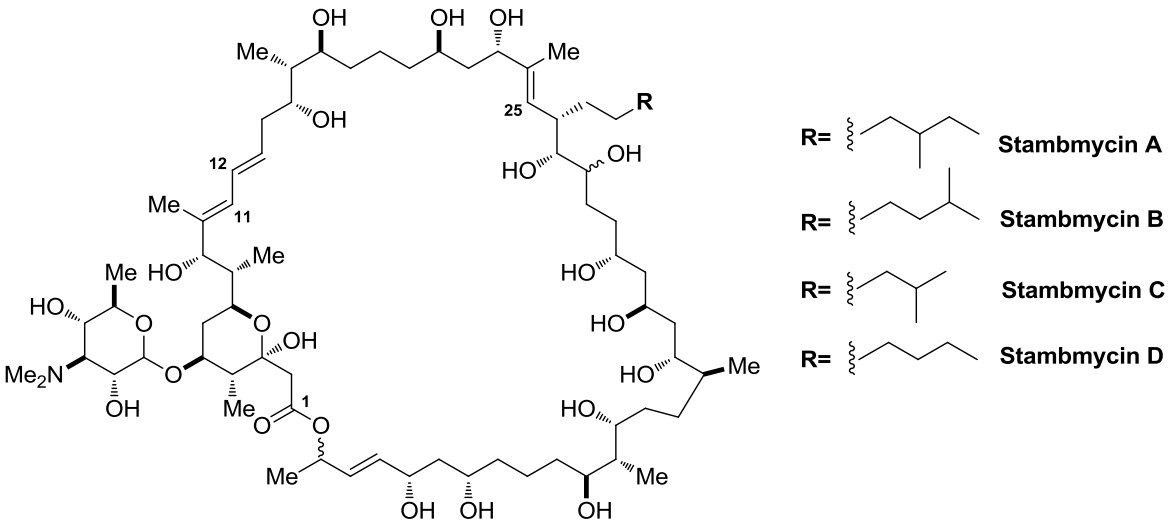
[6] Laureti,L; Song, L.; Huang, S.; Corre, C.; Leblond, P.; Challis, G. L.; Aiglea, B.,*Pnas* **2011**, *108*, 6258-6263

Polyketides are of particular interest because they encompass several different chemical classes, including macrolides, polyenes, aromatics, and polyethers, which have found therapeutic applications as antibiotics, antitumor agents, immunosuppressants, and cholesterol-lowering drugs.[7]

4.1.1 Stambomycins identification

The Stambomycins constitute a unique family of 51-membered glycosylated macrolides with promising antiproliferative activity against human cell lines. Constitutive expression of a gene within the cryptic gene cluster encoding a putative pathway specific activator triggered the expression of the PKS genes (which are not expressed under laboratory growth conditions), providing the key to the identification of the Stambomycins.

Figure 1. *The Stambomycins family*



At first the structure of the fully assembled polyketide chain has been predicted as still attached to the Acyl Carrier Protein (ACP) domain in the last module of the PKS by sequence analyses of the biosynthetic enzymes, suggesting that the assembly of these remarkable macrolides involves unprecedented biosynthetic chemistry. However the structure of the side chain at C-26 could not be predicted in this manner.

[7] Hertweck C. *Angew Chem Int Ed* **2009**, *48*, 4688–4716

In Figure 2, the thus predicted polyketide chain is presented and atoms are colored according to the precursors from which they derive: malonyl-CoA (blue); methylmalonyl-CoA (red).

Figure 2. *Predicted polyketide chain attached to the ACP domain*

Subsequent NMR experiments showed that stambomycins A and B consist of a common 51- membered glycoslated macrolide core containing a tetrahydropyran resulting from the addition of the C-7 hydroxyl group to the C-3 keto group.

Several structural features of the stambomycins were not predictable from sequence analyses of the biosynthetic enzymes, including the nature of the C-26 side chain, which is proposed to be a 4-methyl-n-hexyl derivative, and the sites of g1ycosylation, hydroxylation, and macrocycle formation.

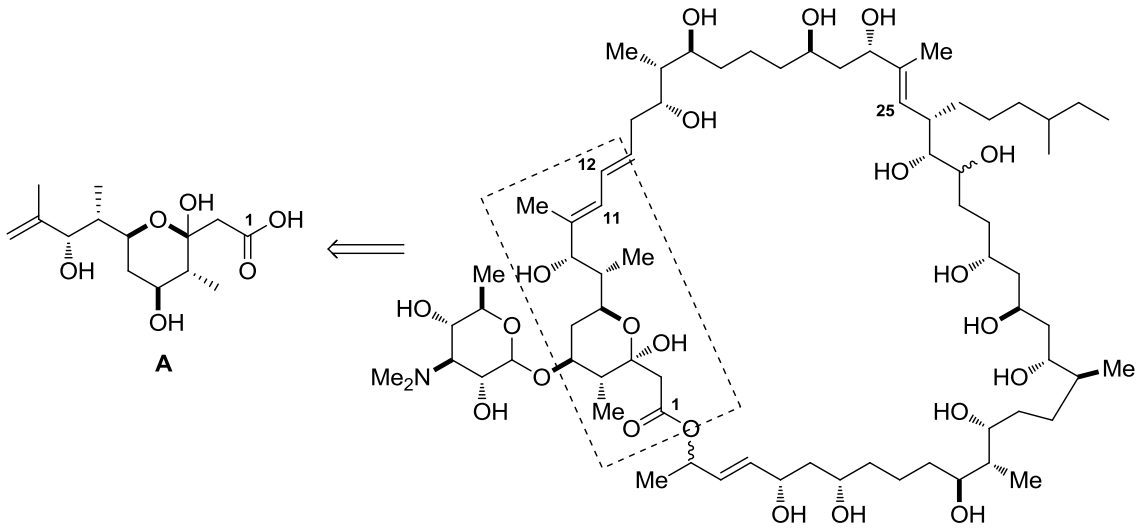
4.1.2 Aim of the work

Among this class of compounds uncovered through genome mining we focused our attention to Stambomycin A (Figure 3)

As largely commented before, its structure has been determined through NMR analysis. However its stereochemistry has been only partly assigned and the majority of the stereocentres contained within this intriguing molecule have been predicted solely through biosynthetic considerations, remaining to be confirmed.

With the aim to begin the stereochemical confirmation by the independent chemical synthesis of fragments of stambomycin which might be accessed through chemical degradation (such as exhaustive cross-metathesis), we focused our attention on C1–C11 fragment **A**.

Figure 3. *C1-C11 fragment of Stambomycin A*



In so doing, the project would deliver a validation of the largest-scale structural prediction of its kind and would revolutionize structural determination chemistry in the polyketide field. Furthermore, synthetic lessons learned en route to stambomycin could lay the basis for a total synthesis of the natural product, other family members, and/or unnatural analogues.

4.2 Retrosynthetic approach to fragment A

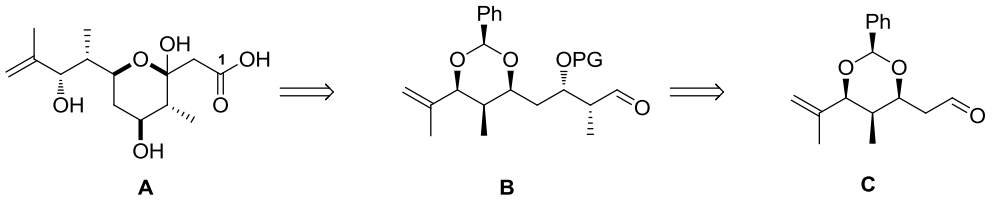
The analysis of the desired fragment **A** pointed the attention on the presence of six stereocenters on a twelve carbon alkyl chain, along with the presence of a pyran ring and a terminal alkene.

By retrosynthetic analysis, the desired fragment **A** could be obtained by homologation and subsequent deprotection and cyclization of intermediate **B**.

At the same time, a strategy for the formation of C-C bonds with the desired stereochemistry would be needed.

With that in mind, we faced the transformation from **C** into **B** (by crotylation, alcohol protection and alkene cleavage) as well as the synthesis of the aldehyde **C** from commercially available starting materials.

Scheme 1



Previous studies within the group towards the C1–C11 fragment of Stambomycin A led to the investigation of different strategies in order to install the requisite methyl stereochemistry at C4 and C8 of the aldehyde intermediate **C**. This followed two failed strategies: a vinylogous Mukaiyama aldol chemistry, and a reductive crotylation reaction developed by Morken.

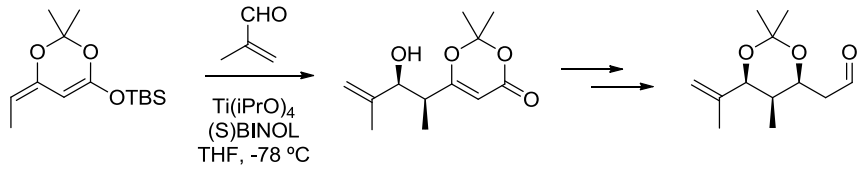
4.2.1 Failed attempts

Mukaiyama aldol reaction

Mukaiyama aldol reaction was first reported in 1975 as a vinilogous alkylation of a silyl dienol ether under activation of $TiCl_4$.[8] Since then, several methods for catalytic, enantioselective, vinilogous aldol reactions have appeared, and the addition of an O-silyl dienolate to aldehydes catalyzed by a chiral Ti (IV) complex was used to afford adducts in good yield and ee.

Therefore, performing a vinilogous Mukaiyama reaction would allow to set two stereocentres in one step, linking an aldehyde and silyl dienol ether, precursors of the intermediate **C** (Scheme 2).

Scheme 2. *Synthetic route based on Mukaiyama aldol reaction*



This sequence is based on an asymmetric catalytic vinylogous Mukaiyama aldol reaction between the dioxenone silyl enol ether (prepared from Meldrum's acid) and methacrolein, using $TiCl_4$ and (S)-BINOL to form the chiral catalyst.

Afterwards, deprotection, selective reduction of the ketone, acetonide protection and reduction would deliver to the corresponding aldehyde.

However, although several attempts of Mukaiyama aldol reaction were carried out performing the reaction on both the enol ether and directly on the dioxenone derivative,

[8] a) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1972**, *13*, 4249. b) Denmark, S. E.; Heemstra, Jr.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682.

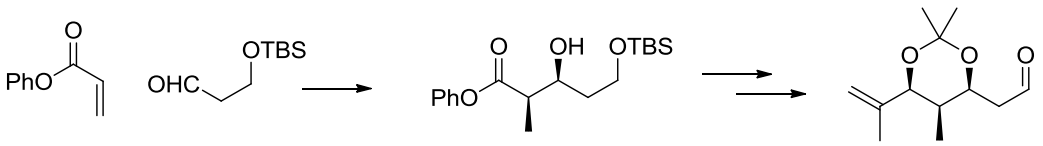
unfortunately no successful results were obtained. Besides, several catalytic loads were tested, even the stoichiometric version, but no desired product was detected.

A possible explanation for these results is the steric hindrance caused by the α-methyl group in methacrolein. Any of aldehydes tested in literature posses this functionality. The methyl group in the dioxenone dienolate derivative is also the cause of unreactivity.

Morken's reductive aldol reaction

An alternative for the first step would be the use of Morken's reductive aldol chemisty,[9] a methodology that would allow to incorporate a propenyl side chain into a selected aldehyde. With this idea in mind the synthetic route would be designed as shown in Scheme 3.

Scheme 3. *Suggested synthesis based on Morken's procedure.*



Therefore, asymmetric catalytic reductive aldol reactions between acrylate esters and aldehydes can be performed by the use of $[(cod)RhCl]_2$ and BINAP, yielding good levels of enantioselectivity.

However when Morken's aldol chemistry was tested no desired compound was obtained, even by screening several reductive agents.

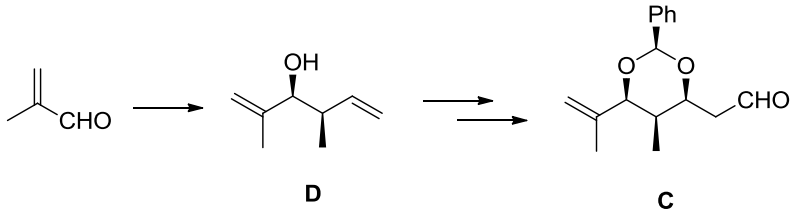
[9] a) Fuller, N. O.; Morken, J. P. *Org. Lett.* **2005**, *7*, 4867. b) Zhao, C.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. c) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528.

4.2.2 New approach: enantioselective crotylation reactions

Regarding the difficulties found in the routes described above, the attention was then focused on a more general procedure that allowed the settlement of the first two stereocentres of our molecule, developing a crotylation strategy.

At first the recourse to Brown crotylation allowed the preparation of aldehyde **C** in very small quantities.

Scheme 4



D **C**

By using methacrolein as starting material, the reaction carried out in the presence of (-)-$(Ipc)_2B(OMe)$, obtained from (+)-α-pinene, afforded compound **D** with the desired stereoselectivity. A following metathesis reaction with methyl acrylate and a conjugate addition with benzaldehyde lead to compund **D**, precursor of the desired intermediate **C**

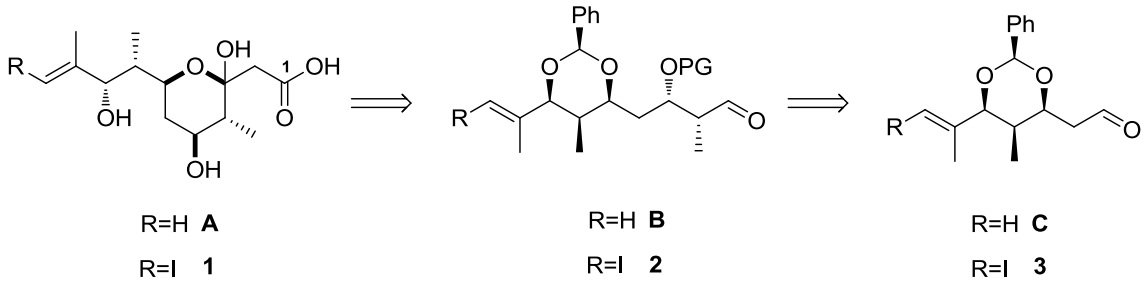
However, the main drawbacks of this strategy are the formation of (Ipc)OH as a side product during Brown crotylation and non optimized reaction conditions for the following reactions (e.g. methatesis with acrolein) that led to compound **C**.

With these promising results in hand as background, we then decided to refine this previous synthesis through: a) introduction of a synthetically useful iodide on the C10–C11 alkene (avoiding the terminal alkene moiety); b) use of Leighton's crotylation chemistry,[10] which should avoid the tedious purification of the Brown crotylation product from the IpcOH byproduct associated with this reaction.

In this vein, we then targeted C1–C11 fragment **1** (containing a vinyl iodide) rather than A, recognising that **1** could be converted to **A** though simple palladium-catalysed deiodination.

[10] a) Hackman, B. M.; Lombarda, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *23*, 4375.; b) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem Soc.***2011**, *133*, 6517–6520

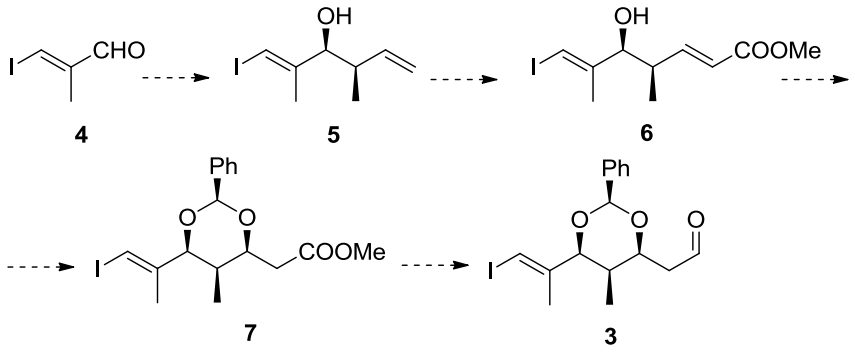
Scheme 5. *New retrosynthetic approach*



R=H **A** R=I **1** R=H **B** R=I **2** R=H **C** R=I **3**

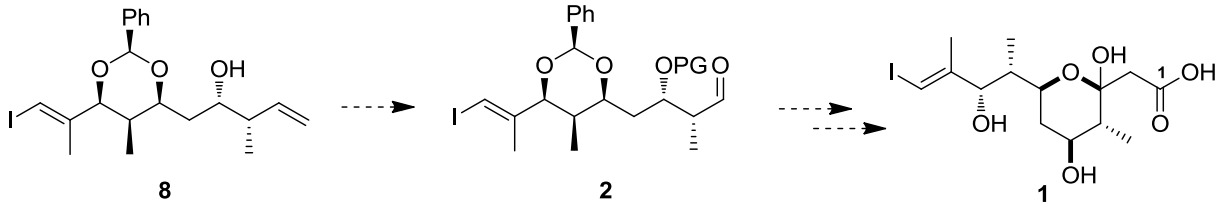
Aldehyde **3** would be then prepared starting from a first Leighton crotylation to give adduct **5**. Afterwards following the original strategy, although not yet perfectly optimised, a rapid chain extension would be accomplished yielding to the desired compound. (Scheme 6)

Scheme 6



A second Leighton crotylation giving adduct **8** would deliver to the setting of all the required stereocentres. The synthesis of **1** should then be completed through alcohol protection, alkene cleavage (to the aldehyde **2**), Roskamp homologation and finally acid mediated acetal cleavage / cyclisation / hydrolysis. (Scheme 7)

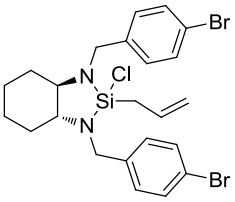
Scheme 7. *Final steps*



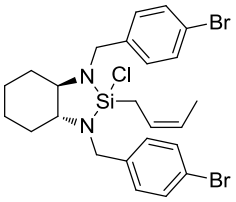
4.3 Results and discussion

Leighton and coworkers recently developed an asymmetric allylation and crotylation of aldehydes by using a new strained chiral reagent, which is practically an allyl or crotyl trichlorosilane tethered to a chiral 1,2-diamine (i.e. cyclohexyldiamine).[10]

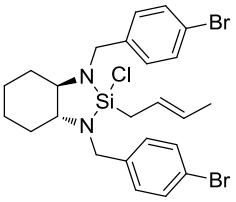
An important feature of these new reagents is that the reaction proceeds without need for any additional catalysts or reagents, yielding the addition to aldehydes on high yields and with excellent diastero- and enantioselectivities.



(R,R)-allylsilane reagent



(R,R)- *cis*-crotylsilane reagent



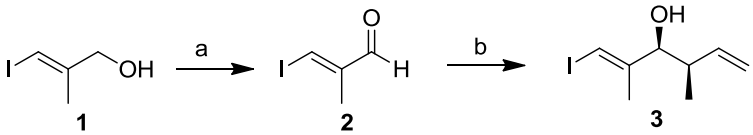
(R,R)- *trans*-crotylsilane reagent

In particular the use of the *cis*-crotyl-reagent afforded exclusively the syn-product, while the *trans*-derivative promoted an *anti*-selective crotylation.

However, since this new methodology is not high performing with aromatic, unsaturated and sterically hindered aldehydes, the addition of a Lewis acid catalysis was found to be crucial to enhance the reactivity on these substrates and $Sc(OTf)_3$ provided the best combination of high enantioselectivity and effective catalysis.[10b]

Thus, the known aldehyde **2**, obtained from oxidation of alcohol **1**, underwent a Leighton crotylation to give adduct **3** in 96%yield and 92%ee. (Scheme 8)

Scheme 8



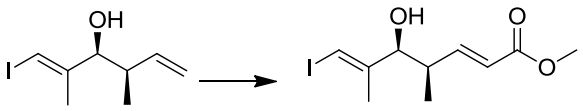
a)MnO_4, Et_2O; b) (R,R)-Leighton Reagent, $Sc(OTf)_3$, DCM

The following elongation of the alkyl chain was performed by a cross metathesis reaction. The presence of the vinyl iodide at one end of the chain let the reaction be regioselective towards the desired double bond. The challenging use of an electron deficient olefin to participate in the reaction is well supported by literature examples.[11] Thus, compound **3** undergoes a metathesis with methyl acrylate in the presence of Hoveyda-Grubbs II

[11] a) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *634*, 216–221; b) Fuwa,H.; Noto, K.; Sasaki, M. *Org Lett* **2010**, *12*,.1636

catalyst. Although the reaction gave good results, different reaction conditions were tested in order to low the catalyst loading (Scheme 9, Table 1).

Scheme 9



3 **4**

Table 1

	Catalytic System	Solvent	T (°C)	Time	%Yield (SM recovered)
1	HG II 2.5%	DCM	RT	24h	78
2	HG II 2.0%	DCM	40 °C	16 h	78
3	HG II 1.0%	DCM	RT	5 d	57 (20)
4	G II 2.0 % CuI 3.0%	Et_2O	40 °C	16 h	89

However, the best results were obtained by using the less expensive 2nd generation Grubbs catalyst in the presence of a catalytic amount of copper iodide. (entry 4) The presence of copper iodide salt is effective in cross metathesis reaction due to a catalyst stabilizing effect prompted by the iodide ion and a phosphine sequestering effect by Copper (I) from ruthenium[12]

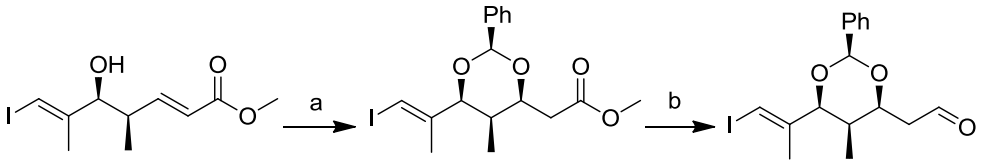
To insert the following oxygen functionality and set another sterocenter, a base catalyzed intramolecular conjugate Michael addition reaction on intermediate **4** was performed. (Scheme 10)

Precedents for the synthesis of protected syn-1,3-diols from δ-hydroxy-α,β-unsaturated esters reported good yields and selectivities.[13] In our case, the reaction of alcohol **4** with benzaldehyde in the presence of *t*-BuOK at low temperature furnished the corresponding benzaylidene acetal. To optimize the reaction several conditions were tested and best results were obtained using THF as solvent at -5 ºC, with excess of benzaldehyde and dropwise addition of *t*-BuOK in solution. As the acetalization is an equilibrium reaction, the slow addition of the base was found to be definitely crucial to avoid side reactions.

[12] Vigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, 76, 4697
[13] Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58,* 2446

However the yields were not great due to the steric hindrance performed by the methyl group on C4 in the emiacetal intermediate

Scheme 10

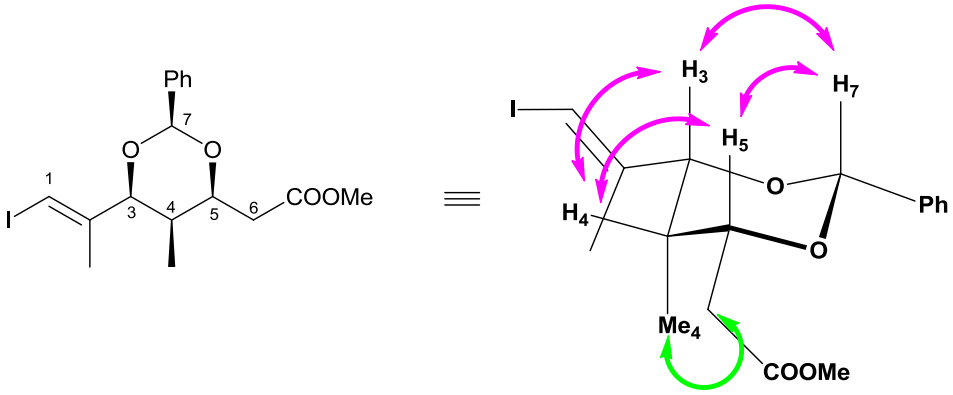


4 **5** (35%) **6** (67%)

a) PhCHO, tBuOK, THF, -5 °C; c) DIBAL-H, DCM, -78 °C.

In order to confirm the absolute configuration of the stereocentres formed, we looked into NOE correlations. Figure 4 shows that there is NOE between H-7 and both H-3 and H-5, which places the three of them in the same face of the conformational chair. There is also NOE between H-4 and both H-3 and H-5, which confirms that the methyl on C4, which is also NOE coupled to H-6, is in axial position.

Figure 4. *NOE correlations*



The following one step reduction performed by using DIBAL-H in DCM at room temperature yield to the desired aldehyde **3**. (Scheme 10).

