New Synthetic Methodologies Using Enyne Olefin Metathesis Application in Natural Product Synthesis

Vorgelegt von
Marta Porta García, M.Sc.
aus Terrassa (Spanien)

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Abstract

The presented investigations deal with three related topics regarding metathesis methodology with amine-containing compounds.

The main focus of this work lies on the application of diastereoselective ring-rearrangement metathesis (enyne *d*RRM) in the synthesis of naturally occurring 5,8-disubstituted indolizidine alkaloids. Starting from cheap chiral-pool-substances such as (*S*)-proline and (*S*)-glutamic acid, different bicyclic substrates containing a prochiral C-3-thethered cycloolefine have been prepared and subjected to metathesis studies. For amide-based compounds, diastereoselectivity can be controlled by means of catalyst choice. A wide range of commercially available complexes as well as recently developed Ru-catalysts have been screened, and values of diastereoselectivity from 1:10 to 4:1 (*cis*:*trans*) have been obtained. For the particular case of amine-based substrates, the Lewis basic character of the nitrogen atom can be overcome by formation of the corresponding ammonium salt to avoid catalyst deactivation. For the first time in metathesis transformations, it has been demonstrated that the counterion of such ammonium salts play an important role in the reaction outcome. After extensive substrate screening it has been possible to control the *dr,* obtaining values from 1:3 (*cis*:*trans*) to complete selectivity towards the desired *cis*-diastereoisomer. These results were next applied in the concise synthesis of C-5 and C-8 epimers of indolizidines 223J, 219F and 223AA. Further investigations towards indolizidine 193E and 1,4-disubstituted quinolizidines have been performed and further synthetic studies have been proposed for the conclusion of such approaches.

The second part of this work is an investigation into the influence of the counterion on metathesis reactions with structurally different ammonium salts, including *d*RRM. From the obtained results it can be concluded that the use of Brønsted acids is a very effective methodology for avoiding catalyst deactivation when unprotected amines are used as substrates in metathesis. Further, it has been proven that the counterion plays an important role in the outcome of the metathesis reaction. For the investigated transformations, ammonium salts derived from HBF_4 and *p*TSA furnished better conversion towards the desired product than the substrates obtained by reaction with HCl. Trifluoromethane sulfonic acid salts have been used for the first time in metathesis reactions and have shown, for certain substrates, to deliver improved results in terms of conversion and selectivity.

The last part of the presented research deals with the development of a hydroamination-alkyne addition-metathesis sequence which is based on the combination of DBI-Zn-complexes with ruthenium-based metathesis catalysts. This methodology enables the formation of unsaturated *N*-heterocycles in an one-pot procedure, and is one of the few examples on both bi-catalyzed hydroamination and bi-catalyzed metathesis one-pot reactions, being the first report of a Zn-Ru sequential catalysis. The described transformation is suitable for benzylic amines, anilines and other heterocyclic amines and the products obtained, as well as further possible synthetic derivatives, are amine-containing compounds that resemble the structural core of different natural products.

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Chapter 1

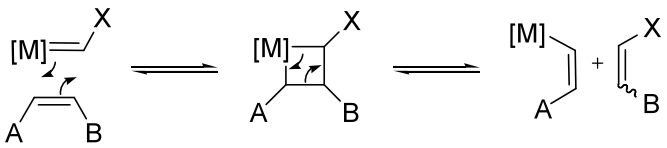
Introduction

Chapter 1: Introduction

1.1 Olefin Metathesis

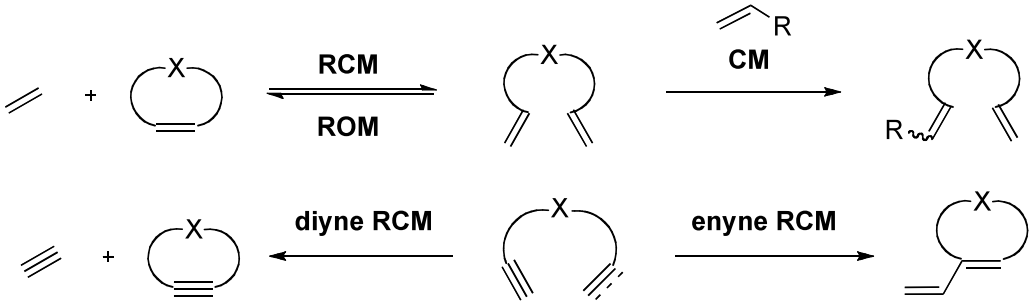
In the field of carbon-carbon bond-forming processes the Grignard (Nobel Prize 1912),[1] Diels Alder (Nobel Prize 1950),[2] and Wittig (Nobel Prize 1979)[3] reactions are three of the most prominent transformations that have played decisive roles in organic chemistry and natural product synthesis. In the last 60 years, two further reactions have been extensively developed which also deserve to be included amongst the most powerful tools of a synthetic chemist: palladium-catalyzed cross-coupling reactions and olefin metathesis (Nobel Prize 2005 to Y. Chauvin, R. H. Grubbs and R. R. Schrock).[4]

Under alkene metathesis is described the metal-catalyzed redistribution of carbon-carbon double bonds *via* a [2+2] cycloaddition-cycloreversion process, whereby the generally accepted mechanism, originally proposed by Chauvin in 1971,[4a] consists of a metal carbene intermediate as key propagating species (Scheme 1).



Scheme 1. General mechanism of olefin metathesis.

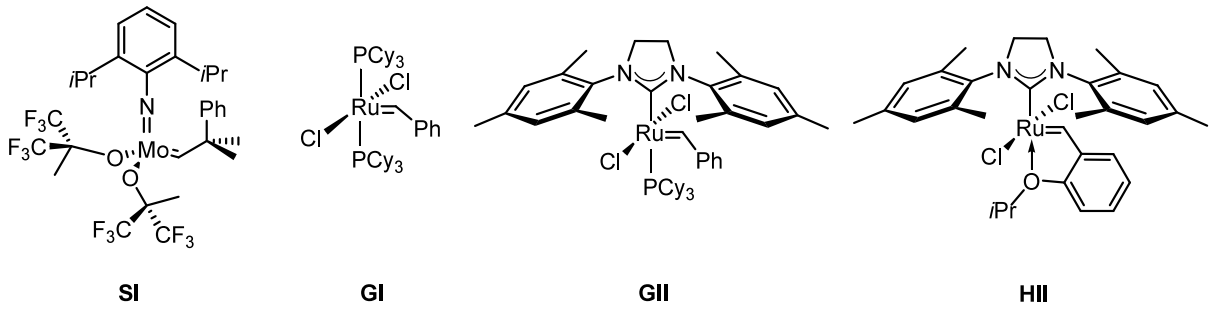
Several synthetically useful intra- and intermolecular variants of this process are known, including the classical ring-opening metathesis (ROM),[5] ring-closing metathesis (RCM),[6] cross metathesis (CM),[7] and polymerization reactions (Scheme 2).[8] Although alkene metathesis constitutes the most widely utilized type of metathesis, alkynes can also be used as substrates, with either an alkene (enyne metathesis)[9] or a second alkyne (diyne metathesis).[10]



Scheme 2. Classification of metathesis reactions.

1.2 Olefin Metathesis Catalysts

At the heart of advancement in metathesis lies the development of effective catalysts. A great variety of olefin metathesis catalysts have been developed over the past 20 years. Nowadays, there are up to 20 catalysts commercially available and several reviews have been published with an overview of the most significant, where their reactivity, stability and selectivity have been addressed.[11] Despite the large number of these carbene complexes, catalyst **SI**,[12] **GI**,[13] **GII**[14] and **HII**[15] are the most widely applied (Figure 1).



SI **GI** **GII** **HII**

Figure 1. Carbene complexes mostly used in metathesis reactions.

Catalyst **SI** exhibits high olefin metathesis activity, but lacks general functional group tolerance and suffers from strong air and moisture sensitivity.

The first generation catalyst **GI**, although less reactive than **SI**, exhibits improved stability towards functional groups. With the replacement of one of the phosphine ligands with an *N*-heterocyclic carbene ligand (NHC), the "second-generation" catalyst **GII** shows an increase in catalytic activity, thermal stability, and functional group tolerance. This improvement in metathesis activity is attributed to an increased rate of catalyst turnover owing to the favorable electron donation and steric bulk of the NHC ligand. Further catalyst tuning through the substitution of the remaining phosphine ligands with an isopropoxystyrene-based ligand provided the complex **HII**, with increased resistance towards high temperatures, together with air-, moisture- as well as chromatographic stability. Functional group compatibility and thermal stability are crucial for the synthesis of complex molecules, thus commercially available Ru-based **GI**, **GII** and **HII** have been utilized in synthesis to a greater extent than **SI**.

1.3 Metathesis as Key Transformation in Organic Synthesis

Olefin metathesis has proven to be a valuable synthetic tool in organic chemistry and is nowadays well established.[4] A number of reviews on this topic have been published during

the last years, focusing on the application of the reaction in organic synthesis,[16] natural product synthesis, [17] and polymer chemistry.[8]

To date, commercially available products constructed by metathesis reactions range from polymers to highly functionalized pharmaceutical agents. In this regard, the combination of reactivity and functional group compatibility of the ruthenium catalyst, with the chemoselectivity and the mild reaction conditions required, enable the use of metathesis at the late stages of a total synthesis, whereby many other reaction transformations cannot be applied.[18] Moreover, the newly formed olefins offer a synthetic handle for further transformations, such as cycloaddition, dihydroxylation, epoxidation, halogenation, or other metal-catalyzed reactions.

Ruthenium metathesis catalysts are also used in tandem reactions as they are stable toward a variety of reaction conditions and reagents increasing the wealth of synthetic transformations that can be accomplished. Additionally, ruthenium catalysts can be modified *in situ*, to promote reduction or oxidation reactions, depending on the substrates and the reaction conditions employed.[19] Olefin metathesis has been recognized as a "green" chemistry, since increases the efficiency in terms of synthetic steps and the lack of contaminating by-products, and opens new routes for the conversion of biomaterials into useful products, which may replace petroleum-based starting materials.

1.4 The Challenges of Alkene Metathesis

Despite the exponential development of metathesis reactions and the status of alkene metathesis as one of the most powerful reactions in the field of C-C bond-forming transformations, there are still many challenges to be faced.

The facile preparation of ruthenium catalysts coupled with their functional group tolerance and stability, has enabled olefin metathesis to realize its broad synthetic potential. Nevertheless, new ligand design is still required in order to improve the catalysts' lifetime and to control enantio-, diastereo- and *cis/trans* selectivity. Mo-based complexes solve some of these challenges, but the lack of tolerance towards moisture, oxygen and certain functionalities hampers its application in organic synthesis.

Development of new methodology is likewise essential in order to broaden the synthetic potential of metathesis reactions. In this regard, investigation of "green" processes, including one-pot procedures towards more friendly reactions are indispensable, especially for industrial applications.

> *"After all the achievements of the last couple of decades, there is still much to do at a fundamental level, and a great deal to do in terms of applications, which in the end*

will depend upon the ability to manipulate and control catalyst activities." R. R. Schrock.[4b]

1.5 Motivation and Objectives

In the presented investigations three related topics regarding metathesis methodology and its application will be discussed.

The main focus of this work is on the combination of different metathesis reactions in a sequence cascade, a process known as ring-rearrangement metathesis (RRM). Enantiomerically pure compounds will serve as metathesis substrates and efforts will be made to control diastereoselectivity, by selecting the adequate reaction conditions and the appropriate metathesis catalyst. The newly developed methodology will next be applied in the synthesis of naturally occurring indolizidine alkaloids. Diastereoselective enyne RRM (enyne *d*RRM) is an unprecedented and as yet unpublished methodology and constitutes an important advancement in this field, since this would enhance the synthetic potential of metathesis transformations.

The second part of this work is an investigation into the effect of different ammonium salts on metathesis reactions, including enyne *d*RRM. Unprotected amines have been shown to interfere with the catalyst activity, due to coordination of the lone pair of the nitrogen atom with the metal center. One strategy to avoid catalyst deactivation employs a Lewis acid additive. The emphasis will be placed on the different parameters that may influence the outcome of the reaction, including catalyst and the type of Lewis acid used, with the intention to overcome drawbacks associated with the use of amine compounds in metathesis.

The final part involves a novel Zn-Ru sequential catalysis. Tandem hydroamination-alkyne addition will be combined with Ru-catalyzed RCM in a one-pot process. Readily available amine compounds will be used as substrates, using the knowledge gained with the above-mentioned investigations, for the synthesis of *N*-heterocyclic compounds.

The three investigated subjects combine results obtained in catalyst development and methodological investigations with applications to the synthesis of potentially bioactive natural products, this being a valuable contribution to the further development of the metathesis reaction.

Chapter 2

Ru-Catalyzed Diastereoselective Enyne RRM and Application in Natural Product Synthesis

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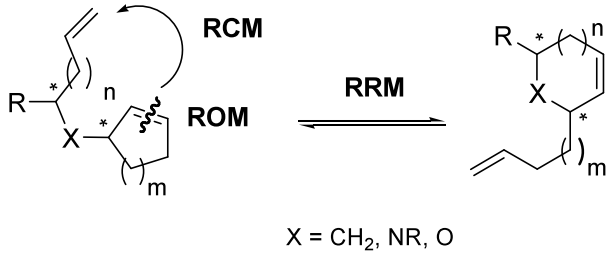
2.1 Introduction and Motivation

2.1.1 Ring-Rearrangement Metathesis (RRM)

The synthetic potential of RCM, ROM and CM can be increased when these transformations are combined in a cascade process. This domino process is classified as ring-rearrangement metathesis (RRM) and allows the facile construction of complex molecules, starting from easily accessible substrates. Generally, in RRM a strained carbo- or heterocyclic alkene is transformed into a new cycle by intramolecular ring-opening ring-closing with an exocyclic double bond, resulting in an interchange in the connectivity of the carbon skeleton (Scheme 3).



Scheme 3. General principle of a RRM cascade.

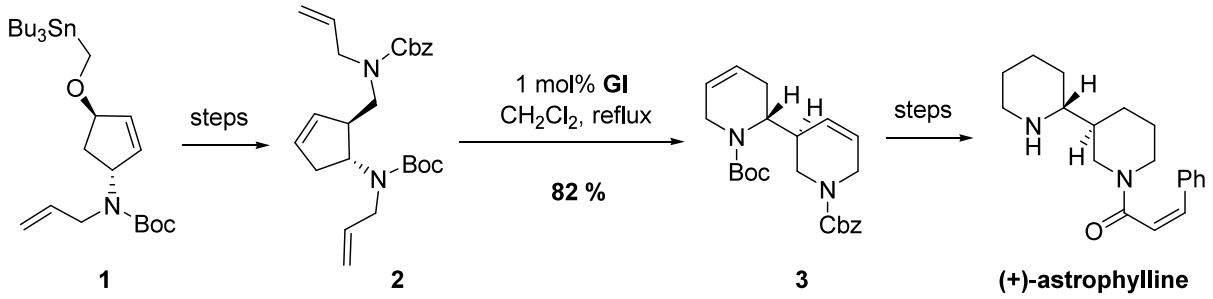
Among all the possible metathesis reactions, this methodology has demonstrated extraordinary synthetic potential concerning the construction of carbon and heterocyclic structures, serving as a key step in an increasing number of natural product syntheses since 1999, when the first application of ruthenium catalysed RRM was published on the synthesis of (-)-halosaline.[20] Since stereocenters remain unchanged during the metathesis reaction, probably the most important feature of RRM is the capacity to transfer any stereochemical information from the starting material into the product. While the application of RCM can be limited by the accessibility of the chiral acyclic precursor, RRM offers the possibility of transferring stereocenters, easily accessible in a ring system, to the side chain or *vice versa*, and thus avoiding complicated multistep syntheses of chiral compounds otherwise difficult to access.

RRM is driven by thermodynamic factors (loss of ring strain or release of a volatile olefin) as well as kinetic effects (such as the formation of a less-reactive carbene complex) and it can be applied to different sized mono and polycyclic structures. Due to the reversibility of this metathesis cascade, the strategic selection of protecting groups, reaction conditions and electronic properties of the reacting parts is crucial in order to shift the equilibrium to the desired product.

2.1.1.1 Application of RRM in the Synthesis of Natural Products

The application of RRM in target oriented synthesis has increased exponentially during the last decade and several articles have been published encompassing a wide variety of natural products.[21]

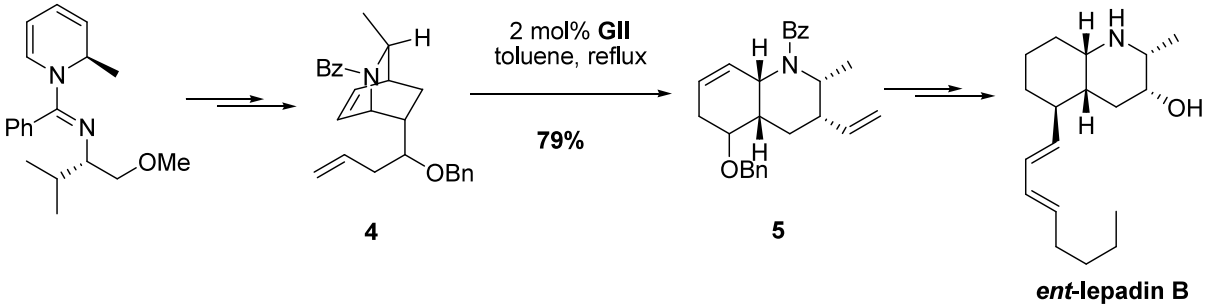
A noteworthy demonstration of the utility of this skeletal reorganisation was described in the first synthesis of (+)-astrophylline performed by Blechert and Schaudt (Scheme 4).[22] The functionalized cyclopentene **2**, in which the stereocontrolled generation of the 1,2-*trans* relative configuration was achieved *via* a *n*-BuLi mediated [2,3]-Wittig-Still rearrangement of **1**, which was successfully transformed into the key intermediate **3** with the use of the second generation catalyst **GII**.



Scheme 4. RRM of the cyclopentene derivate **2** in the synthesis of (+)-astrophylline.

Bicyclic systems deserve special attention among the different types of substrates suitable for metathesis reactions. Owing to the highly strained ring system inherent in such systems, these substrates are highly reactive, and the driving force for the reaction can be clearly attributed to the release of strain energy. The introduction of an external olefin, usually ethylene, is necessary in most of the cases to avoid oligomerization, a common side reaction in RRM. Norbornene derivatives are thus common substrates for ring rearrangement cascades. Because of their highly strained structure, equilibrium is strongly shifted to the product, and due to the highly stereocontrolled norbornene synthesis, easy access to new architectures is possible which otherwise would be difficult to synthesise.

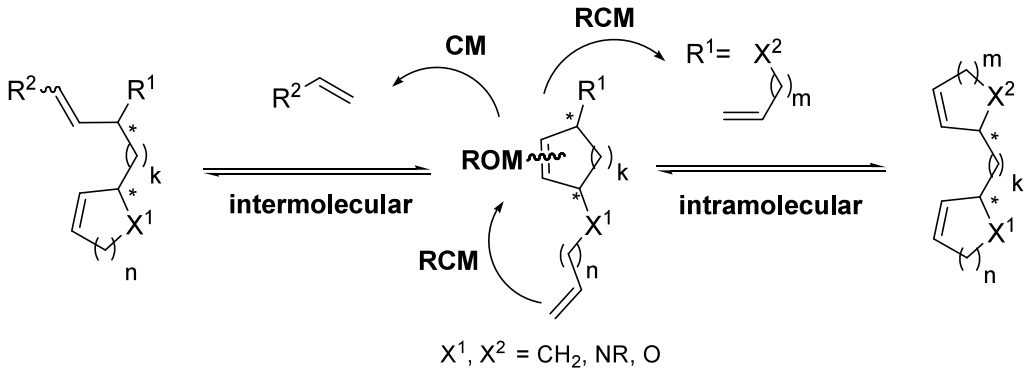
A recent example of this particular RRM was reported by Barbe and Charette in the synthesis of *ent*-lepadin B (Scheme 5).[23] Lepadine was isolated from the tunicate of *Clavelina lepadiformis* and has shown to exhibit significant *in vitro* cytotoxicity against several human cancer cell lines. Subjecting **4** to 2 mol% of catalyst **GII** at 80 °C afforded the desired rearranged product **5** in 79% yield after a reaction time of only 2 minutes.



Scheme 5. Synthesis of *ent*-lepadin B by a RRM cascade.

2.1.1.2 RRM Combined with other Metathesis Reactions

The synthetic potential of RRM can be further augmented with the introduction of a third olefin, permitting access to much more complex structures in one single transformation, by a consecutive intermolecular CM or a second RCM. Two mechanistic pathways can be envisaged for this transformation. The metathesis cascade may involve an initial formation of a ruthenium-alkyliden complex at the terminal olefin, or alternatively, the sequence may begin with [2+2]-cycloaddition of the ruthenium carbene onto the endocyclic double bond, followed by ring-opening ring-closure or cross-metathesis (Scheme 6). None of these possibilities can be ruled out, and the occurrence of one or another may be influenced according to ring strain, steric and electronic properties of the corresponding olefins, as well as by the reaction conditions employed.

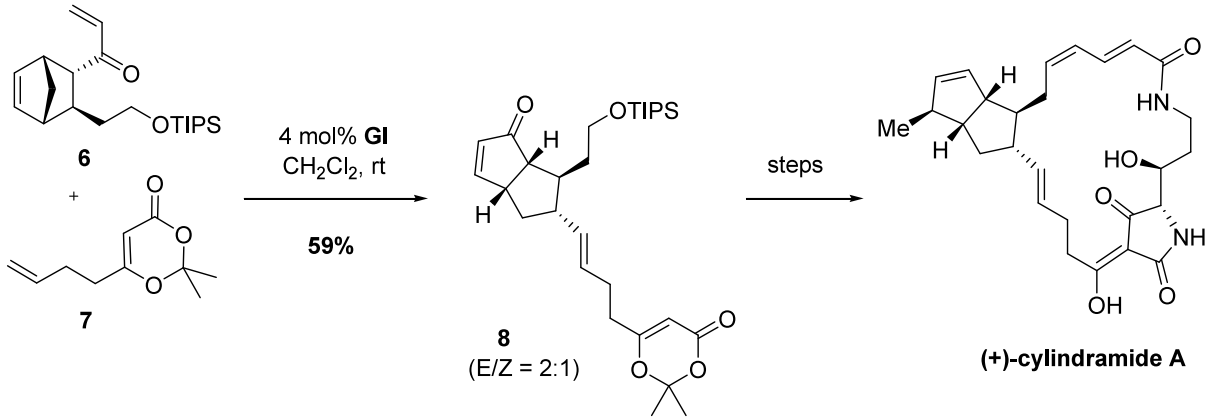


Scheme 6. General concept of the RCM–ROM–RCM and RCM–ROM–CM sequences.

Extension of intramolecular domino metathesis processes with an intermolecular reaction, namely cross metathesis (CM), has also been successfully applied in organic synthesis.

Although CM is afflicted with difficulties in E/Z selectivity and chemoselectivity (three different products may be possible in a reaction of two different olefins), the choice of suitable substrates and catalysts alleviates the limitation of these problems. In this case, however, the loss of ring strain, which usually shifts the metathesis cascade towards the desired product in RRM of bicyclic structures, does not guarantee a clean reaction, since selectivity issues inherent in CM can lead to side reactions.

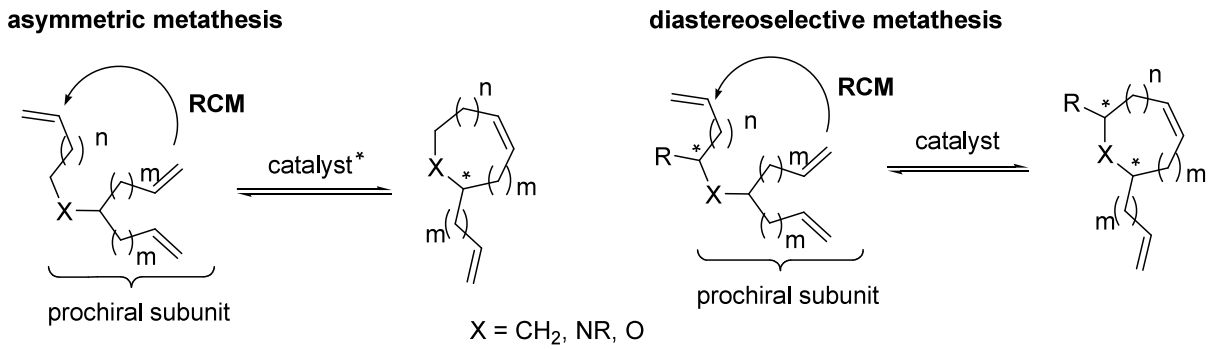
Phillips and coworkers exemplified this metathesis cascade within the synthesis (+)-cylindramide A (Scheme 7).[24] The bicyclic compound **6** served as a metathesis precursor, where reaction with **7** using 4 mol% catalyst **GI** led to the formation of product **8** in 59% yield and with an *E/Z* ratio of 2:1.



Scheme 7. RCM-ROM-CM cascades on bicyclic systems.

2.1.2 Diastereoselective RRM (*d*RRM)

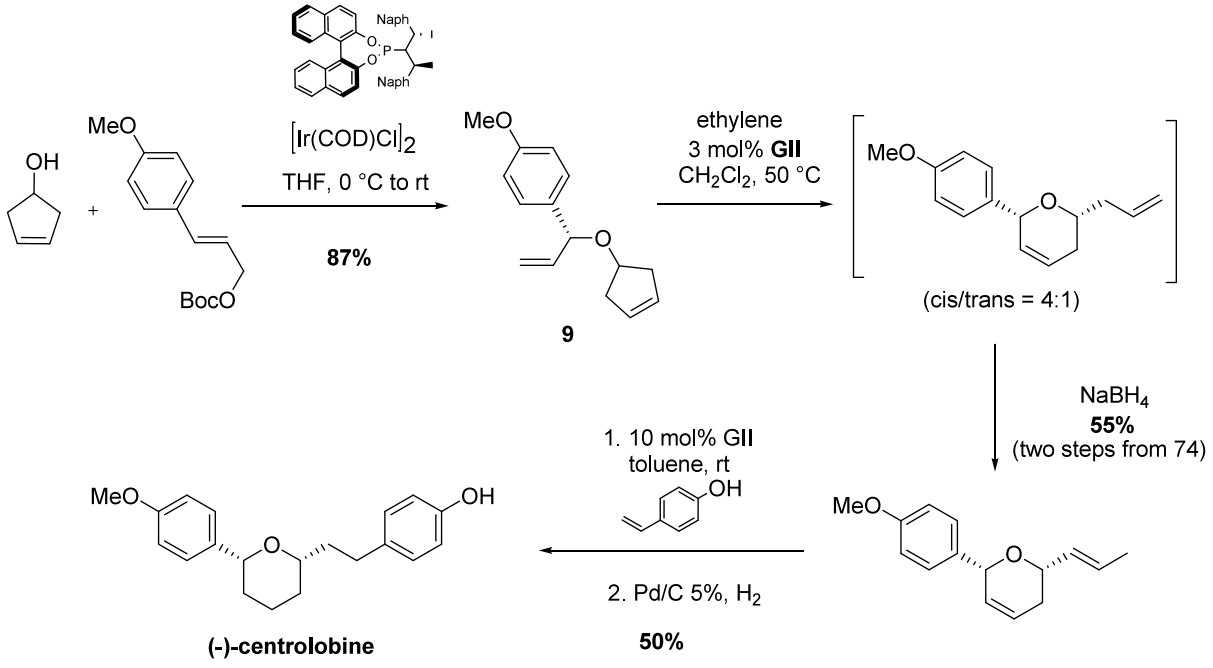
There are two possible pathways for the generation of a new chiral centre using metathesis: asymmetric induction by a chiral metal complex or substrate-controlled diastereoselective induction, whereby the chiral information present in the substrate influences the configuration of the newly formed chiral centre (Scheme 8).



Scheme 8. Two possible alternatives for stereoselective metathesis.

Diastereoselective metathesis allows the construction of new stereocenters with high selectivity, where the challenge consists of shifting the reaction to the desired isomer. The reaction can be kinetically or thermodynamically controlled, and selectivity is mainly catalyst-dependent. Often, the stereoelectronic properties of the activated 14-electron catalytic complex are decisive in the reaction outcome.

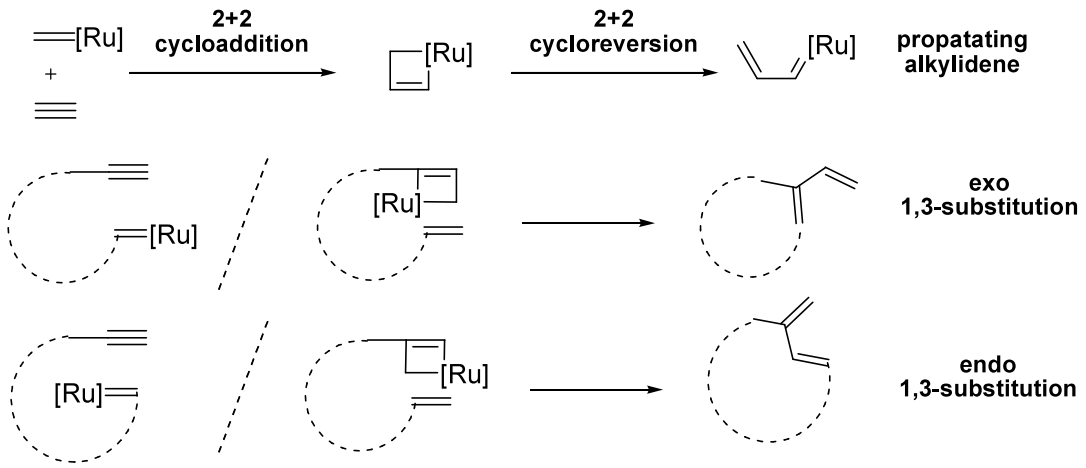
Blechert and coworkers presented in 1996 the fist report on stereocontrolled RCM,[25] a concept which was later on applied in natural product synthesis by Shishido in the preparation of (-)-limaspermine.[26] Except for two publication of stereoselective RCM by Harrity[27] and by Schimdt,[28] and two further relevant reports on RCM and enyne RCM of phosphinates by Gouverneur,[29] the field of diastereoselctive metathesis transformations has been almost exclusively studied in the group of Blechert. The first investigations on diastereoselective RRM (*d*RRM) were presented in 2006, [30] and the first and single reported application on target oriented synthesis was released the same year by Blechert and Böhrsch with the construction of (-)-centrolobine (Scheme 9).[31] The key features of the synthetic approach to this tetrahydropyranic antibiotic involve not only a *d*RRM but three consecutive transformations catalyzed with complex **GII**. The enantiopure metathesis precursor **9**, obtained by asymmetric iridium-catalyzed allylic etherification, underwent a ROM-RCM cascade where the stereocenter at C-5 was established diastereoselectively. Optimized reaction conditions for the *d*RRM were found to be under an ethylene atmosphere in saturated CH_2Cl_2 at 50 °C. A selective double bond isomerization of the terminal alkene with an *in situ* generated Ru-H species followed the metathesis cascade. One-pot CM-hydrogenation procedure completed the synthesis of centrolobine in 5 steps, with 22% overall yield and 98% *ee*.



Scheme 9. *d*RRM cascade in the synthesis of (-)-centrolobine by Blechert and Böhrsch.

2.1.3 Enyne Metathesis

Enyne metathesis is unique among the other metathesis transformations for diverse reasons.[32] Firstly, the product obtained presents a new functionality different from the present in the reactants. Further, the propagating specie generated is able to undergo a consecutive metathesis, which facilitates its application in tandem processes (Scheme 10). The resulting 1,3-diene is also a very attractive synthetic unit and can be used in further transformations such as the Diels-Alder reaction.[33] Additionally, exo/endo-selectivity has to be taken into account to predict the product distribution, especially for macrocyclic systems, as well as functional-group selectivity when more than two alkenes are involved.[32a]



Scheme 10. Mechanism of enyne metathesis and possible product formation.

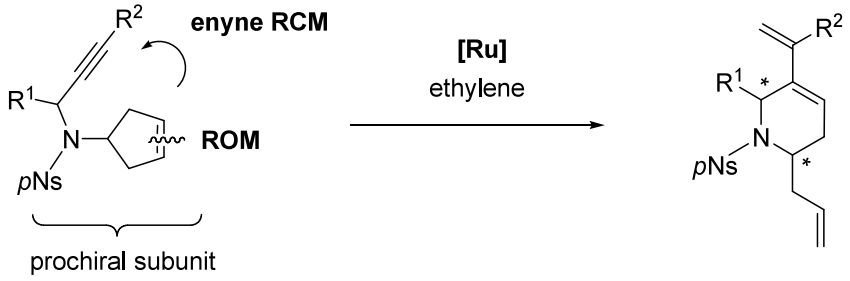
A further peculiarity of enyne metathesis, compared with the analogous alkene metathesis, is the reaction mechanism. Two possible mechanistic pathways can be envisaged dependent upon whether the reaction is initiated at the alkyne or at the alkene part of the enyne substrate. This issue is still a subject of discussion, although experimental and theoretical investigations support the “ene-then-yne“ mechanism.[34] Nevertheless both pathways are possible, and discrimination between both alternatives might be dependant upon substrate, catalyst and reaction conditions.

Finally, unlike the corresponding alkene metathesis reactions, enyne metatheses are wholly atom economical since no olefin-containing by-product is released during the process, and are therefore entropic release plays only a minor role in this reaction. Indeed, the reaction is enthalpically driven by the formation of a more stable conjugated butadiene moiety in the product, making the reaction essentially irreversible.

2.1.4 Diastereoselective Enyne RRM (enyne *d*RRM)

When RRM is performed with enyne substrates, the resulting 'domino' process is typically characterized by reaction of an endocyclic double bond of a cycloolefin with an exocyclic alkyne. As described for enyne RCM, the same selectivity issues must be considered, including exo/endo-cyclization, and the "ene-then-yne" or "yne-then-ene" mechanistic pathways.

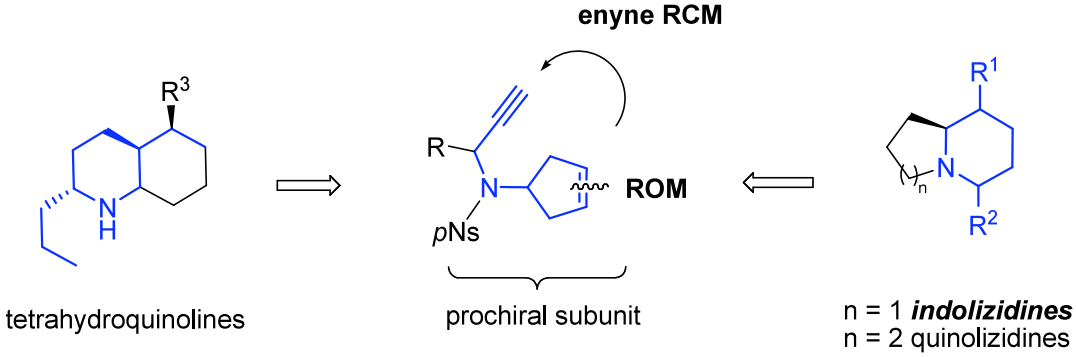
Likewise, when prochiral olefines are used, a new stereocenter is formed, and the metathesis transformation may be performed stereoselectively. The first studies on enyne *d*RRM have been conducted by Blechert and coworkers in the last few years, following the investigations in the group on enyne RRM.[35] The first methodology studies were performed by Schmitt with structurally different propargylamines substituted with C-3-tethered cycloolefins, which after RRM, led to 2,3,6-trisubstituted tetrahydropyridines (Scheme 11).[36] Starting from prochiral substrates, product mixtures with different diastereoisomeric ratios were obtained. For this type of substrates the diastereoselectivity was governed by the catalyst rather than by the substrate, and *cis* substituted tetrahydropyridines were preferentially obtained with the first generation catalyst, whereas an inversion of selectivity was observed when the catalyst type was switched to the second generation. In the investigated substrates, steric and stereolectronic effects of the substituents influenced conversion and selectivity, although the same tendency was observed for all substrates with the commercially available catalysts **GI**, **GII** and **HII** employed.



Scheme 11. Principle of enyne *d*RRM applied on the first investigated substrates.

The results obtained within the investigations of Schmitt and Blechert opened new perspectives in the application of RRM in natural product synthesis. By means of enyne *d*RRM it was now possible to generate highly functionalized heterocyclic structures possessing new stereocenters with high selectivity by selecting the appropriate Ru-complex, offering an alternative to the use of frequently expensive chiral catalysts or reagents. Since chirality is maintained in metathesis reactions, this proof-of-principle would allow the synthesis of 2,6-*cis* or 2,6-*trans* tetrahydropyridines with a high degree in selectivity by starting with enatiomerically enriched propargyl amines.

The concept of *d*RRM developed by Schmitt was therefore conceived as a key synthetic step for the synthesis of different natural products containing such a structural unit (Scheme 12). Alkaloids derived from poisonous frogs were chosen as synthetic targets.[37] Decahydroquinolin alkaloids should be prepared within investigations on natural product synthesis by Torsten Eichhorn, and the synthesis of 5,8-disubstituted indolizidines should be approached in the presented work.



Scheme 12. Proposed application of enyne *d*RRM on natural product synthesis.

2.1.5 Objectives and Motivation

Natural products are the source of the great majority of drugs and drug candidates, whereby alkaloid derived compounds are one of the most important categories. Indeed, 61% of 877 small-molecule new chemical entities introduced worldwide from 1981 to 2002 can be traced to natural products. Most impressive is that 78% percent of the antibacterials and 74% of anticancer compounds are either natural products or inspired by a natural product scaffold.[38] In this regard, the development of new synthetic methodologies that facilitate the preparation of naturally occurring molecules is of great interest, not only for the scientific community but for society.

Domino reactions are economic and elegant transformations to synthesize complex structural scaffolds from easily accessible starting materials in one step. Among them RRM has emerged as one of the most powerful tools for the rapid construction of complex heterocyclic compounds. In the presented research a novel enyne *d*RRM cascade will be used as the key step for the synthesis of 5,8-disubstitued indolizidine alkaloids.

An important focus of this work will be the combination of the latest advancements obtained in metathesis catalyst design with the knowledge gained in previous methodological investigations within the group, for the development of a methodology able to control diastereoselectivity by changing reaction conditions and catalyst complex. The effect of standard reaction parameters such as solvent, temperature, concentration and ethylene pressure will also be explored.

The results obtained in terms of diastereoselectivity might help in the development of new catalysts that are able to perform metathesis reactions with higher stereocontrol of the reaction. Within this project it will be intended to develop a versatile and concise synthesis for the indolizidine alkaloid scaffold, from which various natural product derivatives can be synthesized. The investigations in this divergent synthetic approach should serve for the preparation of other alkaloids such as 1,4-disubstituted quinolizidines, and for the general application of enyne *d*RRM in natural product synthesis.

2.2 Synthesis of Indolizidine Derivatives by Enyne *d*RRM

2.2.1 5,8-Disubstitued Indolizidine Alkaloids

5,8-Disubstitued indolizidines form part of a family of alkaloids, extracted from amphibian skin, and comprise over eight hundred compounds which display diverse biological activities.[36b,36c] The alkaloids in focus of this research are common constituents of skin secretions of poison frogs of the genus *Mantella* found in Madagascar, and their structure differs in the nature of the alkyl chains at position C-5 and C-8 (Figure 2 and 3).

Figure 2. Mantella viridis

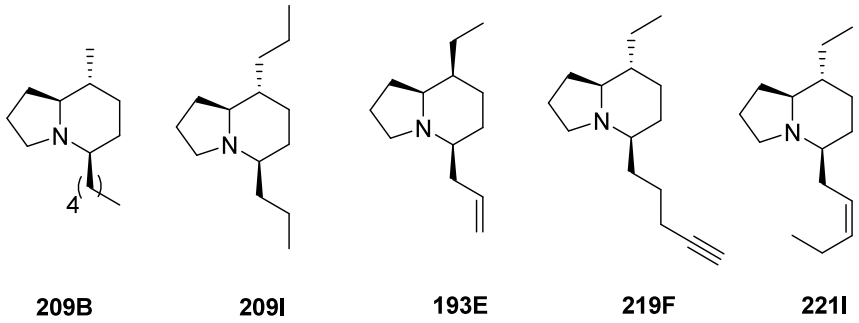


Figure 3. Some examples of isolated 5,8-disubstitued indolizidine alkaloids.

The code-names for these alkaloids were first introduced in 1978 and consist of the nominal molecular weight and an identifying letter. Empirical formulae were determined after extraction from the frogs' skins, by high-resolution chemical ionization mass spectral analysis, while vapor-phase FTIR data provided structural insights into functional groups and stereochemical configurations.

The structure of the first 5,8-disubstituted indolizidines was described in 1987 and at present, they represent a natural product class with about 80 examples, the largest class of alkaloids found in amphibian skin. The mass spectra of 5,8-disubstituted indolizidines are dominated

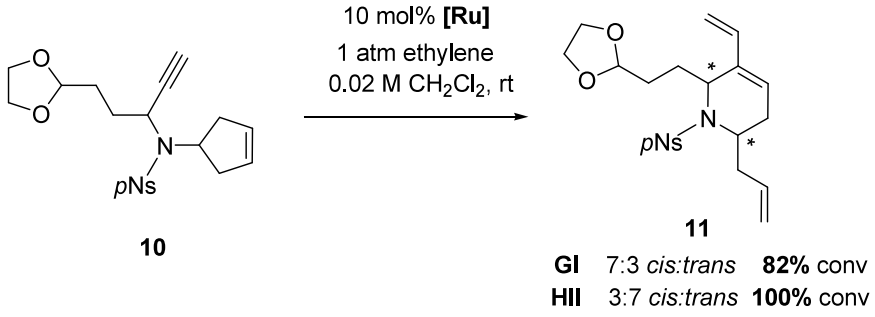
by a base peak due to loss of the R-substituent at the 5-position. A subsequent retro-Diels-Alder elimination yields a diagnostic ion at m/z 96 for all 5,8-disubstituted indolizidines. The vapor-phase FTIR spectra permitted assignment of the relative configuration of the hydrogens at C-5 and C-9, due to a strong, sharp Bohlmann band at about 2789 cm^{-1} that permits assignment of the 5,9-*Z* configuration present in most of these indolizidines.

Despite some syntheses of 5,8-disubsitued indolizidines having been previously reported, for some structures like 193E, a synthetic pathway remains unpublished. Nevertheless, all published syntheses include routes with more then 15 steps,[39] which hamper the preparation of such compounds for toxicity and activity investigations.

Indeed, some of the synthesized indolizidines have been reported as potent noncompetitive blockers of nicotinic receptors and a complete biological evaluation of such compounds might be of great interest.

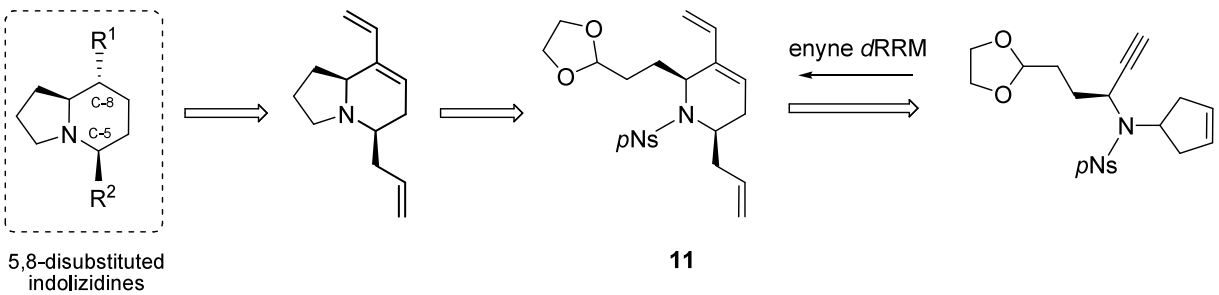
2.2.2 Retrosynthetic Analysis with Enyne *d*RRM as Key Step

The first proposed retrosynthetic analysis was based in the investigations of Schmitt (Scheme 13).[36] Intermediate **11** was prepared from enyne precursor **10** with excellent conversion and variable *dr* depending on the Ru-based catalysts used.



Scheme 13. Previous results on enyne *d*RRM with **10** by Blechert and coworkers.

Thus starting thus from **11**, after double deprotection and condensation, the target molecules could be obtained by derivatization of the alkene chains at C-5 and C-8 (Scheme 14).



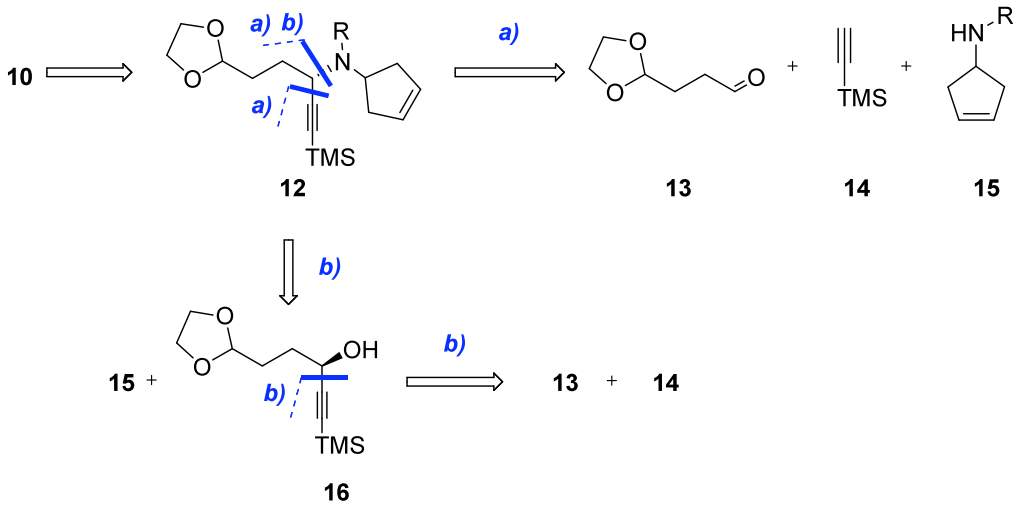
Scheme 14. Initially proposed general retrosynthetic analysis for 5,8-disubstitued indolizidines.

2.3 First Synthetic Approach Towards the Metathesis Substrate

The retrosynthetic analysis of the chosen enyne precursor **10** suggests two convenient disconnections (Scheme 15):

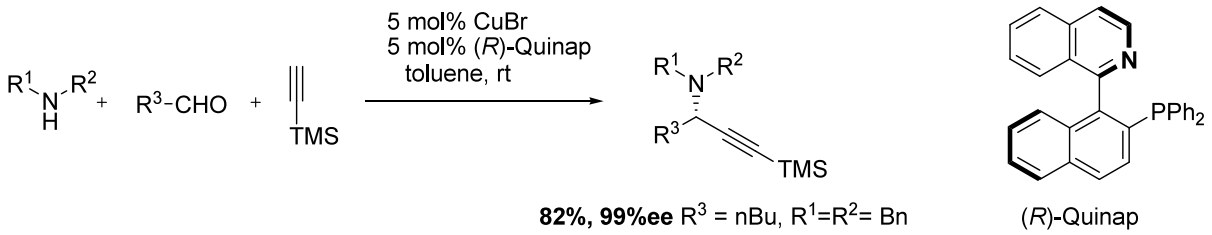
a) One step synthesis of enantiomerically enriched propargyl amines: three component Cu-catalyzed coupling.

b) Two step approach: synthesis of enantiomerically enriched propargyl alcohol **16** followed by Mitsunobu reaction with amine **15**.



Scheme 15. Retrosynthetical analysis for the enyne *d*RRM precursor.

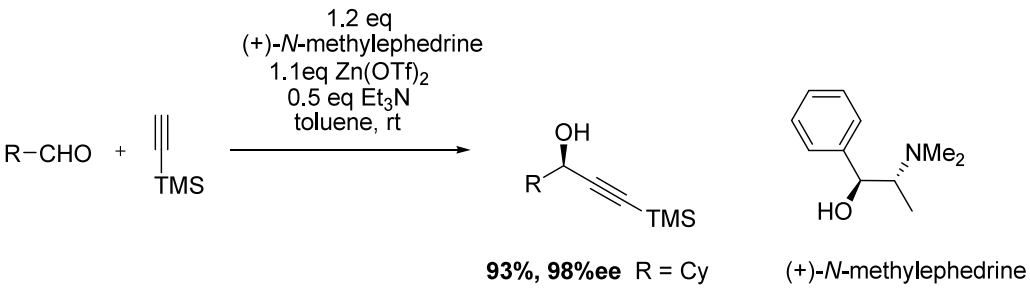
The copper catalyzed three component reaction between aldehydes, amines and terminal alkynes is a type of methodology that has been extensively studied by Knochel and coworkers. The reaction mechanism proceeds through attack of the copper-activated alkyne to the *in situ* generated imine or enamine, using Quinap as chiral ligand and requires electron rich amino-compounds as substrates (Scheme 16).[40]



Scheme 16. Example for the three-component propargylamine formation developed by Knoechel and coworkers.

Pathway **b** (Scheme 15) was proposed as a synthetic alternative for amines **15** that would not be sufficiently electron rich for the copper-catalyzed transformation. This two-step variant was followed by Schmitt with racemic alcohols achieving yields ranging from 43% to 85% over two steps, with commercially available aldehydes and alkynes.[35]

Enantiomerically enriched propargylic alcohols are useful and versatile building blocks in asymmetric synthesis and several methodologies have been developed for their synthesis.[41] There are two main methods for their preparation: asymmetric reduction of an ynone, or by asymmetric metal-catalyzed alkynylation of a carbonyl group. The later is the more convenient, since it avoids extra steps for the synthesis of the ynone, typically by organometallic addition to the corresponding aldehyde, and subsequent oxidation. Some of the most effective methodologies towards propargyl alcohols, by alkynylation of aldehydes, have been described by Pu[42] and Carreira[43]. The first involves a titanium-BINOL-catalyzed enantioselective addition, and Carreira´s methodology is based on the reaction of dialkyl-zincs, where the chiral environment is provided by ephedrine derivatives (Scheme 17). Other remarkable methodologies include different ligands such as bis-oxazoline derivatives,[44] In(III)/BINOL complexes,[45] or the enantioselective alkynylation of aldehydes with organozinc derivatives with Trost's bifunctional ProPhenol catalyst.[46]

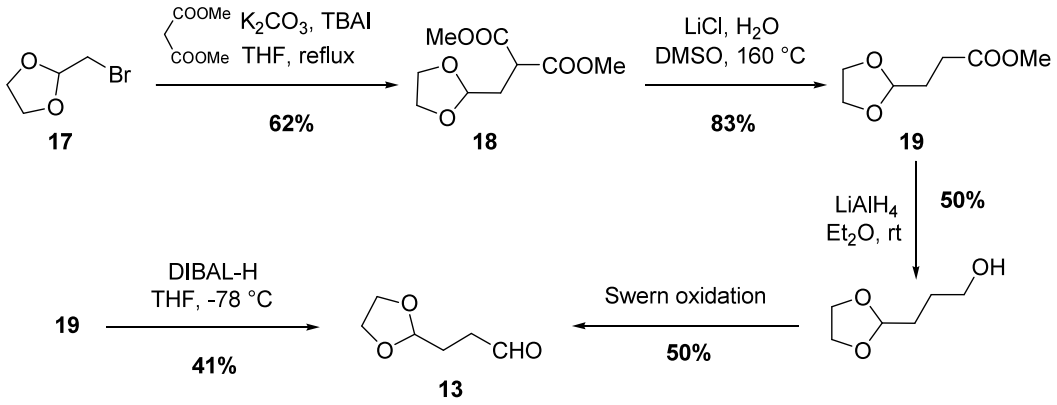


Scheme 17. General scheme for the synthesis of enantiomerically enriched propargylic alcohols by Carreira.

2.3.1 Aldehyde Synthesis

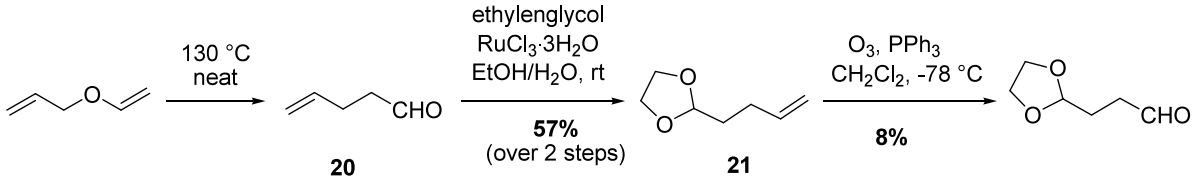
Both above-mentioned proposed synthetic pathways start with the synthesis of a monoprotected succinaldehyde **13**. In the literature there are many possible alternatives described for the preparation of **13**. We were searching for an easy procedure to synthesize **13** on a multigram scale, rapidly and efficiently.