The further functionalization of the side chain followed a second Leighton crotylation. In this case the (S,S)-isomer of the crotylsilane reagent was used in order to install the right stereochemistry and the reaction was conducted in the absence of the $Sc(OTf)_3$ to avoid a Lewis acid-promoted deacetalization. Thus, the desired compound **7** was obtained in good yield. (Scheme 11) The best results were obtained by prolonging the reaction times and performing the reaction at a higher concentration of the Leighton reagent. (Table 2)

Scheme 11

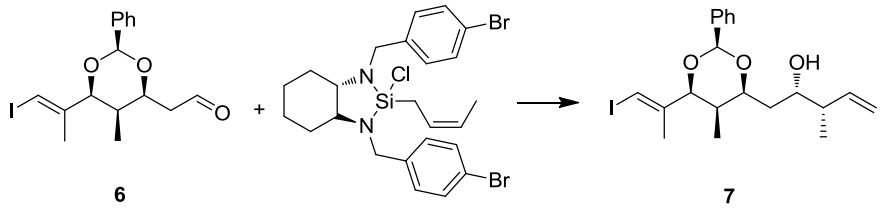


Table 2

	(S,S)-Leighton reagent	DCM	Catalyst	Time (h)	Yield (%)
1	1.2eq	0.1M	$Sc(OTf)_3$ 10%	20	0
2	1.2eq	0.1M	--	20	30
3	2.4eq	0.25M	--	20	65
4	2.4eq	0.25M	--	48	96

Now that all the stereocenter required were successfully set, the further functionalization of the alkyl chain was performed by protection of the alcohol and subsequent alkene cleavage to achieve aldehyde **2**. (Scheme 12)

At first benzoylchloride was chosen as protecting agent, because of it can be easy removed under acidic conditions, thus the deprotection could have been accomplished in the last step of the designed synthesis along with the deacetalization/cyclization sequence. However we found out that the reaction carried out in pyridine was not high yielding and the product difficult to purify. Moreover some problems were detected during the subsequent reaction. (Table 3, entry 1)

Scheme 12

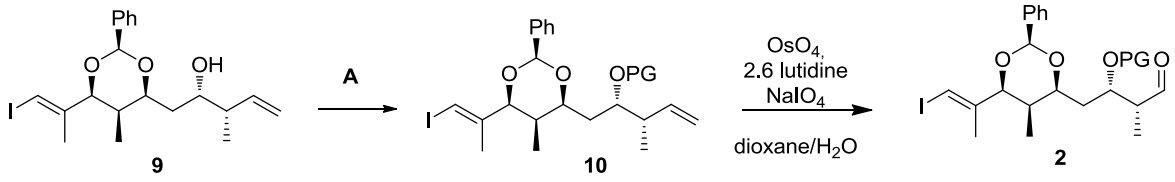


Table 3

	PG	A	**10** (% yield)	**2** (%yield)
1	Bz	BzCl 1.2eq, Py	**10a** (50)	**2a** (30)
2	PMB	PMBCl, NaH, TBAI, THF/DMF	**10b** (72)	**2b** (53)

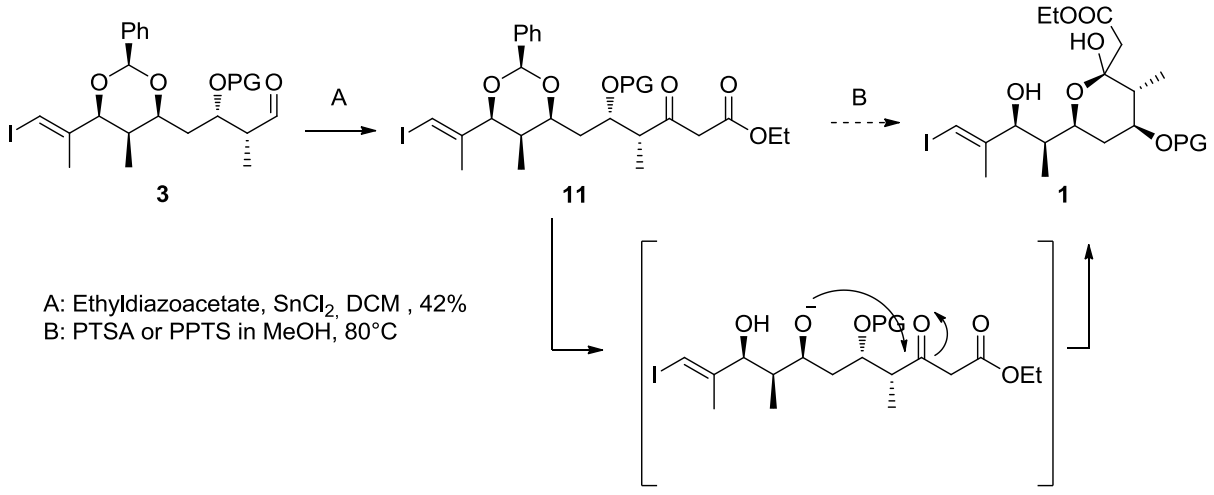
For these reasons, we decided to use *p*-methoxybenzyl as protecting group.

Alcohol **9** was then treated with PMB-Cl in basic conditions (NaH) in THF/DMF as solvent in the presence of tetra-butyl-ammonium iodide to yield the protected product **10b** in good yield. Compound **10b** was then transformed into aldehyde **2b** under oxidative conditions: catalytic amount of OsO_4 and of $NaIO_4$ in dioxane/water. The addition of 2,6-lutidine was used to prevent the formation of oxidation by-products.

At last a Roskamp omologation[14] was performed by insertion of the carbine, generated from ethyl diazoacetate in the presence of $SnCl_2$, into the aldehyde **2b**, obtaining the desired β-ketoester **11** in good yield (80%).

At this point acidic conditions would deliver to the deprotection of the acetal, followed by intramolecular acetalization on the keto-group in order to obtain the cyclized compound **1**. (Scheme 13). However, only small scale test reactions were performed on derivative **11**. The catalytic use of p-toluensulfonic acid (PTSA) in methanol at 80 °C afforded only a mixture of degradation products, while when the reaction was performed with pyridinium *p*-toluensulfonate (PPTS) in methanol the formation of a small amount of the desired product was detected from both TLC analysis and ^{1}H-NMR of the crude mixture.

Scheme 13. *Final steps*



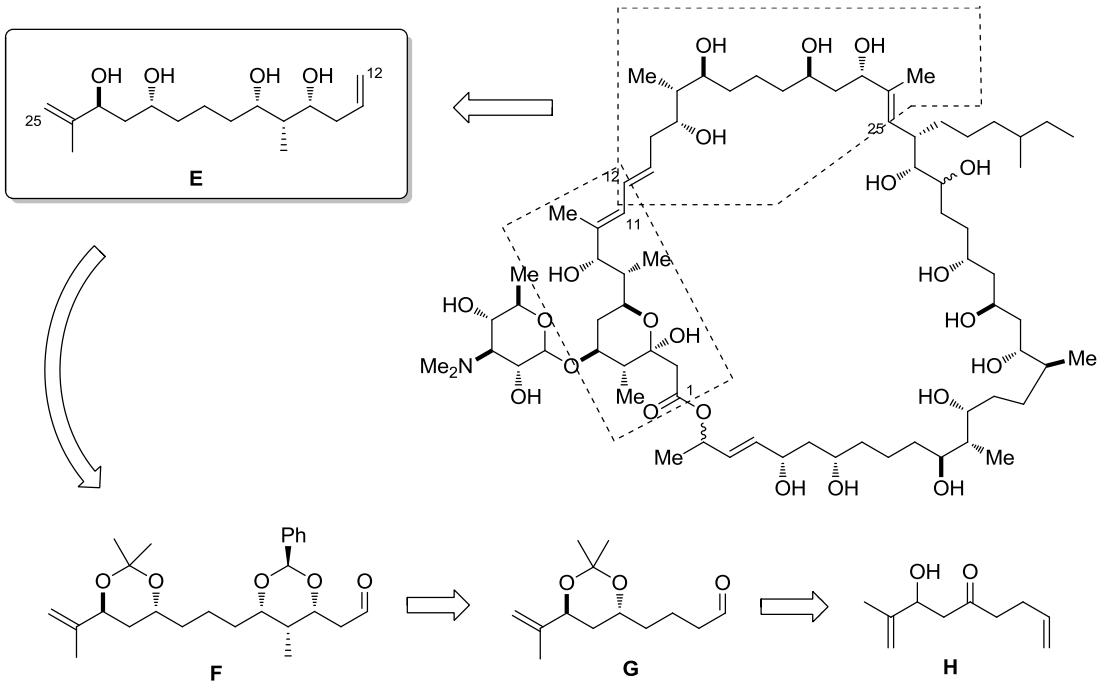
[14] Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

4.4 Conclusions

In summary a convenient route to fragment **A** of Sambomycin A has been developed and partially accomplished. The compound **1** was synthesized with high stereoselectivity and Leighton crotylation chemistry, cross-metathesis and conjugate additions were the synthesis key steps to construct the requisite stereocentres. However, the last step to the desired compound **1** has only been settled and remains to be scaled and the product recovered and purified.

Since this synthesis proved to be successful, the attention can be turned to the C12–C25 fragment **F**, which features two remote areas of stereochemistry (an *anti*-diol and a stereotriad) linked by a -$(CH_2)_3$- chain (Figure 5), recognizing that transformation from **G** to **F** could follow a sequence equivalent to the one settle in this early part of the project towards fragment **A**.

Figure 5. *C12-C25 fragment*



Conclusions

In conclusion, during this research work we have developed transition metal catalyzed strategies resulting in the formation of new C-N bonds.

The interest toward nitrogen containing heterocycles brought us to investigate new synthetic ways towards such structures exploiting Pd catalyzed reactions on unsaturated substrates, ending up with the formation of new two-heteroatom-containing cyclic systems such as imidazoindoles, oxazoles, imidazoles, benzoxazines, oxazepines and isoxazolidines.

Hydroamination and carboamination reactions on different allenes let us to afford the formation of a new five-member ring system bearing a useful vinyl or styryl moiety.

Conversely, the intramolecular hydroamination on alkynes resulted in different regioselectivity when platinum or palladium were used as catalysts.

In the first case, seven-member ring heterocycles were obtained (e.g. benzoxazepines and benzodiazepines) through a 7-*endo* cyclization process, while by using palladium six-member ring systems were formed.

Finally, isoxazolidines were successfully synthesized performing a Pd(II) a halogenation/amination on alkenyl-hydroxylamines.

At last, although not concerning within the project, the experience towards the synthesis of the first fragment of Stambomycin A accomplished at the University of Oxford has revealed to be a good challenge, resulting in the setting of the initial steps of the total synthesis of this macrolacton.

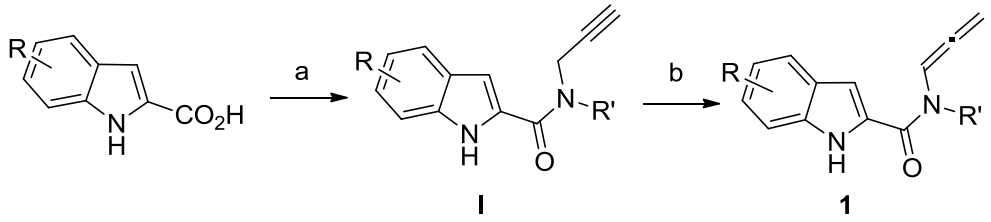
Experimental Section

General details: All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F_{254} thin-layer plates were employed for thin layer chromatography (TLC). Silica gel 40–63 micron/60 Å was employed for flash column chromatography. Melting points were measured with a Büchi B-540 heating unit and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer FT-IR 16 PC spectrophotometer using KBr tablets for solids and NaCl disks for oils. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$, at 200, 300, 400, 500 MHz (with a Varian-Gemini 200 or Brucker 300, 400 and 500 Avance spectrometers), with residual chloroform as the internal reference (δ_H = 7.27 ppm). ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ at 50.3, 75.45, 100 or 125.75 MHz, with the central peak of chloroform as the internal reference (δ_C = 77.3 ppm). The APT or DEPT sequences were used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. Data for ^{1}H NMR are reported as follows: s = singlet, d =doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet, br = broad. Coupling constants (*J*) are reported as values in hertz. All ^{13}C NMR spectra were recorded with complete proton decoupling. Two-dimensional NMR experiments (COSY, NOESY and HMBC) were used, where appropriate, to aid in the assignment of signals in proton and carbon spectra. Low-resolution MS spectra were recorded with a Thermo-Finnigan LCQ advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions. Microwave assisted reactions were performed in a MILESTONE microSYNT multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with an optical fibre sensor.

Column chromatography was performed on a Merck silica gel 60, (mesh size 63-200 μm).

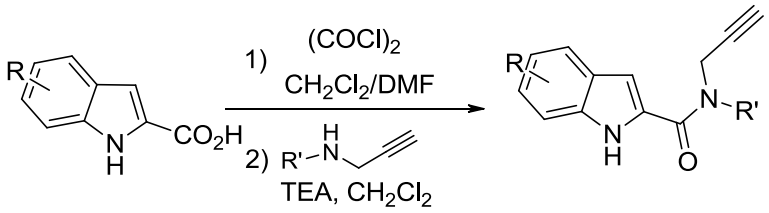
Indole derivatives

The allenamides of 2-indolcarboxylic acid were prepared in near quantitative yields, starting from indole-2-carboxylic acid easily conversted into the propargylamide and followed by prototropic isomerization promoted by *t*-BuOK.



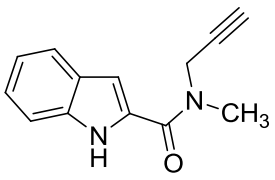
a) $(COCl)_2$, DCM/DMF, then propargylamine, TEA, DCM; b) t-BuOK, THF

General procedure for the preparation of propargylamides



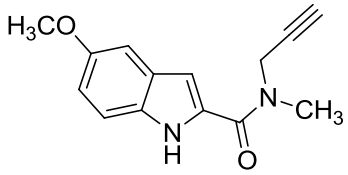
A solution of indole-2-carboxylic acid (6.20 mmol), DMF (0.3 mL) and oxalyl chloride (18.60 mmol) in anhydrous CH_2Cl_2 (40 mL) was stirred at rt for 1 h and refluxed for 1 h. The solvent was evaporated under reduced pressure, the crude residue was diluted with CH_2Cl_2 (40 mL) and a solution of propargylamine (8.24 mmol) and triethylamine (8.24 mmol) in CH_2Cl_2 was added at 0 °C. The solution was stirred at rt for 1 h, then the organic phase was washed with HCl 1M and dried over Na_2SO_4 then the solvent was evaporated under reduced pressure. The resulting crude was purified by flash chromatography to afford the desired product (PE/AcOEt 7:3).

***N*-Methyl-*N*-propargyl-1*H*-indole-2-carboxamide (Ia)**



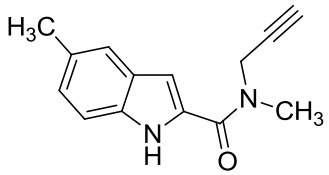
Yield: 96%. White solid. **mp** 145 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3308, 3230, 2116, 1661; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.56 (1H, br s); 7.69 (1H, d, *J* = 8.0 Hz), 7.46 (1H, d, *J* = 8.2 Hz), 7.30 (1H, dd, *J* = 8.2 Hz, 7.1 Hz), 7.15 (1H, dd, *J* = 8.0 Hz, 7.1 Hz), 7.00 (1H, s), 4.49 (2H, s), 3.23 (3H, s), 2.37 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.6 (s), 136.3 (s), 129.0 (s), 127.8 (s), 124.8 (d), 122.3 (d), 120.7 (d), 112.3 (d), 106.4 (d), 78.5 (s), 73.2 (d), 40.3 (t), 35.8 (q). **MS**: *m/z* 212 $[M]^+$. Anal. calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found C, 73.41; H, 5.82; N, 13.34.

5-Methoxy-*N*-methyl-*N*-propargyl-1*H*-indole-2-carboxamide (Ib)



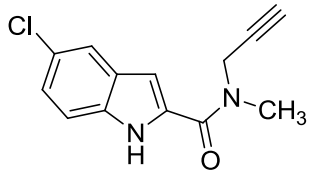
Yield: 94%. White solid. **mp** 143 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3305, 3224, 2114, 1658; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.95 (1H, br s), 7.37 (1H, d, *J* = 8.9 Hz), 7.08 (1H, s), 6.96 (1H, d, *J* = 8.9 Hz), 6.91 (1H, s), 4.48 (2H, s), 3.85 (3H, s), 3.20 (3H, s), 2.38 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.2 (s), 154.5 (s), 131.4 (s), 129.3 (s), 127.9 (s), 116.0 (d), 112.9 (d), 105.7 (d), 102.3 (d), 78.6 (s), 74.5 (d), 55.7 (q), 45.8 (t), 38.7 (q). **MS**: *m/z* 242 $[M]^+$.

***N*-5-Dimethyl-*N*-propargyl-1*H*-indole-2-carboxamide (Ic)**



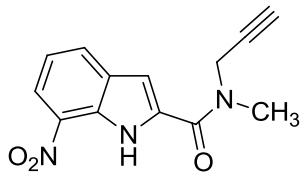
Yield: 65%. White solid. **mp** 136 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3312, 3220, 2118, 1664; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 10.09 (1H, br s), 7.46 (1H, s), 7.39 (1H, d, *J* = 8.4 Hz), 7.14 (1H, d, *J* = 8.4 Hz), 6.93 (1H, s), 4.50 (2H, s), 3.41 (3H, s), 2.47 (3H, s), 2.39 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.3 (s), 134.5 (s), 129.7 (s), 128.9 (s), 127.9 (s), 126.5 (d), 121.3 (d), 111.7 (d), 105.6 (d), 78.6 (s), 73.6 (d), 46.1 (t), 39.4 (q), 21.5 (q). **MS**: *m/z* 226 $[M]^+$

5-Chloro-*N*-methyl-*N*-propargyl-1*H*-indole-2-carboxamide (Id)



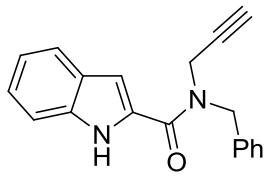
Yield: 65%. White solid. **mp** 152 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3307, 3235, 2120, 1673; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 10.03 (1H, br s), 7.64 (1H, s), 7.40 (1H, d, *J* = 8.7 Hz), 7.24 (1H, d, *J* = 8.7 Hz), 6.92 (1H, s), 4.48 (2H, s), 3.43 (3H, s), 2.39 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.3 (s), 134.5 (s), 129.7 (s), 128.9 (s), 127.9 (s), 126.5 (d), 121.3 (d), 111.7 (d), 105.5 (d), 78.3 (s), 72.8 (d), 47.8 (t), 33.4 (q). **MS**: *m/z* 246 $[M]^+$.

_N_-Methyl-7-nitro-_N_-propargyl-1_H_-indole-2-carboxamide (Ie)



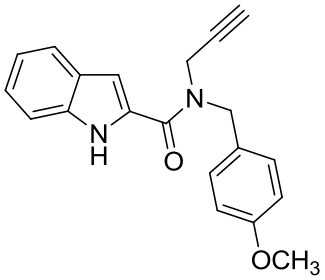
Yield: 74%. White solid. **mp** 161 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3315, 3216, 2112, 1664; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 10.5 (1H, br s), 8.25 (1H, d, *J* = 7.9 Hz), 8.02 (1H, d, *J* = 7.8 Hz), 7.27 (1H, dd, *J* = 7.8 Hz, 7.9 Hz), 7.10 (1H, s), 4.45 (2H, s), 3.12 (3H, s), 2.39 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 161.8 (s), 133.3 (s), 131.6 (s), 131.3 (s), 130.3 (d), 128.8 (s), 121.6 (d), 120.0 (d), 106.5 (d), 78.1 (s), 72.4 (d), 45.8 (t), 38.7 (q). **MS**: *m/z* 257 $[M]^+$.

_N_-Benzyl-_N_-propargyl-1_H_-indole-2-carboxamide (If)



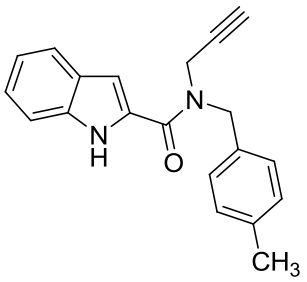
Yield: 59%. White solid. **mp** 163 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3313, 3220, 2116, 1668; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.35 (1H, br s), 7.63-7.66 (1H, m), 7.15-7.45 (8H, m), 7.09-7.14 (1H, m), 5.05 (2H, s), 4.39 (2H, s), 2.37 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 159.0 (s), 30.9 (t), 136.0 (s), 135.8 (s), 128.8 (d), 128.6 (s), 127.8 (d), 127.7 (s), 124.6 (d), 122.4 (d), 122.2 (d), 120.6 (d), 111.7 (d), 105.7 (d), 78.6 (s), 74.1 (d), 52.8 (t). **MS**: *m/z* 288 $[M]^+$.

***N*-(4-Methoxybenzyl)-*N*-propargyl-1*H*-indole-2-carboxamide (Ig)**



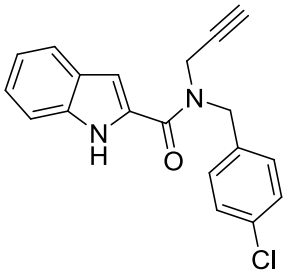
Yield: 98%. White solid. **mp** 138 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3321, 3218, 2108, 1667; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.53 (1H, br s), 7.62-7.65 (1H, m), 7.45 (2H, d, *J* = 8.2 Hz), 7.12-7.33 (4H, m), 6.92 (2H, d, *J* = 8.2 Hz), 5.00 (2H, s), 4.37 (2H, s), 3.83 (3H, s), 2.37 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.3 (s), 159.3 (s), 135.9 (s), 128.7 (s), 127.9 (s), 127.7 (s), 124.7 (d), 122.2 (d), 120.6 (d), 114.3 (d), 111.8 (d), 106.5 (d), 105.7 (d), 78.7 (s), 73.4 (d), 55.3 (q), 53.4 (t), 30.9 (t). **MS**: *m/z* 318 $[M]^+$.

***N*-(4-Methylbenzyl)-*N*-propargyl-1*H*-indole-2-carboxamide (Ih)**



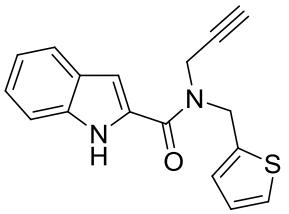
Yield: 98%. White solid. **mp** 138 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3309, 3222, 2120, 1670; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.26 (1H, br s), 7.11-7.65 (9H, m), 5.01 (2H, s), 4.36 (2H, s), 2.38 (4H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.4 (s), 137.6 (s), 135.9 (s), 132.9 (s), 129.6 (d), 128.6 (s), 127.6 (s), 124.7 (d), 122.1 (d), 120.6 (d), 111.8 (d), 106.5 (d), 105.7 (d), 78.7 (s), 72.8 (d), 49.1 (t), 33.9 (t), 21.1 (q). **MS**: *m/z* 302 $[M]^+$.

_N_-(4-Chlorobenzyl)-_N_-propargyl-1_H_-indole-2-carboxamide (Ii)



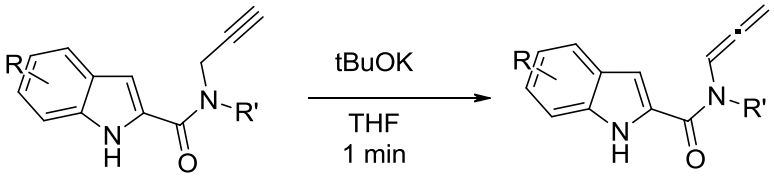
Yield: 58%. White solid. **mp** 166 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3320, 3210, 2109, 1657; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 10.06 (1H, br s), 7.12-7.65 (9H, m), 5.02 (2H, s), 4.42 (2H, s), 2.41 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.6 (s), 136.2 (s), 134.7 (s), 133.7 (s), 129.1 (d), 128.3 (s), 127.5 (s), 124.8 (d), 122.1 (d), 120.6 (d), 112.0 (d), 105.9 (d), 105.8 (d), 78.5 (s), 73.3 (d), 50.3 (t), 34.1 (t). **MS**: *m/z* 322 $[M]^+$.

_N_-Propargyl-_N_-(thiophen-2-ylmethyl)-1_H_-indole-2-carboxamide (Ij)



Yield: 51%. White solid. **mp** 121 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3312, 3220, 2114, 1676; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.87 (1H, br s), 7.68 (1H, d, *J* = 8.0 Hz), 7.48 (1H, d, *J* = 8.3 Hz), 7.27-7.32 (2H, m), 7.09-7.17 (3H, m), 7.00-7.03 (1H, m), 5.15 (2H, s), 4.46 (2H, s), 2.44 (1H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 163.2 (s), 138.4 (s), 136.1 (s), 128.4 (s), 127.6 (s), 127.1 (d), 127.0 (d), 126.9 (d), 126.1 (d), 124.8 (d), 122.2 (d), 112.0 (d), 105.8 (d), 78.6 (s), 73.2 (d), 44.4 (t), 37.6 (t). **MS**: *m/z* 294 $[M]^+$.

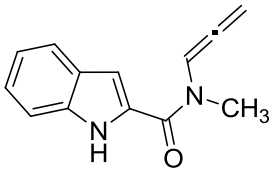
General procedure for the synthesis of allenamides



A solution of propargylamide (1 mmol) in THF (10 mL) was treated with t-BuOK (2.5 mmol). The resulting solution was stirred at rt for 1 min, then filtered on silica gel (AcOEt). The

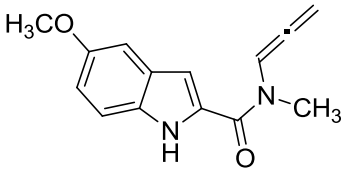
solvent was evaporated under reduced pressure and the residue was used without further purification for the next step.

N-Methyl-N-(propa-1,2-dienyl)-1H-indole-2-carboxamide (1a)



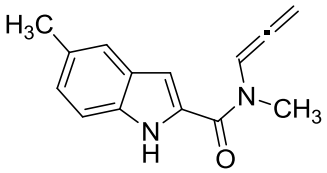
Yield 98%. White solid. **mp** 143 °C (i-Pr_2O); **IR** (ν_{max}/cm^{-1}): 3306, 1940, 1668; **^{1}H-NMR** (400 MHz, CDCl3) δ_H: 9.07 (1H, br s), 7.68 (1H, d, J = 8.8 Hz), 7.44 (1H, d, J = 8.2 Hz), 7.28 (1H, dd, J=8.8 Hz, 7.0 Hz), 7.27-7.72 (1H, m), 7.17 (1H, dd, J = 8.2 Hz, 7.0 Hz), 7.00 (1H, s), 4.49 (2H, d, J = 6.6 Hz), 3.34 (3H, s); **^{13}C-NMR** (100MHz, $CDCl_3$) δ_C: 202.4 (s) 161.7 (s), 136.1 (s), 129.1 (s), 127.9 (s), 125.2 (d), 122.4 (d), 120.9 (d), 112.0 (d), 107.9 (d), 102.7 (d), 87.6 (t), 33.7 (q). **MS** m/z 212 $[M]^+$.

5-Methoxy-*N*-methyl-*N*-(propa-1,2-dienyl)-1*H*-indole-2-carboxamide (1b)



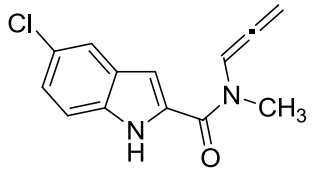
Yield: 85%. White solid. **mp** 143 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3310, 1935, 1672; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.22 (1H, br s), 7.57-7.88 (1H, m), 7.36 (1H, d, *J* = 8.9 Hz), 7.08 (1H, s), 6.99 (1H, d, *J* = 8.9 Hz), 6.92 (1H, s), 5.50 (2H, d, *J* = 6.3 Hz), 3.86 (3H, s), 3.35 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 201.9 (s) 161.6 (s), 154.6 (s), 131.6 (s), 129.3 (s), 127.9 (s), 116.3 (d), 112.8 (d), 106.9 (d), 102.6 (d), 102.3 (d), 87.4 (t), 55.7 (q), 33.2 (q). **MS**: *m/z* 242 $[M]^+$.

***N*,5-Dimethyl-*N*-(propa-1,2-dienyl)-1*H*-indole-2-carboxamide (1c)**



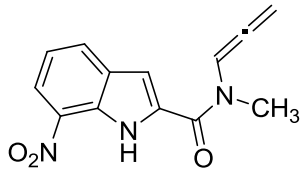
Yield: 88%. White solid. **mp** 135 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3301, 1944, 1660; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.80 (1H, br s), 7.79-7.50 (1H, m), 7.45 (1H, s), 7.36 (1H, d, *J* = 8.4 Hz), 7.13 (1H, d, *J* = 8.4 Hz), 6.92 (1H, s), 5.51 (2H, d, *J* = 6.3 Hz), 3.36 (3H, s), 2.46 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 202.5 (s), 162.0 (s), 134.6 (s), 129.9 (s), 128.9 (s), 127.8 (s), 126.8 (d), 121.9 (d), 121.4 (d), 111.6 (d), 106.8 (d), 87.3 (t), 30.3 (q), 21.4 (q). **MS**: *m/z* 226 $[M]^+$.