The first synthetic approach was inspired by a procedure from Vanderhaeghe[47] and started with **17**, which was alkylated with dimethylmalonate affording **18** in 62% yield after purification by column chromatography (Scheme 18).[48] Compound **19** was smoothly obtained by Krapcho decarboxylation,[49] which was then reduced to obtain the desired aldehyde with 41% yield.[50] Selective reduction was difficult to accomplish and further reduction to the alcohol was obtained as a side-reaction. The isolated alcohol, also accessible from reduction of **19** with lithium aluminium hydride, was next oxidized without further purification to the desired compound **13** *via* Swern oxidation.[51] The reduction-oxidation sequence was not further optimized and more straightforward synthetic approaches were investigated.



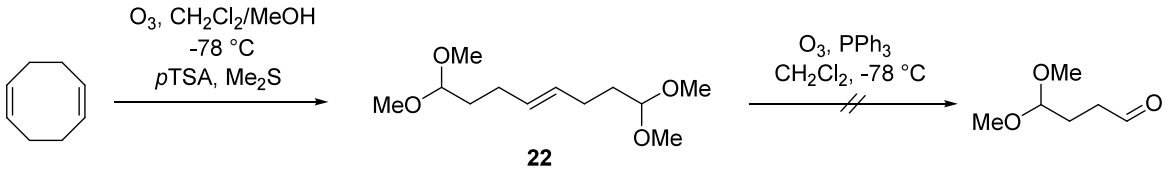
Scheme 18. Synthesis of aldehyde **13** via alkylation of methyl malonate and Krapcho decarboxilation.

13 can be alternatively synthesized from **21** via ozonolysis (Scheme 19).[52] Compound **21** was obtained from allyl vinyl ether after Claisen rearrangement,[53] followed by protection of the resulting aldehyde **20** as its ketal under very mild conditions, with 57% overall yield and without chromatographic purification.[54] Attempts to protect **20** under classic conditions with *p*TSA in toluene resulted in very low yields, probably due to the volatility of compound **20**. Ozonolysis of **21** afforded the desired product in very low yield, and further attempts to optimize this reaction failed.



Scheme 19. Synthesis of aldehyde **13** by Claisen rearrangement of ally vinyl ether.

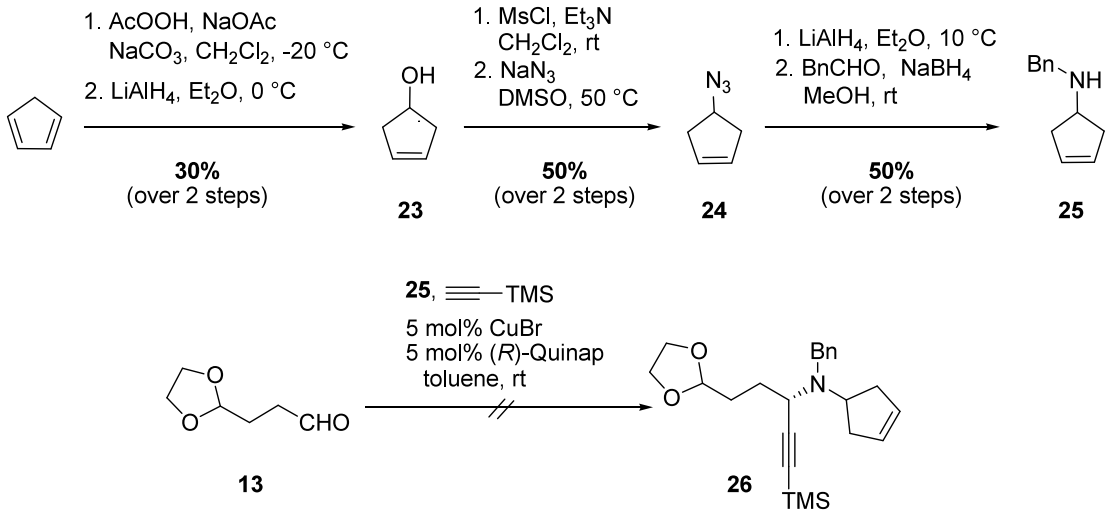
A third synthetic alternative towards the C-4 component was investigated following a published procedure from Nicolaou (Scheme 20).[55] 1,5-cyclooctadiene was reported to be converted into aldehyde **13** through a two-step ozonolysis sequence in 40% overall yield. The first ozonolysis reaction led to an intractable crude mixture containing the desired product, but further reaction with the crude **22** failed. That was in accordance with the observation of Nicolaou and co-workers, who indicated that **22** must be purified in order to obtain the aldehyde **13**. Without further optimization proof-of-principle investigations towards the metathesis substrate **10** were continued, with the obtained aldehyde **13** from the previous approaches



Scheme 20. Approach towards aldehyde **13** from 1,5-cycloocatdiene.

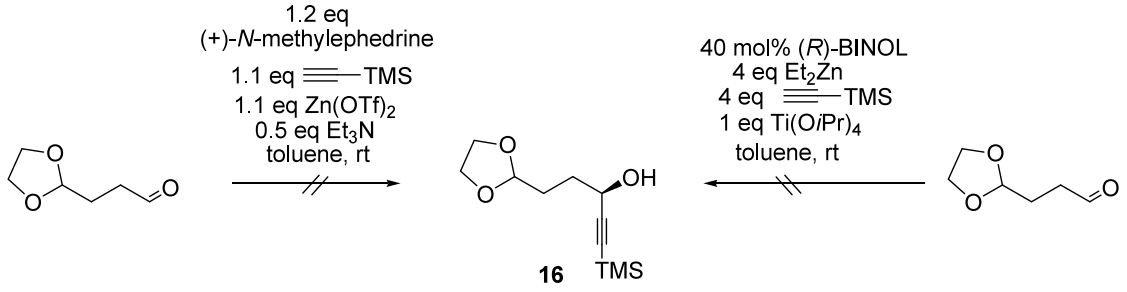
2.3.2 Synthetic Studies Towards Propargyl Amine 10

With enough aldehyde **20** in our hands, we first investigated the synthetic pathway a). Synthesis of benzyl amine **25** was accomplished in a multigram scale using a six-step sequence without chromatographic purification of intermediates with an overall yield of 8% (Scheme 21). The alcohol **23** was obtained from cyclopentadiene in 30% yield following the procedure of Crandall *via* epoxidation with 40% peracetic acid and reduction with lithium aluminium hydride..[56] The obtained alcohol was converted into azide **24** in two steps, and reduction followed by reductive amination with benzaldehyde and $NaBH_4$ furnished the desired benzyl amine **25**. Unfortunately, all attempts to synthesize **26** using Knoechel's methodology failed, and starting materials were partially re-isolated, together with other complex by-products.



Scheme 21. Synthetic approach towards **10** following Knoechel´s methodology.

Next we investigated Carreira's methodology for the synthesis of propargylic alcohol **16** (pathway **b**). Aldehyde addition of the *in situ* formed dialkyne-zinc with (+)-*N*-methylephedrine as chiral ligand likewise failed, and any attempt to improve the yield by careful purification of the reactants, screening of reaction conditions, or changing the reagents' order of addition gave again a mixture of unseparable products (Scheme 22).



Scheme 22. Synthetic approaches towards propargylic alcohol **16**.

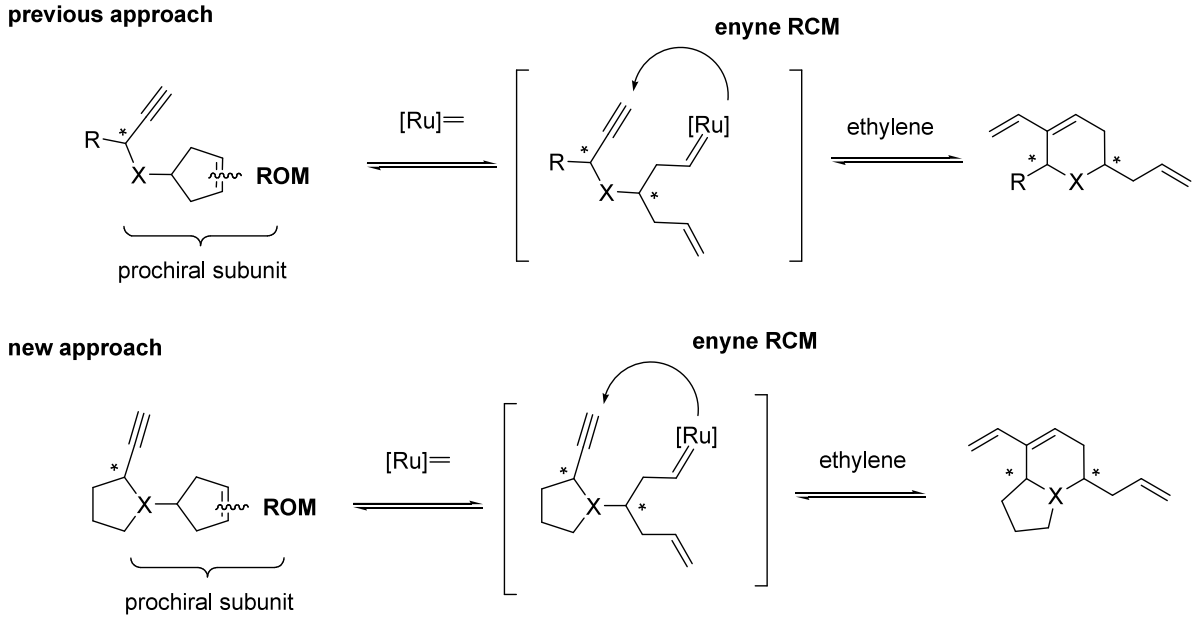
The same result was obtained when Pu's protocol was employed, resulting in as before in a complex mixture of products. Such results have been documented in the literature for facile enolizable unbranched aliphatic aldehydes and for certain aromatic analogues,[57] where Aldol reaction and Cannizzaro disproportion have been detected as the competing reactions.

Due to the failure of the presented reactions, two additional synthetic steps would be necessary in order to obtain **10**. Either by preparing a propargylic amine, with subsequent Mitsunobu reaction on **23**, or by enantioselective reduction to **16** of the corresponding ynone,[58] **10** would be accessible in five steps from aldehyde **13** (at least seven overall steps). At this point, we considered that the proposed synthetic pathway for the synthesis of the metathesis precursor was far too long to provide an elegant synthetic approach towards the presented indolizidines, and an alternative synthesis was envisaged.

2.4 New Synthetic Approach: Bicyclic Enyne Metathesis Substrate

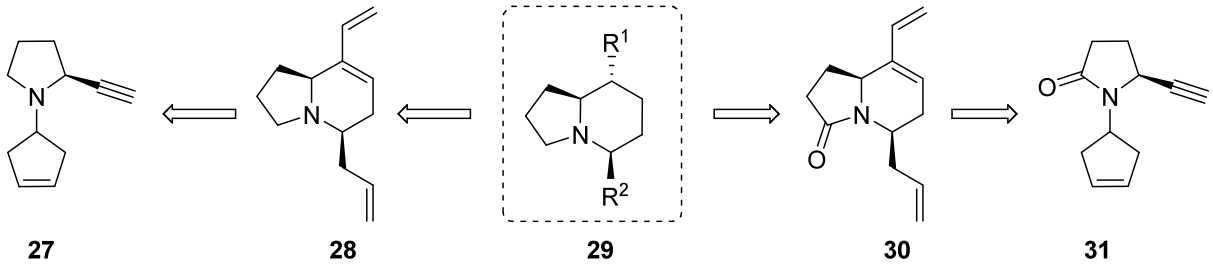
2.4.1 Retrosynthetic Analysis

Introducing the chiral information required in the metathesis substrate by asymmetric synthesis would require several synthetic transformations. Instead, we envisaged that starting with enantiomerically pure chiral pool starting materials would save some steps as well as the need for chiral HPLC chromatographic purification. Moreover, by following the previous approach, further steps after the RRM would be needed in order to form the bicyclic structural core (Scheme 23). Starting from easily accessible bicyclic structures, on the other hand, would lead to the desired indolizidine structural core in fewer steps.



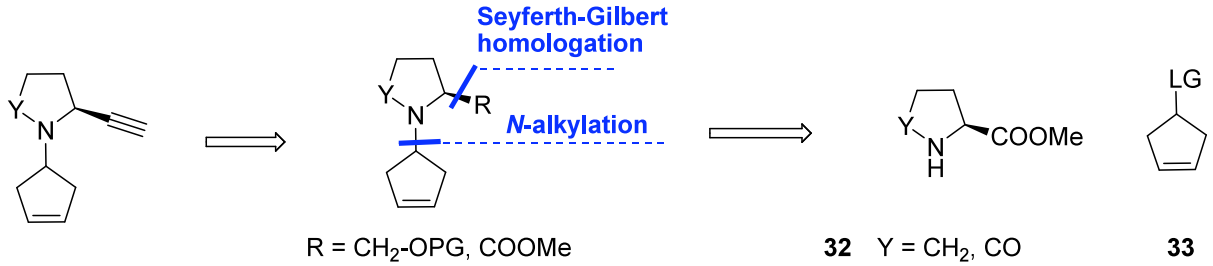
Scheme 23. General scheme in enyne *d*RRM of mono- and bicyclic substrates.

We anticipated that structure **29** could be obtained from two similar intermediates **28** and **30**, generated from amine **27** or the amide analogue **31** (Scheme 24). Thereby decrease of the Lewis basicity of amine **27** could be necessary in the metathesis step, to prevent catalyst deactivation.[59]



Scheme 24. Alternative retrosynthetic analysis for indolizidine derivatives by enyne *d*RRM.

Both metathesis substrates could be prepared using chiral-pool substrates such as the cyclic amino acids (*S*)-proline and (*S*)-pyroglutamic acid. We proposed that the terminal alkyne could be easily synthesized by Seyferth-Gilbert homologation from the corresponding aldehyde, while the desired cyclo-olefin might be introduced by *N*-alkylation of **32** with the appropriate derivative **33** (Scheme 25).



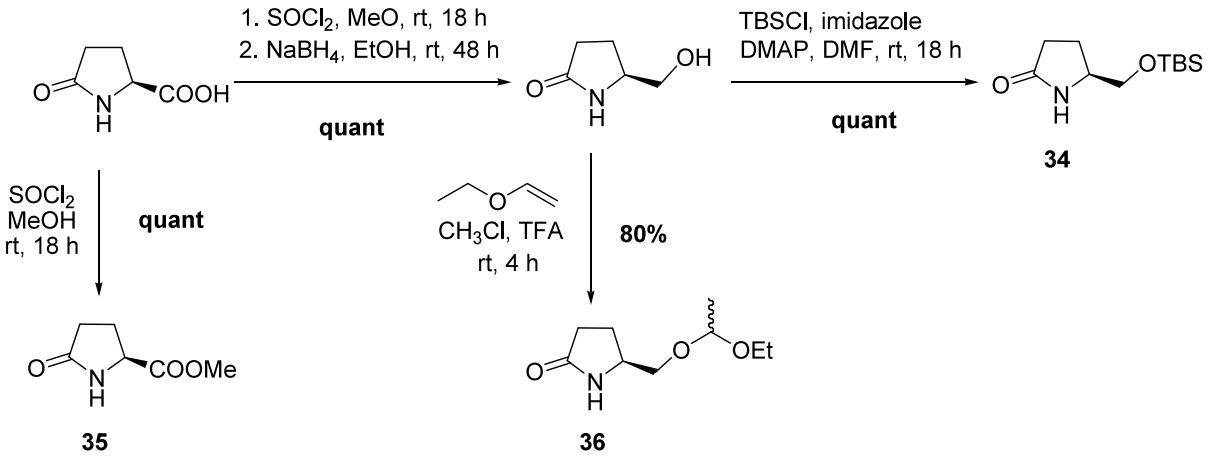
Scheme 25. Retrosynthetic analysis for metathesis precursors **27** and **31**.

2.4.2 Synthesis of (*S*)-1-(cyclopent-3-enyl)-5-ethynylpyrrolidin-2-one 31

Derivatives of pyroglutamic acids are cheap chiral synthons with two different carbonyl entities in the molecule that can be differentially functionalized, and which have served as starting materials for asymmetric synthesis of many natural products.[60] For the synthesis of **31**, it was likewise envisaged that the ester functionality could help to introudce the desired alkyne, and the lactam functionality could be alkylated with the suitable electrophile **33**.

2.4.2.1 *N*-Alkylation Experiments

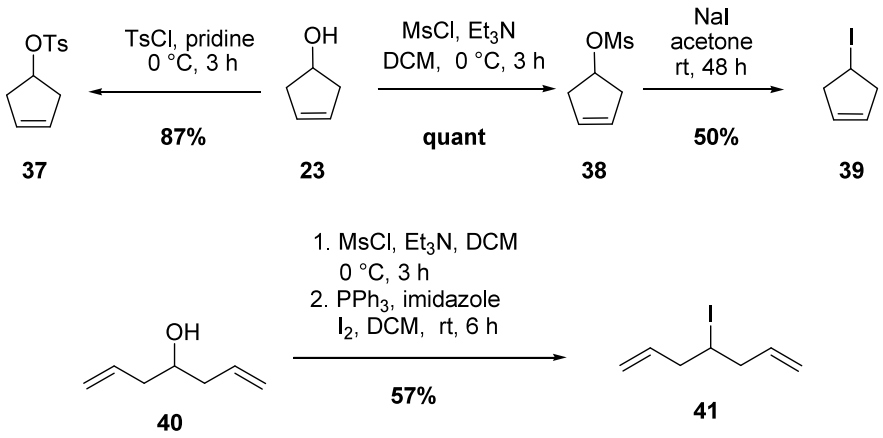
According to previously reported protocols, pyroglutamic acid methyl ester **35** has been successfully *N*-alkylated with allyl bromide in THF using KOH as a base.[61] The corresponding protected alcohol **36** (Scheme 26), likewise served as intermediate for the synthesis of the natural product (-)-stemoamide by reaction with NaH in DMF and a non-activated primary halogenated compound.[62] These two substrates **35**, **36** and the TBS protected analogue **34** were therefore chosen as staring materials for the synthesis of the corresponding *N*-alkylated compound. Esterification of (*S*)-pyroglutamic acid with methanol and reduction to the corresponding alcohol[63] was followed by quantitative protection with TBS,[64] and by formation of the ethyl vinyl ether **36** [65] in 80% isolated yield.



Scheme 26. Synthesis of substrates for the *N*-alkylation reaction.

Cyclopentenyl derivatives **37**-**39** were synthesized as electrophilic components for pyrrolidinones **34**-**36** (Scheme 27). The choice of the leaving group may be crucial for the success of the reaction since derivatives **37**-**39** are secondary homoallylic electrophiles which can undergo elimination under basic conditions. Compounds **37**-**39** have shown satisfactory results in reported *N*-alkylations, whereas the corresponding Br-analogue, for instance, gave rise to elimination.[66]

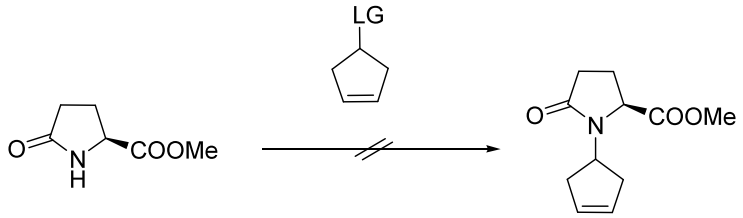
The selected compounds were smoothly synthesized from the secondary alcohol **23** by reaction with TsCl[67] and MsCl,[68] while iodide derivative **39** was afforded by Finkelstein reaction with NaI from the crude mesylate **38**. Diene **41**, which was obtained in a similar manner from the commercially available alcohol **40**,[69] was considered as an alternative to study this reaction, since it should be less prone to undergo elimination. The resulting product after *N*-alkylation, however, cannot be considered as a substrate for RRM, but rather for diastereoselective enyne RCM. In order to obtain a metathesis precursor which would undergo *d*RRM, a RCM step would be necessary.



Scheme 27. Synthesis of the used electrophiles for the *N*-alkylation reaction towards **31**.

The procedures described by Nelson[70] and by Smith[71] were unsuccessful in the alkylation of the pyrrolidine **35** with the electrophiles **37**-**39** or **41** (Table 1). Formation of the desired compound **31** was not detected, and only unreacted starting materials were reisolated and/or detected. Different combinations of bases, solvents, concentrations and temperatures were screened, without success, while increasing either the reaction time or the reaction temperature above 70 °C resulted in decomposition of electrophile **33**. The use of stronger bases such as KH, or LiHMDS for complete deprotonation are not applicable for the pyrrolidinone **35**, given the lower pK_a value at the α-position of the ester functionality.

Table 1. Representative results in the *N*-alkylation of **35**.



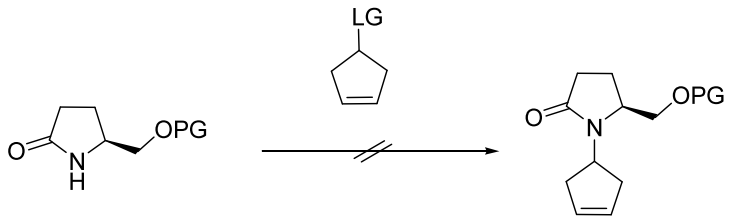
35 **42**

Entry	Electrophile	Base	Conditions
1	**38**, **39**	1 eq KOH	0.1 M THF, 70 °C, 12 h
2	**38**, **39**	2 eq Na_2CO_3	0.3 M DMF, 50 °C, 96 h
3	**41**	2 eq Na_2CO_3	0.1 M THF, 70 °C, 96 h
4	**41**	2 eq Na_2CO_3	0.1 M DMF, 70 °C, 96 h
5	**38**	2 eq Cs_2CO_3	0.1 M DMF, 50 °C, 96 h
6	**37**	4 eq Na_2CO_3	0.3 M THF, 80 °C 48 h

Subsequently, we investigated the use of substrates **34** and **36** as alternative nucleophiles. For this type of substrate, the standard literature procedure for aklylation involves deprotonation with NaH in DMF at room temperature or below, and subsequent reaction with

the electrophile at temperatures between 70 °C and 130 °C.[65,72,73,74] Even though use of the nucleophile **36** and electrophiles **37**-**39** and **41**, have been successfully reported for similar reactions, none of the tested reaction conditions gave the desired product (Table 2), most probably owing to a sterically congested site of reaction and the presence of a weak amide nucleophile. Instead, partial or total decomposition of the substrates took place *via* competing elimination in the electrophile **33**.

Table 2. Summarized results from *N*-alkylation reactions of **36** and **34**.

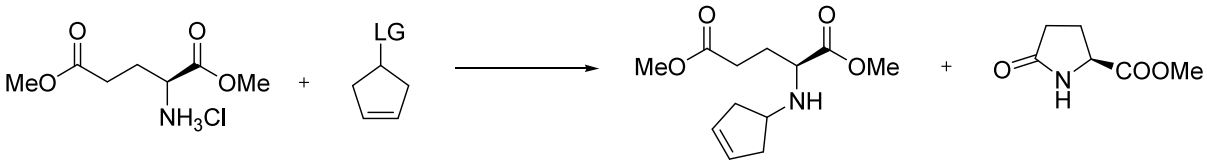


Entry	Substrates		Base	Conditions
1	**34**	**38**	1eq NaH	0.1 M DMF, 130 °C, 3 h
2	**34**	**38**	1eq NaH	0.3 M DMF, 0 °C to rt, 96 h
3	**34**	**41**,**39**,**38**	1eq NaH	0.3 M DMF, 60 °C, 96 h
4	**34**	**41**,**39**,**38**	3 eq Na_2CO_3	0.3 M THF, 70 °C, 72 h
4	**34**/**36**	**37**	1eq NaH	0.3 M DMF, 60 °C, 72 h
5	**34**/**36**	**37**,**39**	1eq NaH	0.3 M DMF, 100 °C, 72 h

We envisaged better results by performing the *N*-alkylation reaction with a primary amine. Glutamic acid methyl ester could serve as the starting material, which after alkylation and intra-molecular cyclization would furnish the desired compound **42**. Conditions were screened in small scale reactions which were analyzed by ^{1}H-NMR of the crude mixture obtained. Initial attempts in different solvents and temperatures resulted only in intra-molecuar cyclization of the starting amino acid to give pyroglutamic ester (entries 1-4, Table 3). With the use of acetonitrile as solvent however, an appreciable amount of starting material was still detected in the mixture after 12 h at 80 °C. Increasing the reaction time to 72 h (entry 5) allowed the product **44** to be detected for the first time, and reaction in acetonitrile (0.4 M) for six days gave **44** in 42% yield after chromatographic purification (entry 7). Different experiments were then performed in order to increase the obtained yield. Both the number of equivalents of base and solvent concentration played an important role (entries 8-13). Higher concentrations resulted in the improvement of the reaction yield. Hoewever during the reaction the mixture became progressively thicker and stirring more difficult when higher concentrations were used. We expected that reducing the amount of base would enable better stirring at higher concentrations, however this resulted in a lower

yield. Despite substrates **37** and **38** furnishing similar results even with the addition of sodium iodide, tosyl derivate **37** appears to be more stable than the mesylate **38** under the reaction conditions and any unreacted electrophile remaining after the reaction could be partially recycled from the crude material. Optimized conditions were found when stirring at reflux a 0.8 M solution of **43** with **37** in acetonitrile for 6 days. This reaction was performed on a multigram scale and showed very reproducible results (entry 13).

Table 3. Summarized results from *N*-alkylation reactions of **42**.