5-Chloro-*N*-methyl-*N*-(propa-1,2-dienyl)-1*H*-indole-2-carboxamide (1d)



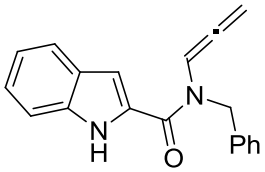
Yield: 85%. White solid. **mp** 145 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3313, 1937, 1655; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 10.16 (1H, br s), 7.23-7.82 (1H, m), 7.64 (1H, s), 7.39 (1H, d, *J* = 8.8 Hz), 7.25 (1H, d, *J* = 8.8 Hz), 6.92 (1H, s), 5.52 (2H, d, *J* = 6.3 Hz), 3.31 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 201.8 (s), 161.4 (s), 134.5 (s), 130.1 (s), 128.4 (s), 126.2 (s), 125.3 (d), 121.8 (d), 121.2 (d), 113.1 (d), 106.6 (d), 87.5 (t), 32.8 (q). **MS**: *m/z* 246 $[M]^+$.

***N*-Methyl-7-nitro-*N*-(propa-1,2-dienyl)-1*H*-indole-2-carboxamide (1e)**



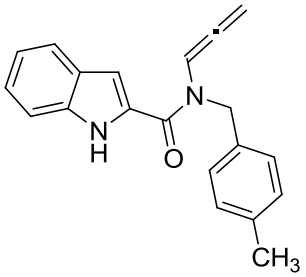
Yield: 80%. White solid. **mp** 128 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3302, 1945, 1667; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 10.50 (1H, br s), 8.25 (1H, d, *J*= 7.4 Hz), 8.02 (1H, d, *J*= 7.8 Hz), 7.47-7.32 (1H, m), 3.27 (3H, s), 7.27 (1H, dd, *J*= 7.8, 7.4 Hz), 6.97 (1H, s), 5.51 (2H, d, *J*= 6.3 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 202.0 (s), 160.1 (s), 133.3 (s), 131.6 (s), 131.1 (s), 130.3 (d), 128.9 (s), 122.1 (d), 121.7 (d), 119.9 (d), 107.6 (d), 87.6 (t), 30.3 (q). **MS**: *m/z* 257 $[M]^+$.

_N_-Benzyl-_N_-(propa-1,2-dienyl)-1_H_-indole-2-carboxamide (1f)



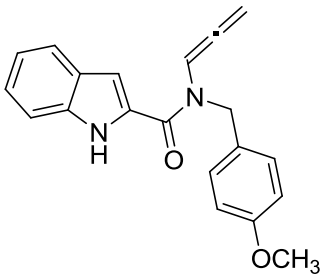
Yield: 69%. White solid. **mp** 145 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3298, 1953, 1669; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.34 (1H, br s), 7.68-7.11 (11H, m), 5.36 (2H, s), 5.01 (2H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 202.8 (s), 161.6 (s), 137.2 (s), 136.0 (s), 128.6 (d), 128.4 (s), 127.8 (s), 127.6 (d), 127.2 (d), 125.0 (d), 122.3 (d), 120.7 (d), 111.7 (d), 107.5 (d), 102.6 (d), 87.5 (t), 49.8 (t). **MS**: *m/z* 288 $[M]^+$.

_N_-(4-Methylbenzyl)-_N_-(propa-1,2-dienyl)-1_H_-indole-2-carboxamide (1g)



Yield: 92%. White solid. **mp** 155 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3310, 1933, 1655; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.62 (1H, br s), 7.77-7.03 (10H, m), 5.38 (2H, s), 4.90 (2H, s), 3.36 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 202.4 (s), 161.5 (s), 158.8 (s), 136.0 (s), 130.0 (s), 129.2 (s), 128.7 (d), 127.6 (s), 125.0 (d), 122.3 (d), 120.7 (d), 114.0 (d), 111.8 (d), 108.2 (d), 102.1 (d), 87.4 (t), 55.3 (q), 47.4 (t). **MS**: *m/z* 302 $[M]^+$.

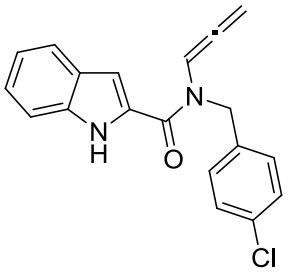
_N_-(4-Methoxybenzyl)-_N_-(propa-1,2-dienyl)-1_H_-indole-2-carboxamide (1h)



Yield: 84%. White solid. **mp** 136 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3310, 1954, 1670; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.41 (1H, br s), 7.43-6.88 (10H, m), 5.39 (2H, s), 4.90 (2H, s), 3.81

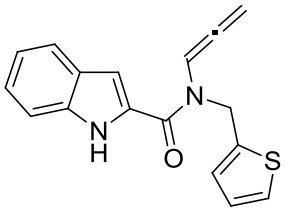
(3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 202.4 (s), 161.5 (s), 158.8 (s), 136.0 (s), 130.0 (s), 129.2 (s), 128.7 (d), 127.6 (s), 125.0 (d), 122.3 (d), 120.7 (d), 114.0 (d), 111.8 (d), 108.2 (d), 102.1 (d), 87.4 (t), 55.3 (q), 47.4 (t). **MS**: *m/z* 318 $[M]^+$.

***N*-(4-Chlorobenzyl)-*N*-(propa-1,2-dienyl)-1*H*-indole-2-carboxamide (1i)**



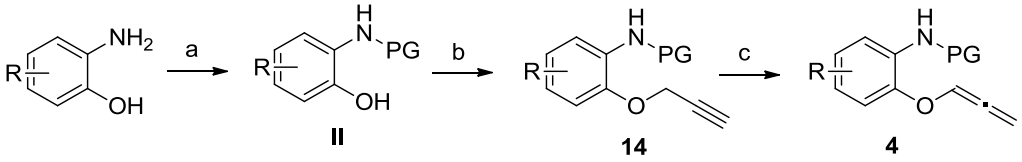
Yield: 92%. White solid. **mp** 167 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3295, 1938, 1652; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.28 (1H, br s), 7.64-6.85 (10H, m), 5.37 (2H, d, *J* = 5.9 Hz), 4.96 (2H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 202.1 (s), 161.6 (s), 136.1 (s), 135.7 (s), 133.1 (s), 129.9 (s), 128.8 (d), 127.5 (s), 127.5 (d), 125.1 (d), 122 (d), 120.8 (d), 111.8 (d), 108.0 (d), 101.9 (d), 87.7 (t), 48.6 (t). **MS**: *m/z* 322 $[M]^+$.

***N*-(Propa-1,2-dienyl)-*N*-(thiophen-2-ylmethyl)-1*H*-indole-2-carboxamide (1j)**

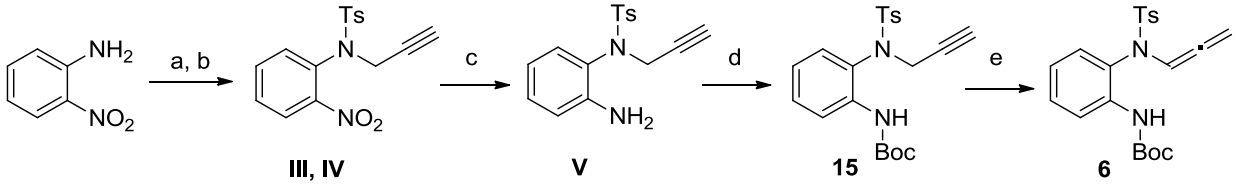


Yield: 95%. White solid. **mp** 166 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3321, 1952, 1654; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 9.47 (1H, br s), 7.67 (1H, d, *J* = 8.0 Hz), 7.43 (1H, d, *J* = 8.3 Hz), 7.31 (1H, dd, *J* = 7.6 Hz, 7.7 Hz), 7.17-7.06 (3H, m), 7.24-7.27 (1H, m), 6.96-6.99 (1H, m), 6.95-7.45 (1H, m), 5.54 (2H, d, *J* = 5.3 Hz), 5.10 (2H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 201.9 (s), 161.2 (s), 139.8 (s), 136.1 (s), 130.3 (s), 128.5 (s), 127.5 (d), 126.5 (d), 125.5 (d), 125.1 (d), 122.3 (d), 120.8 (d), 111.8 (d), 107.7 (d), 101.8 (d), 88.1 (t), 45.5 (t). **MS**: *m/z* 294 $[M]^+$.

For the studies to dihydrobenzoxazoles and dihydrbenzoimidazoles the substrates were synthesized starting from 2-amino-phenol and 2-nitro-aniline following the scheme below:



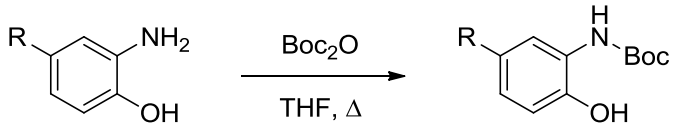
a) Boc_2O, THF or TsCl, DCM; b) propargyl bromide, base, THF/DMF; c) *t*-BuOK, THF



a) TsCl, Py; b) Propargyl alcohol, DIAD, PPh_3, THF; c) Fe, AcOH, EtOH/H_2O; d) Boc_2O, THF; e) *t*-BuOK, THF

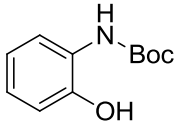
Aminophenol derivatives

General procedure for the preparation of *N*-Boc 2-aminophenol derivatives



To a stirred solution of the suitable 2-aminophenol (1 eq) in THF (6.5 mL / mmol), Boc_2O (1.2 eq) was added at room temperature and the reaction mixture was stirred at room temperature (heated when necessary) hor 16h. The solvent was then removed under reduce pressure, 10 mL of H_2O were added and the solution was extracted with AcOEt (3 x 20 mL). The layers were separated and the organic phases dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel flash column chromatography.

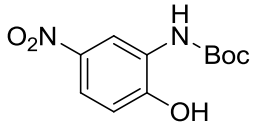
***N*-(*tert*-butoxycarbonyl)-2-aminophenol (IIa)[44]**



Yield: 95% Colourless crystal solid. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.12 (1H, bs), 7.08-6.81 (4H, m), 6.62 (1H, bs), 1.53 (9H, s).

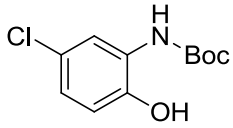
Data are consistent with literature.

***N*-(*tert*-butoxycarbonyl)-5-nitro-2-aminophenol (IIb)**



Yield: 72% Orange solid. **mp**: 141 °C (Et_2O) **IR** (ν_{max}/cm^{-1}): 3361, 3339, 1711, 1532, 1496. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 9.15 (1H, bs), 8.16 (1H, d, *J* = 2.9 Hz), 7.93 (1H, dd, *J*= 8.8, 2.9 Hz), 6.86 (1H, bs), 6.99 (1H, d, *J*= 8.8 Hz), 1.55 (9H, s).**^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 155.1 (s), 153.2 (s), 141.4 (s), 126.3 (s), 121.4 (d), 118.4 (d), 117.0 (d), 83.6 (s), 28.4 (q). **MS** *m/z* 277.0 $[M+Na]^+$

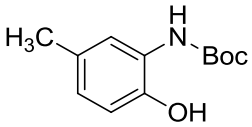
***N*-(*tert*-butoxycarbonyl)- 5-chloro-2-aminophenol (IIc)**



Yield: 97 % Orange oil. **IR** (ν_{max}/cm^{-1}): 3394, 3317, 2981, 1707, 1530. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.86 (1H, bs), 7.33 (1H, d, *J* = 2.2 Hz), 6.93 (1H, dd, *J* = 8.8, 2.9 Hz), 6.81 (1H, d, *J* = 8.8 Hz), 6.80 (1H, bs), 1.56 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 154.6 (s), 145.5 (s), 131.9 (s), 127.1 (s), 124.8 (d), 120.8 (d), 119.0 (d), 82.5 (s), 28.5 (q). **MS** *m/z* 266.1 $[M+Na]^+$.

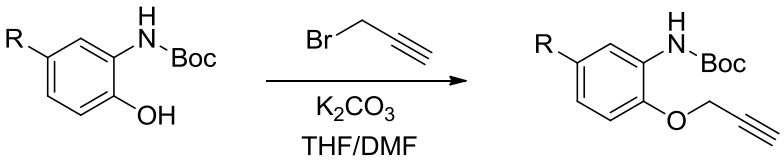
[44] Buon, C.; Chacun-Lefèvre, L.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron* **2000**, *56*, 605.

***N*-(*tert*-butoxycarbonyl)-5-methy-2-aminophenol (IId)** [45]



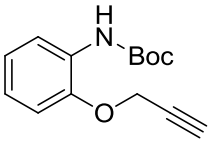
Yield: 99% Colourless solid. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.76 (1H, bs), 6.95 (1H, s), 6.65 (1H, bs), 6.84-6.60 (2H, m), 2.23 (3H, s), 1.51 (9H, s).
Data are consistent with literature.

General procedure for the preparation of *N*-Boc *O*-propargyl ethers intermediates



To a stirred solution of the suitable *N*-(*tert*-butoxycarbonyl)-2-aminophenol (1 eq) in THF/DMF (10 mL / 3 mL) at room temperature, under N_2 atmosphere, was added K_2CO_3 (1.2 eq). The mixture was cooled to 0 °C and a solution of propargyl bromide (80% in toluene, 1.2 eq) was added dropwise. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, brine (15 ml) was added and the mixture was extracted with Et_2O (3 x 20 mL). The organic layers were dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The crude was purified by crystallization or by silica gel flash chromatography.

***N*-(*tert*-butoxycarbonyl)-*O*-(prop-2-ynyl)-2-aminophenol (14a)**

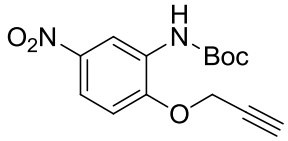


Yield: 97% Yellow oil. **IR** (ν_{max}/cm^{-1}): 3439, 3295, 2979, 2931, 2123, 1728, 1604, 1522, 1454. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.10-8.08 (1H, m), 7.06 (1H, bs), 6.99-6.96 (3H, m), 4.75 (2H, d, *J* = 2.2 Hz), 2.54 (1H, t, *J* = 2.2 Hz), 1.53 (9H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ_C:

[45] Sarkar, A.; Raha Roy, S.; Parikh, N.; Chakraborti, A. K. *J. Org. Chem.* **2011**, *76*, 7132.

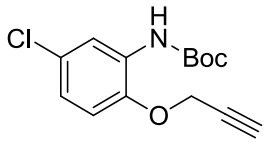
152.9 (s), 145.8 (s), 128.9 (s), 122.5 (d), 122.2 (d), 118.9 (d), 112.2 (d), 80.6 (s), 76.6 (s), 76.4 (d), 56.9 (t), 28.8 (q) **MS** *m/z* 270.0 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-*O*-(prop-2-ynyl)-4-nitro-2-aminophenol (14b)**



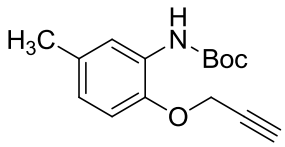
Yield: 80% Yellow solid. **mp**: 111-113 °C (Et_2O) **IR** (ν_{max}/cm^{-1}): 3361, 3258, 2993, 2939, 2120, 1706, 1594, 1535, 1345, 1278. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 9.03 (1H, d, *J* = 2.9 Hz), 7.90 (1H, dd, *J* = 9.2, 2.9 Hz),7.10 (1H, bs), 7.04 (1H, d, *J* = 9.2 Hz), 4.86 (2H, d, *J* = 2.6 Hz), 2.61 (1H, t, *J* = 2.6 Hz), 1.54 (9H, s).**^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.3 (s), 149.9 (s), 142.7 (s), 129.3 (s), 118.4 (d), 113.8 (d), 110.9 (d), 81.8 (s), 77.6 (s), 76.9 (d), 57.0 (t), 28.5 (q). **MS** *m/z* 315.0 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-*O*-(prop-2-ynyl)-4-chloro-2-aminophenol (14c)**



Yield: 62% Dark yellow oil. **IR** (ν_{max}/cm^{-1}): 3436, 3299, 2980, 2933, 2125, 1729, 1598.**^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 8.17 (1H, s),7.05 (1H, bs), 7.00-6.89 (3H, m), 4.73 (2H, d, *J* = 2.6 Hz), 2.55 (1H, t, *J* = 2.6 Hz), 1.53 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.5 (s), 144.2 (s), 129.9 (s), 127.6 (s), 121.8 (d), 118.6 (d), 112,9 (d), 82.9 (s), 81.1 (s), 76.3 (d), 57.0 (t), 28.5 (q). **MS** *m/z* 304.0 $[M+Na]^+$

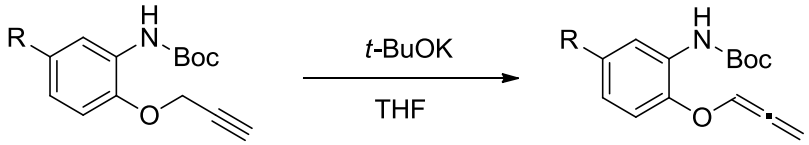
***N*-(*tert*-butoxycarbonyl)-*O*-(prop-2-ynyl)-4-methyl-2-aminophenol (14d)**



Yield: 76% Orange oil. **IR** (ν_{max}/cm^{-1}): 3408, 3276, 2980, 2930, 2129, 1731, 1532. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.95 (1H, s), 7.04 (1H, bs), 6.86 (1H, d, *J* = 8.1 Hz), 6.75 (1H, ddd, *J* = 8.1, 2.0, 0.6 Hz), 4.71 (2H, d, *J* = 2.6 Hz), 2.53 (1H, t, *J* = 2.6 Hz), 2.30 (3H, s), 1.53 (9H, s).

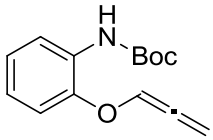
^{13}C-NMR (50 MHz, $CDCl_3$) δ_C: 153.0 (s), 144.7 (s), 132.0 (s), 128.6 (s), 122.7 (d), 119.4 (d), 112.1 (d), 80.5 (s), 78.6 (s), 76.0 (d), 56.9 (t), 28.5 (q), 21.3 (q). **MS** *m/z* 284.1 $[M+Na]^+$

General procedure for the preparation of *O*-allenes



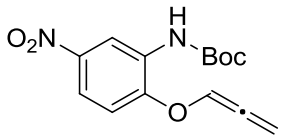
A solution of the suitable tert-butyl (2-(prop-2-yn-1-yloxy)phenyl)carbamate (1 eq) in THF (10 mL) was treated with t-BuOK (2.5 mmol). The resulting solution was stirred at rt for 1-3 min, then filtered on silica gel (AcOEt). The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash chromatography. The products need to be stored at -18 °C.

N-(*tert*-butoxycarbonyl)-*O*-(propa-1,2-dienyl)-2-aminophenol (4a)



Yield: 84% Colourless oil. **IR** (ν_{max}/cm^{-1}): 3440, 2980, 2931, 1965, 1732, 1602, 1522. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.11 (1H, d, *J* = 7.5 Hz), 7.09-6.94 (4H, m), 6.81 (1H, t, *J* = 5.9 Hz), 5.48 (2H, d, *J* = 5.9 Hz), 1.52 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 202.7 (s), 152.8 (s), 145.4 (s), 129.6 (s), 123.7 (d), 122.4 (d), 119.1 (d), 118.4 (d), 115.7 (d), 90.4 (t), 80.7 (s), 28.6 (q). **MS** *m/z* 270.1 $[M+Na]^+$

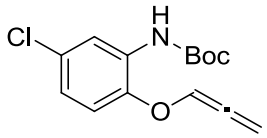
N-(*tert*-butoxycarbonyl)-*O*-(propa-1,2-dienyl)-4-nitro-2-aminophenol tert-butyl (4b)



Yield: 52% Orange solid. **mp**: 117-118 °C (Et_2O) **IR** (ν_{max}/cm^{-1}): 3435, 2974, 2928, 2002, 1733, 1541, 1343. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 9.06 (1H, d, *J* = 2.6 Hz),7.88 (1H, dd, *J* = 9.0, 2.6 Hz), 7.13 (2H, d, *J* = 9.0), 6.84 (1H, t, *J* = 5.9 Hz), 5.56 (2H, d, *J* = 5.9 Hz),1.54 (9H,

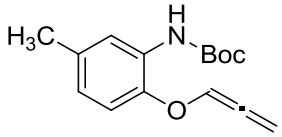
s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 202.7 (s),152.3 (s), 149.7 (s), 143.5 (s), 129.7 (s), 118.2 (d), 116.7 (d), 114.2 (d), 113.8 (d), 91.2 (t), 81.9 (s), 28.5 (q). **MS** *m/z* 315.0 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-*O*-(propa-1,2-dien-1-yl)-4-chloro-2-aminophenol (4c)**



Yield: 66% Yellow oil. **IR** (ν_{max}/cm^{-1}): 3438, 2980, 2933, 1967, 1732, 1600, 1520. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.19 (1H, d, *J* = 2.0 Hz), 7.26 (1H, bs), 6.95–6.92 (2H, m), 6.78 (1H, t, *J* = 5.9 Hz), 5.48 (2H, d, *J* = 5.9 Hz), 1.53 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 202.4 (s), 152.5 (s), 143.7 (s), 130.5 (s), 129.0 (s), 122.0 (d), 118.9 (d), 118.3 (d), 116.6 (d), 91.0 (t), 81.3 (s), 28.5 (q). **MS** *m/z* 304.0 $[M+Na]^+$

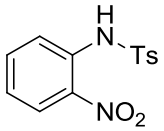
***N*-(*tert*-butoxycarbonyl)-*O*-(propa-1,2-dien-1-yl)-4-methyl-2-aminophenol (4d)**



Yield: 70% Yellow oil. **IR** (ν_{max}/cm^{-1}): 3441, 2978, 2928,1965, 1730, 1602, 1530, 1467. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.95 (1H, d, *J* = 1.3 Hz), 6.98 (1H, bs), 6.93 (1H, d, *J* = 8.1 Hz), 6.79 (1H, t, *J* = 5.9 Hz), 6.75 (1H, dd, *J* = 8.1, 1.3 Hz), 5.45 (2H, d, *J* = 5.9 Hz), 2.30 (3H, s), 1.53 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 202.6 (s), 152.9 (s), 143.2 (s), 133.6 (s), 129.2 (s), 122.8 (d), 119.5 (d), 118.9 (d), 115.8 (d), 90.6 (t), 80.7 (s), 28.6 (q), 21.4 (q). **MS** *m/z* 284.0 $[M+Na]^+$

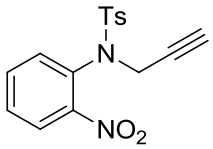
Aminoaniline derivatives

N-(*p*-toluenesulfonyl)-2-nitro-aniline (III) [46]



To a stirred solution of 2-nitroaniline (8 g, 57.92 mmol, 1 eq) in dry pyridine (32 mL) *p*-toluenesulfonylchloride (11 g, 57.92 mmol, 1 eq) was added over a 3 minute period at room temperature. The reaction mixture was stirred for 6 hours at 125 °C. The reaction mixture was concentrated under reduced pressure and the concentrate was poured into ice cold water (500 mL). The resulting reddish brown solid precipitate was filtered, washed with water and dried. Crystallization from EtOH gave **III** (8.62 g, 29.49 mmol) as yellow needle shaped crystals.
Yield: 51% **mp**: 112-113 °C (EtOH) **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 9.85 (1H, s), 8.13-7.10 (8H, m), 2.38 (3H, s).
Data are consistent with literature.

N-(*p*-toluenesulfonyl)-*N*-(prop-2-ynyl)-2-nitro-aniline (IV)



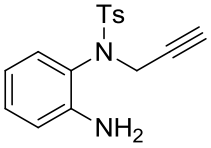
N-(*p*-toluenesulfonyl)-2-nitro-aniline **III** (2.5 g, 8.56 mmol, 1 eq), prop-2-yn-1-ol (0.55 mL, 9.42 mmol, 1.1 eq) and triphenylphosphine (3.368 g, 12.84 mmol, 1.5 eq) were suspended in anhydrous THF (50 mL) under inert atmosphere. The mixture was cooled to 0 °C and a solution of diisopropyl azodicarboxylate (2.49 mL, 12.84 mmol, 1.5 eq) in THF (10 mL) was added dropwise over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 6 hours. After reaction completion, the solvent was removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 (40 mL), washed sequentially with NaOH 2M (3 x 40 mL), HCl 1M (20 mL), saturated sodium bicarbonate

[46] Purushottamachar, P.; Khandelwal, A.; Vasaitis, T. S.; Bruno, R. D.; Gediyaa, L. K.; Njar, V. C. O. *Bioorg. Med. Chem.* **2008**, *16*, 3519.

solution (40 mL) and brine (3 x 40 mL). The organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (CH_2Cl_2) to afford **IV** (2.68 g, 8.11 mmol) as yellow solid.

Yield: 95% **mp**: 88 °C (Et_2O) **IR** (ν_{max}/cm^{-1}): 3436, 3277, 2921, 2123, 1728, 1599, 1532. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.89-7.85 (1H, m), 7.62-7.51 (4H, m), 7.38-7.34 (1H, m), 7.28-7.24 (2H, m), 4.84-4.38 (2H, bs), 2.43 (3H, s), 2.26 (1H, t, *J* = 2.5 Hz). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 149.9 (s), 144.5 (s), 136.2 (s), 131.8 (s), 133.3 (d), 133.1 (d), 130.2 (d), 129.8 (d), 128.1 (d), 125.4 (d), 78.3 (s), 74.6 (d), 41.3 (t), 21.8 (q). **MS** *m/z* 353.1 $[M+Na]^+$

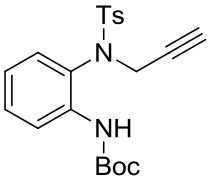
***N*-(*p*-toluenesulfonyl)-*N*-(prop-2-ynyl)-2-amino-aniline (V)**



To a stirred suspension of *N*-(*p*-toluenesulfonyl)-*N*-(prop-2-ynyl)-2-nitro-aniline **IV** (2.68 g, 8.11 mmol) in a mixture of glacial acetic acid (10 mL), ethanol (26 mL) and water (26 mL) was added reduced iron powder (1.81 g, 32.45 mmol). The resulting suspension was heated at reflux (85°C) for 3 hours. After reaction completion the mixture was filtered through a Celite® pad using AcOEt (400 mL) to remove the iron excess. The filtrate was washed with water (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (*n*-hexane / AcOEt 4:1) to afford **8** (1.63 g, 5.43 mmol) as white crystal solid.