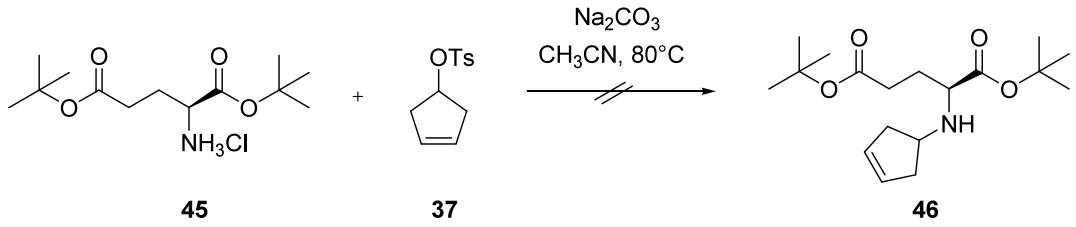


43 **44** **35**

Entry	Electrophile	Base	Conditions	Yield [a]	Ratio 42/35/43 [b]		
1	1.2 eq **37**	4 eq Na_2CO_3	0.5 M THF, 60 °C, 12 h	-	0	1	0
2			0.5 M *n*-butanol, 60 °C, 12 h	-	0	1	0
3			0.4 M DMF, 80 °C, 12 h	-	0	1	0
4			0.4 M CH_3CN, 80 °C, 12 h	-	1	1	0
5			0.4 M CH_3CN, 80 °C, 72 h	-	2	1	1.8
6	1.2 eq **38**		0.4 M CH_3CN, 80 °C, 72 h	-	1	2.1	1.5
7	0.98 eq **37**		0.4 M CH_3CN, 80 °C, 6 d	42%	-	-	-
8	0.5 eq **38**		0.4 M CH_3CN, 80 °C, 5 d	30%	-	-	-
9			0.4 M CH_3CN, NaI, 80 °C, 5 d	30%	-	-	-
10			0.8 M, CH_3CN, 80 °C, 5 d	37%	-	-	-
11		2 eq Na_2CO_3	0.4 M CH_3CN, 80 °C, 5 d	22%	-	-	-
12	0.5 eq **37**	4 eq Na_2CO_3	0.4 M CH_3CN, 80 °C, 6 d	30%	-	-	-
13	0.5 eq **37**	4 eq Na_2CO_3	0.8 M CH_3CN, 80 °C, 6 d	48%	-	-	-

[a] Isolated yield after column chromatography; [b] Analyzed by ^{1}H-NMR spectroscopy of the crude mixture obtained.

In order to sterically hinder intramolecular cyclization as a side reaction and thus increase the yield of the alkylated product, the *tert*-butyl analog **45** was used. Unfortunately the steric hindrance provided by the *t*Bu group also appeared to impede nucleophilic substitution on the tosylate **37**, and the desired compound **46** was detected only in trace amounts by ^{1}H-NMR analysis of the crude mixture. It was our expectation that (*S*)-5-tert-butyl-1-methyl-2-aminopentanedioate would give better results, but the possible increase in yield would not justify the extra synthetic steps required to give the desired product.



45 **37** **46**

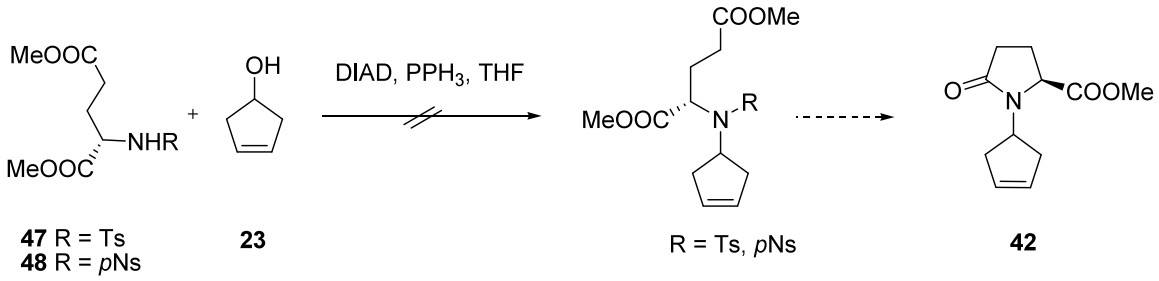
Scheme 28. Reaction of glutamic acid *t*But ester with **37** to avoid formation of **35** by intramolecular cyclization.

Having assessed the important role of the solvent and the reaction concentration in the *N*-alkylation with **43**, experiments with **34**-**36** under the same reaction conditions were conducted (Table 4). Methyl pyroglutamate failed again (entry 1), but under the optimized conditions, alkylation with TBS protected alcohol **34** and **35**, furnished 49% and 61% yield respectively.

Table 4. *N*-alkylation reaction of **34**-**36** with **37** under the new reaction conditions.

Entry	Substrates		Base	Conditions	Yield [a]
1	**35**	**37**	4 eq Na_2CO_3	0.8 M CH_3CN, 80 °C, 96 h	0%
2	**34**	**37**	4 eq Na_2CO_3	0.8 M CH_3CN, 80 °C, 96 h	49%
3	**36**	**37**	4 eq Na_2CO_3	0.8 M CH_3CN, 80 °C, 96 h	61%

Parallel to these investigations Mitsunobu reactions were performed with derivatives **47** and **48** using alcohol **23** (Scheme 29). Standard Mitsunobu conditions using DIAD and PPh_3 were first chosen, which should be applicable for the lowered pK_a value of tosylamide **47** and nosylamide **48**. Under the employed reaction conditions only complex mixtures including starting material and decomposition products of the used reagents were isolated. Further attempts with more reactive Mitsunobu reagents were discarded,[75] since parallel investigations in the group with very similar compounds indicated that the alcohol **23** was not an adequate substrate for Mitsunobu reactions.[76]



47 R = Ts
48 R = *p*Ns

23

R = Ts, *p*Ns

42

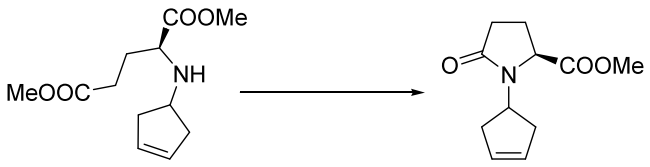
Scheme 29. Attempts to synthesize **42** by Mitsunobu reaction.

2.4.2.2 Preparation of 31 from 44 and 51.

With **44** in our hands we initiated investigations to find optimal reaction conditions for the cyclization towards lactam **42**. First attempts in boiling xylene (Table 5, entry 1) resulted in complete reisolation of the starting material.[77] Cyclization in refluxing acetic acid,[78] on the other hand, afforded the desired compound in quantitative yield (entry 2). According to the published protocol, very diluted conditions are necessary to avoid intermolecular condensation. When the reaction was scaled up, however, the required work-up to remove the solvent by successive extractions became tedious and higher concentrations were investigated in order to use less acetic acid (entries 3-5). Nevertheless, on reactions performed with 10-20 g of substrate **44**, the extraction procedure became too laborious, and was often accompanied by a decrease in yield.

Alternatively, catalytic amounts of *p*TSA in refluxing toluene[79] were sufficient to afford complete condensation (entry 6), and lactam **42** was isolated in very high yields, even in a multigram scale (entry 7).

Table 5. Summarized results obtained from cyclisation reactions of **44**.

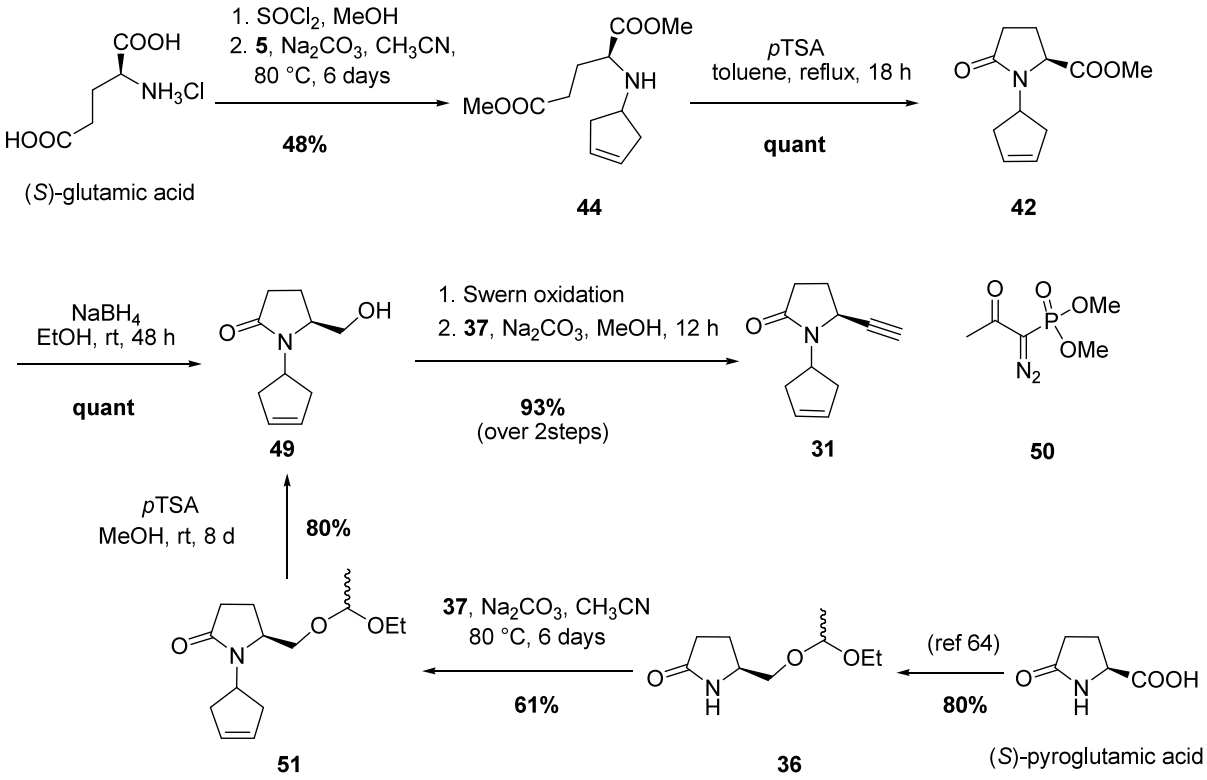


44 **42**

Entry	Reaction Conditions	Yield
1	0.2 M xylene, reflux, 12h	0%
2	0.006 M, AcOH, 100°C, 12h	quant [a]
3	0.015 M, AcOH, 100°C, 12h	85% [b]
4	0.023 M, AcOH, 100°C, 12h	97% [c]
5	0.029 M, AcOH, 100°C, 12h	60% [d]
6	*p*TSA (cat), 0.2 M toluene, reflux, 12h	quant [e]
7	*p*TSA (cat), 0.2 M toluene, reflux, 12h	91% [d]

[a] 0.2 mmol; [b] 5.8 mmol; [c] 5.7 mmol; [d] 41 to 62 mmol; [e] 2.1 mmol.

Alcohol **49** was prepared from methyl ester **42**, by selective reduction with $NaBH_4$, and from the ether **51** by deprotection of the ethoxyethyl group with *p*TSA (Scheme 30). The synthesis of alkyne **31** was then accomplished in very few steps by sequential Swern oxidation–Seyferth-Gilbert homologation in 93% yield from **49** and without chromatographic purification of the aldehyde intermediates.



Scheme 30. Two possilbe synthetic pathways for metathesis substrate **31**.

To summarize, the metathesis substrate **31** was accessible by two different routes:

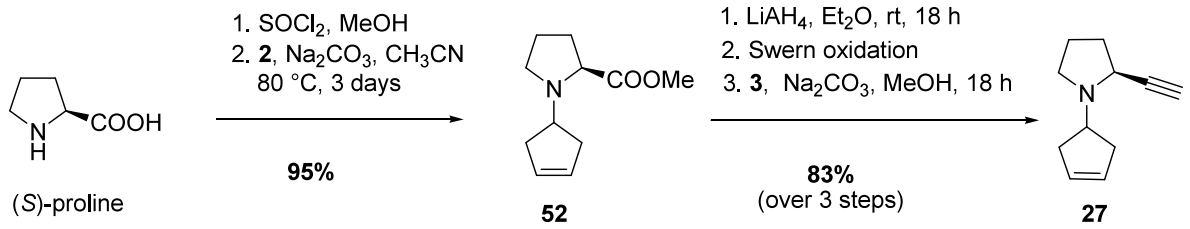
- In six steps from commercially available glutamic acid, with an overall yield of 44%, in a multigram scale synthesis requiring only two chromatographic purifications (for **44** and for the final product **31**).
- Starting from (*S*)-pyroglutamic acid in seven synthetic steps, with an overall yield of 36% and with four chromatographic purifications.

Even though the synthesis of **31** by the second route could be further optimized, the first synthetic pathway was favored since this involves less labor and reduced cost. The protection and deprotection to **36** and **49** respectively introduce one more step to the synthesis of **49** when compared with the other alternative. Additionally, the first route requires less chromatographic purifications, and the major loss of product takes place at the very beginning of the synthesis with a cheap starting material.

2.4.3 Synthesis of (*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidine 27

The synthesis of the enyne homologue **27** was approached in the same way as described for **31** (Scheme 31). In this case, due to the higher nucleophilic character of proline derivatives,

N-alkylation with (*S*)-proline afforded the desired bicyclic compound **52** with very high yield. Reduction to the corresponding alcohol was performed quantitatively with $LiAlH_4$,[80] and the alcohol was obtained as a storable yellowish solid. The synthesis of the metathesis substrate was completed by sequential Swern oxidation–Seyferth-Gilbert homologation, affording compound **27** with an overall yield of 79% in very few synthetic transformations and with only two chromatographic purifications.



Scheme 31. Synthesis of metathesis precursor **27**.

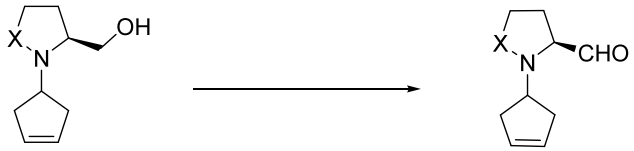
The combination of Swern oxidation of the corresponding alcohol **52**, followed by the addition of the phosphorazide reagent **50** was chosen as a synthetic strategy for the synthesis of the desired alkyne intermediate, since, according to the literature, is one of the most used procedures for such substrates.[81] To overcome this reduction-oxidation sequence from the ester **52**, its selective reduction with DIBAL-H directly to the aldehyde was also examined.[82] First attempts indicated the challenge of conducting this reduction with enough selectivity, avoiding over-reduction to the corresponding alcohol. Even though reduction with $LiAlH_4$ and subsequent selective oxidation to the aldehyde introduces an extra synthetic step, both transformations are high yielding and experimentally much more easy to handle, in comparison with the DIBAL-H reduction.

2.4.3.1 Alternatives to Swern Oxidation

Despite the successful results obtained with the described methodology, due to the required basic reaction conditions for the Swern oxidation, substrates such as **54** can suffer from epimerization (Table 6). In these cases, other oxidation methodologies are recommended employing, for example, PCC,[83] the Dess-Martin reagent,[84] TEMPO[85] or TPAP/NMO (Ley oxidation).[86] Due to the basic character of tertiary amine **53** however, all these methodologies failed. Additionally, parallel experiments with the corresponding amide **49** were performed (entries 2 and 5). All methodologies failed under the standard reaction conditions, while all attempts to perform the reaction decreasing the Lewis basicity of the amine by *in situ* protonation, resulted in no conversion to the desired product **54**. *N*-oxide

derivatives were instead isolated when PCC and TEMPO were used, and in the case of the Ley oxidation and oxidation with DMP, almost all of the starting material was recovered.

Table 6. Investigation of the oxidation of alcohols **49** and **53** to aldehyde **54** using standard oxidizing agents.



53 X = CH_2
49 X = CO

54 X = CH_2
55 X = CO

Entry	Substrate	Oxidation Method	Conv to 54/55 [a]
1	**53**	PCC in CH_2Cl_2, rt	0%
2	**49**		100%
3	**53**	i) 1 eq HCl	0%
4	**53**	NMO, TPAP, 4 Å MS, CH_2Cl_2, 40 °C	9%
5	**49**		100%
6	**53**	i) 1 eq *p*TSA	0%
7	**53**	TEMPO (cat), TCICA, CH_2Cl_2, rt	0%
8	**53**	DMP in CH_2Cl_2, rt	0%

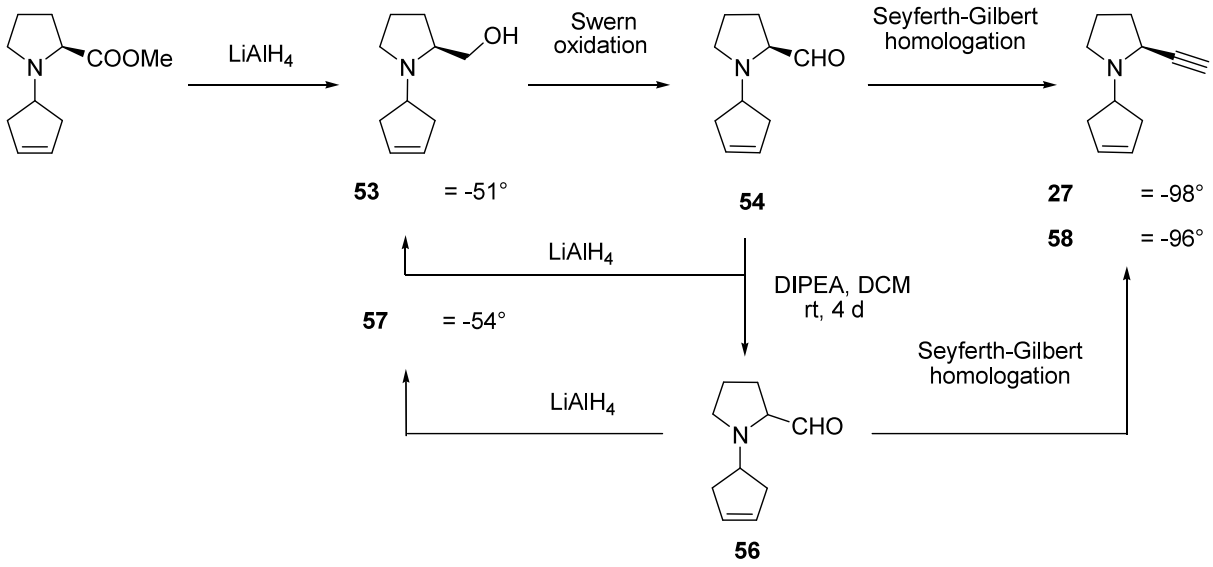
[a] Determined by ^{1}H-NMR spectroscopic analysis.

According to the literature, immediate use of the generated aldehyde in the next step is sufficient to avoid epimerization.[87] In order to determine, if epimerization was taking place and to what extent, different experiments were performed. Samples of **27**, **53**, and **54** purified by column chromatography and bulb-to-bulb distillation, and were analyzed by chiral GC. Under all explored chromatographic conditions only one signal was detected, indicating an ee > 99.5%.[88]

Nevertheless, in order to support the obtained analytical data, a_D^{20} values of differently synthesized samples were compared (Scheme 32). According to Sudau and Nubbemeyer,[89] storage of an aldehyde structurally similar to **54** at room temperature led to partial epimerization, whereas any epimerization was avoided when the compound was processed immediately after its isolation. The authors thus reacted their aldehyde with DIPEA in CH_2Cl_2 at rt, and after 4 days almost complete racemization was obtained as observed by HPLC analysis.

The same experiment was performed on **54**, and **56** was subsequently both reduced to alcohol **57** and reacted with **50** to obtain alkyne **58**. By comparing the values of the samples' optical rotations, it was found that the obtained results were extremely dependent on the purity of the sample. By purifying all the samples by distillation almost identical optical

rotations were obtained, supporting the previous data obtained, indicating that no epimerization had taken place.



Scheme 32. Performed experiments to determine if epimerization during the Swern oxidation had taken place.

2.5 Investigations on Enyne *d*RRM with Bicyclic Enyne Metathesis Substrates

2.5.1 Generalities

An important objective of the presented work was to investigate all possible parameters which could influence selectivity in enyne *d*RRM, and ideally, to be able to direct selectivity by changing the reaction conditions. In this regard, solvent, concentration, temperature, catalyst, additives and ethylene pressure were the variables investigated in enyne *d*RRM of both amine **27** and the corresponding amide **31**.

Previous studies in our group showed that, for a given substrate, diastereoselectivity in *d*RRM reactions is strongly influenced by the neutral ligand that remains bound on the metal center in the Ru-propagating species.[30] This can be reasoned by the shape of the phosphine and the NHC ligands which provide a different steric environment around the metal.[90] In this regard, when steric properties of the NHC ligand are modified, a change in the diastereoisomeric ratio can be expected.

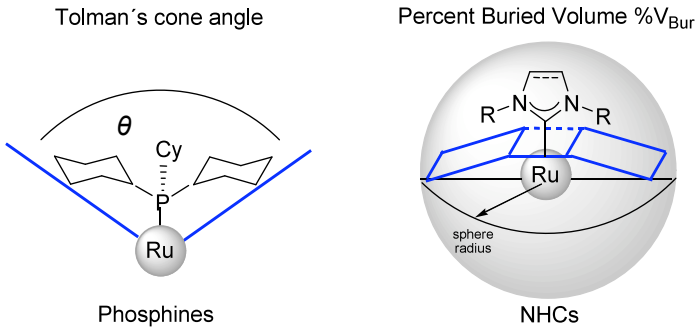


Figure 4. Different shape of NHCs compared with phosphine ligands.

Different parameters are used for the classification of the steric environment imposed by ligands in organometallic molecules. In the case of phosphine complexes, the phosphine substituents point away from the metal center, forming a cone (Figure 4), where the Tolman´s cone angle (*θ*) is used as a suitable descriptor of the steric demand.[91]

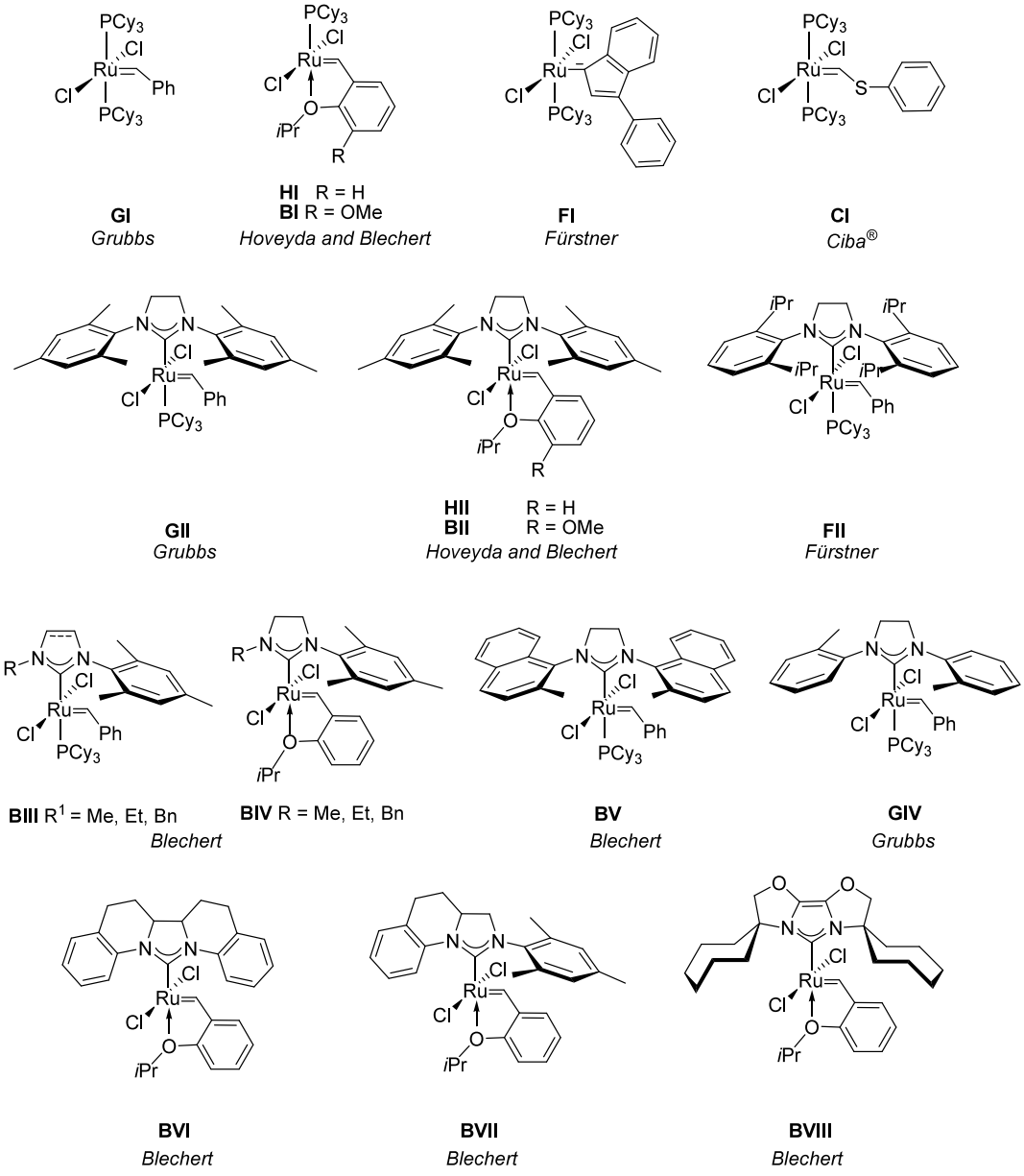


Figure 5. Selected Ru-complexes for the catalyst screening for *d*RRM of **27** and **31**.

The shape of NHCs significantly differs from that of the phosphine ligands, and in transition-metal NHC complexes the substituents bound to the carbene's nitrogen atoms point toward the metal, thereby surrounding thereby the active center. In order to quantify the steric bulk of the NHC ligand, the concept of the so-called "percent buried volume" ($\%V_{Bur}$) is used.[92] This parameter defines the occupied space of a ligand bound to a metal in its coordination sphere within a radius of 3 Å, and enables the comparison between the steric bulk of both NHC and phosphine ligands: $\%V_{Bur}$ PCy_3 = 32, **FII**-NHC = 29, **GII**-NHC = 27.

In Figure 5 are depicted the ruthenium catalysts used in the presented enyne *d*RRM investigations with **27** and **31**. Diverse first generation catalysts **GI**, **HI**,[93] **BI**,[94] **FI**[95] and **CI**[96] were screened with the aim of also studying the influence of the initiation rate and the pre-catalyst stability on the conversion and yield obtained. The same objective was behind using different second generation catalysts **GII**, **HII** and **BII**.[97] We envisaged that catalysts **FII**,[98] **BVI**,[99] **BVII**[100] and **BVIII**[101] could furnish enhanced selectivity due to a major steric bulk around the Ru, whereas complexes **BIII**,[102] **BIV**, **BV**[103] and **GIV**[104] could lead to the inverted result due to a reduced steric demand of the NHC compared to **GII**.

Other parameters which might influence diastereoselectivity will be studied. Within previous investigations in the group,[105] increasing the ethylene pressure demosnstrated a positive effect on the *dr* in alkene *d*RRM. Any variable capable of influencing the micro-reversibility of the metathesis reaction can lead to a change in the product distribution. In this regard, different temperatures, concentrations and solvents will be likewise screened. The chosen cross partners, due to electronic and steric effects, can lead to very different results in comparison with ethylene and will be also investigated within the total synthesis of indolizidine alkaloids.