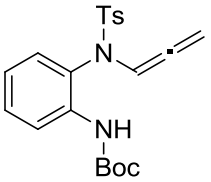
Yield: 67% **mp**: 103 °C; **IR** (ν_{max}/cm^{-1}): 3446, 3362, 3303, 2921, 1911, 1617, 1498, 1335. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 8.3 Hz, ArTs), 7.28 (2H, d, *J* = 8.3 Hz, ArTs), 7.11 (1H, ddd, *J* = 8.2 Hz, 6.8 Hz, 1.4 Hz, Ar), 6.78 (1H, dd, *J* = 8.2 Hz, 1.4 Hz, Ar), 6.62-6.49 (2H, m, Ar), 4.54 (1H, bd, *J* = 16.9 Hz, CH_2), 4.23 (3H, m, CH_2 and NH_2), 2.44 (3H, s, CH_3), 2.16 (1H, t, *J* = 2.5 Hz, C*H*). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 146.5 (s), 144.1 (s), 135.8 (s), 124.8 (s), 130.1 (d), 129.6 (d), 128.6 (d), 124.8 (d), 118.1 (d), 116.9 (d), 78.3 (s), 73.7 (d), 41.0 (t), 21.8 (q).; **MS** *m/z* 301.0 $[M]^+$

***N'*-(*p*-toluenesulfonyl)-*N'*-(prop-3-ynyl)-2-amino-*N*-(*tert*-butoxycarbonyl)-aniline (15)**



To a stirred solution of *N*-(*p*-toluenesulfonyl)-*N*-(prop-2-ynyl)-2-amino-aniline **V** (1.63 g, 5.43 mmol, 1 eq) in THF (60 mL), 1.41 g of Boc_2O (6.52 mmol, 1.2 eq) were added at room temperature. The reaction mixture was heated at reflux (90 °C) for 24 hours. Every 8 hours 1.2 eq of Boc_2O were added. After reaction completion the solvent was removed under reduced pressure, 20 mL of H_2O were added to the residue and the solution was extracted with AcOEt (3 x 20 mL). The organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (*n*-hexane/AcOEt 5:1) to afford 2**9** (2.16 g, 5.39 mmol) as white crystal solid. Yield: 67% **mp**: 127 °C (Et_2O); **IR** (ν_{max}/cm^{-1}): 3395, 3266, 2999, 2968, 2930, 2120, 1722, 1525, 1445, 1338. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.14 (1H, dd, *J* = 8.4, 1.3 Hz), 7.59 (2H, d, *J* = 8.3 Hz), 7.40 (1H, bs), 7.34-7.25 (3H, m, *J* = 8.3 Hz), 6.82 (1H, td, *J* = 7.7, 1.5 Hz), 6.66 (1H, dd, *J* = 8.0, 1.5 Hz), 4.40 (1H, bs), 4.34 (1H, bs), 2.44 (3H, s), 2.17 (1H, t, *J* = 2.5 Hz), 1.52 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 153.0 (s), 144.6 (s), 138.5 (s), 134.8 (s), 127.6 (s), 130.1 (d), 130.0 (d), 128.8 (d), 128.7 (d), 122.6 (d), 120.8 (d), 80.9 (s), 77.6 (s), 73.4 (d), 41.9 (t), 28.6 (q), 21.8 (q). **MS** *m/z* 423.2 $[M+Na]^+$

***N'*-(*p*-toluenesulfonyl)-*N'*-(propa-1,2-dienyl)-2-amino-*N*-(*tert*-butoxycarbonyl)-aniline (6)**

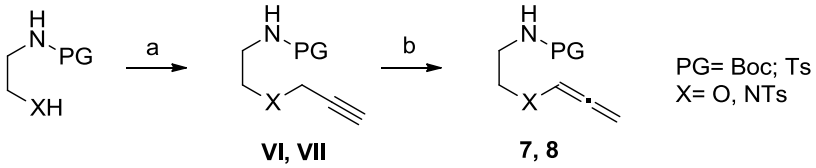


A stirred solution of *N'*-(*p*-toluenesulfonyl)-*N'*-**(**prop-3-ynyl)-2-amino-*N*-(*tert*-butoxycarbonyl) -aniline **15** (629 mg, 1.57 mmol, 1 eq) in THF (25 mL) was cooled to 0 °C with an ice bath. *t*-BuOK (352 mg, 3.14 mmol, 2 eq) was added to the solution in one portion. The reaction mixture was stirred for 25 minutes. The crude mixture was filtered through a silica gel pad washing with AcOEt/MeOH (9:1) (150 ml). The solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (CH_2Cl_2) yelding compound **6** (414 mg, 1.07 mmol) as yellow solid. The product has to be stored in at -18 °C.

Yield: 68% **mp**: 125-126 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 3422, 2981, 1728, 1595, 1516, 1445, 1355. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.17 (1H, dd, *J* = 8.4, 1.3 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 7.32-7.22 (3H, m), 7.18 (1H, bs), 7.10 (1H, t, *J* = 6.2 Hz), 6.75 (1H, td, *J* = 7.7, 1.5 Hz), 6.34 (1H, dd, *J* = 8.0, 1.5 Hz), 5.02 (2H, d, *J* = 6.2 Hz), 2.46 (3H, s), 1.52 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 201.2 (s), 152.8 (s), 144.7 (s), 138.0 (s), 134.6 (s), 125.4 (s), 130.1 (d), 129.5 (d), 129.9 (d), 128.3 (d), 122.0 (d), 120.3 (d), 102.2 (d), 88.2 (t), 81.0 (s), 28.5 (q), 21.9 (q). **MS** *m/z* 423 $[M+Na]^+$

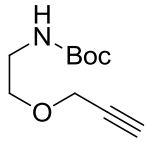
Aliphatic derivatives

For the studies to dihydroxazole, dihydroimidazole and isoxazolidine derivatives the precursors were synthetised following the scheme below.



a) propargyl bromide, NaH, THF/DMF; b) *t*-BuOK, THF

N-(*tert*-butoxycarbonyl)-*O*-(prop-2-ynyl)-1,2-amminoethanol (VI)[47]



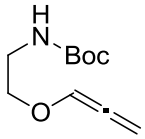
To a suspension of NaH (60% mineral oil, 1 eq) in THF at 0 °C was added a solution of *N*-(*tert*-butyloxycarbonyl)-aminoethanol (3 g, 18.61 mmol, 1 eq) in 15 ml of DMF and stirred for 30 minutes. Then a solution of propargylbromide (2 eq) in THF was added dropwise and the reaction was stirred overnight at room temprature. After reaction completion, 20 ml of water were added, extracted with CH_2Cl_2. The organic layers were then washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (*n*-hexane / AcOEt 5:1)

Yield: 85% Pale yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 5.04 (1H, br s), 3.96 - 4.01 (2H, m), 3.43 (2H, t, *J* = 2.8 Hz), 3.17 (2H, br s), 2.35 (1H, s), 1.28 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ_C: 155.9 (s), 79.3 (s), 75.8 (s), 74.8 (d), 68.9 (t), 58.0 (t), 40.1 (t), 28.2 (q). **MS** (*m/z*): 199 $[M]^+$

Data are consistent with literature.

[47] CTIBIO, *Patent WO2009/113828 A2*, **2009**

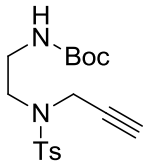
_N_-(_t_-butoxycarbonyl)-_O_-(1,2-propadienyl)-aminoethanol (7)



To a stirred solution of *N*-(*tert*-butoxycarbonyl)-*O*-(prop-2-ynyl)-1,2-amminoethanol **VI** (500 mg, 2.53 mmol) in 40 mL of THF, *t*-BuOK (2 eq) was added and after 1 minute the mixture was filtered on a silica gel pad with AcOEt (250 ml) The solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (Petrol Ether/AcOEt 7:3) yelding compound **7** (382 mg, 1.92 mmol).

Yield: 76% Colorless oil. **IR** (ν_{max}/cm^{-1}): 3287, 1956, 1704 **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 6.66 (1H, t, *J* = 5.9 Hz), 5.37 (2H, d, *J* = 5.9 Hz), 4.98 (1H, br s), 3.55 (2H, dd, *J* = 10.2, 5.1 Hz), 3.32 (2H, dd, *J* = 10.2, 5.1 Hz), 1.38 (9H, s); **^{13}C-NMR** (50MHz, $CDCl_3$): δ_C: 200.9 (s), 155.8 (s), 121.3 (d), 90.9 (t), 79.2 (s), 67.7 (t), 39.8 (t), 28.3 (q). **MS** (*m/z*): 199 $[M]^+$

_N_-(_t_-butoxycarbonyl)-_N'_-tosyl-propargylethylen-1,2-diamine (VII)[48]



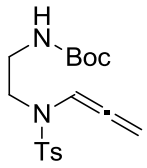
To a suspension of NaH (60% mineral oil, 178 mg, 2.72 mmol) in THF at 0 °C was added a solution of *N*-(*tert*-butyloxycarbonyl)-*N*-(*p*-toluenesulfonyl)-ethylendiamine (858 mg, 2.72 mmol, 1 eq) in 7 ml of DMF and stirred for 30 minutes. Then a solution of propargylbromide (0.31 mL, 4.08 mmol, 2 eq) in THF (5 ml) was added dropwise and the reaction was stirred overnight at room temprature. After reaction completion, 5 ml of water were added and extracted with CH_2Cl_2. The organic layers were then washed with brine, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography (Petrol Ether/AcOEt 8:2).

Both the alkynyl (**VII**) and the allene (**8**) derivatives were formed.

[48] Li, H.; Widenhoefer, R. A. *Org. Lett.*, **2009**, *11*, 2671

Yield: 31% Colorless oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H:: 7.71 (2H, d, *J* = 8.4 H), 7.28 (2H, d, *J* = 8.4 Hz), 4.93 (1H, s), 4.14 (2H, d, *J* = 2.4 Hz,), 3.35-3.31 (4H, m), 2.41 (3H, s), 2.05 (1H, t, *J* = 2.2 Hz), 1.44 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ_C: 156.2 (s), 143.9 (s), 137.9 (s), 135.6 (d), 133.5 (d), 129.7 (d), 127.8 (d), 79.6 (s), 76.7 (s), 74.2 (d), 21.7 (q), 46.4 (t), 38.5 (t), 37.3 (t), 28.5 (q). **MS** (*m/z*): 353 $[M]^+$

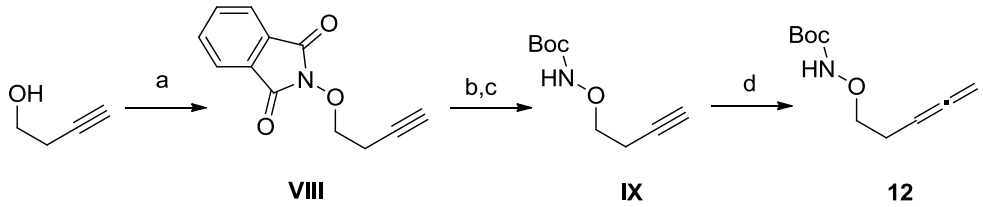
***N*-(*t*-butoxycarbonyl)-*N'*-tosyl-(1,2-propadienyl)-ethylendiamine (8)**



Yield: 63% Colorless oil. **IR** ($\nu_{max/}$ cm^{-1}): 1950, 1634; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.66 (2H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 8.0 Hz), 6.83 (1H, t, *J* = 6.2 Hz), 5.34 (2H, dd, *J* = 12.6, 6.2 Hz), 4.92 (1H, br s, 1H), 3.47 (2H, br s), 3.27 (2H, br s), 2.41 (3H, s), 1.45 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 200.1(s), 154.6 (s), 143.9 (s), 134.5 (s), 129.8 (d), 129.2 (d), 127.6 (d), 127.1 (d), 100.4 (d), 88.2 (t), 80.6 (s), 38.6 (t), 37.7 (t), 28.3 (q), 21.5 (q). **MS** (*m/z*): 352 $[M]^+$

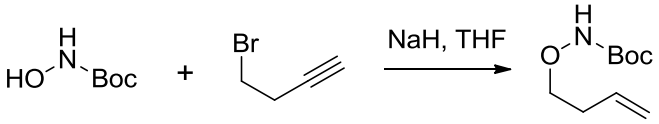
Hydroxylamine derivatives

For the studies to isoxazolidine derivatives the precursors were synthetised following the schemes below.



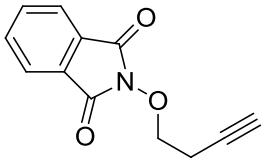
VIII **IX** **12**

a) N-hyroxyphthalimide, DIAD, PPh_3, THF; b) NH_2NH_2, DCM; c) Boc_2O, NaOH, DCM, d) $(CH_2O)_n$, Cy_2NH, CuI, dioxane



28

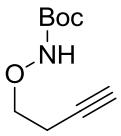
2-(but-3-yn-1-yloxy) isoindoline-1,3-dione (VIII)



To a stirred solution of 3-butyn-1-ol (1.5 g, 21.4 mmol) in THF (40 mL) under nitrogen atmosphere triphenylphosphine (6.74 g, 25.7 mmol) and *N*-hydroxyphtalimide (4.19 g, 25.7 mmol) were added sequentially. The mixture was then cooled to 0 °C and a solution of diisopropyl azodicarboxylate (4.98 mL, 5.19 g, 25.7 mmol) in THF (5 mL) was added dropwise. After stirring the reaction at room temperature overnight, the solvent was removed under reduced pressure and the residue suspended with Et_2O. The white precipitate was filtered off, the solvent removed and the crude mixture purified by silica gel chromatography (*n*-hexane/AcOEt 4:1) yielding the desired compound (4.45g, 20.66 mmol) as a white solid.
Yield: 96.5%. White solid. **mp** 103 °C (Et_2O); **IR** (ν_{max}/cm^{-1}): 3269, 2127, 1734; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.90-7.68 (4H, m), 4.32-4.30 (2H, m), 2.73 (2H, td, *J*= 7.1, 2.7 Hz),

1.98 (1H, t, *J*= 2.7 Hz); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 163.9 (s), 134.9 (d), 129.3 (s), 124.0 (d), 75.9 (t), 70.6 (d), 19.2 (t). **MS** (*m/z*): 215 $[M]^+$

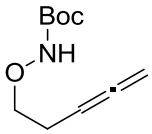
_O_-(but-3-ynyl)-_N_-(_tert_-butoxycarbonyl)-hydroxylamine (IX)



To a stirred solution of 2-(but-3-yn-1-yloxy)isoindoline-1,3-dione **VIII** (2.2 g, 10.6 mmol) in DCM (10 mL) 1.54 mL of hydrazine hydrate (1.59 g, 31.8 mmol) were added and the mixture was stirred at room temperature. After 1h30 the reaction mixture was filtered on a Celite® pad. 10 mL of water, solid NaOH (932 mg, 23.32 mmol) and Boc_2O (2.77 g, 12.72 mmol) were then added to the filtrate and the mixture was stirred at room temperature overnight. After reaction completion, the layers were separated and extracted with AcOEt (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude was then purified via silica gel chromatography (n-Hexane/AcOEt 5:1 the desired compound (1.62 g, 8.75 mmol) as a colorless oil.

Yield: 82%; Colorless oil. **IR** (ν_{max}/ cm^{-1}): 3269, 2127, 1695; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H : 7.18 (1H, br s), 3.97 (2H, t, *J* = 6.8 Hz), 2.56 (2H, t, *J* = 6.8 Hz), 1.99 (1H, t, *J* = 6.8 Hz), 1.48 (9H, s); **^{13}C-NMR** ($CDCl_3$) δ_C: 156.9 (s), 80.5 (s), 75.6 (d), 74.1 (t), 69.7 (t), 28.8 (q), 18.3 (t). **MS** (*m/z*): 185 $[M]^+$

_O_-(penta-3,4-dien-1-yl)-_N_-(tert-butoxycarbonyl)-hydroxylamine (8)

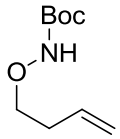


To a stirred solution of tert-butyl but-3-yn-1-yloxycarbamate (300 mg, 1.62 mmol) in dioxane (2 mL) under nitrogen atmosphere freshly distilled diisopropyl amine (0.46 mL, 328 mg, 3.24 mmol) was added, followed by 97 g of paraformaldehyde (3.24 mmol) an 122 mg of CuI (0.81 mmol).

The mixture was then heated to 80 °C and stirred for 16h. The solvent was then removed and the residue purified by silica gel chromatography (*n*-Hexane/AcOEt 10:1) yielding the desired compound (93 mg, 0.45 mmol) as a pale yellow oil.

Yield 28%. Pale yellow oil. **IR** (ν_{max}/ cm^{-1}): 3315,1632,1564; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 7.30 (1H, br s), 5.14-5.07 (1H, m), 4.67 (2H, dt, *J* = 6.5, 3.1 Hz, 2H), 3.89 (2H, t, *J* = 6.7 Hz), 2.35-2.28 (2H, m), 1.42 (9H, s); **^{13}C-NMR** ($CDCl_3$) δ_C: 208.9 (s), 156.9 (s), 86.1 (d), 81.6 (s), 75.6 (t), 75.1 (t), 28.2 (q), 27.1 (t). **MS** (*m/z*): 199 $[M]^+$

***N*-(*tert*-butoxycarbonyl)-*O*-(but-3-en-1-yl)-hydroxylamine 28[49]**



To a stirred suspension of NaH (60% on mineral oil, 71 mg, 1.8 mmol), in (THF 5 ml) under inert athmosphere at 0 °C, *N*-(*tert*-butoxycarbonyl)- hydroxylamine (200 mg, 1.5 mmol) was added. After 15 minutes a solution of 4-bromo-but-1-ene (0.17 ml, 227 mg, 1.65 mmol) was added dropwise and the reaction stirred at room temperature overnight.

After reaction completion, the solvent was removed under reduced pressure, 10 ml NH_4Cl solution added and exctracted with AcOEt (15 ml x 3).

The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude was then purified via silica gel chromatography (*n*-hexane/AcOEt :1) and the desired compound (112 mg, 0.61 mmol) was afforded as a colorless oil.

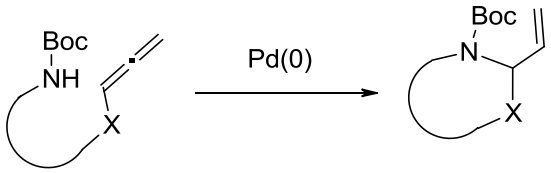
Yield 40%. Colorless oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 7.12 (1H, s), 5.83 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz), 5.23–4.95 (2H, m), 3.91 (2H, t, *J* = 6.7 Hz), 2.40 (2H, qt, *J* = 6.7, 1.4 Hz), 1.50 (9H, s).

Data are consistent with literature.

[49] Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.*, **2009**, *74*, 2533–2540

Chapter 2: Hydroamination reactions

General procedure for the hydroamination reactions on allene derivatives



	Catalyst	Additive	Solvent	Temperature	Time
1	$Pd(PPh_3)_4$ 8% mol	---	Toluene	150 °C (MW)	60’
2	$Pd(PPh_3)_4$ 8% mol	---	CH_3CN	120 °C (MW)	40’
3	$Pd(PPh_3)_4$ 8% mol	---	THF	120 °C (MW)	40’
4	$Pd(PPh_3)_4$ 8% mol	---	DMF	120 °C (MW)	40’
5	$PdCl_2(CH_3CN)_2$ 5% mol	---	CH_3CN	120 °C (MW)	40’
6	$Pd_2(dba)_3$ 5% mol	---	THF	120 °C (MW)	40’
7	$Pd(PPh_3)_4$ 15% mol	PPh_3 10% mol	Toluene	110°C	2-5h
8	$Pd(PPh_3)_4$ 15% mol	PPh_3 10% mol	Toluene	90°C (MW)	40’
9	$Pd(PPh_3)_4$ 8% mol	PPh_3 10% mol	Toluene	90°C (MW)	40’
10	$Pd(PPh_3)_4$ 5% mol	PPh_3 5% mol	Toluene	90°C (MW)	40’

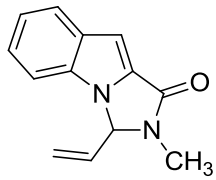
Procedure with microwave irradiation

A mixture of allene (0.4-1 mmol) and the suitable catalist dissolved in the suitable solvent (5 mL) were transferred in a microwave reactor and heated according to the data reported in the table above (temperature and time) under microwave irradiation maintaining the power between 400-500 W. The mixture was then filtered on a Celite® layer, the solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography.

Procedure with conventional heating (entry 7)

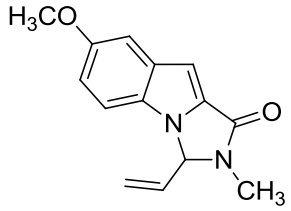
$Pd(PPh_3)_4$ (8% mol) and PPh_3 (10% mol) were added to a solution of the suitable allene (0.4 mmol) in toluene (5 ml). The reaction mixture was stirred at reflux at 110 °C for 2-5h. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash chromatography.

2-Methyl-3-vinyl-2,3-dihydro-1H-imidazo[1,5-a]indol-1-one (2a)



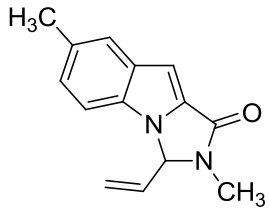
Yield 71% (entry 1), Colorless oil; **IR** (ν_{max}/cm^{-1}):1645; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.75 (1H, d, J=8.1Hz), 7.32-7.25 (2H, m), 7.10 (1H, dd, *J* = 7.8, 7.0 Hz), 6.92 (1H, s), 5.96-5.88 (1H, m), 5.77-5.30 (3H, m), 3.07 (3H, s); **^{13}C-NMR**(100MHz,$CDCl_3$) δ_C: 160.5 (s), 133.5 (d), 133.0 (s), 131.9 (s), 131.4 (s), 124.4 (t), 123.8 (d), 123.6 (d), 121.0 (d), 110.1 (d), 97.9 (d), 75.2 (d), 26.8 (q). **MS** (*m/z*) 212 $[M]^+$.

7-Methoxy-2-methyl-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2b)



Yield: 67%. (entry 1). White solid. **mp** 138 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1638; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.16 (1H, d, *J* = 8.9 Hz), 7.13 (1H, d, *J* = 2.3 Hz), 6.91 (1H, dd, *J* = 8.9, 2.3 Hz), 6.80 (1H, s), 5.89-5.85 (1H, m), 5.73-5.59 (3H, m), 3.83 (3H, s), 3.03 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.5 (s), 154.8 (s), 133.6 (d), 132.3 (s), 131.9 (s), 128.4 (s), 124.3 (t), 115.1 (d), 110.8 (d), 103.9 (d), 97.3 (d), 75.1 (d), 55.7 (q), 26.7 (q). **MS**: (*m/z*) 242 $[M]^+$.

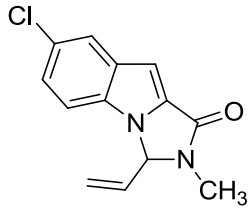
2,7-Dimethyl-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2c)



Yield: 78%. (entry 1).White solid. **mp** 122 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1655; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.51 (1H, s), 7.17 (1H, d, *J* = 8.5 Hz), 7.09 (1H, d, *J* = 8.5 Hz), 6.82 (1H, s), 5.91-5.85 (1H, m), 5.74-5.60 (3H, m), 3.04 (3H, s), 2.44 (3H, s); **^{13}C-NMR** (100

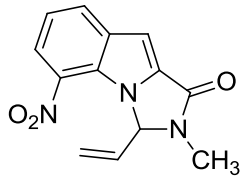
MHz, $CDCl_3$) δ_C: 160.6 (s), 133.6 (d), 133.2 (s), 132.2 (s), 131.5 (s), 130.3 (s), 125.6 (d), 124.2 (t), 122.9 (d), 109.7 (d), 97.2 (d), 75.1 (d), 26.7 (q), 21.4 (q). **MS**: (*m/z*) 226 $[M]^+$.

7-Chloro-2-methyl-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2d)



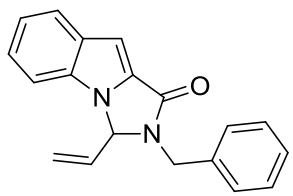
Yield: 85% (entry 1). White solid. **mp** 144 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1632; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.67 (1H, s), 7.17 (2H, s), 6.79 (1H, s), 5.93-5.60 (4H, m), 3.04 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.0 (s), 133.1 (d), 132.7 (s), 132.6 (s), 131.2 (s), 126.6 (s), 124.8 (t), 124.3 (d), 122.6 (d), 111.0 (d), 97.2 (d), 75.1 (d), 26.8 (q). **MS**: (*m/z*) 246 $[M]^+$.

2-Methyl-5-nitro-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2e)



Yield: 58% (entry 1). White solid. **mp** 170 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1652; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 8.11 (1H, d, *J* = 8.0 Hz), 8.06 (1H, d, *J* = 7.9 Hz), 7.27 (1H, dd, *J* = 7.9, 8.0 Hz), 7.09 (1H, s), 6.37 (1H, d, *J* = 7.6 Hz), 5.61-5.51 (2H, m), 5.45-5.37 (1H, m), 3.12 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 158.9 (s), 136.1 (s), 135.2 (s), 135.1 (s), 133.3 (d), 130.7 (d), 125.1 (s), 124.1 (t), 121.6 (d), 120.3 (d), 99.3 (d), 76.8 (d), 27.0 (q). **MS**: (*m/z*) 257 $[M]^+$.

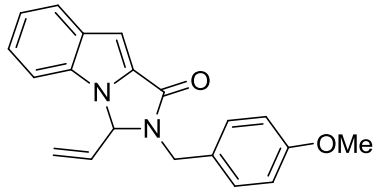
2-Benzyl-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2f)



Yield: 63% (entry 1). White solid. **mp** 111 °C (*i*-Pr_2O). **IR**: 1648 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.75 (1H, d, *J* = 8.0 Hz), 7.36-7.17 (8H, m), 6.98 (1H, s), 5.77-5.64 (4H,

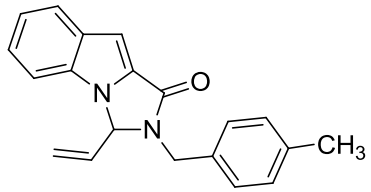
m), 5.35 (1H, d, *J* = 15.2 Hz), 4.14 (1H, d, *J* = 15.2 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.3 (s), 136.2 (s), 133.4 (d), 133.0 (s), 131.9 (s), 131.1 (s), 128.9 (d), 128.3 (d), 128.0 (d), 124.5 (t), 123.9 (d), 123.6 (d), 121.0 (d), 110.1 (d), 98.2 (d), 72.9 (d), 43.6 (t). **MS**: (*m/z*) 288 $[M]^+$.