2.5.2 Enyne *d*RRM Studies with Amine 27

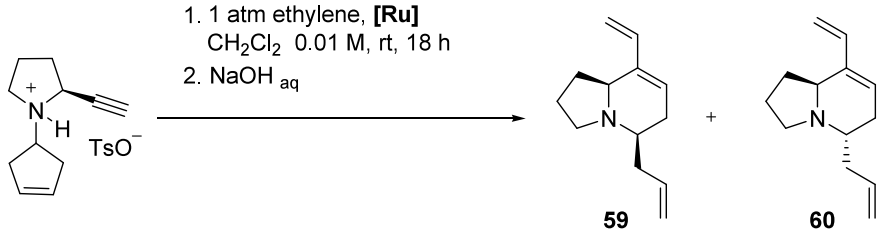
2.5.2.1 Catalyst Screening

Initial studies, with commercially available ruthenium-based pre-catalysts under various reaction conditions, showed that compound **27** was not able to undergo metathesis due to the ability of the amine free electron pair to coordinate to ruthenium and interfere with the catalytic activity.[59] By forming its corresponding ammonium salt with *p*TSA,[(*)] however, it was possible to prevent this interaction and the metathesis reaction was conducted with 100% conversion with complex **HII**.[106]

[(*)] HCl and *p*TSA are the acids most commonly used in such cases. *p*TSA was chosen for the diasteroseletivity investigations, since the corresponding HCl salt showed no conversion in preliminary studies with **GI**.

Metathesis studies on **27**·*p*TSA were carried out with different catalysts, solvents, concentrations and temperatures as well as at variable ethylene pressure (Table 7). As previously expected, the diastereoisomeric ratio was determined by the neutral ligand which remains in the catalytic species. We found that 'first generation' catalysts furnished a *dr* of 2:3, although unfortunately, conversions were relatively low even with 10 mol% catalyst (entries 1-3). 'Second generation' catalysts, instead, led to complete conversion with 5 mol% catalyst loading and an inverted selectivity of 7:4 (entry 4).

Table 7. Catalyst screening in the enyne *d*RRM of **27**·*p*TSA.



Entry	[Ru]	mol%	*dr* [a]	Conv
1	**FI/BII**	5	2:3	< 10%
2	**GI**	10	2:3	53%
3	**HI**	10	2:3	40%
4	**GII/HII/BII**	5	7:4	100%
5	**GIV**	10	1:1	50%
6	**BV**	8	1:1	19%
7	**FII**	5	8:3	100%
8	**BVIII**	-	-	0%
9	**BVI**	-	-	0%
10	**BVII**	10	1:1	29%
11	**BIII**	10	1:1	77-100%
12	**BIV**	15	3:5	100%

[a] Conversion and *dr* determined by ^{1}H-NMR spectroscopic analysis.

In order to further investigate the influence of the catalyst ligand on selectivity, we decided to study catalyst **GIV**, which presents a considerably reduced steric bulk in comparison with **GII**. Remarkably, with an acceptable formation of product, no selectivity was observed, and a *dr* near to 1:1 was obtained (entry 5). To corroborate this result we performed the same reaction with catalyst **BV**. This Ru-complex also possesses a less crowded steric environment at the ruthenium center, and has shown to deliver even better results than **GIV**, in RCM of sterically demanding substrates leading to tetrasubstituted cyclic olefins. As expected, the same result was obtained in terms of selectivity, although with significantly less conversion (entry 6).

The general trend in these results suggests that reducing the steric bulk around the metal center leads to a decrease in the diastereoselectivity. First generation catalysts, whose ligands present a higher percentage buried volume, lead surprizingly to an inverted diastereoisomeric ratio (entries 1-3).

In any case, we expected to obtain a higher diastereoisomeric ratio with pre-catalyst **FII** than with the commercially available complexes **GII** and **HII**, due to its higher steric demand (calculated percentage buried volumes for the NHC ligand of **FII** is 29%; for **GII**, 27%). Indeed, selectivity did increase and a *dr* of 8:3 was obtained with 100% conversion (entry 7). Any attempts to increase this selectivity by using more sterically demanding Ru-complexes **BVI** and **BVIII** failed to give any conversion (entries 8 and 9).

Complex **BVII** was also considered as an attractive pre-catalyst for *d*RRM investigations since it combines an unsymmetrical substitution on the NHC ligand, with a structurally rigid backbone, through hindered rotation and a torsional angle of approximately 45°. This structural feature, according to previous investigations regarding **BVI**, exerts a greater anisotropy around the metal center leading to higher selectivity. Following the same tendency as the other unsymmetrical pre-catalysts, **BVII** showed no selectivity for the described reaction, and relatively low formation of the rearranged product, probably due to certain instability of **BVII** under the ethylene atmosphere (entry 10).

Next, we became interested in studying the selectivity of unsymmetrical NHC derived ruthenium catalysts **BIII** and **BIV**. These types of NHC ligands present a 'variable' percentage buried volume which is dependent upon the bulkiness of the *N*-substituent (Me, Ph, Bn, etc), and, additionally, due to the unsymmetrical distributed bulk around the metal centre, they have been shown to give a different E/Z selectivity compared with commercially available complexes in CM reactions. Catalysts bearing a saturated unsymmetrical NHC ligand did not show high diastereoselectivity on the reaction outcome having a *dr* of 1:1 or very close, and this was independent of the non-mesityl *N*-substituent (entry 11). The use of the unsaturated ligands, remarkably, showed a small but significant change in *dr* (entry 12). Unsaturated NHC ligands are structurally less flexible than the saturated ones, and the implicitly superior directing properties of these ligands could explain the higher selectivity observed.

2.5.2.2 Experimental Analysis of the *d*RRM Reaction and *dr* Determination

The diastereoisomeric ratio was calculated by integrating the corresponding signals for the vinylic proton on the diene moiety (Figure 6). Any attempt to calculate the ratio by GC-MS spectrometry or by HPLC failed, since the reaction products could not be reliably quantified by these methods.

In order to determine the relative stereochemistry of the two stereoisomers, spectroscopic analysis *via* NOE with **59** and **60** were performed. Even though correlation between protons could be observed, due to signal overlapping it could not be unequivocally assigned which of the stereoisomers possessed the desired *cis* alignment.

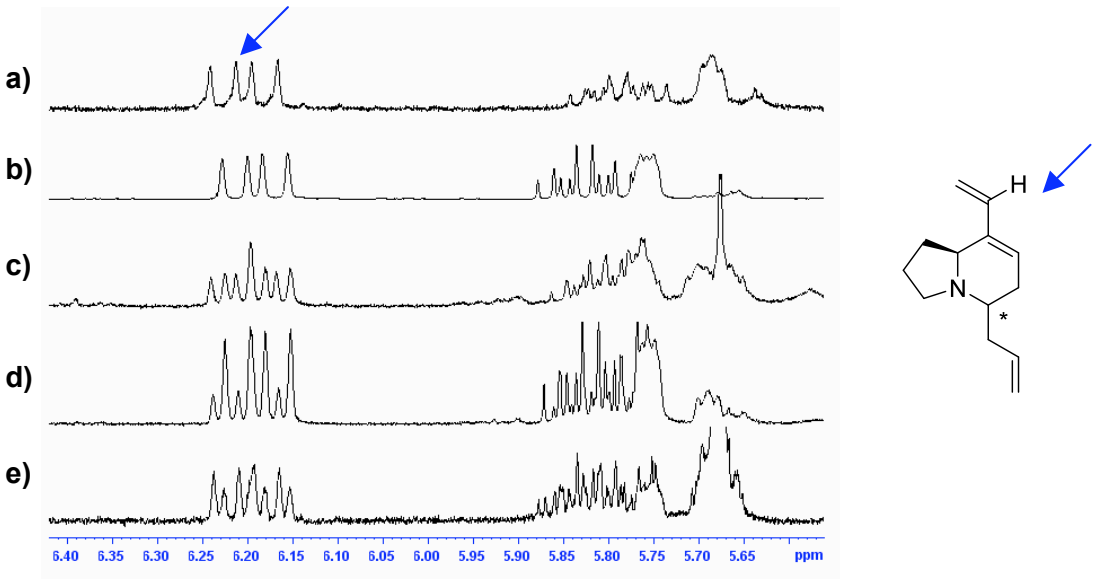


Figure 6. In blue are indicated the signals used to calculate the *dr* on the *d*RRM reaction. Both spectra on the top represent the two different isomers (a and b). ^{1}H-NMR spectra c) represents a crude metathesis reaction with **BIII**, d) with **FII** and e) with **HI**.

2.5.2.3 Investigations with Different Brønsted Acids

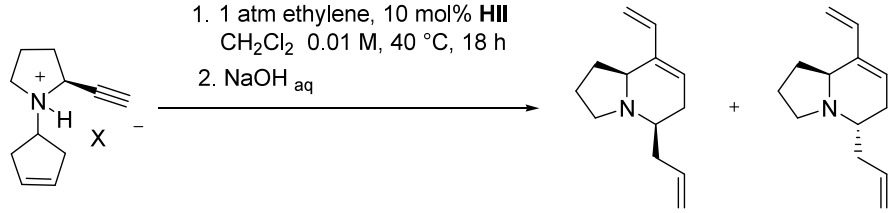
Since parameters such as solvation, coordination capacity of the counterion, pK_a, and general electrostatic effects may play an important role in the reaction outcome, we decided to perform metathesis experiments with a range of ammonium salts derived from different Brønsted acids (Table 8). Despite protonation of amines being a common strategy in metathesis to avoid catalyst deactivation, there are few reports discussing the reaction outcome when different Brønsted acids are applied.[107] The most noteworthy report is a recent publication by Vanderwaal and coworkers, in the synthesis of the alkaloid (-)-nakadomarin, describing a modest but significant increase in the *E/Z* selectivity during macrocyclization by using camphorsulfonic acid (CSA) in comparison when no acid was employed.[108]

In our case we found that although 'first generation' catalysts showed low conversions,[(*)] for 'second generation' catalysts, however, complete conversion was achieved and surprisingly, the diastereoisomeric ratio was found to be counterion dependent.

[(*)] Except for **27**·TsOH and **27**·TfOH (Tables 7 and 9 respectively) less than 10% conversion was generally obtained with **GI**.

When HBF_4, TFA and HCl salts were used, high diastereoselectivities were obtained (entries 1-3). For HPF_6, MsOH, CSA and *p*TSA selectivity appeared to be lower (entries 4-7), and, surprisingly, for fluorinated sulfonic acids the diastereoselectivity was inverted (entries 8 and 9). Moreover, reactions performed with the triflate salt proceeded with an increased reaction rate in comparison for instance with the corresponding *p*TSA salt, and underwent complete conversion within less than 20 minutes, a point at which with the *p*TSA salt 42% conversion was achieved. Remarkably, the use of the acetic acid salt, with a lower pK_a value of 4.7, resulted in complete reisolation of the starting material.

Table 8. Enyne *d*RRM studies on tertiary amine **27**. Representative results in the Brønsted acid influence in diastereoselectivity**.**



Entry	Substrate	*dr* [a]	pK_a [b]	Conv
1	**27**·HBF_4	10:1	-5	100%
2	**27**·TFA	10:1	-0.25	100%
3	**27**·HCl	6:1	-8	100%
4	**27**·HPF_6	2:1	-20	100%
5	**27**·MsOH	2:1	-2.6	100%
6	**27**·CSA	7:2	-	100%
7	**27**·*p*TSA	7:4	-6	100%
8	**27**·$C_2HF_4SO_3H$	2:3	-	100%
9	**27**·TfOH	1:3	-14	100% [c]

[a] Conversions and diasteromeric ratio determined *via* ^{1}H-NMR after basic work up; [b] Measured in water; [c] Complete conversion was achieved within 20 min.

The presented results cannot be explained from the pK_a values or the coordination character of the counterions: HBF_4 and *p*TSA (pK_a of -5 and -6 respectively) show significantly different diastereoisomeric ratios (entries 1 and 7), and HBF_4 and HPF_6 differ also in *dr*, whereby both counterions are non-coordinative ions.

Seeking experimental support to explain the observed diastereocontrol, the corresponding quaternary ammonium salts were analyzed by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Interestingly, dependent upon the salts two different resonance patterns could be attributed to the alkyne proton, whereby the reproducibility of the spectrum after repeated sample purifications excluded any other impurities. For ammonium salts synthesized with HCl, HBF_4 and TFA, only one isomer was detected (Figure 7). For fluorinated sulfonic acids such as

TfOH, however, two different diastereoisomers could be clearly observed in the ^{1}H-NMR and ^{13}C-NMR spectra.(*)

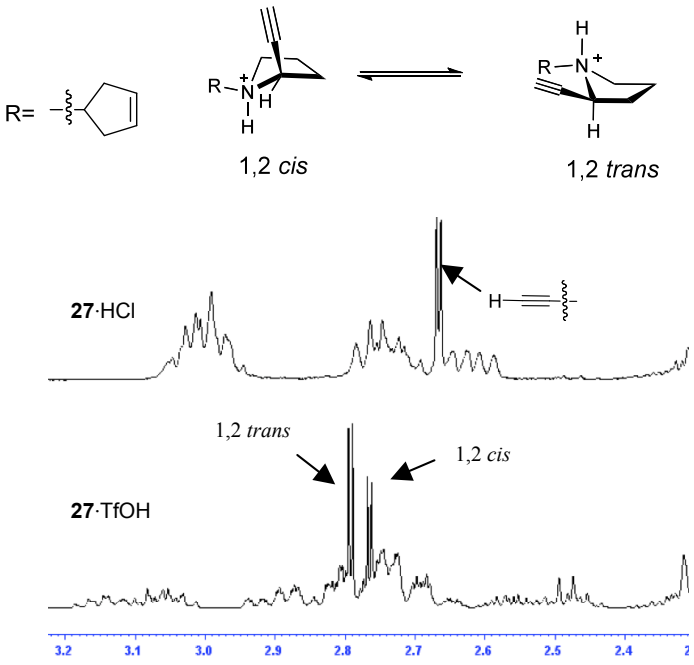


Figure 7. Fragment of the ^{1}H-NMR spectra ($CDCl_3$) corresponding to the alkyne resonance in **27**·HCl salt and **27**·TfOH salt.

The non-equivalence of the *N*-methyl groups in *trans*-1,2-dimethylpyrrolidine hydrochloride and other heterocycles has been extensively discussed by Closs and McKenna, among others.[109] Since our cyclic tertiary amine hydrochlorides have tetrahedral geometry and can exist in two configurations, the proton magnetic resonance spectrum can exhibit two signals associated with the two differently oriented substituents. These are differently shielded in each conformation and hence come into resonance at different applied fields. According to previous reports from both Closs and McKenna, the alkyne proton's resonance of the conformer where the alkyne and the cyclopentene are orientated *trans* to each other should appear at lower field, and the corresponding *cis* ammonium salt at higher field. The inversion of substituents on trivalent nitrogen in relatively unstrained ring systems is known to be a process of low activation energy and it can be expected that the two isomers exist in solution in rapid equilibrium, whereby at pH 6 the rate of interconversion of the two stereoisomers would be expected to be such that independent signals for each isomer are not seen. The investigations of Closs and McKenna were performed at pH 1, conditions where the relative intensities of the signals should give an indication of the proportions of the two configurations, and thus the relative stability of the conformers.

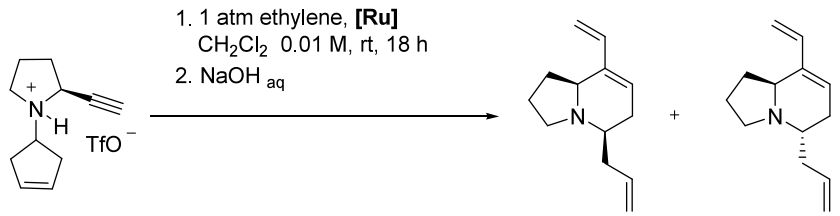
(*) For more detailed information concerning ^{1}H-NMR and ^{13}C-NMR spectroscopic data for all synthesized ammoniums salts see Chapter 5.

For ammonium salts **27**·TfOH, **27**·$C_2HF_4SO_3H$, **27**·MsOH, and **27**·HPF_6 the *cis* and *trans* conformers present different stability, with an interconversion rate low enough to be observed by ^1H and ^{13}C-NMR spectroscopy. Remarkably, for these specific substrates the diastereoselectivities observed are inverted. A correlation between the signal integrations and the *dr* obtained was unfortunately not possible, since overlapping with other proton signals was observed in the majority of substrates. The fact that even at a pH value near to 6 two different diastereoisomers were observed, is an indication that **27** is indeed a relatively strained system.(*)

In order to confirm the influence of the counterion in the selective formation of 1,2-*cis/trans*-isomers the following experiment was performed: **27**·HCl was synthesized by adding anhydrous 2.5 M methanolic HCl to an anhydrous solution of **27** in CH_2Cl_2. After concentration under vacuum, the sample was suspended in C_6D_6 and AgOTf was added under inert conditions. Spectroscopic analysis showed clearly the formation of two isomers, reproducing the ^1H-NMR obtained in **27**·TfOH samples synthesized by direct addition of TfOH to a solution of **27** in CH_2Cl_2.

The observed selectivity in the metathesis reaction outcome could be thus rationalized by arguing that the different 1,2-conformers in ammonium salts of amine **27** preferentially furnish different *cis/trans* substituted bicyclic transitions states according to the corresponding conformational preferences. Such equilibrium may also be strongly influenced by pH of the reaction mixture and the reversibility of protonation, as well as solvation.[110] Besides, it must be taken in account that metathesis reaction rates toward products may be significantly different for each conformer, and that the electronic properties and sterics of the catalytic species also play an important role in the diastereoisomeric ratio obtained.

Table 9. Catalyst screening in the enyne *d*RRM of **27**·TfOH.



Entry	[Ru]	mol%	*dr* [a]	Conv
1	**GI**	10	3 : 5	67%
2	**BIV**	10	3 : 4	50%
3	**HII/HIV/GII**	5	1 : 3	100%
4	**FII**	10	7 : 1	100%

[a] Conversions and diasteromeric ratio determined *via* ^1H-NMR after basic work up.

(*) The used salts were synthesized by using 1.05 eq acid and where purified by column chromatography prior to use, to eliminate the excess of Brønsted acid.

Nevertheless, according to the results presented, it can be concluded that in pyrrolidinic derivatives diastereoselectivity can be directed with Brønsted acids by means of stabilizing the appropriate conformer.

We next aimed to investigate the reaction outcome with **27**·TfOH and different catalysts, aiming to observe if selectivity could be also controlled and if even higher values than 1:3 could be obtained (Table 9). The reactions were performed at room temperature, since the catalysts showed higher stability under these conditions. First generation catalyst (entry 1) and unsymmetrical complexes (entries 2) furnished lower *dr* values as **HII** or **GII**, while surprisingly diastereoselectivity was inverted with catalyst **FII** (entry 4).

Apparently, pre-catalyst **FII** leads preferentially to the same diastereoisomer independently of the Brønsted acid used. Thus, we became interested in investigating the influence of this catalyst on the *dr* when the previously outlined Brønsted acids were screened (Table 10). All the obtained results showed the same selectivity, with a similar tendency as observed for catalyst **HII**. Surprisingly, while in this case **27**·HBF_4 led to a 1:1 *dr*, the corresponding HPF_6 ammonium salt, furnished complete selectivity.

Table 10. Results on the Brønsted acid influence on diastereoselectivity with catalyst **FII**.

Entry	Substrate	FII *dr* (HII *dr*) [a]	Conv
1	**27**·HBF_4	1:1 (10:1)	100%
2	**27**·MsOH	5:2 (2:1)	100%
3	**27**·CSA	3:2 (7:2)	6%
4	**27**·TsOH	3:1 (7:4)	100%
5	**27**·HCl	4:1 (6:1)	50%
6	**27**·TfOH	7:1 (1:3)	100%
7	**27**·TFA	8:1 (10:1)	100%
8	**27**·HPF_6	> 20:1 (2:1)	100%

[a] Reaction conditions: 10 mol% catalyst, CH_2Cl_2, 40 °C, 12 h. Conversions and diasteromeric ratio determined *via* ^{1}H-NMR after basic work up. In brackets appears the *dr* obtained with **HII**.

With the purpose of rationalizing the obtained results, a detailed static and dynamic characterization of NHC ligands in Ru-complexes recently reported by Cavallo and coworkers was taken into account.[111] According to Cavallo, analysis of the dynamic trajectories indicates that the nature of the *N*-substituent can result in extremely different flexibilities of the Ru complexes. In almost all the cases the *N*-substituent *trans* to the Ru-ylidene bond is severely folded so that it protects the vacant coordination position at the Ru center. Limited flexibility is instead associated with the *N*-substituent on the side of the Ru-ylidene bond. Analysis of the dynamic trajectories in terms of buried volume indicate that the real bulkiness of these systems can be somewhat modulated, and this flexibility is a key feature that allows NHCs to adapt their encumbrance around the metal in order to make

room for substrates. According to the molecular dynamics simulations performed by the group of Cavallo, for the specific case of **FII** the rotation of the *N*-substituent on the side of the Ru-ylidene bond is comparable to the less sterically hindered **GIV**, due to the steric interaction between the *i*Pr substituents and the halide ligands, which causes the rotation angle to oscillate between 60-120°. For the *N*-substituent bond opposite to the Ru-methylidene bond, catalyst **FII** presents the most limited rotation among all catalysts studied. According to this, and supported by experimental observations by Grubbs and coworkers,[112] the flexibility of both *N*-substituents, which is contrary to that expected with **GII**, together with the increased steric bulk of the *i*Pr group provides the complex **FII** with a special sterically hindered environment at the Ru-center which may be responsible for the obtained selectivities (Figure 8).

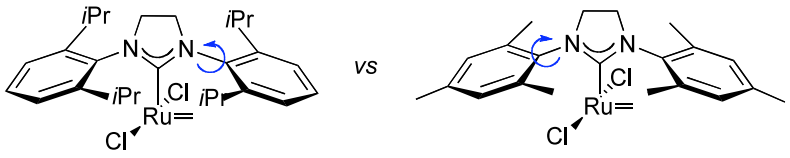


Figure 8. Comparison between the active species derived from **FII** and **GII**. With blue arrowas are indicated *N*-substituents with increased rotation capacity. This differencated NHC flexibility, along with increased $\%V_{Bur}$, might be one of the factors responsible for the measured *dr*.

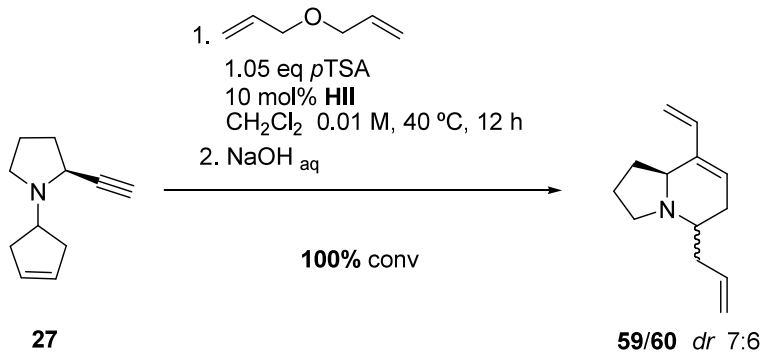
2.5.2.4 Ethylene Influence and Reproducibility of the Obtained Results

Neither temperature, concentration or solvent type showed to have a significant influence on the reaction outcome(*) and complete conversions were achieved within 12 h. The applied ethylene pressure, on the other hand, appeared to be an important feature. At values higher than 1 bar, formation of **59**/**60** decreased, obtaining at 3 bar only a 40% conversion. On the other hand, an equimolar amount of ethylene, generated *in situ* through RCM of diallyl ether, was sufficient to allow complete transformation to the rearranged product (Scheme 33) with **27**, whereby the same selectivity was observed.[113]

In terms of diastereoselectivity, the ethylene pressure and the amount of added acid showed to have influence in the reproducibility of the obtained results. All metathesis test screenings were performed in 10 ml Schlenk tubes with salts purified by column chromatography. When the salt is synthesized *in situ* with an excess of acid, the pH of the obtained solution influences the protonation reversibility and the **59**/**60** distribution, with a consequent influence on the observed *dr*. Besides, for strong acids such as TfOH, HBF_4 and HPF_6 the stability of the catalyst in solution under ethylene atmosphere is significantly reduced, and an excessive

(*) With the exception of the **27**·TfOH ammonium salt, whereby due to diminished solubility in toluene, only starting material was recovered after performing the *d*RRM reaction.

amount of acid can lead to immediate catalyst decomposition. An exception is *p*TSA (pK_a value of -6), whereby even with the use of 1.5 eq acid the same results regarding yield and selectivity were obtained as with equimolar quantities.

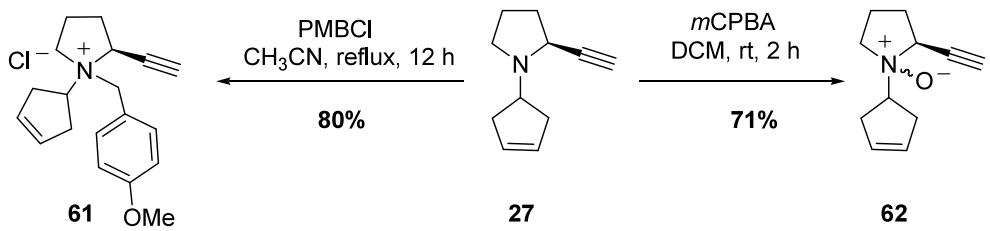


Scheme 33. *d*RRM of **27** substituting the ethylene atmosphere for equimolar quantities of ethylene generated by RCM of diallyl ether.

Further, for a given reaction scale, when the form or the volume of the flask changed, and thus the relative surface solution-atmosphere, for HPF_6 and TfOH, problems to reproduce the *dr* were observed. The scaled up reaction, was therefore performed in 50-100 ml Schlenk tubes with "finger" form to reproduce the shape of the 10 ml Schlenk tube.
Under this conditions and 5 mol% catalyst **HII,** a 97% yield with **27**·TfOH and 95% yield with **27**·TFA was obtained, with the same selectivities indicated in Table 7.