2-(4-Methoxybenzyl)-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2g)



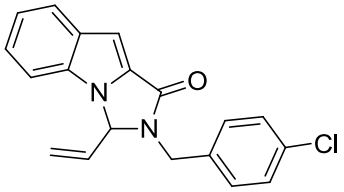
Yield: 89% (entry 1).White solid. **mp** 113 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1659; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.74 (1H, d, *J* = 8.0 Hz), 7.26-7.22 (4H, m), 7.18-7.14 (1H, m), 6.96 (1H, s), 6.89-6.87 (2H, m), 5.73-5.64 (4H, m), 5.27 (1H, d, *J* = 15.0 Hz), 4.08 (1H, d, *J* = 15.0 Hz), 3.79 (3H, s); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.3 (s), 159.3 (s), 133.4 (d), 133.0 (s), 131.8 (s), 131.3 (s), 129.7 (d), 128.3 (s), 124.5 (t), 123.9 (d), 123.5 (d), 121.0 (d), 114.3 (d), 110.1 (d), 98.1 (d), 72.8 (d), 55.3 (q), 43.1 (t). **MS**: (*m/z*) 318 $[M]^+$.

2-(4-Methylbenzyl)-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2h)



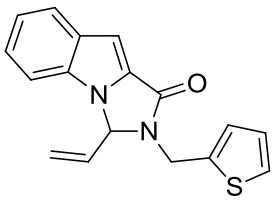
Yield: 69% (entry 1). White solid. **mp** 138 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1648; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.77-7.74 (1H, m), 7.27-7.15 (7H, m), 6.98 (1H, s), 5.82-5.63 (4H, m), 5.32 (1H, d, *J* = 15.1 Hz), 4.10 (1H, d, *J* = 15.1 Hz), 2.36 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.3 (s), 137.7 (s), 133.4 (d), 133.2 (s), 133.0 (s), 131.9 (s), 131.2 (s), 129.7 (d), 128.3 (d), 124.5 (t), 123.9 (d), 123.5 (d), 121.0 (d), 110.1 (d), 98.1 (d), 72.8 (d), 43.4 (t), 21.1 (q). **MS**: (*m/z*) 302 $[M]^+$.

2-(4-Chlororbenzyl)-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2i)



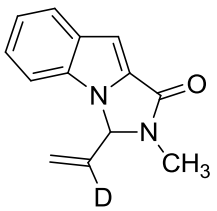
Yield: 85% (entry 1). White solid. **mp** 131 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1650; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.75 (1H, d, *J* = 8.0 Hz), 7.35-7.30 (2H, m), 7.27-7.24 (4H, m), 7.20-7.16 (1H, m), 6.98 (1H, s), 5.82-5.63 (4H, m), 5.24 (1H, d, *J* = 15.4 Hz), 4.16 (1H, d, *J* = 15.4 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.3 (s), 134.8 (s), 133.9 (s), 133.3 (d), 133.1 (s), 131.8 (s), 130.8 (s), 129.7 (d), 129.1 (d), 124.7 (t), 124.1 (d), 123.6 (d), 121.1 (d), 110.1 (d), 98.4 (d), 73.0 (d), 43.0 (t). **MS**: (*m/z*) 322 $[M]^+$.

2-(Tiophen-2-ylmethyl)-3-vinyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2j)



Yield: 72% (entry 1). White solid. **mp** 112 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1656; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.74 (1H, d, *J* = 8.0 Hz), 7.27-7.23 (3H, m), 7.19-7.15 (1H, m), 7.05-7.04 (1H, m), 6.99-6.97 (2H, m), 5.90-5.67 (1H, d, *J* = 16.4 Hz), 5.40 (1H, d, *J* = 15.7 Hz), 4.38 (1H, d, *J* = 15.7 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 159.9 (s), 138.5 (s), 133.2 (d), 133.1 (s), 131.8 (s), 130.9 (s), 127.3 (d), 127.1 (d), 126.0 (d), 124.9 (t), 124.0 (d), 123.6 (d), 121.1 (d), 110.1 (d), 98.4 (d), 72.8 (d), 38.0 (t). **MS**: (*m/z*) 294 $[M]^+$.

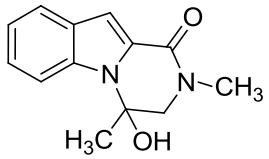
3-(1-Deutheriumvinyl)-2-methyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (2k)



Yield: 68% (entry 1). Colorless oil. **IR**: 1639 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.76-7.73 (1H, m), 7.30-7.19 (3H, m), 6.90 (1H, s), 5.92-5.89 (1H, m), 5.75-5.70 (2H, m), 3.07 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 158.5 (s), 133.5 (s), 132.9 (s), 131.7 (s), 124.3

(t), 123.8 (d), 123.6 (d), 123.2 (s), 121.0 (d), 110.3 (d), 97.9 (d), 75.1 (d), 26.8 (q). **MS**: (*m/z*) 213 $[M]^+$.

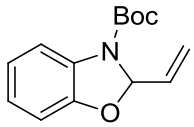
4-Hydroxy-2,4-dimethyl-3,4-dihydropyrazino-[1,2-a]indol-1(2H)-one (3).



A mixture of allenamide **1** (1 mmol) in toluene (10 mL) was heated at 150 °C for 1 h under microwave irradiation, or refluxed for 24 h, then filtered on a Celite® layer. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography.

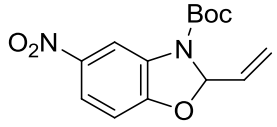
Yield 41%. White solid, **mp** 134 °C (*i*-Pr_2O); **IR** 3313, 1652 cm-1; **^{1}H-NMR** (400 MHz, $CDCl_3$) $\delta_{H:}$ 7.83 (1H, d, *J* = 8.5 Hz), 7.52 (1H, d, *J* = 7.9 Hz), 7.22 (1H, dd, *J* = 7.9, 7.4 Hz), 7.10 (1H, dd, *J* = 8.5, 7.4 Hz), 7.03 (1H, s), 4.92 (1H, br s), 3.67 (1H, d, *J* = 12.6 Hz), 3.49 (1H, d, *J* = 12.6 Hz), 2.93 (3H, s), 1.78 (3H, s). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.1 (s), 135.8 (s), 128.2 (s), 128.1 (s), 124.7 (d), 122.6 (d), 120.9 (d), 113.3 (d), 108.0 (d), 82.9 (s), 60.7 (t), 34.1 (q), 24.7 (q). **MS**: (*m/z*) 230 $[M]^+$.

***N*-(*tert*-Butoxy carbonyl) 2-vinyl-2,3-dihydro-benzo[d]oxazole (5a)**



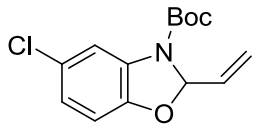
Yield 70% (entry 5). Colourless oil. **IR** (ν_{max}/cm^{-1}): 3417, 2978, 2103, 1711, 1490. **^{1}H-NMR** (300 MHz, DMSO) δ_H: 7.36 (1H, bs), 6.95-6.84 (3H, m), 6.47 (1H, d, *J* = 6.1 Hz), 5.96 (1H, ddd, *J* = 16.9, 10.3 Hz, 6.1 Hz), 5.50 (1H, d, *J* = 16.9, Hz), 5.39 (1H, d, *J* = 10.3 Hz), 1.49 (9H, s). **^{13}C-NMR** (75 MHz, DMSO) δ_C: 150.5 (s), 150.2 (s), 133.8 (d), 129.7 (s), 124.1 (d), 122.1 (d), 120.6 (t), 114.4 (d), 109.5 (d), 93.8 (d), 82.6 (s), 28.7 (q). **MS** (*m/z*) 270.1 $[M+Na]^+$

***N*-(*tert*-Butoxy carbonyl) 5-nitro-2-vinyl-2,3-dihydro-benzo[d]oxazole (5b)**



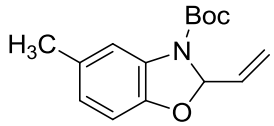
Yield: 40% (entry 9). Colorless oil. **IR** (ν_{max}/cm^{-1}): 3413, 3131, 2980, 2931, 2853, 2425, 2303, 1875, 1721, 1600, 1525, 1493. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.30 (1H, br s), 7.92 (1H, dd, *J* = 8.7, 2.4 Hz), 6.80 (1H, d, *J* = 8.7 Hz), 6.52 (1H, br d, *J* = 6.0 Hz), 5.96 (1H, ddd, *J* = 16.5, 10.2, 6.0 Hz), 5.57 (1H, d, *J* = 16.5, Hz), 5.44 (1H, d, *J* = 10.2 Hz), 1.57 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 155.5 (s), 149.8 (s), 142.9 (s), 132.1 (d), 130.8 (s), 121.8 (d), 120.8 (t), 109.8 (d), 108.1 (d), 95.9 (d), 83.8 (s), 28.4 (q). 21b, **MS** (*m/z*) 315.1 $[M+Na]^+$

***N*-(*tert*-Butoxy carbonyl) 5-chloro-2-vinyl-2,3-dihydro-benzo[d]oxazole (5c)**



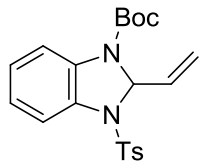
Yield 91% (entry 7). Colourless oil. **IR** (ν_{max}/cm^{-1}): 2979, 2932, 1716, 1599, 1489, 1430, 1383, 1297. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.50 (1H, br s), 6.85 (1H, dd, *J* = 8.4, 2.2 Hz), 6.66 (1H, d, *J* = 8.4 Hz), 6.38 (1H, br d, *J* = 6.4 Hz), 5.94 (1H, ddd, *J* = 17.0, 10.8, 6.4 Hz), 5.52 (1H, d, *J* = 17.0 Hz), 5.38 (1H, d, *J* = 10.8 Hz), 1.55 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.1 (s), 149.2 (s), 130.6 (s), 126.4 (s), 132.7 (d), 119.9 (t), 122.9 (d), 114.7 (d), 109.3 (d), 94.6 (d), 83.0 (s), 28.5 (q). **MS** (*m/z*) 304 $[M+Na]^+$

***N*-(*tert*-Butoxy carbonyl) 5-methyl-2-vinyl-2,3-dihydro-benzo[d]oxazole-3(2*H*) (5d)**



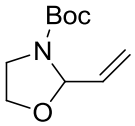
Yield 71% (entry 7). Yellow oil. **IR** (ν_{max}/cm^{-1}): 2977, 2930, 1713, 1645, 1498, 1388. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.65 (1H, br s), 6.72-6.63 (2H, m), 6.34 (1H, br d, *J* = 5.4 Hz), 5.94 (1H, ddd, *J* = 17.0, 10.7, 6.0 Hz), 5.51 (1H, d, *J* = 17.0 Hz), 5.35 (1H, d, *J*= 10.7 Hz), 2.28 (3H, s), 1.55 (9H, s). **^{13}C-NMR** (50 MHz, CDCl3) δ_C: 150.4 (s), 148.3 (s), 131.1 (s), 129.4 (s), 133.1 (d), 119.4 (t), 123.5 (d), 115.1 (d), 108.4 (d), 93.8 (d), 82.4 (s), 28.5 (q), 21.4 (q). **MS** (*m/z*) 262 $[M+H]^+$

***N*-(*tert*-Butoxy carbonyl)-*N'*-tosyl-2-vinyl-2,3-dihydro-1*H*-benzo[d]imidazole (9)**



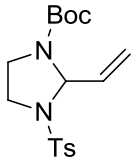
Yield 79% (entry 7). Yellow oil. **IR** (ν_{max}/cm^{-1}): 3645, 3412, 3069, 2979, 2932, 1919, 1714, 1598, 1486, 1385. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.62-6.99 (8H, m), 6.22 (1H, m), 5.85 (1H, ddd, *J* = 17.0, 10.1, 4.7 Hz), 5.46 (1H, d, *J* = 17.0 Hz), 5.27 (1H, dt, *J* = 10.1, 1.1 Hz), 2.32 (3H, s), 1.42 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.2 (s), 144.7 (s), 134.3 (s), 133.5 (s), 131.6 (s), 118.1 (t), 132.9 (d), 129.7 (d), 127.5 (d), 126.7 (d), 123.5 (d), 119.1 (d), 115.5 (d), 77.3 (d), 82.3 (s), 28.4 (q), 21.6 (q). **MS** (*m/z*) 423 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)–2-vinyloxazolidine (10)**



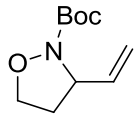
Yield 76% (entry 5). Colorless oil- **IR** (ν_{max}/cm^{-1}): 1685. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 5.77-5.70 (1H, m), 5.40-5.29 (2H, m), 5.21 (1H, d, *J* = 10.3 Hz), 3.98-3.89 (2H, m), 3.60-3.56 (1H, m), 3.35-3.30 (1H, m), 1.40 (9H, s) **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.9 (s), 134.7 (d), 117.7 (t), 80.2 (s), 88.2 (d), 65.3 (t), 44.2 (t), 28.3 (q),**MS** (*m/z*): 199 $[M]^+$

***N*-(*tert*-butoxycarbonyl)–*N'*-(*p*-toluenesulfonyl)-2-vinylimidazolidine (11)**



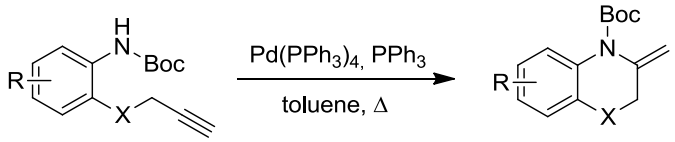
Yield 61% (entry 5) Colorless oil. **IR** (ν_{max}/cm^{-1}): 1689 **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 7.31 (2H, d, *J* = 8.2 Hz), 7.28 (br s, 2H), 5.83-5.76 (2H, m), 5.33 (1H, d, *J* = 16.8 Hz), 5.24 (1H, d, *J* = 9.8 H), 3.72 (1H, br s), 3.42-3.49 (1H, m), 3.15 (1H, t, *J* = 6.9 Hz),2.93 (1H, br s), 2.42 (3H, s), 1.45 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.2 (s), 144.4 (s), 133.9 (s), 129.9 (d), 129.7 (d), 127.4 (d), 127.1 (d), 116.9 (t), 80.7 (s), 73.2 (d), 45.4 (t), 43.3 (t), 28.3 (q), 21.6 (q). **MS** (*m/z*) 341 $[M]^+$

***N*-(*tert*-butyl carbonyl) 3-vinylisoxazolidine (13)**



Yield 74% (entry 5). Colorless oil. **IR** (ν_{max}/cm^{-1}): 1689 **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 5.82 (1H, ddd, *J*= 16.9, 10.1, 6.5 Hz), 5.27 (1H, d, *J* = 16.9 Hz), 5.12 (1H, d, *J* = 10.1 Hz), 4.59 (1H, dd, *J* = 13.8, 6.5 Hz), 4.06 (1H, td, *J* = 7.8, 4.2 Hz), 3.78 (1H, dd, *J* = 15.3, 7.8 Hz), 2.56-2.37 (1H, m), 2.17-1.96 (1H, m), 1.50 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 157.3 (s). 137.7 (d), 115.8 (t), 82.2 (s), 68.9 (t), 61.2 (d), 35.4 (t), 28.5 (q), **MS** (*m/z*): 199 $[M]^+$

General procedure for the Pd-catalyzed hydroamination reactions on alkyne derivatives

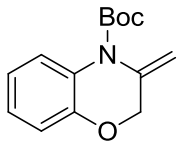


X=O **14a-d**
X=NTs **15**

16a-d
17

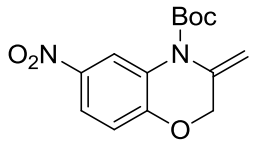
$Pd(PPh_3)_4$ (8% mol) and PPh_3 (10% mol) were added to a solution of the suitable propargyl derivative (0.4 eq) in toluene (5 mL) under nitrogen atmosphere. The reaction mixture was stirred at reflux at 90 °C for 4h. The reaction mixture was filtered under reduced pressure through a Celite® pad washing with AcOEt. The solvent was removed under reduced pressure and the crude purify by silica gel chromatography. (*n*-hexane/AcOEt 10:1)

***N*-(*tert*-butoxycarbolnyl)-3-methylene-3,4-dihydro-2H-benzo[b][1,4]oxazine (16a)**



Yield: 58%. Yellow oil. **IR** (ν_{max}/cm^{-1}): 3433, 3058, 2979, 2932, 2870, 1717, 1602, 1494. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.01-6.76 (4H, m), 5.34 (1H, s), 5.13 (1H, s), 4.56 (2H, s), 1.53 (9H, s); **^{13}C-NMR** (50 MHz, CDCl3) δ_C: 152.0 (s), 147.2 (s), 133.7 (s), 131.6 (s), 24.7 (d), 123.6 (d), 120.9 (d), 117.1 (d), 107.9 (t), 82.5 (s), 69.8 (t), 28.4 (q). **MS** (*m/z*) 270.1 $[M+Na]^+$, 249.0 $[M]^+$

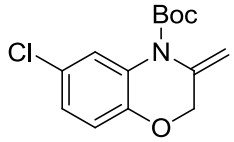
***N*-(*tert*-buoxycarbonyl)-3-methylene-6-nitro-3,4-dihydro-2H-benzo[b][1,4]oxazine (16b)**



Yield: 76%. Orange oil. **IR** (ν_{max}/cm^{-1}): 3436, 3128, 2986, 2923, 2851, 2626, 1926, 1721, 1588, 1513; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.76 (1H, d, *J* = 2.7 Hz), 7.89 (1H, dd, *J* = 9.0, 2.7 Hz), 6.93 (1H, d, *J* = 9.0 Hz), 5.43 (1H, s), 5.35 (1H, s), 4.66 (2H, s), 1.57 (9H, s);

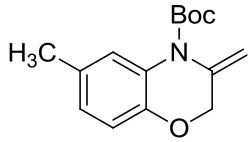
^{13}C-NMR (50 MHz, $CDCl_3$) δ_C: 152.4 (s), 151.6 (s), 143.0 (s), 134.0 (s), 129.6 (s), 120.3 (d), 119.6 (d), 117.3 (d), 111.5 (t), 81.8 (s), 69.7 (t), 28.5 (q). **MS** *m/z* 315.0 $[M+Na]^+$

***N*-(*tert*-buoxycarbonyl)-3-methylene-6-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine (16c)**



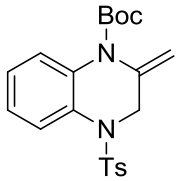
Yield: 45%. **IR** (ν_{max}/cm^{-1}): 3422, 3086, 2979, 2930, 2333, 1858, 1719, 1601; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.79 (1H, m, d, *J* = 2.4 Hz), 6.94 (1H, dd, *J* = 8.7, 2.4 Hz), 6.79 (1H, d, *J* = 8.7 Hz), 5.35 (1H, d, *J* = 0.5 Hz), 5.19 (1H, d, *J* = 0.5 Hz), 4.54 (2H, d, *J* = 0.5 Hz), 1.54 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 151.5 (s), 145.5 (s), 135.7 (s), 127.7 (s), 125.7 (s), 124.5 (d), 123.2 (d), 118.0 (d) 109.0 (t), 83.0 (s), 69.5 (t), 28.3 (q). **MS** (*m/z*) 281.0 $[M]^+$

***N*-(*tert*-buoxycarbonyl)-3-methylene-6-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (16d)**



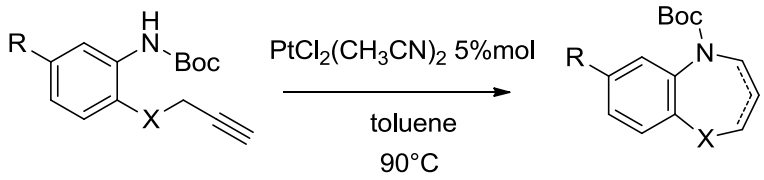
Yield: 70%. **IR** (ν_{max}/cm^{-1}): 3432, 3056, 2977, 2928, 1715; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.53 (1H, s), 6.95-6.67 (2H, m), 5.34 (1H, s), 5.15 (1H, s), 4.54 (2H, d, *J* = 0.6 Hz), 2.30 (3H, s), 1.54 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.0 (s), 145.0 (s), 136.9 (s), 133.8 (s), 126.8 (s), 125.3 (d), 123.8 (d), 116.7 (d), 107.6 (t), 82.4 (s), 69.8 (t), 28.4 (q), 21.13 (q). **MS** (*m/z*) 279.0 $[M+H_2O]^+$

***tert*-Butyl 2-methylene-4-tosyl-3,4-dihydroquinoxaline-1(2*H*)-carboxylate (17)**



Yield: 83%. **IR** (ν_{max}/cm^{-1}): 3422, 2979, 2330, 1920, 1720; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.71-7.38 (4H, m), 7.26-7.13 (4H, m), 5.14 (1H, d, *J* = 0.8 Hz), 4.53 (1H, d, *J* = 0.8 Hz), 4.36 (2H, s), 2.30 (3H, s), 1.34 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 151.8 (s), 143.7 (s), 138.5 (s), 134.7 (s), 133.8 (s), 131.7 (s), 129.6 (d), 127.7 (d), 127.4 (d), 126.6 (d), 124.8 (d), 124.7 (d), 98.8 (t), 82.6 (s), 53.1 (t), 28.1 (q), 21.8 (q). **MS** *m/z* 423.0 $[M+Na]^+$

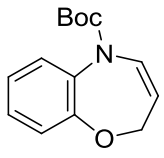
General procedure for the Pt-catalyzed hydroamination reactions on alkyne derivatives.



X=O **14a-d** **19a-e**
X=NTs **15** **20**

$PtCl_2(CH_3CN)_2$ (5% mol) and PPh_3 (10% mol) were added to a solution of the suitable propargyl derivative (0.4 eq) in toluene (5 mL) under nitrogen atmosphere. The reaction mixture was stirred at reflux at 90 °C for 4-24h. The reaction mixture was filtered under reduced pressure through a Celite® pad washing with AcOEt. The solvent was removed under reduced pressure and the crude purify by silica gel chromatography. (*n*-hexane/AcOEt 10:1)

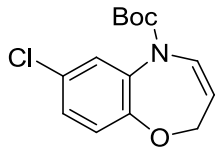
***N*-(*tert*-butoxycarbonyl)-2,5-dihydrobenzo[b][1,4]oxazepine (19a)**
(major isomer)



ab255

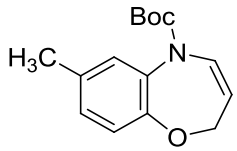
Yield: 40%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3425, 2970, 1920, 1720; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.91 (1H, d, *J* = 8.2 Hz), 6.93 (1H, br s), 6.84 (1H, t, *J* = 7.9 Hz), 6.64 (1H, dd, *J* = 7.5, 1.4 Hz), 6.41 (1H, dt, *J* = 9.9, 1.8 Hz), 5.76 (1H, dt, *J* = 9.9, 3.5 Hz), 4.83 (2H, dd, *J* = 3.5, 1.9 Hz), 1.54 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.9 (s), 141.8 (s), 127.1 (s), 124.9 (d), 123.3 (d), 121.6 (d), 121.4 (d), 120.3 (d), 118.7 (d), 80.5 (s), 66.0 (t), 28.6 (q). **MS** (*m/z*) 270.0 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-7-chloro-2,5-dihydrobenzo[b][1,4]oxazepine (19c)**
(major isomer)



Yield: 15% Colorless oil. **IR** (ν_{max}/cm^{-1}): 3432, 2979, 2930, 1728; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.99 (1H, s), 6.94 (1H, s), 6.63 (1H, d, *J* = 2.5 Hz), 6.34 (1H, dt, *J* = 9.9, 1.9 H), 5.81 (1H, dt, *J* = 9.9, 3.5 Hz), 4.84 (2H, dd, *J* = 3.5, 1.9 Hz), 1.54 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 152.58 (s), 140.12 (s), 128.8 (d), 126.6 (s), 124.1 (d), 122.8 (d), 122.6 (s), 119.7 (d), 118.2 (d), 81.1 (s), 66.1 (t), 28.52 (q). **MS** (*m/z*) 304.0 $[M+Na]^+$

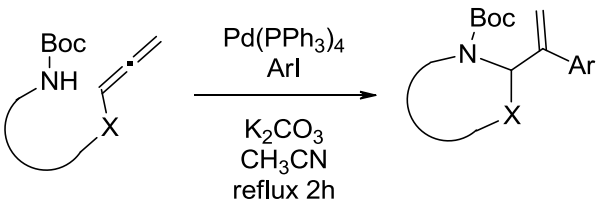
***N*-(*tert*-butoxycarbonyl)-7-methy-2,5-dihydrobenzo[b][1,4]oxazepine (19d) (major isomer)**



Yield: 60%. Yellow oil. **IR** (ν_{max}/cm^{-1}): 3436, 2977, 2920, 1728; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: δ 7.72 (1H, d, *J* = 16.2 Hz), 7.00–6.76 (1H, m), 6.46 (1H, s), 6.37 (1H, dt, *J* = 9.8, 1.7 Hz), 5.75 (1H, dt, *J* = 9.8, 3.5 Hz), 4.79 (2H, dd, *J* = 3.5, 1.8 Hz) 2.24 (3H, s), 1.53 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 153.0 (s), 139.7 (s), 130.9 (s), 130.0 (d), 126.7 (s), 125.0 (d), 121.8 (d), 120.8 (d), 119.0 (d), 80.5 (s), 65.9 (t), 28.5 (q), 21.2 (q). **MS** (*m/z*) 384.0 $[M+Na]^+$

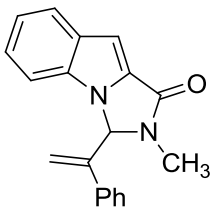
Chapter 3: Domino reactions

General procedure for the carboamination reaction



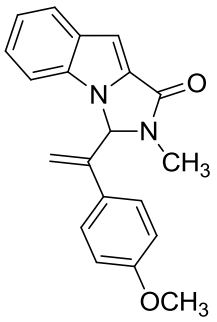
K_2CO_3 (4 mmol), aryl iodide (1.5 mmol), and $Pd(PPh_3)_4$ (5% mol) were added to a solution of allenamide (1 mmol) in acetonitrile (10 mL). The resulting solution was heated at reflux for 2-8 h. The solvent was evaporated under reduced pressure, then the resulting crude mixture was diluted with brine and extracted with AcOEt (3 x 20 mL). The organic phase was dried over Na_2SO_4 and the product was purified by flash chromatography.