2.5.2.5 Investigations with Other Amine Derivatives

In view of the satisfactory results obtained in metathesis reactions with ammonium salts from **27**, we became interested in performing the same reaction with other quaternary amines. We chose derivate **61** (Scheme 34) as model substrate from a family of compounds that could include diverse benzyl derivatives, with different electronic and steric properties. The synthesis of **61** was approached following a published procedure in THF[114] and in acetone,[115] but only starting material was reisolated. By conducting the reaction in acetonitrile at reflux, **61** was successfully isolated as mixture of diastereoisomers. On the other hand, *N*-oxide **62**,

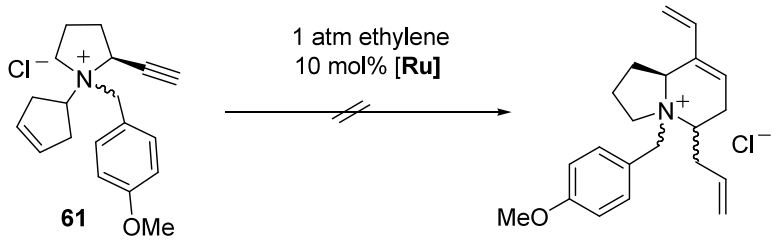


Scheme 34. Synthesis of quaternary amines **61** and **62**.

prepared by treatment with *m*CPBA, appeared to be an interesting substrate, since metathesis reactions with such compounds have never been reported.

Metathesis experiments with ammonium salt **61** resulted in complete reisolation of the starting material (Table 11), which would indicate a too sterically strained intermediate in comparison with the ammonium counter parts.

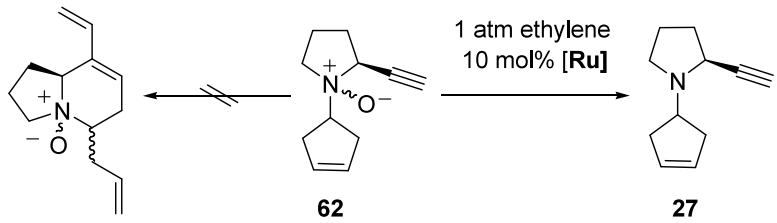
Table 11. Reaction conditions on metathesis experiments with quaternary ammonium salt **61**.



Entry	Catalyst	Solvent	T
1	**GI**	CH_2Cl_2	40 °C
2	**GII**	CH_2Cl_2	40 °C
3	**GII**	toluene	80 °C

Similar experiments where performed with *N*-oxide **62**, using catalysts **GI**, **GII** and **HII**. With both first and second-generation catalyst the formation of the desired rearranged product could not be detected, instead complete isolation of amine **27** was obtained (Table 12). In view of these results, the *N*-oxide behaves as an oxidation agent decomposing the ruthenium-complex leading to the reduced compound **27**. Since amine **27** was reisolated almost quantitatively, a redox transformation must take place, whereby ethylene might be oxidated to acetaldehyde and the formed RuO_2 may be acting as catalyst.[116]

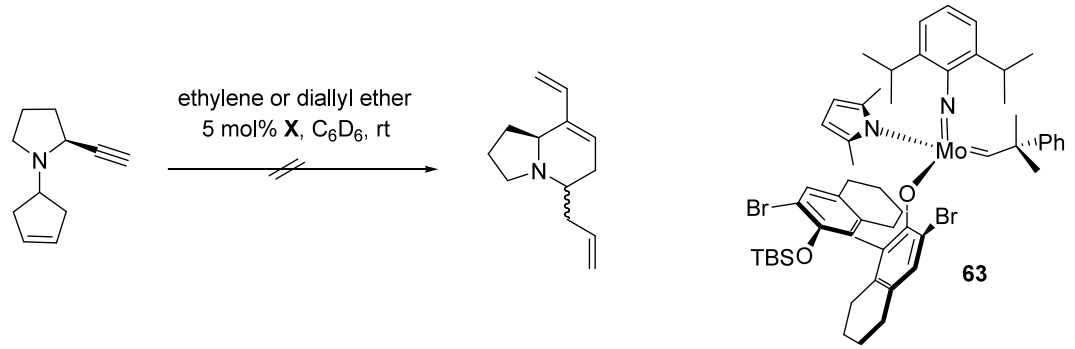
Table 12. Result obtained when substrate *N*-oxide **62** was subjected to metathesis conditions under an ethylene atmosphere.



Entry	Catalyst	Solvent	T
1	**GI**	CH_2Cl_2	40 °C
2	**GII**	CH_2Cl_2	40 °C
3	**HII**	CH_2Cl_2	40 °C

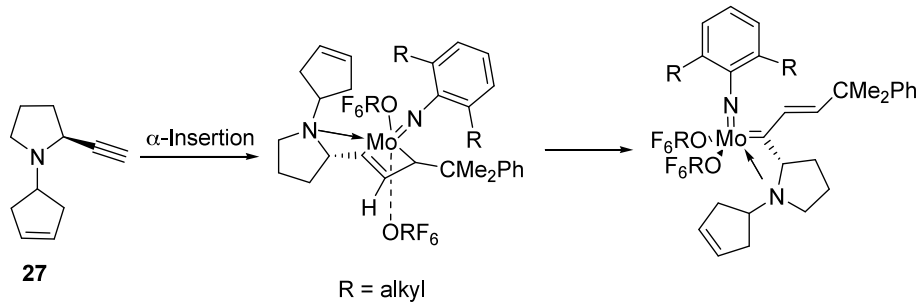
2.5.2.6 Investigations with Mo-based Metathesis Catalysts

Molybdenum-based complexes are generally tolerant towards tertiary amines and have been used successfully in the synthesis of different natural products such as the *Aspidosperma* alkaloid (+)-quebrachamine.[117] The same catalyst **63** was synthesized in Blechert´s group by Matthias Grabowski and tested in the enyne *d*RRM of **27**. Unfortunately, no product formation was detected under the used reaction conditions (Scheme 35).



Scheme 35. Metathesis results performed with **27** in Blechert´s group with molybdenum based metathesis catalysts **63** developed by Schrock and coworkers.

Other molybdenum -based catalysts were also tested on alkyne **27** in collaboration with Prof. Buchmeiser. Several experiments where conducted with catalysts which were developed in his group, but again, the desired product could not be isolated and instead polymerization took place through the alkyne moiety. Interestingly *via* spectroscopic analysis it was possible to detect the formation of a relative stable intermediate resulting from complexation and insertion of the molybdenum catalyst and the substrate (Scheme 36)



Scheme 36. Proposed structure for the new complex observed in molybdenum-catalyzed RRM with substrate **27**, according to Buchmeiser.

2.5.3 Enyne *d*RRM of Amide 31

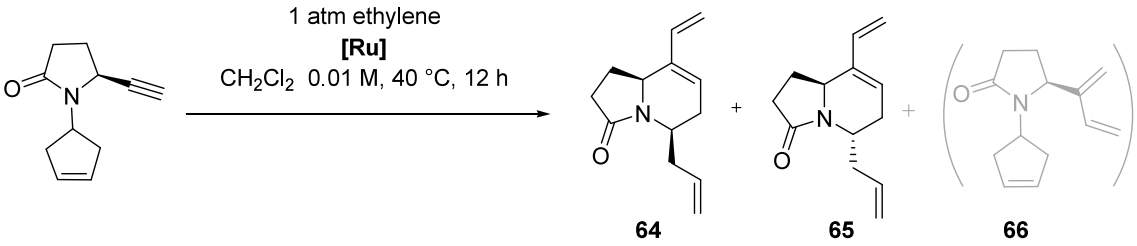
2.5.3.1 Catalyst Screening

Metathesis studies on **31** were also performed with different catalysts, solvents, and at different temperatures. The best results in terms of diastereoselectivity were found with PCy_3

based ruthenium catalysts with a *dr* of 1:10 (Table 13), except for the catalyst **CI**,[118] where no conversion towards products was detected.

Second generation catalysts, due to their higher reactivity, afforded a complex mixture of products including the desired compounds, compound **66**, and mainly oligomerizated products. Complex **FII** showed improved chemoselectivity when compared to **GII** or **HII**, leading to a 1:7:2 mixture of products **64**, **65** and **66**, no oligomerizated compounds and a similar diastereoisomeric ratio (entry 4). Unsymmetrical catalysts **BIII** and **BIV** delivered again no selectivity and a *dr* of 1:1 was obtained (entry 5).

Table 13. Catalyst screening results in enyne *d*RRM of **31**.



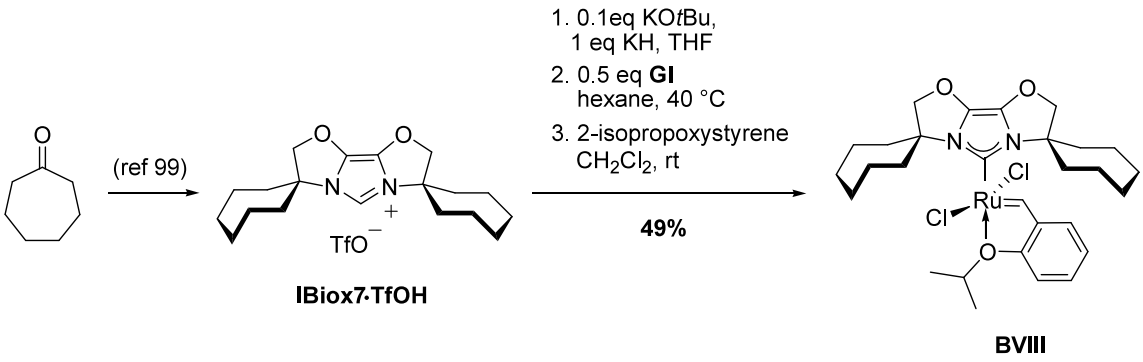
Entry	[Ru]	mol%	*dr*	Conv [a]
1	**GI/HI/FI**	5	1:10	100%
2	**CI**	10	-	0%
3	**GII/HII**	5	-	product mixture
4	**FII**	10	1:7	100% [b]
5	**BIII/BIV**	5-15	1:1	50-65%
6	**BVI**	5	1:2	20%
7	**BVII**	10	-	0%
8	**BVIII**	10	-	0%
9	**BVIII** [c]	10	4:1	38%
10	**BV**	5	-	0%
11	**GIV**	10	3:1	100%

[a] Determined by ^{1}H-NMR spectroscopic analysis. [b] A ratio 1:7:2 of **64**:**65**:**66** was obtained. [c] Reaction performed under N_2 atmosphere and with 2 eq diallyl ether.

In view of to the obtained results, sterically hindered phosphine-derived catalysts favored a high diastereoselectivity. To further study the influence of the catalyst steric bulk in the *dr* obtained catalyst **BVI**, **BVII** and **BVIII** developed in Blechert´s group were also investigated.

Ruthenium-complex **BVI**, which had shown excellent results in previous investigations on *d*RRM, presented good selectivity but very low activity under the chosen reactions conditions (entry 6). Catalyst **BVII**, due to reduced stability under an ethylene atmosphere, showed no conversion towards the desired product (entry 7).

Very significant results were obtained with the more sterically hindered pre-catalyst **BVIII**. **BVIII** was synthesized according to the published procedure (Scheme 37), and showed very low stability when converted to the corresponding active species in ethylene atmosphere (entry 8). As mentioned in section 2.5.2.4, ethylene can also be generated *in situ* by RCM of diallyl ether. Under these reaction conditions an improved conversion of 38% was obtained, and remarkably, with an inverted diastereoselectivity of 4:1 (entry 9).



Scheme 37. Synthesis of pre-catalyst **BVIII**.

With the aim of finding further experimental support to relate $\%V_{Bur}$, NHC flexibility and selectivity, we became interested in performing the *d*RRM reaction with **BV**. Unfortunately the corresponding active species was unable to perform the desired reaction (entry 10). Catalyst **GIV**, which is also less sterically hindered when compared with **GII**, showed on the other hand complete conversion, and also an inverted selectivity of *dr* 3:1 (entry 11).

From the presented results, it can be concluded that less sterically hindered ruthenium- pre-catalysts such as **BIII** and **GIV** furnish low or inverted selectivities in comparison with the phosphine-based catalysts. A special case is complex **BVIII**, due to the nature of his flexible steric bulk (Figure 9). According to Glorius and coworkers, the different conformational possibilities of the IBiox6·TfOH ligand (the cyclohexyl homologue) exhibit a buried volume from 31.1 to 39.3, which is similar to those of the most sterically demanding monodentate ligands.[119] In this regard, similar or even superior selectivity than with the phosphine ligands should be obtained.

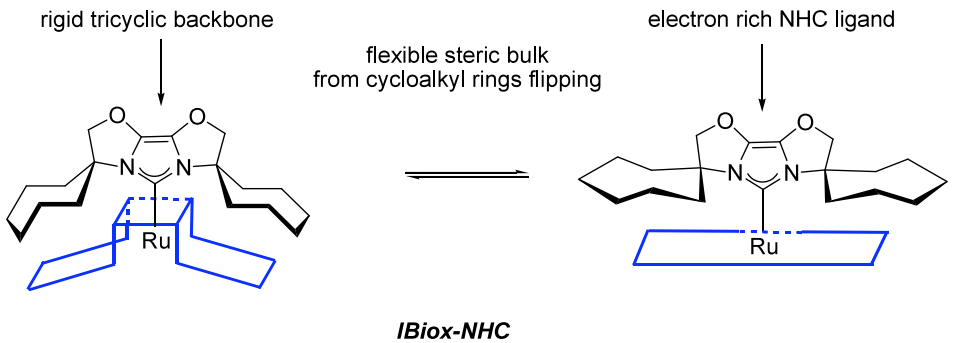


Figure 9. Two of the four possible conformations of the IBiox-NHC ligand.

According to the presented results, despite that the values of $\%V_{Bur}$ can help to predict selectivity, the flexibility of the NHC ligand and its *N*-substituents play a most significant role. The four structural conformations that the NHC in **BVIII** can embrace, provide this catalyst with unique qualities, and hence, studying its behavior in *d*RRM is of high interest.

2.5.3.2 Optimization of the Reaction Conditions

Analogously to the results obtained with amine **27**, in terms of diastereoselectivity, neither temperature, concentration or solvent type showed to have an influence on the reaction outcome. With all first generation catalyst, except for the catalyst **CI**, complete conversion as achieved with 5 mol% at 40 °C in CH_2Cl_2 in a 2-10 mg scale.

In order to find optimal reaction conditions for the enyne dRRM of amide substrate **31**, different experiments were performed in a 100-500 mg scale. As pre-catalytic species commercially available complex **GI** was first chosen for being most readily available compared to **HI** and **HIII**. With this catalyst, we found out that catalyst loading, temperature and concentration played a decisive role in the isolated product yield after chromatographic purification (Table 14). By decreasing the temperature and increasing the concentration better conversions were achieved (entry 3). Optimized results where found with catalyst **FI** under 1 bar ethylene atmosphere, using a 0.03 M solution of the metathesis substrate in CH_2Cl_2 and performing the reaction at room temperature over night. Under this conditions, rearranged products **64** and **65** were obtained in 95% yield as a chromatographic separable diastereoisomeric mixture (entries 4 and 5).

Table 14. Selected reaction optimization results for enyne *d*RRM of alkyne **31**.

Entry	Catalyst	Solvent	T	[mol/l]	Conv [a]	Yield [b]
1	5 mol% **GI**	CH_2Cl_2	40	0.01	78%	75%
2	5 mol% **GI**	CH_2Cl_2	40	0.02	95%	76%
3	5 mol% **GI**	CH_2Cl_2	rt	0.03	100%	71%
4	5 mol% **FI**	CH_2Cl_2	rt	0.03	100%	93%
5	3 mol% **FI** [c]	CH_2Cl_2	rt	0.03	100%	95%

[a] Determined by ^{1}H-NMR spectroscopic analysis. [b] Isolated yield after column chromatography. [c] Added in two portions.

2.6 Synthesis of Indolizidine Alkaloids

Having obtained reaction conditions to steer the selectivity towards both diastereoisomers for amine **27** and for amide **31** (Table 15), we next directed our synthetic investigations towards natural occurring indolizidine alkaloids.

Table 15. Summarized results obtained in enyne *d*RRM.

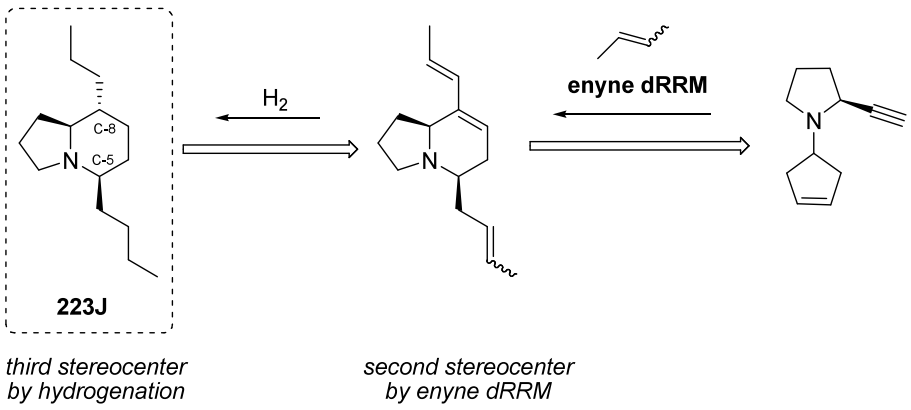
Entry	Substrate	Catalyst	*dr* [a]	Yield [b]	Entry	Substrate	Catalyst	*dr* [a]	Yield [b]
1	**27**·HPF_6	5 mol% **FII**	>20:1	85%	3	**31**	5 mol% **GIV**	3:1	- [c]
2	**27**·TfOH	5 mol% **HII**	1:3	97%	4		3 mol% **FI**	1:10	95%

[a] Determined by ^{1}H-NMR spectroscopic analysis. [b] Isolated yield after column chromatography. [b] 100% conv, non-optimized yield

2.6.1 Synthesis of Indolizidines 5-*epi*-223J and 8-*epi*-223J

2.6.1.1 Retrosynthetic Analysis

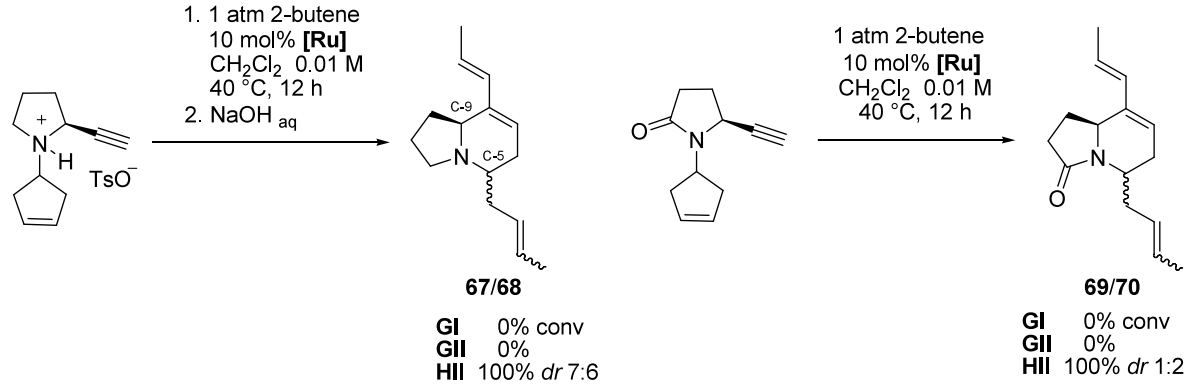
With the intention of establishing the relative stereochemistry obtained in the metathesis studies, we chose to synthesize an indolizidine alkaloid with described spectroscopic data. Indolizidine 223J exhibits a fully saturated structure, bearing a butyl and a propyl rest at C-5 and C-8 respectively. To build-up such a structure, we reasoned that by conducting the enyne *d*RRM under an atmosphere of 2-butene instead of ethylene it would be possible to introduce the methyl fragments at the desired positions and establish the second stereocenter of the target molecule. Subsequent hydrogenation of the formed triene would finally lead to the desired compound with all three stereogenic centers (Scheme 38).



Scheme 38. Envisaged retrosynthetic analysis for indolizidine 223J.

2.6.1.2 Proof-of-Principle Experiments

Metathesis reactions were successfully achieved with both substrates **27** and **31**, leading to the desired compounds with 100% conversion and with a *dr* of 7:6 and 1:2 respectively (Scheme 39). Although the same tendency was observed as with ethylene, the influence of the cross partner in the enyne *d*RRM was shown to be significant, leading to a decrease of selectivity, due to the increased steric bulk of the propagating species. Surprisingly, in this case ruthenium-complexes **GI** and **GII** were unable to successfully perform the *d*RRM with **31** and **27**·*p*TSA, while the isopropoxystirene analogue **HII** gave complete conversion in both cases.



Scheme 39. Enyne *d*RRM with **27**·*p*TSA ammonium salt and alkyne **31** in a 2-butene atmosphere.

Both chromatographic separable diastereoisomers obtained with alkynes **27**·*p*TSA and **31** were analyzed by 1D-NOE spectroscopy (Figure 10), finding for one of the amine isomers 2% NOE enhancement between the protons at C-5 and C-9, which is indicative of a *cis* arrangement. The desired *cis* diastereoisomer was found to be the one favored with **27**, whereby amide **31** led to the favored formation of the *trans* isomers. The sterochemical information in **69**/**70** was determined analogously to **67**/**68** by considering the relative chemical shifts of the hydrogen atom at C-5.(*)

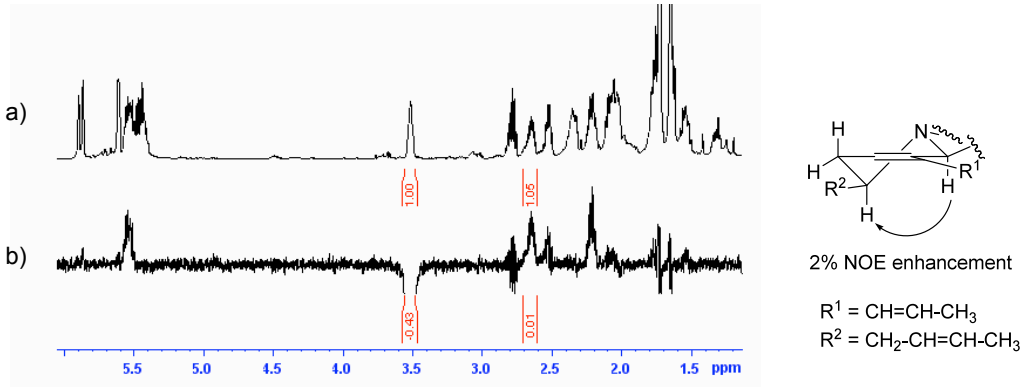


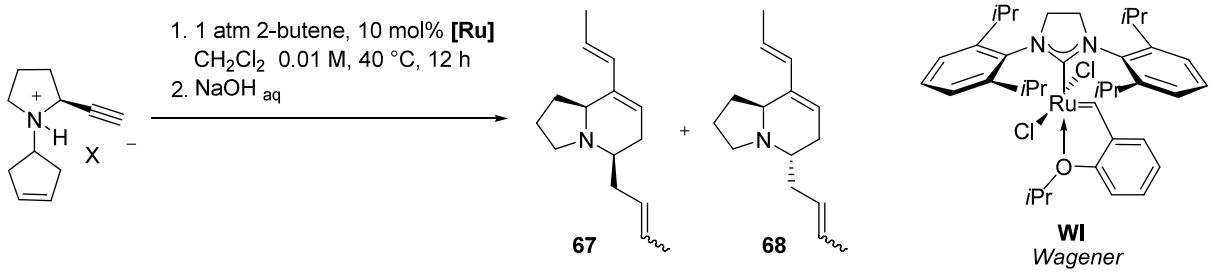
Figure 10. a) ^{1}H-NMR spectra from *cis* diastereoisomer; b) 1D-NOE measurement. The obtained NOE enhancement that indicates a *cis* arrangement is marked with an arrow.

(*) For further analytic data see Section 5.2.2.

2.6.1.3 Counterion and Catalyst Screening

Having proved the viability of performing the enyne *d*RRM with 2-butene as cross-partner, amine **27** was chosen as substrate for the total synthesis of indolizidine 223J, since only one more hydrogenation step after the metathesis reaction would lead to the target natural product. With the aim of increasing the selectivity in the *d*RRM reaction, metathesis reactions were performed with different ammonium salts and ruthenium catalysts (Table 16). Except for substrates **27**·HCl and **27**·HPF_6 (entries 2 and 3), the same tendency in diastereoisomeric ratio was obtained as with ethylene, although with significantly less selectivity. The results with **27**·TFA ammonium salt were on the contrary excellent, leading to a mixture 5:1 towards the desired *cis* isomer (entry 6).

Table 16. Substrate and catalyst screening in enyne *d*RRM experiments with ammonium salts of **27** and 2-butene as cross-partner.



Entry	Substrate	*HII cis/trans* [a]	*WI cis/trans* [a]
1	**27**·TfOH	5:7	-
2	**27**·HCl	6:7	-
3	**27**·HPF_6	6:7	3:2
4	**27**·TsOH	7:6	-
5	**27**·HBF_4	7:6	-
6	**27**·TFA	5:1	> 20:1

[a] *dr* determined by ^{1}H-NMR spectroscopic analysis. All reactions proceeded with 100% conv.

Since the catalyst **FII** had furnished increased selectivities with the use of ethylene, we expected also in this case to obtain improved results. Catalyst **FII**, however, in analogy to **GII** afforded 0% conversion. Pre-catalyst **WI** was therefore synthesized following the protocol from Wagener,[120] and was tested with the TFA and HPF_6 ammonium salts of **27** (entries 3 and 6). Employing 2-butene as cross-partner exclusive formation of the *cis*-isomer was obtained with **27**·TFA, while **27**·HPF_6 led to an improved but lower *dr* towards the desired compound. As it can be observed in Figure 11, with TfOH and TFA also better chemoselectivities were obtained, and the formation of the by-product **71** was suppressed (characteristic signals at 6.20 ppm).