2-Methyl-3-(1-phenylvinyl)-2,3-dihydro-1H-imidazo[1,5-a]indol-1-one (21a)



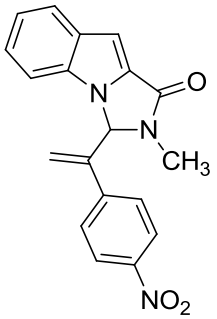
Yield 74%. White solid. **mp** 178 °C (*i*-Pr_2O); **IR** (ν_{max}/cm^{-1}):1670; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.76 (1H, d, *J* = 8.0Hz), 7.34 (1H, d, *J* = 8.2 Hz), 7.27-7.24 (1H, m), 7.19-7.16 (2H, m), 7.10 (2H, dd, *J* = 7.7 Hz, 7.2 Hz), 6.90 (1H, s), 6.73 (2H, d, *J* = 7.4 Hz), 6.01 (1H, s), 5.86 (1H, s), 5.82 (1H, s), 2.99 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 161.0 (s), 144.2 (s), 135.9 (s), 133.2 (s), 132.1 (s), 132.0 (s), 128.9 (d), 128.8 (d), 127.1 (d), 124.2 (d), 123.8 (d), 123.6 (t), 121.3 (d), 110.5 (d), 98.3 (d), 77.5 (d), 27.1 (q). **MS** (*m/z*) 288 $[M]^+$.

3-(1-(4-Methoxyphenyl)vinyl)-2-methyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (21b)



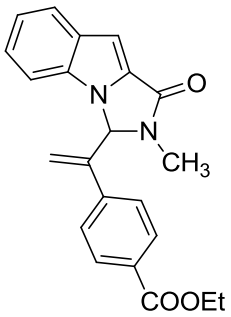
Yield: 88%. White solid. **mp** 140 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1666; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.74 (1H, d, *J* = 8.0 Hz), 7.35 (1H, d, *J* = 8.2 Hz), 7.25 (1H, dd, *J* = 8.2 Hz, 7.6 Hz), 7.17 (1H, dd, *J* = 8.0 Hz, 7.6 Hz), 6.91 (1H, s), 6.79-6.62 (4H, m), 6.03 (1H, s), 5.80 (1H, s), 5.77 (1H, s), 3.68 (3H, s), 2.99 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.8 (s), 159.8 (s), 143.3 (s), 133.0 (s), 131.8 (s), 128.6 (s), 128.0 (d), 127.8 (s), 123.9 (d), 123.6 (d), 122.3 (t), 121.0 (d), 114.0 (d), 110.3 (d), 97.9 (d), 77.4 (d), 55.1(q), 26.8 (q). **MS**: (*m/z*) 318 $[M]^+$.

2-Methyl-3-(1-(4-nitrophenyl)vinyl)-2,3-dihydro-1H-imidazo[1,5-*a*]indol-1-one (21c)



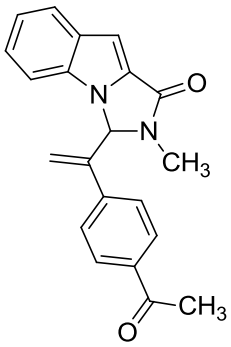
Yield: 68%. White solid. **mp** 190 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1654; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.93 (2H, d, *J* = 8.7 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.33 (1H, d, *J* = 8.1 Hz), 7.27 (1H, dd, *J* = 8.2 Hz, 7.1 Hz), 7.18 (1H, dd, *J* = 8.0 Hz, 7.1 Hz), 6.89 (1H, s), 6.84 (2H, d, *J* = 8.7 Hz), 6.09 (1H, s), 6.07 (1H, s), 5.94 (1H, s), 3.03 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 160.6 (s), 147.8 (s), 142.5 (s), 142.0 (s), 132.8 (s), 131.9 (s), 131.3 (s), 127.9 (d), 125.9 (t), 124.5 (d), 123.9 (d), 123.7 (d), 121.4 (d), 109.9 (d), 98.6 (d), 76.9 (d), 26.9 (q). **MS**: (*m/z*) 333 $[M]^+$.

2-Methyl-3-(1-(4-ethoxycarbonylphenyl)vinyl)-2,3-dihydroimidazo[1,5-*a*]indol-1-one (21d)



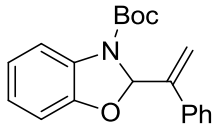
Yield: 72%. Yellow oil. **IR** (ν_{max}/ cm^{-1}): 1659; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.76 (2H, d, *J* = 8.5 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 8.2 Hz), 7.23 (1H, dd, *J* = 6.9 Hz, 8.2 Hz), 7.16 (1H, dd, *J* = 6.9 Hz, 8.0 Hz), 6.87 (1H, s), 6.75 (2H, d, *J* = 8.5 Hz), 5.95 (1H, s), 5.92 (1H, s), 5.85 (1H, s), 4.27 (2H, q, *J* = 7.1 Hz), 2.97 (3H, s), 1.30 (3H, t, *J* = 7.1 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 165.9 (s), 160.6 (s), 143.2 (s), 140.0 (s), 132.9 (s), 131.8 (s), 131.6 (s), 130.5 (s), 129.7 (d), 126.9 (d), 124.7 (t), 124.2 (d), 123.6 (d), 121.2 (d), 110.1 (d), 98.2 (d), 76.9 (d), 61.0 (t), 26.8 (q), 14.2 (q). **MS**: (*m/z*) 360 $[M]^+$.

3-(1-(4-Acetylphenyl)vinyl)-2-methyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (21e)



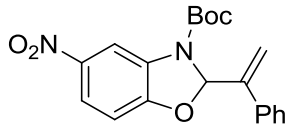
Yield: 76%. Yellow oil. **IR** (ν_{max}/ cm^{-1}): 1652; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.71 (2H, d, *J* = 8.6 Hz), 7.71 (1H, d, *J* = 8.1 Hz), 7.29 (1H, d, *J* = 8.2 Hz), 7.23 (1H, dd, *J* = 6.9 Hz, 8.2 Hz), 7.16 (1H, dd, *J* = 6.9 Hz, 8.1 Hz), 6.88 (1H, s), 6.76 (2H, d, *J* = 8.6 Hz), 5.99 (1H, s), 5.97 (1H, s), 5.88 (1H, s), 2.97 (3H, s), 2.44 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 197.4 (s), 160.7 (s), 143.1 (s), 140.2 (s), 136.8 (s), 132.9 (s), 131.8 (s), 131.5 (s), 128.5 (d), 127.1 (d), 124.9 (t), 124.2 (d), 123.7 (d), 121.3 (d), 110.1 (d), 98.3 (d), 76.8 (d), 26.9 (q), 26.5 (q). **MS**: (*m/z*) 330 $[M]^+$.

N-(*tert*-butyloxycarbonyl)-2-(1-phenylvinyl)-2,3-dihydrobenzo[d]oxazole (22a)



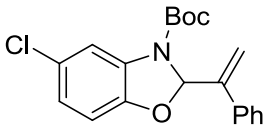
Yield: 70%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3411, 2970, 2930, 1722, 1600, 1489, 1384. **^{1}H-NMR** (300 MHz, DMSO) δ_H: 7.48-7.35 (6H, m), 6.95-6.87 (4H, m), 5.57 (1H, s), 5.50 (1H, s), 1.48 (9H, s). **^{13}C-NMR** (75 MHz, DMSO) δ_C: 150.4 (s), 144.5 (s), 137.5 (s), 130.5 (s), 129.2 (d), 129.0 (d), 127.7 (d), 124.2 (d), 122.1 (d), 114.1 (d), 113.9 (s), 109.5 (d), 118.2 (t), 94.8 (d), 82.6 (s), 28.6 (q). **MS** (*m/z*) 346.4 $[M+Na]^+$

***N*-(*tert*-butyloxycarbonyl)-5-nitro-2-(1-phenylvinyl)-2,3-dihydrobenzo[d]oxazole (22b)**



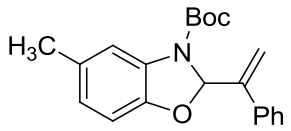
Yield: 38%. Orange oil. **IR** (ν_{max}/cm^{-1}): 3423, 2978, 2933, 1721, 1524; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.28 (1H, bs), 7.90 (1H, dd, *J* = 8.7, 2.4 Hz), 7.39-7.26 (5H, m), 6.87 (1H, bs), 6.77 (1H, d, *J* = 8.7 Hz), 5.57 (1H, s), 5.53 (1H, s), 1.53 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 155.5 (s), 149.8 (s), 144.2 (s), 142.9 (s),
136.9 (s), 131.4 (s), 132.2 (d), 128.7 (d), 128.6 (d), 127.5 (d), 121.2 (d), 118.7 (t), 109.5 (d), 108.1 (d), 97.2 (d), 83.9 (s), 28.3 (q). **MS** *m/z* 391.0 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-5-chloro-2-(1-phenylvinyl) 2,3-dihydrobenzo[d]oxazole (22c)**



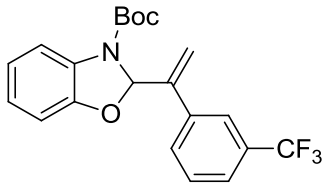
Yield: 62%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3415, 2980, 2930, 1720, 1598. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.65-7.26 (6H, m), 6.85 (1H, dd, *J* = 8.4, 2.2 Hz), 6.75 (1H, s), 6.65 (1H, d, *J* = 8.4 Hz), 5.53 (1H, s), 5.48 (1H, s), 1.49 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.1 (s), 149.0 (s), 144.7 (s), 137.4 (s), 131.6 (s), 126.4 (s), 128.6 (d), 128.4 (d), 127.5 (d), 123.0 (d), 114.4 (d), 109.3 (d), 117.7 (t), 95.8 (d), 83.1 (s), 28.4 (q). **MS (***m/z*) 380 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-5-methyl-2-(1-phenylvinyl) 2,3-dihydrobenzo[d]oxazole (22d)**



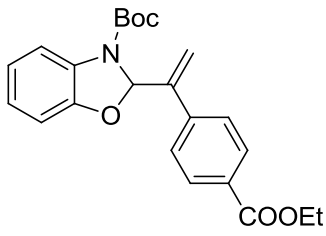
Yield: 54%. Colourless oil. **IR** (ν_{max}/cm^{-1}): 3436, 2976, 2920, 1708, 1496. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.46-7.26 (6H, m), 6.73-6.63 (3H, m), 5.52 (1H, d,), 5.48 (1H, d), 2.30 (3H, s), 1.50 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.5 (s), 148.1(s), 145.0 (s), 137.8 (s), 131.1 (s), 130.3 (s), 128.6 (d), 128.2 (d), 127.4 (d), 123.6 (d), 114.9 (d), 108.4 (d), 117.1 (t), 94.9 (d), 82.4 (s), 28.4 (q), 21.4 (q). **MS** (*m/z*) 360 $[M+Na]^+$, 338 $[M]^+$

***N*-(*tert*-butoxycarbonyl)-2-(1-(3-(trifluoromethyl)phenyl)vinyl)-2,3-dihydrobenzo[d] oxazole (22e)**



Yield: 68%. Yellow oil. **IR** (ν_{max}/cm^{-1}): 3400, 3000, 2940, 1720. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.97-7.87 (1H, m), 7.69-7.19 (5H, m), 6.95-6.75 (3H, m), 5.60 (1H, s), 5.56 (1H, s), 1.51 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.1 (s), 148.1 (s), 143.9 (s), 138.5 (s), 130.0 (s), 126.9 (s), 121.5 (s), 130.9 (d), 128.8 (d), 125.0 (d), 124.7 (d), 123.7 (d), 121.7 (d), 114.1 (d), 109.0 (d), 119.0 (t), 94.7 (d), 82.8 (s), 28.4 (q). **MS** (*m/z*) 414 $[M+Na]^+$

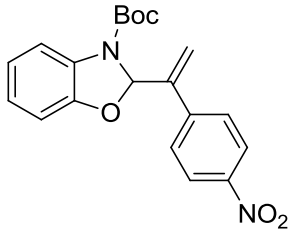
***N*-(*tert*-butoxycarbonyl)-2-(1-(4-(ethoxycarbonyl)phenyl)vinyl)-2,3-dihydrobenzo[d] oxazole (22f)**



Yield: 71%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3415, 3059, 2979, 1712, 1609, 1489. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.00-7.94 (2H, m), 7.50-7.44 (3H, m), 6.91-6.74 (4H, m), 5.59 (1H, s), 5.58 (1H, s), 4.36 (2H, q, *J* = 7.1 Hz), 1.50 (9H, s), 1.38 (3H, t, *J* = 7.1 Hz). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 166.5 (s), 150.5 (s), 150.1 (s), 144.3 (s), 142.2 (s), 130.2 (s), 130.1

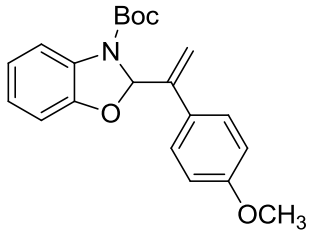
(s), 129.8 (d), 127.5 (d), 123.6 (d), 121.6 (d), 114.1 (d), 109.0 (d), 118.9 (t), 94.7 (d), 82.7 (s), 61.2 (t), 28.4 (q), 14.5 (q). **MS** (*m/z*) 418 $[M+Na]^+$

N-(*tert*-butoxycarbonyl)-2-(1-(4-nitrophenyl)vinyl) 2,3-dihydrobenzo[d]oxazole (22g)



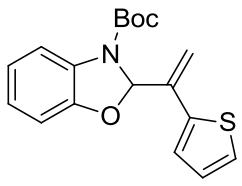
Yield: 78%. Orange oil. **IR** (ν_{max}/cm^{-1}): 3412, 3073, 2978, 2933, 1711, 1598. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.18-8.11 (2H, m), 7.59-7.53 (2H, m), 7.49-7.29 (1H, br s), 6.95-6.74 (4H, m), 5.67 (1H, s), 5.63 (1H, s), 1.51 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.5 (s), 149.9 (s), 147.8 (s), 144.3 (s), 143.5 (s), 129.9 (s), 128.5 (d), 123.8 (d), 123.7 (d), 121.8 (d), 114.2 (d), 109.1 (d), 120.4 (t), 94.5 (d), 83.0 (s), 28.4 (q). **MS** (*m/z*) 391 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-2-(1-(4-methoxyphenyl)vinyl) 2,3-dihydrobenzo[d]oxazole (22h)**



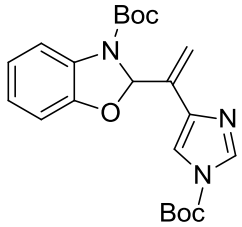
Yield: 65%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3414, 2977, 2933, 1713, 1608. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.66-7.44 (1H, br s), 7.40-7.35 (2H, m), 6.95-6.75 (6H, m), 5.48 (1H, s), 5.42 (1H, s), 3.79 (3H, s), 1.52 (9H). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 159.8 (s), 150.5 (s), 150.3 (s), 144.3 (s), 130.4 (s), 130.2 (s), 128.6 (d), 123.5 (d), 121.4 (d), 114.1 (d), 114.0 (d), 109.0 (d), 116.0 (t), 95.0 (d), 82.4 (s), 55.4 (q), 28.5 (q). **MS** (*m/z*) 376 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-2-(1-(thiophen-2-yl)vinyl) 2,3-dihydrobenzo[d]oxazole (22i)**



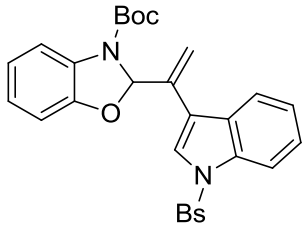
Yield: 64%. Colorless oil. **IR** (νmax / cm-1): 3410, 3072, 2977, 2931, 1713, 1599, 1489, 1393. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.66-7.37 (1H, br s), 7.20 (1H, dd, *J* = 5.1, 1.1 Hz), 7.10 (1H, d, *J* = 3.2 Hz), 6.98-6.76 (4H, m), 6.72 (1H, br s), 5.65 (1H, s), 5.41 (1H, s), 1.50 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.5 (s), 150.3 (s), 139.5 (s), 138.3 (s), 130.3 (s), 127.6 (d), 25.5 (d), 125.4 (d), 123.6 (d), 121.6 (d), 114.1 (d), 109.1 (d), 116.3 (t), 94.8 (d), 82.7 (s), 28.4 (q). **MS** (*m/z*) 352 $[M+Na]^+$

***N*-(*tert*-butoxycarbonyl)-2-(1-(1-(*tert*-butoxycarbonyl)-1H-imidazol-4-yl)vinyl) 2,3-dihydrobenzo[d]oxazole (22j)**



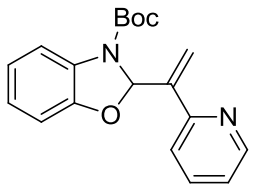
Yield: 25%. Yellow oil. **IR** (ν_{max}/cm-1): 3400, 2958, 2929, 1724, 1489. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.40 (1H, d, *J* = 1.1 Hz), 7.71-7.41 (1H, br s), 7.17 (1H, br s), 6.98-6.74 (4H, m), 6.10 (1H, s), 5.46 (1H, s), 1.56 (18H, br s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 153.2 (s), 150.3 (s), 147.0 (s), 138.6 (s), 136.3 (s), 131.2, (s), 123.7 (d), 121.6 (d), 117.5 (d), 114.2 (d), 113.6 (d), 109.0 (d), 116.4 (t), 94.3 (d), 85.9 (s), 82.7 (s), 28.4 (q), 28.1 (q). **MS** (*m/z*) 414 $[M+Na]^+$, 436 $[M]^+$

***N*-(*tert*-butoxycarbonyl)-2-(1-(1-(phenylsulfonyl)-1H-indol-3-yl)vinyl)-2,3-dihydrobenzo[d] oxazole (22k)**



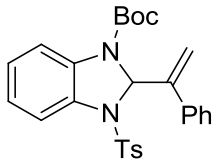
Yield: 67%. Orange oil. **IR** (ν_{max}/cm^{-1}): 3414, 2977, 2931, 1711. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.91 (1H, dd, *J* = 6.9, 1.8 Hz), 7.68-7.19 (10H, m), 7.00-6.80 (3H, m), 6.67 (1H, bs), 5.78 (1H, s), 5.70 (1H, s), 1.47 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.5 (s), 120.5 (s), 138.3 (s), 136.3 (s), 135.1 (s), 130.5 (s), 127.4 (s), 117.91 (s), 134.1 (d), 129.7 (d), 127.2 (d), 125.3 (d), 124.5 (d), 123.9 (d), 123.8 (d), 121.7 (d), 120.8 (d), 114.2 (d), 113.8 (d), 109.0 (d), 120.5 (t), 96.5 (d), 82.7 (s), 28.6 (q). **MS** (*m/z*) 525 $[M+Na]^+$

***N*-(*tert*-butoxycarboyl)-2-(1-(pyridin-2-yl)vinyl) 2,3-dihydrobenzo[d]oxazole (22l)**



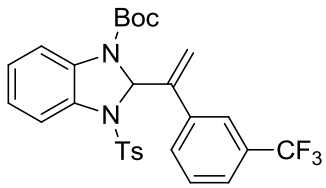
Yield: 30%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3434, 3058, 2978, 2292, 1716. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.67-8.63 (1H, m), 7.73-7.54 (3H, m), 7.29-7.19 (2H, m), 6.92-6.74 (3H, m), 6.03 (1H, s), 5.63 (1H, s), 1.52 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 155.5 (s), 150.3 (s), 149.4 (d), 144.4 (s), 136.7 (d), 130.9 (s), 123.6 (d), 122.9 (d), 121.38 (d), 121.0 (d), 119.9 (s), 117.6 (t), 114.1 (d), 109.4 (d), 92.2 (d), 82.5 (s), 80.5 (s), 28.4 (q). **MS** (*m/z*) 347.1 $[M+Na]^+$

***N*-(*p*-toluenesulfonyl)--*N'*-(*tert*-butoxycarbonyl)-2-(1-phenylvinyl)-2,3-dihydro-1H-benzo[d] imidazole (23a)**



Yield: 86%. Orange solid. **mp**: 99-101 °C (Et_2O) **IR** (ν_{max}/cm^{-1}): 3402, 2973, 2928, 1709. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.53 (1H, dd, *J* = 7.1, 1.5 Hz), 7.49-7.26 (8H, m), 7.13-6.95 (4H, m), 6.60 (1H, bs), 5.38 (1H, s), 5.24 (1H, s), 2.31 (3H, s), 1.35 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.1 (s), 145.4 (s), 144.8 (s), 138.0 (s), 135.3 (s), 133.3 (s), 131.9 (s), 29.7 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.8 (d), 127.6 (d), 127.0 (d), 123.5 (d), 119.6 (t), 115.2 (d), 82.3 (s), 78.6 (d), 28.2 (q), 21.7 (q). **MS** (*m/z*) 499 $[M+Na]^+$

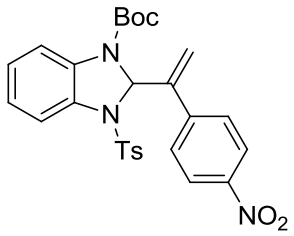
***N*-(*p*-toluenesulfonyl)--*N'*-(*tert*-butoxycarbonyl)-2-(1-(3-(trifluoromethyl)phenyl) vinyl)-2,3-dihydro-1H-benzo[d]imidazole (23b)**



Yield: 65%. Yellow oil. **IR** (ν_{max}/cm^{-1}): 3436, 2980, 2930, 2359, 2342, 1716. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.55-7.37 (8H, m), 7.14-6.95 (4H, m), 6.57 (1H, br s), 5.49 (1H, s),

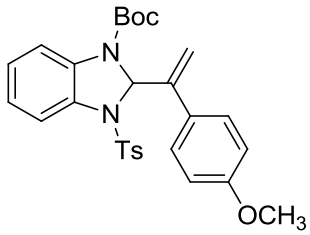
5.30 (1H, s), 2.31 (3H, s), 1.36 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.0 (s), 144.8 (s), 144.5 (s), 138.7 (s), 135.0 (s), 132.3 (s), 130.9 (s), 130.2 (s), 121.5 (s), 131.8 (d), 129.7 (d), 128.6 (d), 127.6 (d), 127.0 (d), 125.4 (d), 125.3 (d) 124.7 (d), 119.5 (d), 115.3 (d), 118.7 (t), 82.6 (s), 78.6 (d), 28.2 (q), 21.6 (q). **MS** (*m/z*) 566.1 $[M+Na]^+$

_N_-(_p_-toluenesulfonyl)--_N'_-(_tert_-butoxycarbonyl)-2-1-(4-nitrophenyl)vinyl)-2,3-dihydro -1H-benzo[d]imidazole (23c)



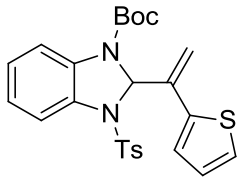
Yield: 86%. Orange oil. **IR** (ν_{max}/cm^{-1}): 3071, 2979, 2932, 2258, 1925, 1713. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.14 (2H, d, *J* = 8.4 Hz), 7.53-7.35 (5H, m), 7.4-6.98 (5H, m), 6.58 (1H, br s), 5.67 (1H, s), 5.63 (1H, s), 2.32 (3H, s), 1.38 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.0 (s), 147.7 (s), 145.0 (s), 144.7 (s), 143.9 (s), 134.8 (s), 132.9 (s), 131.7 (s), 129.8 (d), 129.4 (d), 127.6 (d), 127.2 (d), 123.8 (d), 123.4 (d), 119.7 (d), 115.3 (d), 119.4 (t), 82.9 (s), 78.3 (d), 28.3 (q), 21.7 (q). **MS** (*m/z*) 544 $[M+Na]^+$

_N_-(_p_-toluenesulfonyl)--_N'_-(_tert_-butoxycarbonyl)-2-(1-(4-methoxypheny)lvinyl)-2,3-dihydro-1H-benzo[d]imidazole (23d)



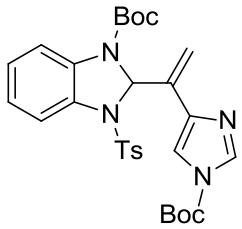
Yield: 65%. Orange oil. **IR** (ν_{max}/cm^{-1}): 3402, 2982, 2931, 1709, 1513. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.55-7.25 (6H, m), 7.12-6.95 (4H, m), 6.80 (2H, d, *J* = 8.7 Hz). 6.58 (1H, br s), 5.28 (1H, s), 5.19 (1H, s), 3.77 (3H, s), 2.31 (3H, s), 1.37 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 159.6 (s), 150.0 (s), 144.7 (s), 135.4 (s), 133.3 (s), 132.0 (s), 130.3 (s), 113.4 (s), 129.6 (d), 129.5 (d), 127.6 (d), 127.0 (d), 123.4 (d), 119.8 (d), 115.1 (d), 113.6 (d), 116.4 (t), 82.3 (s), 78.7 (d), 55.4 (q), 28.3 (q), 21.7 (q). **MS** (*m/z*) 529 $[M+Na]^+$

_N_-(_p_-toluenesulfonyl)--_N'_-(_tert_-butoxycarbonyl)-2-(1-(thiophen-2-yl)vinyl)-2,3-dihydro-1H-benzo[d]imidazole (23e)



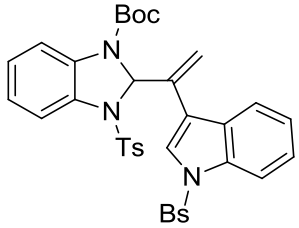
Yield: 36%. Yellow solid. **mp**: 141-142 °C (Et_2O) **IR** (ν_{max}/cm^{-1}): 3429, 2971, 2921, 1709, 1593. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.57-6.93 (11H, m), 6.61 (1H, br s), 5.47 (1H, s), 5.23 (1H, s), 2.33 (3H, s), 1.39 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 150.0 (s), 144.9 (s), 139.3 (s), 138.6 (s), 135.5 (s), 133.1 (s), 132.0 (s), 129.7 (d), 127.7 (d), 127.6 (d), 127.0 (d), 126.3 (d), 125.4 (d), 123.5 (d), 19.6 (d), 114.9 (d), 116.8 (t), 82.6 (s), 78.5 (d), 28.3 (q), 21.8 (q). **MS** (*m/z*) 505 $[M+Na]^+$

_N_-(_p_-toluenesulfonyl)--_N'_-(_tert_-butoxycarbonyl)-2-(1-(1-(_tert_-butoxycarbonyl)-1_H_-imidazol-4-yl)vinyl)-2,3-dihydro-1H-benzo[d]imidazole (23f)



Yield: 10% Colorless oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.17 (1H, dd, *J* = 8.4 Hz, 1.1 Hz), 7.60 (2H, d, *J* = 8.3 Hz), 7.33-7.07 (6H, m), 6.75 (1H, td, *J* = 7.7, 1.4 Hz), 6.33 (1H, dd, *J* = 7.7, 1.4 Hz), 5.04 (1H, s), 5.01 (1H, s), 2.46 (3H, s), 1.52 (18H, s).