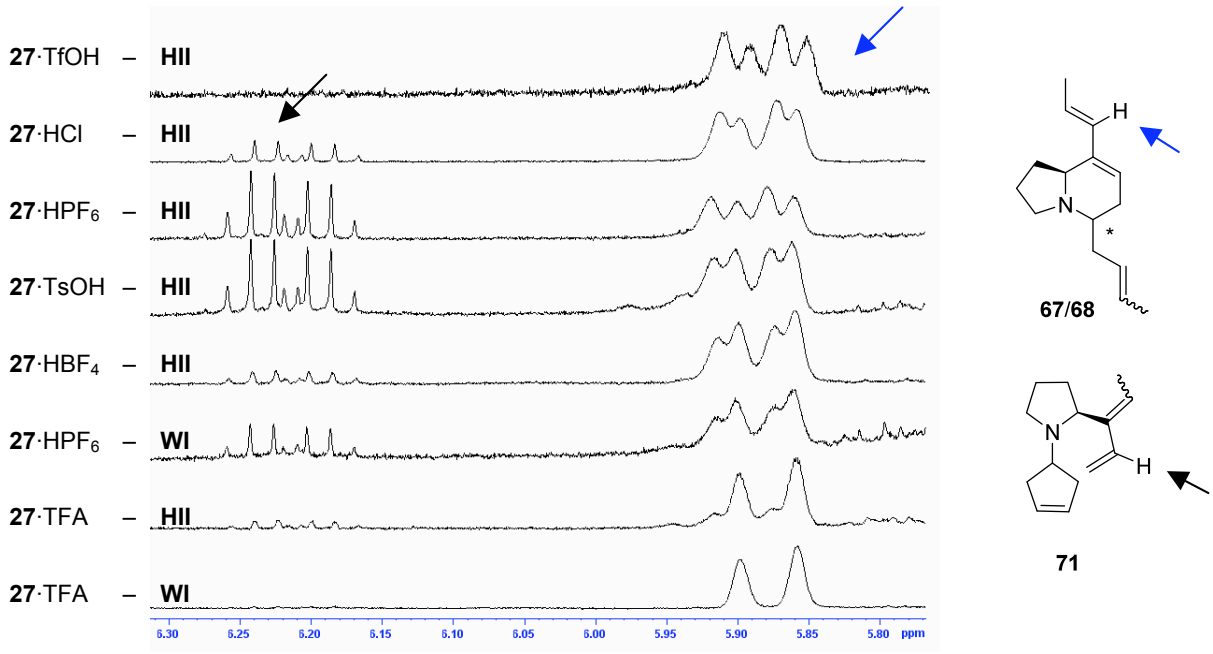


Figure 11. Fragment from ^{1}H-NMR spectra of the crude metathesis reaction with **27**. The blue arrow indicates the proton signals used to calculate the *dr* and the black arrow the characteristic signals corresponding to the by-product **71**.

2.6.1.4 Hydrogenation Experiments

To unequivocally assign the stereochemistry of the obtained isomers, hydrogenation experiments were conducted with both diastereoisomers (Figure 12).

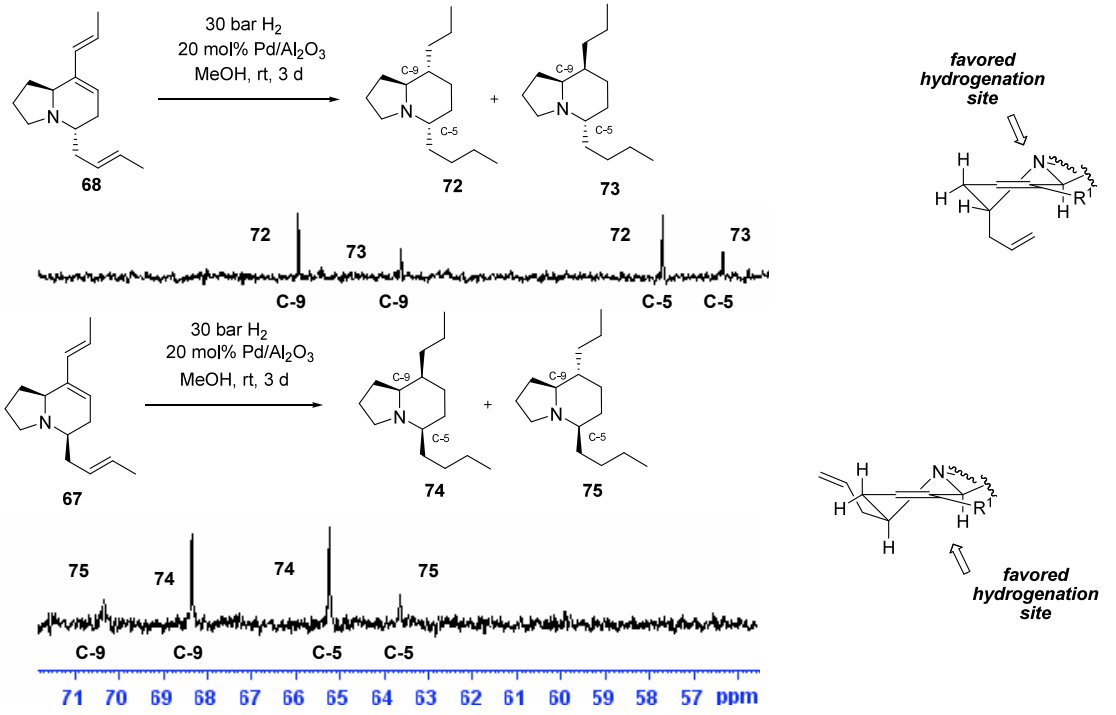


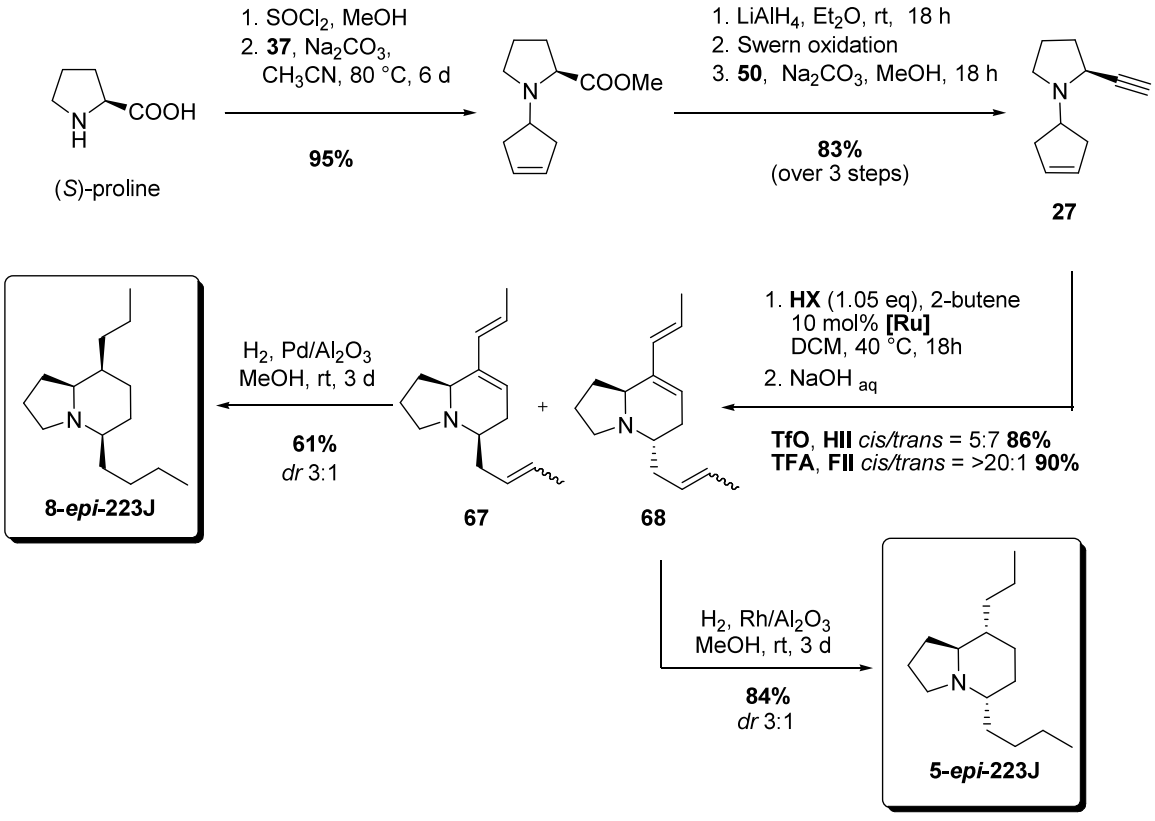
Figure 12. Hydrogenation experiments with trienes **67** and **68** and fragments of the ^{13}C-NMR spectra corresponding to C-5 and C-9.

For both substrates, hydrogenation over Pd/Al_2O_3 delivered a diastereoisomeric mixture. As expected, compound **67** led to both indolozidine 223J and its C-8 epimer, confirming the hypothesis extracted from the NOE experiments. Since the obtained compounds were not detectable by GC-MS and HPLC and the ^{1}H-NMR presented series of overlapping signals, it was not possible to quantify the obtained *dr*. Nevertheless, from the ^{13}C-NMR spectra it can be estimated a *dr* of approx. 3:1 for both compounds (**72**:**73** and **74**:**75**).

With the purpose of controlling the stereochemistry in the hydrogenation step, experiments with different homogeneous catalysts were performed with **59**/**60** and **64**/**65** as model substrates. Unfortunately, with the commonly used Wilkinsons's and Crabtree's catalyst, in all synthetic attempts with conditions including H_2 pressures from 5 to 30 bar, and temperatures between room temperature and 60 °C, the complete hydrogenation of the starting material failed.

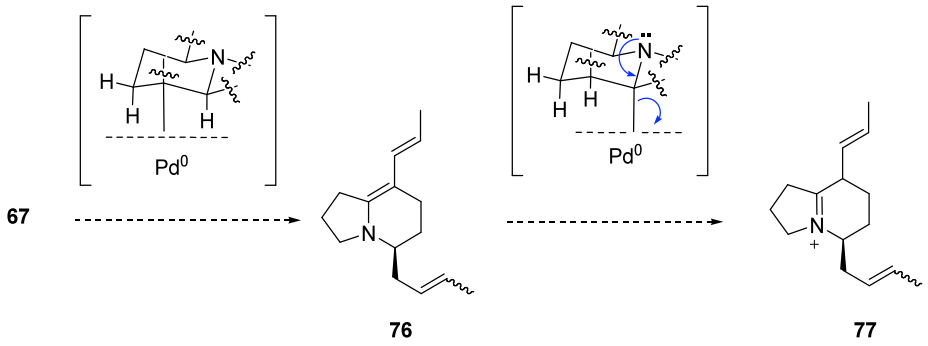
2.6.1.5 Final Steps

The total synthesis of 5-*epi*-223J and 8-*epi*-223J was completed within six steps from proline methyl ester hydrochloride in an overall yield of 40% and 43% respectively (Scheme 40). These results constitute a significant improvement in terms of synthetic efficiency, compared to the previous 15 steps synthesis and 35% overall yield obtained by Rassat and co-workers in the indolizidine 223J previous synthesis.[121]



Scheme 40. Total synthesis of indolizidines 5-*epi*-223J and 8-*epi*-223J by enyne *d*RRM.

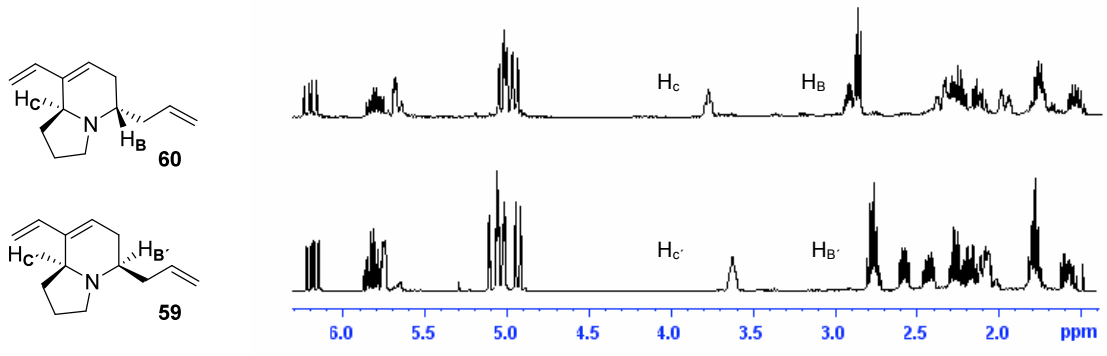
The rearranged product **68** was initially hydrogenated over Rh/Al_2O_3 and purified on silica gel chromatography affording **72** and **73** as a separable mixture of diastereoisomers in 84% yield. Since such hydrogenation reactions proceed normally with complete conversion, in order to increase the amount of product recovered, isomer **67** was hydrogenated on the milder Pd/Al_2O_3 and purified rapidly on Al_2O_3 to avoid possible decomposition. Despite all precautions, the crude mixture containing **71** was isolated in the moderate yield of 61%. Due to the reversibility of the hydrogenation reaction, the intermediate **76** can possibly form the iminium compound **77**, unstable under the used reaction conditions, and responsible for the decrease in isolated **74**. This side reaction may be favored on diastereoisomer **67**, possibly because of steric reasons (Scheme 41).



Scheme 41. Possible decomposition mechanism responsible for the low isolated yield of **74**.

2.6.2 Assignment of the Relative Configuration of the Metathesis Products

In view of the presented spectroscopic data obtained with **67** and **68** it was possible to unequivocally assign the relative configuration of the sterocenters in **59**/**60** and **64**/**65**. In the *trans* isomer **60** the proton attached at C-5 resonates at lower field than the one in the *cis* isomer, whereby in the amide analogue **65** this difference is even more remarkable due to the shielding effect of the carbonyl group. By correlating the chemical shift of the protons attached to C-5 (H_B and $H_{B'}$ in Figure 13), was possible to establish that with amine **27**, the desired *cis*-isomer was favored using the corresponding TFA and HPF_6 ammonium salts as a substrates, whereas alkyne **31** favored the formation of the *trans* isomer with catalyst **GI**, and the *cis* with the NHC-based complexes **BVIII** and **GIV** (Table 17).



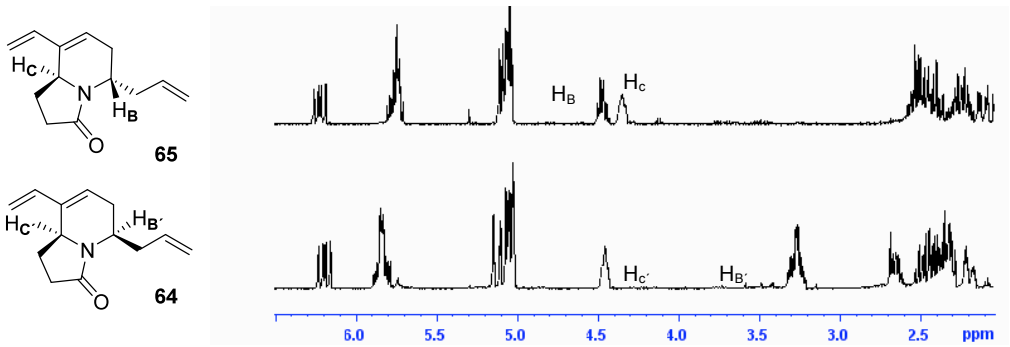


Figure 13. [1]H-NMR of the isolated diastereoisomers and proton signals used for the *cis*/*trans* structural assignment.

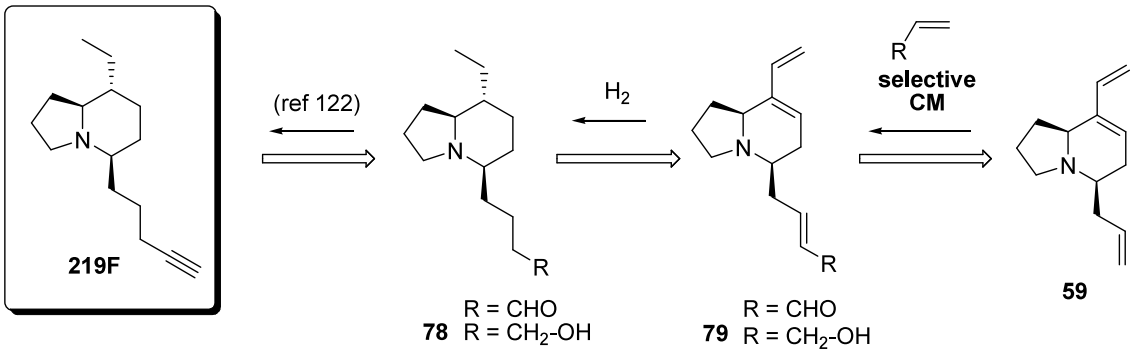
Table 17. Representative results presented in Tables **7** and **9** with the established diastereochemistry.

Entry	Substrate	Catalyst	*cis:trans*	Entry	Substrate	Catalyst	*cis:trans*
1	**27**·HPF_6	**FII**	> 20:1	6		**GI**	1:10
2	**27**·HBF_4		10:1	7		**GIV**	1:2
3	**27**·HCl		6:1	8	**31**	**BIII**	1:1
4	**27**·MsOH	**HII**	2:1	9		**GIV**	3:1
5	**27**·TfOH		1:3	10		**BVIII**	4:1

2.6.3 Formal Synthesis of Indolizidine 5-*epi*-209F

2.6.3.1 Retrosynthetic Analysis

After the successful application of enyne *d*RRM in the short synthesis of indolizidines 5-*epi*-223J and 8-*epi*-223J, we next aimed to study the versatility of the methodology for the synthesis of other alkaloid derivates.

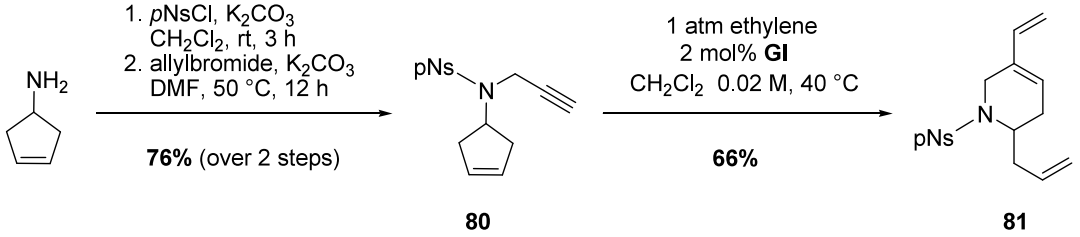


Scheme 42. Proposed retrosynthetic analysis for indolizidine 219F.

We envisaged that indolizidine 219F could be approached from triene **59** by selective CM with a suitable olefin, followed by hydrogenation, leading to intermediate **78** which has been previously used as precursor for the synthesis of this natural product (Scheme 42).[122]

2.6.3.2 Proof-of-Principle Experiments

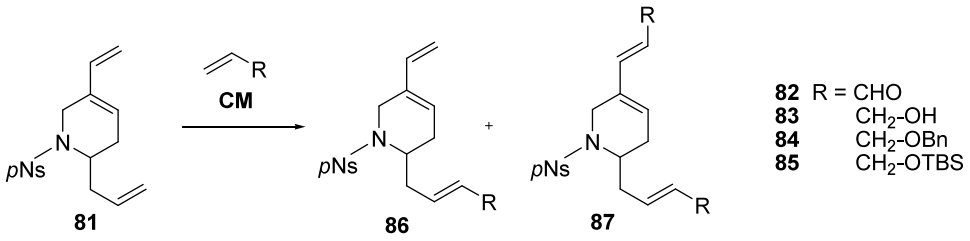
In order to study the viability of performing the CM reaction selectively at the non-conjugated terminal double bound, triene **81** was used as a model substrate for the metathesis experiments (Scheme 43). Compound **81** is readily available from **80** in few transformations and possesses the key structural elements required for the synthesis of **79**.



Scheme 43. Synthesis of substrate **81** for the investigation of selective CM at the terminal non-conjugated olefin.

CM experiments were performed with four different alkenes: acrolein (**82**), allyl alcohol (**83**) and the corresponding Bn (**84**) and TBS protected analogues (**85**) (Table 18). CM experiments began using olefine **82** as cross-partner. Reactions with acrolein were conducted with catalyst **HII**, since it has proven to furnish the best results when electron poor alkenes are used.[123] First experiments indicated the favoured formation of compound **87**,

Table 18. Summarized results from CM experiments with **81**.



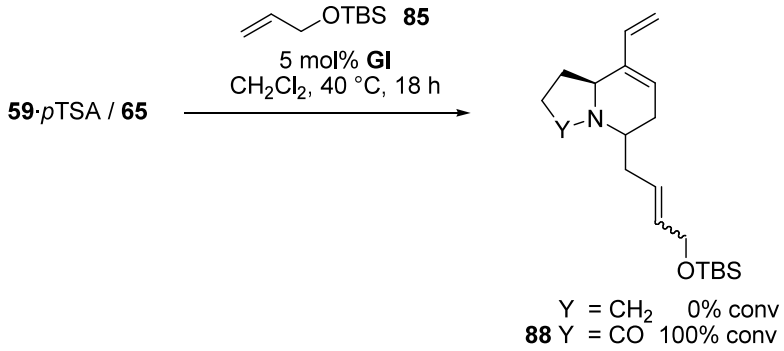
Entry	Cross-partner	Catalyst	Solvent	T	Time	Ratio 81:86:87 [a]
1	2 eq **82**	5 mol% **HII**	CH_2Cl_2	40 °C	3 h	0:0:1
2	1 eq **82**		CH_2Cl_2	rt	6 h	2:1:1
3			CH_2Cl_2	rt	18 h	1:0:1
4			CH_2Cl_2	0 °C to rt	18 h	1:0:0
5	10 eq **83**	5 mol% **HII**	CH_2Cl_2	40 °C	18 h	1:0:0
6		5 mol% **GI**	CH_2Cl_2	40 °C	18 h	1:0:0
7	3 eq **84**	5 mol% **HII**	CH_2Cl_2	40 °C	18 h	1:0:0
8		5 mol% **GI**	CH_2Cl_2	40 °C	18 h	1:0:0
9	2 eq **85**	5 mol% **HII**	CH_2Cl_2	40 °C	18 h	complex mixture [b]
10		5 mol% **GI**	CH_2Cl_2	40 °C	18 h	1:1:0

[a] Determined by ^{1}H-NMR spectroscopic analysis. Reaction conditions: 5 mol% catalyst, 0.06 M **81** in CH_2Cl_2. [a] A complex mixture containing oligomerized compounds, products **86** and **87** and starting material was isolated.

result from CM at both external olefins (entry 1). By decreasing the number of equivalents of cross-partner and the reaction temperature, a mixture of products was obtained (entry 2), while all further attempts to perform the metathesis selectively failed (entries 3-4), even with the use of catalysts **GI** or **GII**. When allyl alcohol, or the corresponding benzyl protected derivate, were employed only starting material was recovered (entries 5-8). On the other hand, alkene **85** led to 50% conversion towards the desired product with 5 mol% catalyst **GI**, in non-optimized conditions, indicating that alkene **85** was a suitable substrate to approach the synthesis of the synthetic intermediate **79** (entry 10).

2.6.3.3 CM Optimization

Under the same reaction conditions substrates **59** and **65** were subjected to CM with **85**. For the corresponding *p*TSA ammonium salt of the amine **59** no formation of the target compound was detected and only starting material was recovered. CM with the amide **65**, however, delivered 100% conversion to a crude mixture containing mostly compound **88**, along with oligomerized material (Scheme 44).



Scheme 44. CM experiments with cross-partner **85** and trienes **59** and **65**.

Since the CM reaction with substrate **59** towards the desired 209F could not be achieved, the synthetic studies were then continued with the analogue **65** to obtain 5-*epi*-209F. In order to increase the chemoselectivity and the obtained yield, different commercially available Ru-complexes were screened. Because of its improved reactivity and stability, second generation catalyst furnished a mixture of compounds containing mainly oligomerized products from **65**. First generation catalysts led to better results under the same conditions, although dimerization of **65** was still detected. The decrease of the reaction temperature to rt, resulted in almost 0% conversion to the desired product and CM at 60 and 80 °C led to an increased amount of oligomeric by-products. At 40 °C in CH_2Cl_2, catalysts **GI**, **FI** and **HI** gave the same results according to analysis of the crude reaction by GC-MS and ^{1}H-NMR. Under this conditions and 5 mol% catalyst **GI** the desired product was isolated in 38% yield (entry 1,

Table 19). Reaction optimization studies were further performed with **GI**, since commercially available pre-catalyst **FI** led to lower formation of product **88** (entry 2). By increasing the amount of catalyst and the equivalents of alkene **85**, an improved yield of 65% was obtained, which was increased to 85% by adding the catalyst in two portions of 5 mol% each.

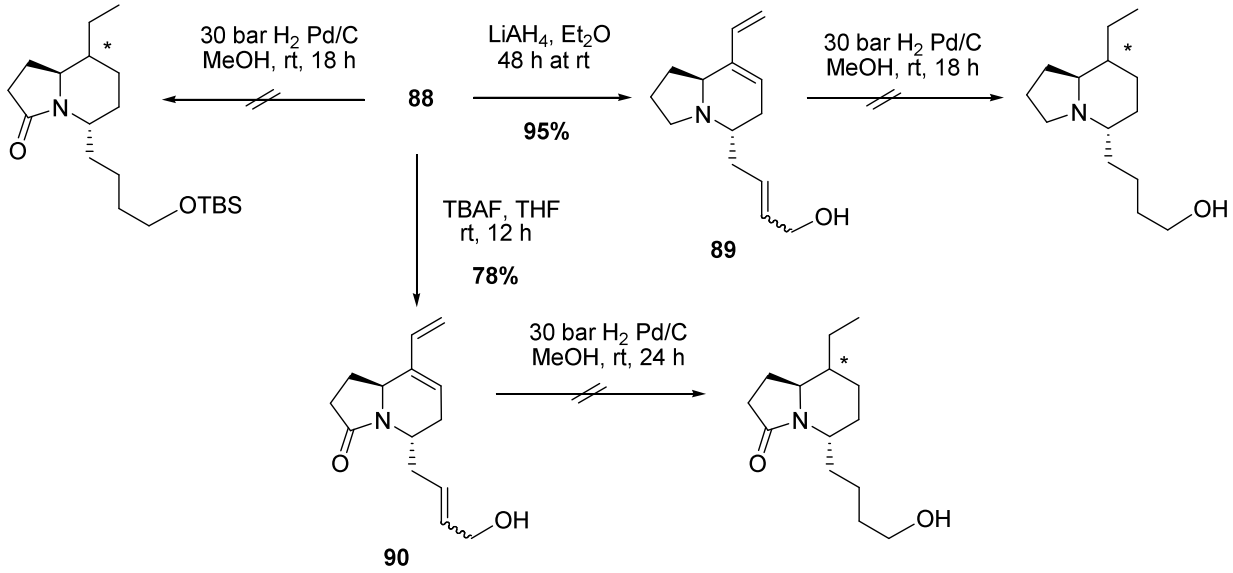
Table 19. CM optimization studies with **65** and **85**.

Entry	Eq 85	Catalyst [b]	Yield [b]
1	2	5 mol% **GI**	38%
2	2	9 mol% **FI**	34%
3	4	10 mol% **GI**	65%
4	4	10 mol% **GI** [c]	85%

[a] Reaction conditions: Catalyst, 0.06 M **65** in CH_2Cl_2, 40 °C, 18 h. [b] Isolated after chromatographic purification on SiO_2. [c] Added in two portions.