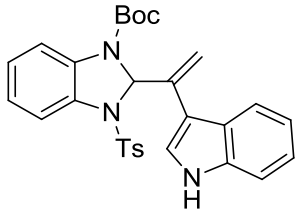
_N_-(_p_-toluenesulfonyl)--_N'_-(_tert_-butoxycarbonyl)-2-(1-((1-(phenylsulfonyl)-1H-indol-3-yl)vinyl)-2,3-dihydro-1H-benzo[d]imidazole (23g)



Yield: 7% Colorless oil. **IR** (ν_{max}/cm^{-1}): 3436, 2975, 2929, 2336, 1714, 1635, 1598. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.92-7.01 (18H, m), 6.55 (1H, br s), 5.56 (1H, s), 5.51 (1H,

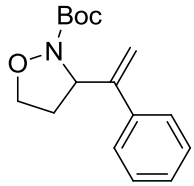
s), 2.32 (3H, s), 1.37 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 144.8 (s), 143.9 (s), 138.3 (s), 136.2 (s), 135.2 (s), 134.8 (s), 132.1 (s), 130.5 (s), 118.8 (s), 118.2 (s), 133.9 (d), 129.7 (d), 129.5 (d), 127.6 (d), 127.3 (d), 126.9 (d), 126.1 (d), 124.9 (d), 123.6 (d), 120.7 (d), 119.4 (t), 115.1 (d), 113.6 (d), 82.6 (s), 79.1 (d), 28.3 (q), 21.7 (q). **MS** *m/z* 803 $[M+3Na]^+$

_N_-(_p_-toluenesulfonyl)--_N'_-(_tert_-butoxycarbonyl)-2-(1-((1H-indol-3-yl)vinyl)-2,3-dihydro-1H-benzo[d]imidazole (23g')



Yield: 12%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 3411, 2976, 2926, 1712, 1622, 1598. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.17 (1H, br s), 7.70 (1H, m), 7.56-7.01 (12H, m) 6.61 (1H, bs), 5.52 (1H, s), 5.40 (1H, s), 2.31 (3H, s, C*H3*), 1.35 (9H, s, *t*-Bu). **MS** (*m/z*) 538 $[M+Na]^+$, 514 $[M]^-$

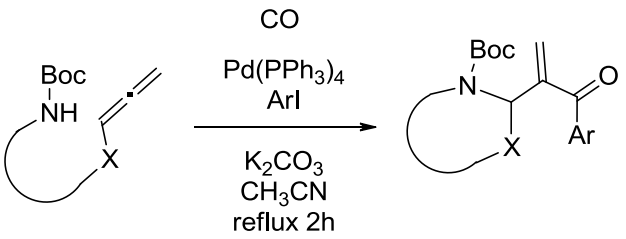
***N*-(*tert*-butoxycarbonyl)-3-(1-phenylvinyl)isoxazolidine (24)**



Yield: 55%. Colorless oil. **IR** (ν_{max}/cm^{-1}): 1689. **^{1}H-NMR** (300 MHz, DMSO) δ_H: 7.49–7.21 (5H, m), 5.44 (1H, s), 5.34 (1H, s), 5.15 (1H, dd, *J* = 8.7, 5.1 Hz), 4.06 (1H, td, *J* = 7.6, 4.5 Hz), 3.97–3.74 (1H, m), 2.65–2.32 (1H, m), 2.21–1.89 (1H, m), 1.659 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: ^{13}C NMR (50 MHz, cdcl$_3$) δ 157.2 (s), 147.5 (s), 139.5 (s), 128.6 (d), 128.0 (d), 127.0 (d), 112.9 (t), 82.2 (s), 69.1 (t), 61.8 (d), 35.6 (t), 28.48 (q).. **MS** *m/z* 298 $[M+Na]^+$

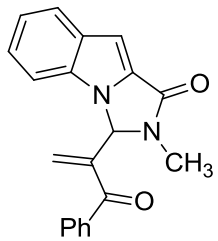
Carbonilations

General procedure for the carbonilation reaction



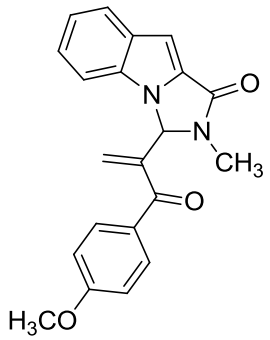
$Pd(PPh_3)_4$ (8% mol), aryl iodide (1.5 mmol), and K_2CO_3 (4 mmol) were added to a solution of the suitable allene (1 mmol) in acetonitrile (10 mL) under CO atmosphere (balloon). The resulting suspension was stirred at rt for 48 h. The solvent was evaporated under reduced pressure, then the crude mixture was diluted with brine and extracted with AcOEt (3 x 20 mL). The organic phase was dried over Na_2SO_4 and the product was purified by flash chromatography.

2-Methyl-3-(3-oxo-3-phenylprop-1-en-2-yl)-2,3-dihydro-1*H*-imidazo[1,5-a]indol-1-one (25a)



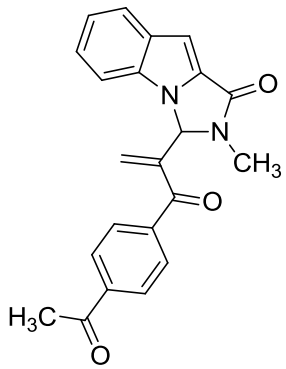
Yield 45%. White solid, **mp** 133 °C (*i*-Pr_2O); **IR** (ν_{max}/cm^{-1}): 1730, 1640; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.81-7.74 (3H, m), 7.64-7.60 (1H, m), 7.51-7.45 (2H, m), 7.27-7.10 (3H, m), 6.97 (1H, s), 6.57 (1H, s), 6.10 (1H, s), 5.88 (1H, s), 3.10 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 195.3 (s), 27.5 (q), 70.5 (d), 98.3 (d), 110.3 (d), 121.1 (d), 123.7 (d), 124.2 (d), 128.7 (d), 129.6 (d), 160.7 (s), 142.0 (s), 136.1 (s), 133.5 (d), 132.5 (s), 132.0 (s), 131.7 (s), 131.2 (t). **MS** m/z 316 $[M]^+$.

3-(3-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)-2-methyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (25b)



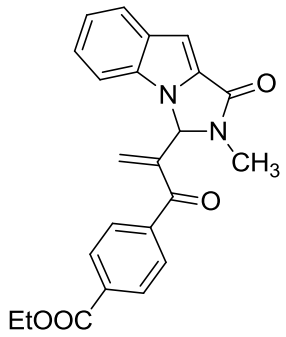
Yield: 31%. White solid. **mp** 163 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1724, 1633 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.84 (2H, d, *J* = 9.0 Hz), 7.76 (1H, d, *J* = 7.8 Hz), 7.17-7.23 (3H, m), 6.97 (1H, s), 6.96 (2H, d, *J* = 9.0 Hz), 6.03 (1H, s), 6.56 (1H, s), 5.78 (1H, s), 3.89 (3H, s), 3.10 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 206.9 (s), 193.7 (s), 164.1 (s), 142.2 (s), 132.5 (s), 132.2 (d), 131.9 (s), 129.2 (t), 128.6 (s), 124.1 (d), 123.7 (d), 121.1 (d), 114.0 (d), 110.4 (d), 110.0 (s), 98.3 (d), 70.8 (d), 55.6 (q), 27.5 (q). **MS**: *m/z* 346 (M^+).

3-(3-(4-acetylphenyl)-3-oxoprop-1-en-2-yl)-2-methyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-one (25c)



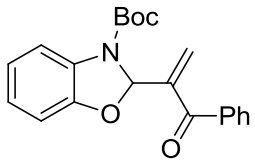
Yield: 28%. White solid. **mp** 145 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1738, 1636; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 8.04 (2H, d, *J* = 8.4 Hz), 7.85 (2H, d, *J* = 8.4 Hz), 7.77 (1H, d, *J* = 8.0 Hz), 7.27-7.18 (3H, m), 6.99 (1H, s), 6.60 (1H, s), 6.12 (1H, s), 5.96 (1H, s), 3.12 (3H, s), 2.66 (3H, s); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 197.1 (s), 194.7 (s), 160.6 (s), 142.1 (s), 140.4 (s), 139.6 (s), 135.0 (s), 132.4 (s), 132.0 (t), 131.6 (s), 129.7 (d), 128.5 (d), 124.3 (d), 123.8 (d), 121.2 (d), 110.1 (d), 98.5 (d), 70.4 (d), 27.5 (q), 26.8 (q). **MS** (*m/z*) 358 $[M]^+$.

3-(3-(4-ethoxycarbonylphenyl)-3-oxoprop-1-en-2-yl)-2-methyl-2,3-dihydro-1*H*-imidazo[1,5-a]indol-1-one (25d)



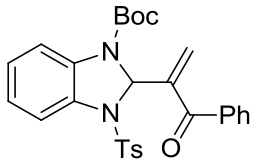
Yield: 33%. White solid. **mp** 121 °C (*i*-Pr_2O). **IR** (ν_{max}/cm^{-1}): 1732, 1655; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ_H: 7.79 (2H, d, *J* = 8.4 Hz), 7.74 (1H, d, *J* = 8.1 Hz), 7.35 (1H, d, *J* = 8.0 Hz), 7.27 (1H, dd, *J* = 7.0 Hz, 8.1 Hz), 7.18 (1H, dd, *J* = 7.0 Hz, 8.0 Hz), 6.91 (1H, s), 6.80 (2H, d, *J* = 8.4 Hz), 6.12 (1H, s), 5.99 (1H, s), 5.90 (1H, s), 4.30 (2H, q, *J* = 7.1 Hz), 3.03 (3H, s), 1.33 (3H, t, *J* = 7.1 Hz); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 165.9 (s), 160.7 (s), 143.4 (s), 140.0 (s), 132.9 (s), 131.9 (s), 131.6 (s), 130.6 (s), 129.8 (d), 129.7 (s), 126.9 (d), 124.5 (t), 124.2 (d), 123.7 (d), 121.2 (d), 110.1 (d), 98.4 (d), 77.1 (d), 61.0 (t), 26.9 (q), 14.2 (q). **MS** (*m/z*) 388 $[M]^+$.

_N_-(_tert_-butoxycarbonyl)-2-(3-oxo-3-phenylprop-1-en-2-yl)-2,3-dihydrobenzo[d] oxazole (26)



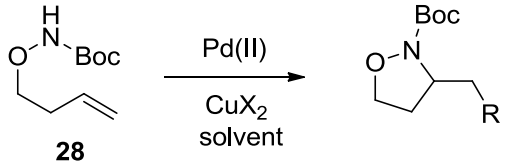
Yield: 27%. Yellow oil. **IR** (ν_{max}/cm^{-1}): 3435, 3060, 2978, 2932, 2254, 1714, 1662.**^{1}H-NMR** (300 MHz, DMSO) δ_H: 7.83-7.78 (2H, m), 7.61-7.40 (4H, m), 6.98-6.77 (4H, m), 5.84 (1H, s), 6.10 (1H, s), 1.49 (9H, s). **^{13}C-NMR** (75 MHz, DMSO) δ_C: 195.3 (s), 150.4 (s), 144.1 (s), 137.2 (s), 129.7 (s), 133.1 (d), 129.9 (d), 128.6 (d), 128.4 (d), 126.4 (t), 123.8 (d), 121.7 (d), 114.3 (d), 109.1 (d), 83.0 (s), 28.4 (q). **MS** (*m/z*) 374.0 $[M+Na]^+$

_N_-(_p_-toluenesulfonyl)-_N_-(_tert_-butoxycarbonyl)-2-(3-oxo-3-phenylprop-1-en-2-yl)-2,3-dihydrobenzo[d] imidazole (27)



Yield: 20%. Yellow oil. **IR** (ν_{max}/cm^{-1}): 3413, 3066, 2980, 2930, 2592, 1919, 1715, 1668, 1598. **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 7.82-7.38 (9H, m), 7.18-7.01 (4H, m), 6.73 (1H, s), 5.96 (1H, br s), 5.64 (1H, s), 2.33 (3H, s), 1.35 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 194.5 (s), 151.2 (s), 144.9 (s), 144.6 (s), 137.2 (s), 134.5 (s), 133.2 (d), 132.7 (s), 131.9 (s), 130.0 (d), 129.8 (d), 128.5 (d), 127.7 (d), 126.6 (d), 123.7 (d), 118.5 (d), 115.2 (d), 82.9 (s), 75.8 (d), 28.3 (q), 21.7 (q). **MS** (*m/z*) 527.6 $[M+Na]^+$

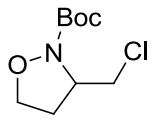
General procedure for the domino alkylation/halogenation reactions



28

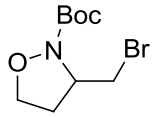
To a stirred solution of **28** (80 mg, 0.43 mmol) in a suitable solvent and in the presence of 4Å molecular sieves under nitrogen atmosphere, were added sequentially $PdCl_2$ (10% mol) or $PdCl_2(CH_3CN)_2$ (10% mol) and the suitable oxidant copper salt (3eq) according to the Table 4 and 5 of Chapter 3. The reaction mixture was then stirred at room temperature for 2-4h. After reaction completion, the solvent was removed under reduced pressure and, brine was added and the mixture extracted with Et_2O. The organic layers were dried over Na_2SO_4, the solvent removed and the product purified by flash chromatography (*n*-hexane/AcOEt 10:1)

N-(tert-butoxycarbonyl)-3-(chloromethyl)isoxazolidine (29)



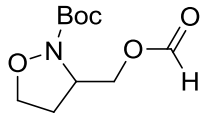
Yield: 48%. Colorless oil. **IR** (ν_{max}/ cm^{-1}): 3386, 2982, 2938, 2875, 1701, 1430; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 4.22 (1H, m), 4.08 (2H, m), 3.90 (1H, ddd, *J* = 11.8, 8.4, 3.3 Hz), 3.63 (1H, dd, *J* = 14.4, 8.4 Hz), 2.27 (1H, m), 2.03 (1H, m), 1.50 (9H, s). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ_C: 154.6 (s), 82.3 (s), 68.7 (t), 53.2 (t), 51.8 (d), 34.6 (t), 28.5 (q). **MS** (*m/z*): 244 $[M+Na]^+$

N-(tert-butoxycarbonyl)-3-(bromomethyl)isoxazolidine (30)



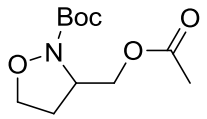
Yield: 43%. Yellow oil. **IR** (ν_{max}/ cm^{-1}): 3292, 2981, 2935, 1783, 1754, 1478; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H 4.17 (1H, m), 3.92 (1H, ddd, *J* = 11.9, 8.6, 3.3 Hz,), 3.69 (1H, dd, *J* = 14.5, 9.0 Hz), 2.44–2.05 (2H, m), 1.50 (9H, s); **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 153.8 (s), 83.4 (d), 82.3 (s), 70.0 (d), 53.5, 42.8, 35.4, 28.2. **MS** (*m/z*): 288.0 $[M+Na]^+$

N-(tert-butoxycarbonyl)- isoxazolidin-3-ylmethyl formate (31)



Yield: 35%. Colorless oil. **IR** (ν_{max}/ cm^{-1}) 3435, 2978, 2933, 1724; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 8.04 (1H, s), 5.15–4.93 (1H, m), 4.21 (1H, ddd, *J* = 12.1, 9.0, 3.3 Hz), 4.02–3.81 (2H, m), 3.74 (1H, dd, *J* = 14.1, 3.0 Hz), 2.21-2.09 (1H, m), 1.99–1.78 (m, 1H), 1.48 (9H, s). **^{13}C-NMR** (50 MHz, $CDCl_3$) δ_C: 160.2 (d), 155.1 (s), 82.1 (s), 67.0 (t), 65.2 (d), 49.5 (t), 29.6 (t), 28.4 (q). **MS** (*m/z*): 254.0 $[M+Na]^+$.

N-(*tert*-butoxycarbonyl)- isoxazolidin-3-ylmethyl acetate (32)



Yield: 20%. Colorless oil. **IR** (ν_{max}/ cm^{-1}): 3430, 2988, 2930, 1725; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ_H: 4.96–4.78 (1H, m), 4.28–4.10 (2H, m), 3.92-3.82 (1H, m), 3.70 (1H, dd, *J* = 14.2, 2.9 Hz), 2.24–2.09 (1H, m), 2.07 (3H, s), 1.93–1.72 (1H, m), 1.49 (9H, s).**MS** (*m/z*): 268 $[M+Na]^+$

Chapter 4: Studies towards the C1-C11 fragment of Stambomycin A

General details

NMR Spectra: ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using an interna deuterium lock for the residual protons in $CDCl_3$ (δ 7.26), C_6D_6 (δ 7.16), d8-toluene (δ 2.31) and CD_3OD (δ 3.31) at ambient probe temperatures on the following instruments: Bruker AV400 (400
MHz), Varian Inova Unity 400 (400 MHz), Bruker AMX 500 (500 MHz), Bruker AVANCE III 500 (500 MHz), Bruker DRX500 (500 MHz) or Varian Inova 600 (600 MHz). Data are presented as follows: chemical shift, peak multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants and interpretations. Chemical shifts are expressed in ppm on a δ scale relative to δTMS (δ = 0 ppm) and coupling constants, *J*, are given in Hz. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, by analysis of 2D NMR (COSY, HSQC, HMBC, NOESY) and irradiation of protons in nOe experiments, or by analogy to fully interpreted spectra for structurally related compounds. ^{13}C NMR Spectra were recorded using an internal deuterium lock using solvents $CDCl_3$ (δ 77.0), C_6D_6 (δ 128.6) and d8-toluene (δ 21.4) at ambient probe temperatures on the following instruments: Bruker AV400 (101 MHz), Varian Inova Unity 400 (101 MHz), Bruker AMX 500 (126 MHz), Bruker AVANCE III 500 (126 MHz), Bruker DRX500 (126 MHz) or Varian Inova 600 (151 MHz).

Infra-red spectra: Recorded on a Perkin Elmer Paragon 1000 spectrometer or a Perkin Elmer Spectrum One spectrometer, with the sample prepared as a thin film between NaCl plates, or using a PIKE-Miracle Diamond /Universal ZnSe ATR module

Mass spectra: Low resolution mass spectra (*m/*z) were recorded on a Micromass LCT Premier Open Access. Accurate mass (HRMS) data was determined under the conditions of ESI on a Bruker MicroTOF (resolution = 5000 FWHM) using tetraoctylammonium bromide as a lock-mass in both positive and negative ion modes, or under the conditions of CI on a Micromass GCT (resolution = 7000 FWHM) using isoamyl acetate as a lock-mass. High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Reactions were monitored by thin layer chromatography (TLC). TLC was conducted on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254) or on pre-coated glass-backed plates (Macherey-Nagel SIL G-25 with fluorescent indicator UV254). Spots were visualized either by quenching of UV fluorescence or by staining with potassium permanganate or vanillin.

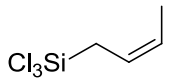
Flash chromatography was performed manually with silica gel 60 (0.040-0.063 mm) (MN Kieselgel 60M) applying head pressure by means of nitrogen.

Materials: All reagents, obtained from Acros, Aldrich, Fluka, Lancaster, Strem and Fluorochem fine chemicals suppliers were used directly as supplied or purified by the methods described by Amerago and Chai. All non-aqueous reactions were performed in oven dried apparatus under argon or nitrogen atmospheres, using anhydrous solvents, at room temperature unless otherwise indicated.

The anhydrous solvents were purchased as sure-seal bottles from Aldrich or dried by pre-storing over activated 3Å molecular sieves and then passing through an activated alumina column on a solvent tower.

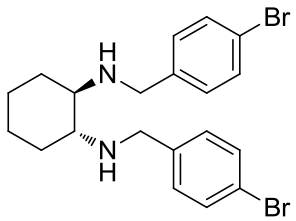
Procedure for the preparation of the Leighton reagent

(Z)-Crotyltrichlorosilane[1]



In a sealed tube, equipped with a side-arm and magnetic stirring bar, was condensed 1,3-butadiene (1.99 0g, 36.91 mmol, 1 eq) at –78 °C, under argon. To this tube were sequentially added $Pd(PPh_3)_4$ (106 mg, 0.0925 mmol, 0.025 eq) and $HSiCl_3$ (3.72 ml, 36.91 mmol, 1.0 equiv) at –78 °C. The side arm was then removed, the tube sealed, and the reaction mixture was allowed to warm at room temperature and stirred overnight. The solution was purified by distillation at atmospheric pressure under argon. The title compound was isolated as a colorless oil. **bp**: 142-144°C (142°C lit.) **^{1}H-NMR** (500 MHz, C_6D_6) δ_H 5.83-5.63 (1H, m, H-3), 5.51-5.35 (1H, m, H-2), 2.36 (2H, dq, *J*= 8.1, 0.8 Hz, C*H*$_2$), 1.67 (3H, ddt, *J*= 6.8, 1.7, 0.8 Hz). Data are consistent with literature.

(1R,2R)-N1,N2-bis(4-bromobenzyl)cyclohexane-1,2-diamine[2]



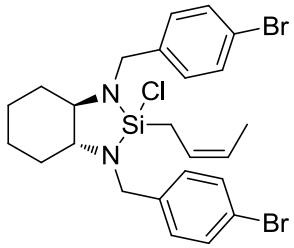
To a stirred suspension of (1R,2R)-cyclohexane-1,2diamine.L-tartrate (13.92 g, 52.7 mmol, 1 eq) in water (250 ml) was added K_2CO_3 (14.56 g, 105.3 mmol, 2 eq). To this mixture was added EtOH (125 ml) and a solution of 4-bromobenzaldehyde (19.48 ml, 105.3 mmol, 2 eq) and methanesulfonic acid (0.428 ml, 6.324 mmol, 0.12 eq) in DCM (250 ml). The biphasic mixture was stirred overnight at room temperature then heated at reflux for 1 hour. The reaction was concentrated in vacuo and the residue diluited with water. The mixture was filtered and the solid residue dissolved in MeOH (150 ml). The solution was cooled to 0 °C and $NaBH_4$ (4.48 g, 118.5 mmol, 2.25 eq) added. After gaseous evolution had ceased the reaction was heated to reflux for 1 hour. The reaction was allowed to cool, concentrated *in vacuo* and 1N NaOH (70 ml), EtOAc (50 ml) and petrol ether (50 ml) added. The layers were separated and the aqueous layer extracted with AcOEt/petrol ether (1:1, 2 x 50 ml). The combined organic layers were washed with brine

[1] Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett*. **1989**, *30*, 1099

[2] B. M. Hackman, P. J. Lombardi, J. L. Leighton, *Org Lett*, **2004**, 6, 4375-4377

(50 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (4:1 petrol ether/AcOEt to 1:1:01 petrol ether/AcOEt/Et_3N) to leave pure diamine (18.16 g, 40.16 mmol, 76%) as a colorless oil. **^{1}H-NMR** (500 MHz, C_6D_6) δ_H 7.4 (4H, dt, *J*= 8.5, 2.0 Hz), 7.04 (4H, dt, *J*= 8.5, 2.0 Hz), 3.63 (2H, d, *J*= 14.0 Hz), 3.43 (2H, d, *J*= 14.0 Hz), 2.19-2.12 (2H, m), 2.01-1.95 (2H, m), 1.70-1.62 (2H, m), 1.47 (2H, bs, N*H*), 1.21-1.11 (2H, m), 0.98-0.88 (2H, m); **^{13}C-NMR** (125 MHz, C_6D_6) δ_C 140.9, 131.6, 130.0, 120.8, 61.2, 50.4, 31.6, 25.2. Data are consistent with literature.[b]

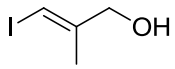
(3aR,7aR)-1,3-bis(4-bromobenzyl)-2-((Z)-but-2-en-1-yl)-2-chlorooctahydro-1H-benzo[d][1,3,2] diazasilole



To a stirred solution of (Z)-crotyltrichlorosilane (1.8 g, 9.5 mmol, 1.2 eq) and freshly distilled 1,8-diazabicyclo[5,4,0]undec-7-ene (2.83 ml, 18.98 mmol, 2.4 eq) in anhydrous DCM (40 ml) at 0 °C under argon was added a solution of the above diamine (3.55 g, 7.90 mmol, 1 eq) in DCM (10 ml) *via* syringe pump over 45 minutes. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated by vacuum distillation. The residue was diluted with pentane (50 mL) and vigorously stirred for 3 h to ensure complete precipitation of all DBU salts. The suspension was filtered under argon and the solvent removed *in vacuo* yielding **4** (4.42 g, 7.7 mmol, 82%) as a pale yellow oil. **^{1}H-NMR** (500 MHz, C_6D_6) δ_H 7.42-7.44 (4H, dd, *J*= 8.3, 3.2, Ar-*H*), 7.17-7.20 (4H, dd, *J*= 8.3, 4.5, Ar-*H*), 5.48-5.50 (2H, m, $SiCH_2CH$=C*H*Me), 3.99-3.92 (2H, m, two of $ArCH_2N$), 3.64-3.52 (m, 2H, two of $ArCH_2N$), 2.73-2.69 (2H, m, two C*H*N), 1.79-1.31 (9H, m, $SiCH_2$, CH=CHCH_3, and 2 x CH_2), 0.96-0.84 (4H, m, 2 xCH_2); **^{13}C-NMR** (125 MHz, C_6D_6) δ_C 141.5, 140.7, 131.6, 130.1, 129.3, 125.1, 122.3, 66.5, 65.7, 48.2, 31.0, 30.7, 24.8, 22.7.0, 18.7, 13.1. Data are consistent with literature.

The same procedure was applied for the synthesis of the S,S enantiomer using (1S,2S)-cyclohexane-1,2-diamine-D-tartrate as starting material.

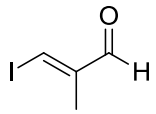
(E)- 3-iodo-2-methyl-prop-2-en-1-ol (1) [3]



To a stirred suspension of $ZrCp_2Cl_2$ (913 mg, 3.125 mmol, 0.25 eq) in DCM (40 ml) at room temperature under argon was added trimethyl alluminium (18.75 ml 2.0M solution in *n*-Hexane, 37.5 mmol, 3 eq) and the mixture was then cooled to 0°C. A solution of propynol (0.738 ml, 12.5 mmol, 1 eq) in DCM (40 ml) was added via cannula and the mixture was allowed to warm at room temperature and stirred for 15h.

The mixture was cooled to -30°C, a solution of iodine (4.75g, 18.75 mmol, 1.5 eq) in Et_2O (10 ml) was added and, after stirring for 30 minutes at -30°C, the mixture was allowed to warm at 0°C. The reaction was quenched by transfer of the solution in a mixture of saturated Na K Tartrate (50 ml) and pentane (300 ml). The mixture was stirred vigorously for 10 minutes, the layers were separated, and the aqueous layer extracted with Et_2O. The organic phases were washed with brine and dried on $MgSO_4$. The solvent was removed and the crude purified by chromatography to afford **1** (1.48 g, 7.48 mmol, 60%). $\mathbf{R_f}$ 0.41 (Petrol Ether/AcOEt (7:3)); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 6.29 (1H, q, *J*= 1.1, H-1), 4.14 (2H, s, CH_2-3), 1.85 (3H, s, CH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 147.2, 77.4, 67.8, 21.36. Data are consistent with Literature.

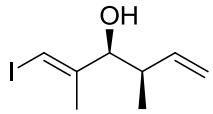
(E)-3-iodo-2-methylpropenal (2)[3]



To a solution of **1** (950 mg, 4.8 mmol, 1 eq) in Et_2O is added MnO_2 (4.17 g, 48.0 mmol, 10 eq) and the mixture stirred for 45 minutes at room temperature. Celite® is then added and the mixture is stirred for other 30 minutes before filtration on Celite to remove MnO_2. The solution is concentrated *in vacuo* yielding **2** (835 mg, 4.26 mmol, 89%) that is used for the next step without further purification. $\mathbf{R_f}$ 0.55 (Petrol Ether / AcOEt (4:1)); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 9.53(1H,s, CHO), 7.82 (1H, q, *J*= 1.1, H-1), 1.92 (3H, d, *J*= 1.1 Hz, CH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 189.6, 150.8, 109.8, 16.4. Data are consistent with literature.

[3] J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. Nylund Kolz, B. W. Phillips *J. Org. Chem.*, **2002**, *67*, 7750–7760

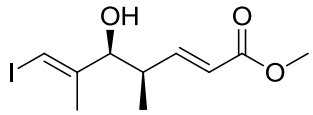
(3S,4R,E)-1-iodo-2,4-dimethylhexa-1,5-dien-3-ol (3)



A solution of aldehyde **2** (713 mg, 3.64 mmol, 1 eq) in DCM (25 ml) was cooled, under argon, to 0 °C. A solution of (3aR,7aR)-1,3-bis(4-bromobenzyl)-2-((Z)-but-2-en-1-yl)-2-chlorooctahydro-1H-benzo[d][1,3,2] diazasilole (2.45 g, 4.3 mmol, 1.2 eq) in DCM was added, followed by $Sc(OTf)_3$ (89 mg, 0.182 mmol, 0.05 eq). The mixture was stirred at 0 °C for 1 hour, then at room temperature overnight.

Solid TBAF $3H_2O$ (1.15 g, 3.64 mmol, 1 eq) was added and the mixture stirred for 1 hour. The solvent was removed and the crude purified on silica gel chromatography (10:1 petrol ether/AcOEt to1:1:0.1 petrol ether/AcOEt/Et_3N to recover the diamine), yielding **3** as a pale yellow oil (880 mg, 3.49 mmol, 96%). $\mathbf{R_f}$ 0.46 (Petrol / AcOEt (5:1)); $\mathbf{[a]_D^{25}}$ –15.29° (c=1.02, $CHCl_3$), **IR** (thin film, ν_{max} / cm^{-1}) 3413, 3077, 2975, 2917, 1725,1639, 1454, 1376, 1266, 1009, 916; ^{1}**H-NMR** (500 MHz, $CDCl_3$) δ_H 6.267 (1H,t, *J*= 1.05 Hz, H-1), 5.73 (1H, ddd, *J* = 17.3, 10.5, 7.1 Hz, H-5), 5.10 (1H, dt, *J* = 9.5, 1.4 Hz, HA-6), 5.07 (1H, m, HB-6), 4.04 (1H, dd, *J* = 5.9, 3.5 Hz, H-3), 2.45 (1H, q, *J* = 6.8 Hz, H-4), 2.05 (3H, s, Me-2), 1.80 (1H, d, *J*= 1.03 Hz, OH) 1.02 (3H, d, *J* = 6.8 Hz, Me-4); ^{13}**C-NMR** (125 MHz, $CDCl_3$) δ_C 148.2, 139.96, 115.4, 79.63, 78.92, 40.97, 20.59, 13.88; **HRMS** (FI^+) calc. for $C_8H_{13}IO$ $[M+1]^+$ 252.0011, found 252.0006

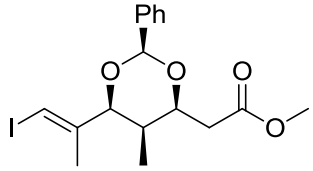
Methyl (3S,4R) 5-hydroxy-7-iodo-4,6-dimethylhepta-2,6-dienoate (4)



Compound **3** (1.01 g, 4.03 mmol) and methyl acrylate (2.17 mL, 24.18 mmol) were dissolved in DCM (12 mL) and the solution was degassed for 15 min. Then Hoveyda-Grubbs catalyst II (50 mg, 0.08 mmol) was added and the reaction mixture was stirred at 40º C until full conversion by TLC. The solvent was removed under pressure and the crude purified on silica gel chromatography yielding compound **4** (1.04 g, 3.35 mmol, 78%). $\mathbf{R_f}$ 0.27 (Petrol ether/AcOEt (5:1)); $\mathbf{[a]_D^{25}}$ –10.69° (c=1.02, $CHCl_3$), **IR** (thin film, ν_{max} / cm^{-1}) 3459, 3056, 2951, 2874, 2357, 1703, 1654, 1436, 1229, 1145, 943, 686; ^{1}**H-NMR** (500 MHz, $CDCl_3$) δ_H 6.87 (1H, dd, *J* = 15.7, 7.6 Hz, H-3), 6.32 (1H, s, H-7), 5.84 (1H, dd, *J* = 15.7, 1.1 Hz, H-2), 4.13 (1H, dd, *J* = 5.6, 3.9 Hz, H-5), 3.73 (1H, s, Me-1), 2.58 (1H, m,

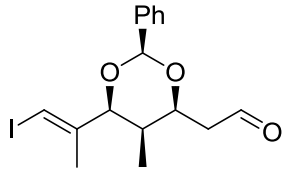
H-4), 1.96 (1H, d, *J*= 3.8 Hz, OH), 1.79 (3H, s, Me-6), 1.07 (3H, d, *J* = 6.8 Hz, Me-4); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 166.9, 150.3, 147.8, 121.2, 79.6, 79.0 51.6, 40.0, 20.6, 13.8; **HRMS** (ES^+) calc. for $C_{10}H_{15}IO_3$ $[M+Na]^+$ 332.9958, found 332.9956

Methyl 2-((4S,5R,6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)acetate (5)



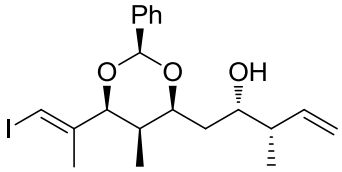
Compound **4** (330 mg, 1.06 mmol, 1 eq) was dissolved in THF (5 mL) under argon and the solution was cooled to -5 ºC. Then freshly distilled benzaldehyde (0.27 mL, 2.66 mmol, 2.5 eq) was added, followed by tBuOK/THF 0.5M (0.21 mL, 0.106 mmol, 0.1 eq). The addition of the solution tBuOK/THF was dropwise and it was repeated three times every 20 minutes. The resulting red solution was quenched with pH 7 phosphate buffer. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (petrol ether/AcOEt 10:1) afforded **5** (130 mg, 0.31 mmol, 30%) as a colourless oil. **R_f** 0.42 (Petrol / AcOEt (5:1)); **$[a]_D^{25}$** – 18.89° (c=0.99, $CHCl_3$), **IR** (thin film, ν_{max} / cm^{-1}) 3468, 3091, 3034, 2974, 2874, 2358, 1737, 1624, 1347, 1101, 1028, 758, 699; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 7.48-7.59 (2H, m, Ph), 7.34-7.40 (3H, m, Ph), 6.35 (1H, s, H-1), 5.63 (1H, s, C*H*Ph), 4.48 (1H,ddd, *J*=7.8, 5.8, 2.2 Hz, H-5), 4.13 (1H, s, H-3), 3.72 (1H, s, Me-7), 2.74 (1H, dd, *J*= 7.8, 15.9 Hz, H-6A), 2.52 (1H, dd, *J*= 15.9, 5.8 Hz, H-6B), 1.87-1.91 (1H, m, H-4), 1.81 (1H, s, Me-2), 0.87 (3H, d, *J* = 6.9 Hz, Me-4); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 171.1, 143.7, 138.5, 128.9, 128.3, 128.2, 126.2, 101.35, 83.4, 78.2, 51.9, 37.8, 33.1, 21.4, 6.2; **HRMS** (ES^+) calc. for $C_{17}H_{21}IO_4$ $[M+Na]^+$ 439.0377, found 439.0374

2-((4S,5R,6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)acetaldehyde (6)



To a solution of **5** (174 mg, 0.432 mmol, 1 eq) in DCM (4 mL), cooled to -78 ºC and under inert atmosphere, was added DIBAL-H 1.0M Hex (0.475 mL, 0.475 mmol, 1.1 eq). The solution was stirred at low temperature for 2 hours. Then, MeOH was added and the solution was poured in a flask containing a mixture of saturated Na K Tartrate and ethyl acetate. After stirring for 1 hour the layers were separated, the aqueous extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to afford a crude that was purified by chromatography on silica gel (petrol/AcOEt 5:1) yielding **6** (110 mg, 0.285 mmol, 66%) as a colourless oil. **R_f** 0.24 (Petrol / AcOEt (5:1)); **$[a]_D^{25}$** –40.24° (c=0.83, $CHCl_3$), **IR** (thin film, ν_{max} / cm^{-1}) 3429, 3034, 2974, 2848, 2733, 2365, 1726, 1624, 1454, 1346, 1133, 1028, 769, 699; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 9.85 (1H, t, *J*= 1.6 Hz, C*H*O), 7.48-7.50 (2H, m, Ph), 7.36-7.40 (3H, m, Ph), 6.36 (1H, t, *J* = 1.6 Hz, H-1), 5.65 (1H, s, C*H*-Ph), 4.57 (1H, ddd, *J* = 7.1, 4.7, 2.3 Hz, H-5), 4.45 (1H, s, H-3), 2.88 (1H, ddd, *J*= 17.3, 8.4, 1.6, H-6A), 2.55 (1H, ddd, *J*= 17.3, 4.7, 1.6, H-6B), 1.85-1.90 (1H, m, H-4), 1.81 (3H, s, Me-2), 0.88 (3H, d, *J* = 6.9 Hz, Me-4); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 200.0, 143.5, 137.9, 129.1, 128.3, 126.2, 101.4, 83.4, 78.3, 75.2, 46.7, 33.3, 21.4, 6.3; **HRMS** (ES^+) calc. for $C_{16}H_{20}IO_3$ $[M+Na+MeOH]^+$ 441.0533, found 441.0544

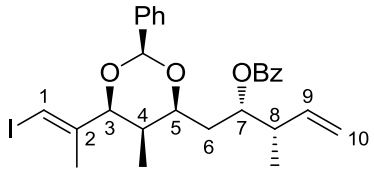
(2S,3S)-1-((4S,5R,6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-ol (7)



A solution of **6** (100 mg, 0.259 mmol, 1 eq) in DCM (2.5 ml) under inert atmosphere was cooled to 0 °C and a solution of (3S,7S)-1,3-bis(4-bromobenzyl)-2-((Z)-but-2-en-1-yl)-2-chlorooctahydro-1H-benzo[d][1,3,2] diazasilole (176 mg, 0.1 mmol, 1.2 eq) in DCM was added. The mixture was allowed to warm at room temperature and stirred for 48h. The reaction was then quenched adding solid TBAF 3H2O (82 mg, 0.259 mmol, 1 eq) and after stirring for 1h, the solvent was removed and the crude purified on silica gel cromatograpphy yielding an inseparable mixture of starting material and product **7** (35 mg, product/SM 3:1). **R_f** 0.22 (Petrol / DCM (1:1)); **$[a]_D^{25}$** –35.5° (c=1.00, $CHCl_3$), **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 7.48-7.52 (2H, m, Ph), 7.36-7.41 (3H, m, Ph), 6.33 (1H, s, H-1), 5.80 (1H, ddd, *J* = 17.5, 10.2, 7.3 Hz, H-9), 5.62 (1H, s, C*H*-Ph), 5.12 (2H, d, *J* = 14.1 Hz,

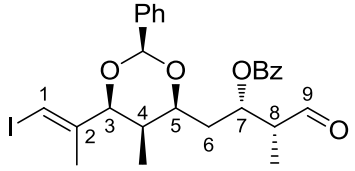
H-10), 4.41 (1H, s, H-3), 4.27 (1H, dt, *J*= 10.1, 2.1 Hz, H-5), 3.82 (1H, t, *J*= 4.2 Hz, H-7), 2.32 (1H, m, H-8), 1.87 (1H, ddd, *J*= 14.3, 9.7, 2.3 Hz, H-6A), 1.79 (3H, s, Me-2), 1.76 (1H, dt, *J*= 6.9, 2.3 Hz, H-4), 1.43 (1H, ddd, *J*= 14.3, 9.9, 2.2 Hz, H-6B), 1.06 (3H, d, *J*= 6.9 Hz, Me-8), 0.86 (3H, d, *J* = 6.9 Hz, Me-4); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 144.0, 140.6, 129.1, 128.9, 128.3, 126.2, 115.7, 101.3, 83.8, 77.9, 77.2, 70.8, 43.7, 37.4, 34.5, 21.4, 14.0, 6.4. **HRMS** (ES^+) calc. for $C_{20}H_{27}IO_3$ $[M+Na]^+$ 465.0897, found 465.0886

(2S,3S)-1-((2S,4S,5R,6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-yl benzoate (10a)



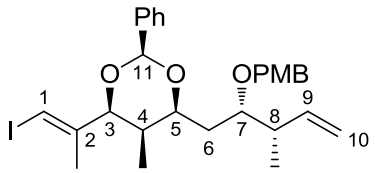
To a solution of **7** (35 mg, 0.08 mmol, 1 eq) in pyridine (0.2 ml) under inert atmosphere was added benzoyl chloride (11microL, 13 mg, 0.09 mmol, 1.2 eq). The mixture was stirred at room temperature for 16h. The reaction was then quenched adding water and extracting with DCM. The organic layers were then washed with HCl 1M, dried over $MgSO_4$, filtered, the solvent removed and the crude purified on silica gel cromatography yielding product **7** (22 mg, 0.04 mmol, 50%). $\mathbf{R_f}$ 0.31 (Petrol / AcOEt (20:1)) **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 8.09 (2H, m, Ph), 7.36-7.61 (8H, m, Ph), 6.35 (1H, t, *J* = 1.2 Hz, H-1), 5.85 (1H, ddd, *J* = 17.5, 10.4, 7.3 Hz, H-9), 5.51 (1H, s, C*H*-Ph), 5.48 (1H, ddd, *J* = 9.9, 5.4, 2.5 Hz, H-7), 5.09 (2H, m, H-10), 4.30 (1H, s, H-3), 3.98 (1H, dt, *J*= 10.1, 2.1 Hz, H-5), 2.60 (1H, dq, *J*= 13.6, 6.9 Hz, H-8), 2.06 (1H, ddd, *J*= 14.7, 9.8, 2.6 Hz, H-6A), 1.80-1.64 (2H, m, H-6B, H-4), 1.72 (3H, s, H-2), 1.12 (3H, d, *J*= 6.9 Hz, Me-8), 0.85 (3H, d, *J* = 6.9 Hz, Me-4); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 166.1, 143.9, 139.5, 138.3, 133.0, 130.4, 129.6, 128.7, 128.4, 128.1, 126.1, 115.7, 101.0, 83.5, 77.9, 77.1, 74.2, 41.9, 35.2, 34.2, 21.3, 15.0, 6.3.**HRMS** (ES^+) calc. for $C_{27}H_{31}IO_3$ $[M+Na]^+$ 569.1159, found 569.1163

(2S,3R)-1-((2S,4S,5R,6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-3-methyl-4-oxobutan-2-yl benzoate (2a)



6 μl of 2,6-lutidine (5.8 mg, 0.054mmol, 2eq), 5.48 mg of a OsO_4 (2.5% solution in *t*-BuOH, $5.4 \cdot 10^{-4}$mmol, 0.02 eq) and 23 mg of $NaIO_4$ (0.108 mmol, 4 eq) were added sequentially to a solution of **10a** (15 mg, 0.027 mmol, 1 eq) in dioxane/H_2O (0.2 ml/ 0.06 ml). The mixture was stirred at room temperature for 2h30. The reaction was then quenched adding H_2O and extraceted with Et_2O. The organic layers were then dried over $MgSO_4$, filtered, the solvent removed and the crude purified on silica gel cromatography yielding product **2a** (9 mg, 0.016 mmol, 61%). $\mathbf{R_f}$ 0.41 (Petrol / AcOEt (5:1))**, ^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 9.8 (1H, s, H-9), 8.03 (2H, d, *J* = 7.0 Hz, Ph), 7.60 (2H, t, *J* = 7.4 Hz, Ph), 7.53 (2H, dd, *J* = 7.9, 1.4 Hz, Ph), 7.47 (2H, t, *J* = 7.9 Hz, Ph), 7.43 – 7.34 (2H, m, Ph), 6.36 (1H, s, H-5), 5.90 (1H, dt, *J* = 8.9, 3.4 Hz, H-7), 5.53 (1H, s, C*H*Ph), 4.35 (1H, s, H-3), 4.06 (1H, dt, *J* = 10.0, 2.3 Hz, H-5), 2.78 (1H, dq, *J* = 7.0, 3.4 Hz, H-8), 2.6 (1H, ddd, *J*= 14.6, 10.0, 4.0 Hz, H-6A), 1.93 (1H, ddd, *J* = 14.6, 8.9, 2.3 Hz, H-6B), 1.82 – 1.71 (4H, m, H-4, Me-2), 1.24 (3H, d, *J* = 7.0 Hz, Me-8), 0.87 (3H, d, *J*=6.9Hz, Me-4). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 201.9, 165.8, 143.7, 138.1, 133.3, 129.7, 128.9, 128.5, 128.4, 128.2, 126.1, 101.1, 83.5, 78.1, 76.9 70.3, 50.7, 36.0, 34.1, 21.3, 8.0, 6.3. **HRMS** (ES^+) calc. for $C_{27}H_{33}IO_6$ $[M+Na+MeOH]^+$ 603.1214, found 603.1209

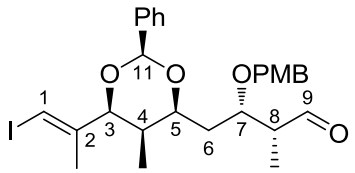
(2S,4S,5R,6S)-4-((E)-1-iodoprop-1-en-2-yl)-6-((2S,3S)-2-((4-methoxybenzyl)oxy)-3-methylpent-4-en-1-yl)-5-methyl-2-phenyl-1,3-dioxane (10b)



32 mg of NaH (60% mineral oil, 0.81 mmol, 3 eq) were suspend in THF (4 ml)/DMF (0.2 mml) under inert atmosphere. A solution of **7** (120 mg, 0.27 mmol, 1 eq) in THF (2.5 ml) was added dropwise followed by tetrabutylamonium iodide (20 mg, 0.054 mmol, 0.2 eq) and 110 μl of *p*-methoxy-benzyl chloride (127 mg, 0.81 mmol, 3 eq) The reaction was stirred at room temperature for 16h. Methanol was then added and the mixture stirred for 15 minutes, diluted with water and extracted with Et_2O. The organic layers were then washed with brine., dried over $MgSO_4$, filtered, the solvent removed and the crude purified by on silica gel cromatography yielding product **10b** (110 mg, 0.19 mmol, 72%). $\mathbf{R_f}$ 0.34 (Petrol / AcOEt (9:1)); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 7.45 (2H, dd, *J* = 7.8, 1.6 Hz, Ph), 7.41 – 7.34 (3H, m, Ph), 7.30 – 7.27 (2H, d, *J* = 8.7 Hz, PMB), 6.89 (2H, d, *J* = 8.7 Hz,

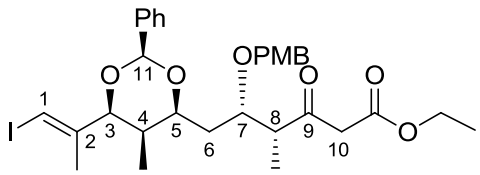
PMB), 6.31 (1H, s, H-1), 5.93 (1H, ddt, *J* = 13.0, 10.0, 7.6 Hz, H-9), 5.36 (1H, s C*H*Ph,), 5.13 – 5.03 (2H, m, H-10), 4.66 (1H, d, *J* = 11.0 Hz, CH_2 *p*-MeOPh), 4.41 (1H, d, , *J* = 11.0 Hz, CH_2 *p*-MeOPh), 4.29 (1H, s, H-3), 4.06 (1H, dt, *J* = 10.3, 2.0 Hz, H-5), 3.74 (3H, s, OCH_3), 3.68 – 3.60 (1H, m, H-7), 2.58 (1H, td, *J* = 13.6, 6.8 Hz, H-8), 1.82 – 1.71 (4H, m, Me-2, H-6A), 1.72 – 1.65 (1H, m, H-4), 1.47 – 1.30 (1H, m, H-6B), 1.05 (3H, d, *J* = 6.9 Hz, Me-8), 0.80 (3H, d, *J* = 6.9 Hz, Me-4). **^{13}C-NMR** (125 MHz, $CDCl_3$) $\delta_{C:}$ 159.2, 144.1, 140.3, 138.6, 130.8, 129.70, 128.1, 126.1, 114.8, 113.8, 113.7, 100.9, 83.9, 78.2, 77.8, 72.0, 55.2, 40.3, 35.1, 34.2, 21.3, 15.1, 6.3.**HRMS** (ES^+) calc. for $C_{28}H_{35}IO_4$ $[M+Na]^+$ 585.1472, found 585.1467

(2R,3S)-4-((2S,4S,5R,6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-3-((4-methoxybenzyl)oxy)-2-methylbutanal (2b)



33 µl of 2,6-lutidine (31 mg, 0.284 mmol, 2eq), 29 mg of OsO_4 (2.5% solution in *t*-BuOH, 0.028 mmol, 0.02 eq) and 121 mg of $NaIO_4$ (0.568 mmol, 4 eq) were added sequentially to a solution of **10b** (80 mg, 0.142 mmol, 1 eq) in dioxane/H_2O (1 ml/ 0.4 ml). The mixture was stirred at room temperature for 2 hours. The reaction was then quenched adding H_2O and extraceted with Et_2O. The organic layers were then dried over $MgSO_4$, filtered, the solvent removed and the crude purified on silica gel cromatography yielding product **2b** (41 mg, 0.075 mmol, 53%). $\mathbf{R_f}$ 0.42 (Petrol / AcOEt (5:1)); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 9.85 (1H, s, CHO), 7.52 – 7.34 (4H, m, Ph), 7.30 – 7.21 (2H, m, PMB), 6.89 – 6.82 (2H, m, PMB), 6.32 (1H, s, H-1), 5.39 (1H, s, C*H*Ph), 4.58 (1H, d, *J* = 11.3 Hz, CH_2 *p*-MeOPh), 4.40 (1H, d, *J* = 11.3 Hz, CH_2 *p*-MeOPh), 4.32 (1H, s, H-3), 4.17 – 4.12 (1H, m, H-7), 4.08 (1H, dt, *J* = 10.3, 2.0 Hz, H-5), 3.75 (3H, s, OMe), 2.71 – 2.61 (1H, m, H-8), 1.84 – 1.78 (1H, m, H-6A), 1.77 (3H, s, Me-2), 1.74 – 1.66 (1H, m, H-4), 1.63 – 1.58 (1H, m, H-6B), 1.14 (3H, d, *J* = 6.9 Hz, Me-8), 0.82 (3H, d, *J* = 6.9 Hz, Me-4); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ_C 204.5, 159.4, 143.8, 138.3, 129.7, 128.8, 128.2, 126.1, 113.9, 101.0, 83.8, 78.0, 76.5, 74.5, 67.1, 60.4, 55.2, 50.2, 36.4, 34.1, 21.3, 8.4, 6.3. **HRMS** (ES^+) calc. for $C_{28}H_{37}IO_6$ $[M+Na+MeOH]^+$ 619.1527, found 619.1519

(4R, 5S)-ethyl 6-((2S, 4S, 5R, 6S)-6-((E)-1-iodoprop-1-en-2-yl)-5-methyl-2-phenyl-1,3-dioxan-4-yl)-5-((4-methoxybenzyl)oxy)-4-methyl-3-oxohexanoate (11)



To a stirred solution of ethyldiazoacetate (34 μl, 0.054 mmol, 2 eq) and of $SnCl_2$ (0.5 mg 0.0027 mmol, 0.1 eq) in DCM (0.5 ml) under inert atmosphere a solution of 15 mg of aldehyde **2b** (0.027 mmol, 1 eq) in DCM was slowly added over 5 minutes, observing the evolution of N_2 and then the mixture was stirred overnigh.t

The reaction was then washed with brine and extracted with Et_2O (x3) The organic layers were then dried over $MgSO_4$, filtered, the solvent removed and the crude purified on silica gel cromatography yielding product **11** (15 mg, 0.023 mmol, 42%). $\mathbf{R_f}$ 0.37 (Petrol / AcOEt (5:1)); ^{1}**H-NMR** (500 MHz, $CDCl_3$) δ_H 7.54-7.17 (6H, m, Ph), 6.95-6.76 (2H, m, PMB), 6.30 (1H, s, H-1), 5.32 (1H, s, C*H*-Ph), 4.63 (1H, d, *J* = 11.2 Hz, CH_2 *p*-MeOPh), 4.43 (1H, d, *J* = 11.2 Hz, CH_2 *p*-MeOPh), 4.29 (1H, s, H-3), 4.19 (2H, q, *J*= 7.14 Hz, CH_2(Et)), 4.04-3.95 (1H, m, H-7), 3.95-3.84 (1H, m, H-5), 3.73 (3H, s, OMe), 3.60 (2H, s, H-10), 3.14 (1H, dd, *J*= 7.0, 3.8 Hz, H-8), 1.87-1.60 (4H, m, H-6A, Me-2), 133-1.24 (4H, m, CH_3(Et), H-4), 1.10 (3H, d, *J*= 6.9 Hz, Me-8), 0.79 (3H, d, *J* = 6.9 Hz, Me-4).