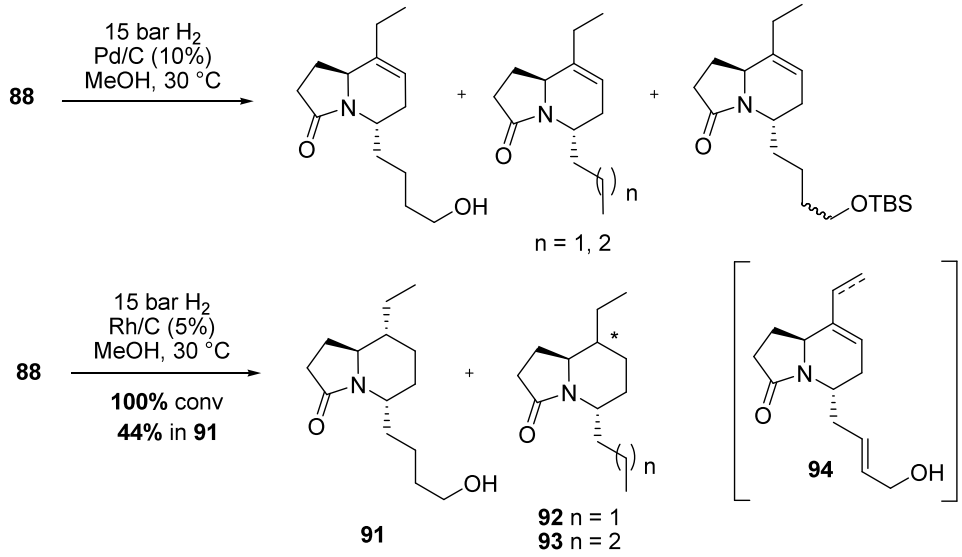
2.6.3.4 Hydrogenation experiments

With intermediate **88** in our hands, the hydrogenation step was next investigated. We envisaged that different results in terms of reactivity and selectivity could be obtained starting from the amine analogue **89**, and from both, the TBS protected alcohol **88** and the deprotected **90** (Scheme 45). Reduction of **88** with $LiAlH_4$ led to **89** in very good yield, and deprotection with TBAF afforded the desired alcohol **90**. When all these substrates were subjected to hydrogenolitic conditions, a complex product mixture was obtained and the target compounds where only detected in the crude material in very low amount.



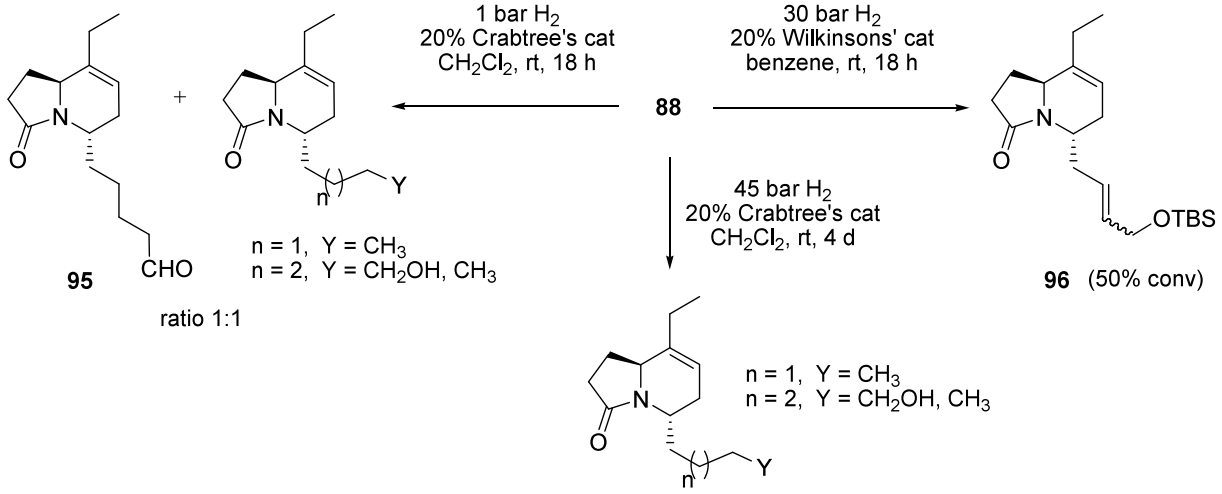
Scheme 45. Hydrogenation experiments with triene **88** and derivatives.

With the intention of controlling the reaction and finding out the origin of the instability of **88**, or the corresponding products, the same experiment with **88**was performed with the H-Cube Tutor ™ hydrogenation equipment. Reaction of a 0.03 M solution of **88** in MeOH at 30 °C with 15 bar hydrogen pressure, over 10% Pd/C and 1ml/min flow, resulted in complete conversion to a mixture of partially hydrogenated compounds (Scheme 46). Catalyst Rh/C was required to hydrogenate the tri-substitued double bound and under these conditions **91** was isolated in 44% yield. MS and NMR spectroscopic analysis showed that the main by-product formed resulted from the dehydroxylation and isomerization-deformylation of **94** and subsequent reduction of the formed alkenes (compounds **92** and **93** respectively).[124]



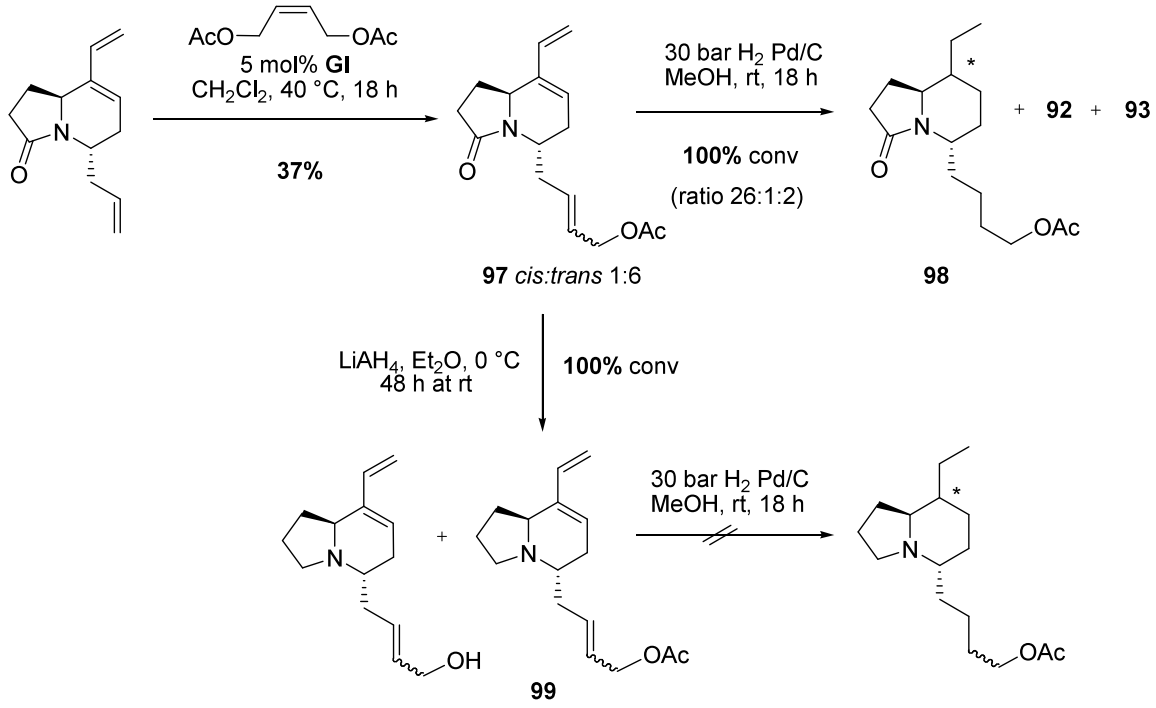
Scheme 46. Hydrogenation experiment with triene **88** performed with the H-Cube Tutor™ hydrogenation device.

Since all attempts to improve the obtained result by changing the reaction conditions or the used catalyst under heterogenic conditions failed, hydrogenation with homogeneous catalyst was next investigated (Scheme 47). Reaction of **88** with the Wilkinsons' catalyst afforded



Scheme 47. Hydrogenation experiment with triene **88** under homogeneous catalysis.

only the partially hydrogenated compound **96**. The Crabtree's complex showed improved reactivity but, like in heterogeneous conditions, poor selectivity. After 18 h under 30 bar H_2 at rt a mixture of partially hydrogenated compounds was obtained, whereby aldehyde **95** was detected for the first time, in a 1:1 mixture approximately. Iridium-hydrogenation catalysts are known to easily undergo isomerization of silyloxy allyl compounds,[125] and we speculated if this side-reaction could be of benefit and save a step towards the synthesis of 5-*epi*-209F. Unfortunately, further reaction resulted in decomposition of the aldehyde **95**, and no hydrogenation of the sterically hindered tri-substituted double bond.



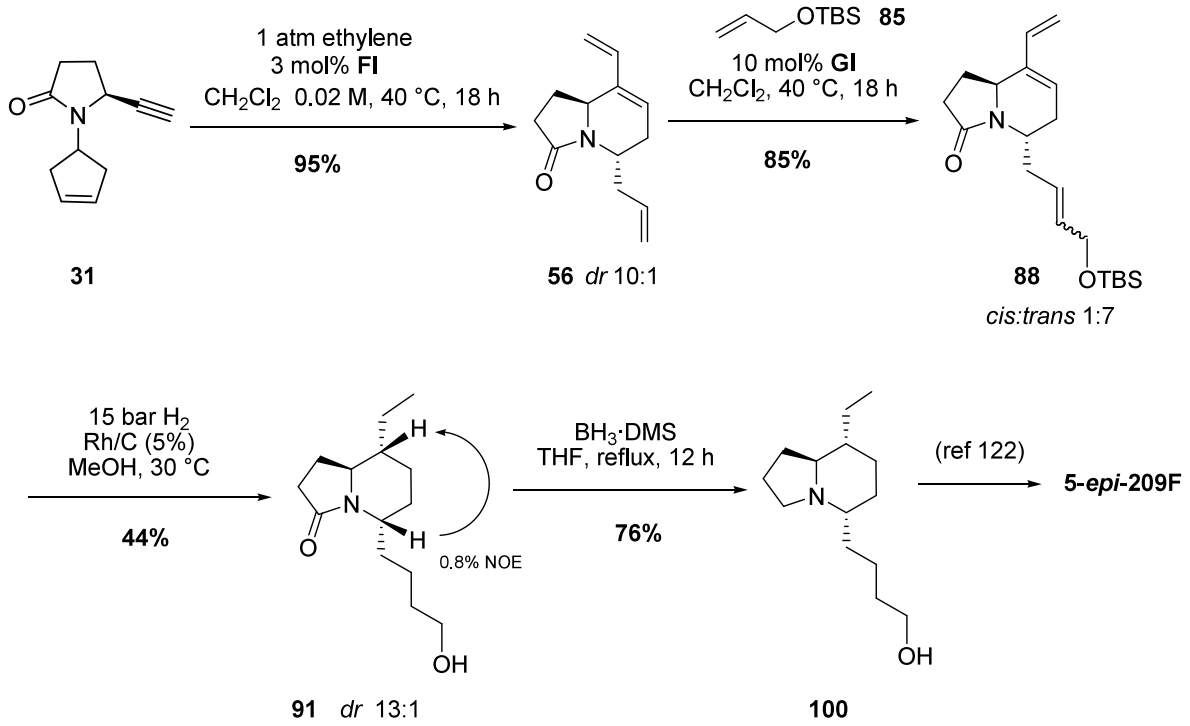
Scheme 48. Hydrogenation experiments with **97** and **99**.

With the aim of preventing alcohol deprotection and subsequent decomposition, we pondered if compound **97** would be more stable under hydrogenolitic conditions. **97** was afforded by CM with a non-optimized yield of 37% (Scheme 48) and the performed hydrogenation showed indeed improved results. Compound **98** was obtained as a crude mixture containing small amounts of **92** and **93**, according to MS-analysis. The reaction yield however could not be detrmined, since the hydrogenated product **98** showed instability when purified on SiO_2. On the other hand, the corresponding amine derivate **99**, gave the same results as the previous substrates, and failed to give the desired hydrogenated product.

2.6.3.5 Final Steps

The formal synthesis of indolizidine 5-*epi*-209F was finalized within four steps from amide **31** after reduction of the amide functionality in alcohol **91** by treatment with BH_3·DMS in THF

(Scheme 49). The reaction delivered the target compound **100** in 76% yield as diastereoisomeric mixture, which could not be successfully separated by column chromatography with SiO_2, Al_2O_3 or C_{18}-SiO_2.

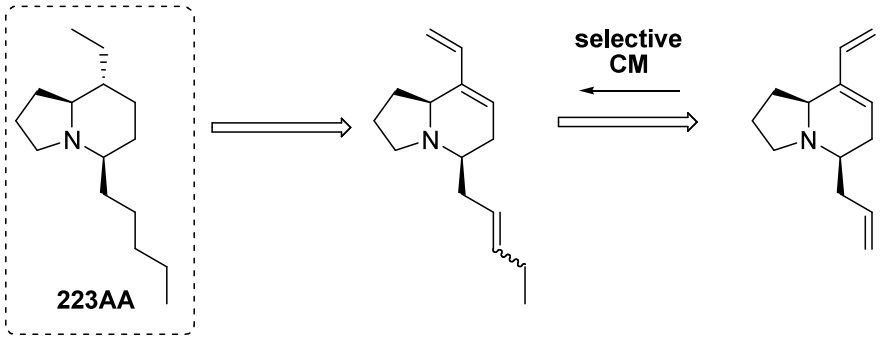


Scheme 49. Formal synthesis of indolizidine 5-*epi*-209F.

2.6.4 Synthesis of indolizidine 5-*epi*-223AA

2.6.4.1 Retrosynthetic Analysis

Following the same strategy as for indolizidine 209F, we reasoned that the synthesis of indolizidine 223AA could be approached by selective CM with 3-hexene (Scheme 50).

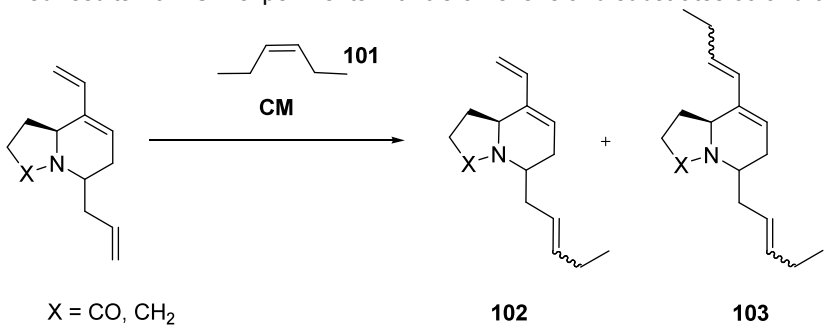


Scheme 50. Proposed retrosynthetic analysis for indolizidine 223AA.

2.6.4.2 Proof-of-Principle Experiments

In analogy to the results outlined before in Table 18, metathesis experiments were performed with amine **59**, and amide **65** with *cis*-3-hexene (**101**). First attempts with substrate **65** and catalyst **GII** resulted in complete formation of the double CM-product **103** (entries 1 and 2, Table 20), whereby under the same reaction conditions, the first generation Ru-complex **GI** led to the desired product **102** with 75% conversion (entry 3). Optimal reaction conditions were found with catalyst **GII** by decreasing the reaction temperature to rt (entry 4). When the same reaction conditions were applied to the amine counterpart **65**, complete reisolation of the starting material was obtained (entry 5). Increasing the temperature to 40 °C resulted in formation of the undesired product **103** (entry 6), while the employment of pre-catalyst **GI**, again, led to complete recovery of the starting material (entry 7).

Table 20. Summarized results from CM experiments with *cis*-3-hexene and substrates **59** and **65**.



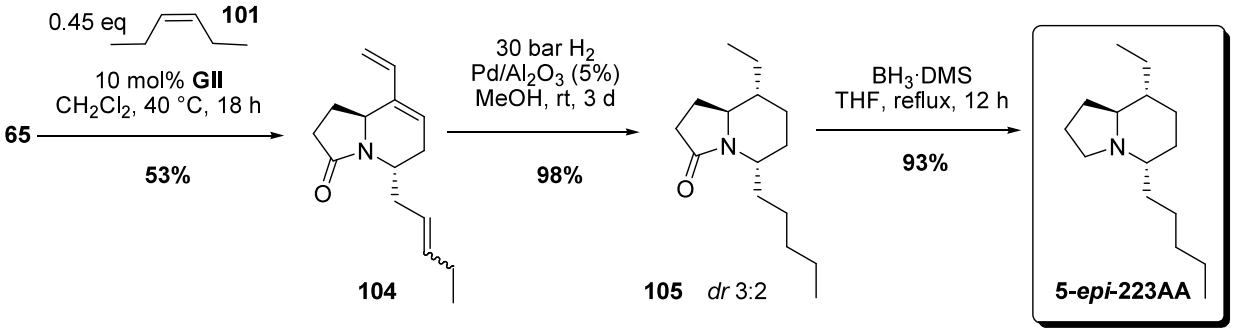
Entry	Substrate	eq 101	Catalyst	Solvent	T	Ratio Substrate:102:103 [a]
1	Amide **65**	1	4 mol% **GII**	CH_2Cl_2	40 °C	0:0:1
2		0.5	4 mol% **GII**	CH_2Cl_2	40 °C	0:0:1
3		0.5	6 mol% **GI**	CH_2Cl_2	40 °C	1:3:0
4		0.5	4 mol% **GII**	CH_2Cl_2	rt	0:1:0
5	Amine **59**	0.6	5 mol% **GII**	CH_2Cl_2	rt	1:0:0
6		0.6	5 mol% **GII**	CH_2Cl_2	40 °C	0:0:1
7		0.5	5 mol% **GI**	CH_2Cl_2	40 °C	1:0:0

[a] Determined by ^{1}H-NMR spectroscopic analysis. Reaction conditions: 0.05 M of substrate in CH_2Cl_2, 12 h, for amine derivative **59** with 1.05 eq *p*TSA.

2.6.4.3 Final Steps

Since only the amide derivative **65** served as suitable substrate for the desired CM with *cis*-3-hexene, the synthesis of the C-5 epimer of 223AA was thus approached. The final steps of the synthesis of this indolizidine alkaloid are outlined in Scheme 51. When the CM reaction was scaled-up reproducibility problems appeared and quenching of the reaction mixture with

ethyl vinyl ether was necessary to avoid further reaction to the undesired **103**. Optimal reaction conditions where found with 0.45 eq of cross-partener **101** which led to 80% conversion and 53% yield of isolated product **104** after chromatographic purification on SiO_2. The low obtained yield may be attributed to certain instability under the used chromatographic conditions, since the analysis of the crude material did not indicate the presence of other by-products. Hydrogenation of **104**, led to a mixture of diastereoisomers (3:2) which could not be separated by column chromatography. Remarkably, the substitution pattern in **104**, in comparison with **88**, resulted in lower selectivity due to decreased steric bulk at C-5. Further reduction of the hydrogenated amide **105** with BH_3·DMS delivered the target compound in 93% yield as diastereoisomeric mixture, that could not be separated on Al_2O_3 or C_{18}-SiO_2, and decomposed on SiO_2.

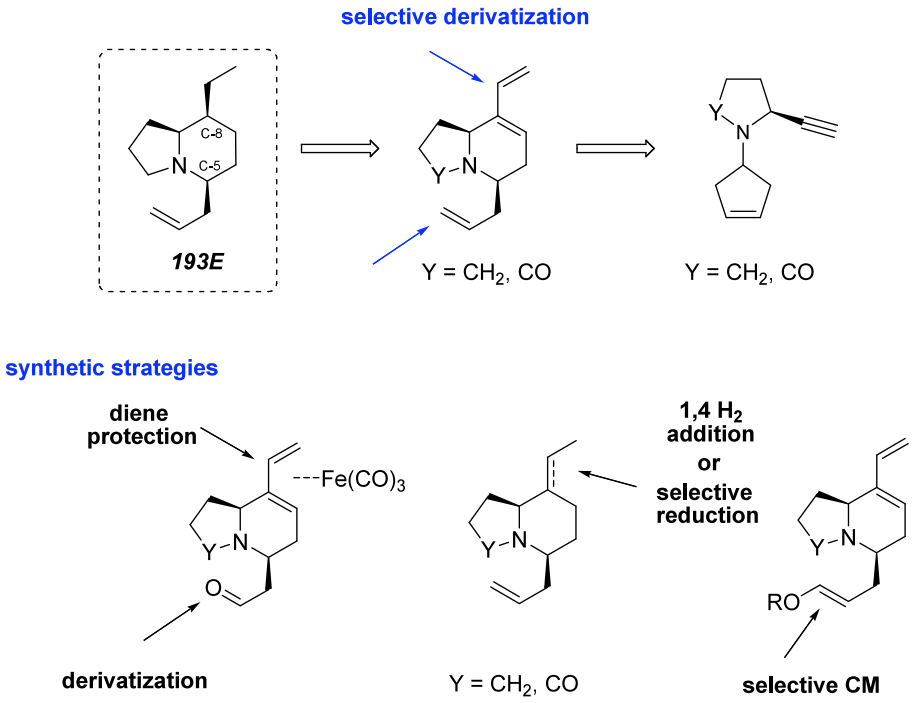


Scheme 51. Synthesis of indolizidine 5-*epi*-223AA by a selective enyne *d*RRM-CM sequence.

2.6.5 Synthetic Studies Towards Indolizidine 193J

2.6.5.1 Retrosynthetic Analysis

In the presented synthetic approaches towards indolizidine alkaloids, it was not possible to conduct the hydrogenation of the diene moiety with complete diastereoselectivity, given that the homogeneous catalysts employed were unable to fully hydrogenate the substrate, and heterogeneous catalysts failed to provide complete diasterodiscrimination. In this regard, we became interested in indolizidine 193E, because, due to its 9,8-*cis* arrangement, we speculated that complete diastereoselctivity towards the desired 5,8-*cis* conformation could be achieved in the hydrogenation step. Indeed, this natural product has not been synthesized yet since all synthetic approaches published towards 5,8-disubstituted indolizidines afford a 5,8-*trans* structure.[39] Furthermore, the *d*RRM step delivers already the structural frame of the synthetic target, and reduction of the diene moiety leads to the natural product 193E. Chemo- and stereoselective transformations are thus required in order to differentiate between the electron rich 1,3-conjugated diene and the terminal olefin (Scheme 52).



Scheme 52. General retrosynthetic analysis for indolizidine 193J and initial proposed synthetic strategies.

Different strategies came into consideration. The first one included the protection of the diene moiety as an iron carbonyl complex, which would allow performing reactions selectively on the terminal double bond. Oxidation to the corresponding aldehyde by ozonolysis or by diol oxidative cleavage would permit the selective hydrogenation of the diene unit, while the terminal alkene could be next reconstructed by a Wittig reaction.

On the other hand, due to the conjugated character of 1,3-dienes, selective 1,4 addition of H_2 by a chrom-catalyzed hydrogenation can be performed leading to a non-conjugated dienic substrate with much more structurally differentiated exocyclic olefins.[126] Selective hydrogenation[127] or oxidation might be then more easily achieved, and indolizidine 193E could be accessible in few synthetic steps.

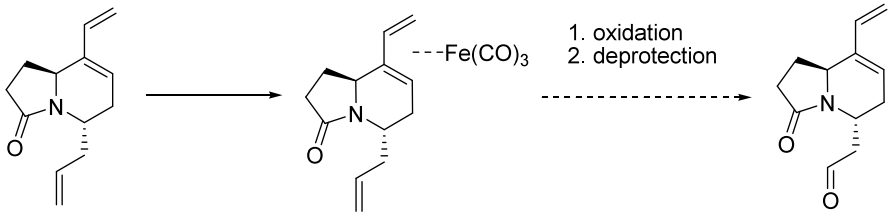
The third possible strategy to investigate would be based on a CM reaction that, as outlined in the previous syntheses of indolizidine alkaloids, is a useful methodology to selectively derivatize the non-conjugated olefin. The introduction of oxigenated functionalities by CM could allow the construction of the target molecule after hydrogenation followed by an elimination reaction.

2.6.5.2 Protection of the Diene Moiety as an Ironcarbonyl Complex

Formation of ironcarbonyl complexes is a well known methodology to protect 1,3-conjugated dienes.[128] The classical procedure for the preparation of tricarbonyliron-diene complexes is based on the complexation of dienes by direct reaction with the binary carbonyliron

compounds pentacarbonyliron, nonacarbonyldiiron, or dodecacarbonyltriiron using thermal conditions. Diene protection as iron complex is known to be sometimes problematic due to the harsh conditions required for the complexation. To prove the viability of this synthetic route amide **65** was chosen as substrate, since the amine analog might be incompatible with the use of this Lewis acid. Treatment with $Fe(CO)_5$ to generate a tricarbonyliron-diene complex usually requires about 140 °C. Treatment of **65** at this temperature failed to give the desired compound **106**, while no remaining starting material was detected in the reaction crude (entry 1, Table 21).

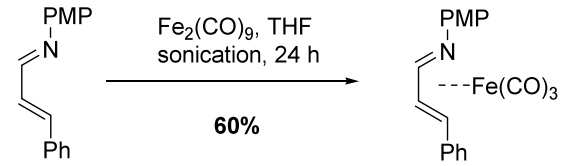
Table 21. Reaction conditions used on the complexation of amide **65** as carbonyliron compound.



65 **106**

Entry	Substrate	Conditions
1	Amide **65**	$Fe(CO)_5$, xylene, reflux, 12 h
2		$Fe_2(CO)_9$, 13 mol% **107**, DME, 85 °C, 12 h
3		1 eq **108**, THF, 65 °C, 12 h
4		3 eq **108**, THF, 65 °C, 12 h

Alternatively, complexation can be achieved under much milder reaction conditions by using tricarbonyliron transfer reagents such as **108** (Scheme 53). These reagents are complexes of tricarbonyliron with ligands which show only weak coordination to the metal. Because of the lability of these complexes, they readily generate 16-electron species which can then bind to one of the double bonds of a 1,3-diene. This coordination initiates the transfer of the metal fragment to the 1,3-diene, and therefore offer a useful alternative for the preparation of tricarbonyliron complexes of dienes which are sensitive towards heat. The imine condensation of cinnamaldehyde with $PMPNH_2$ provided the desired 1-azabuta-1,3-diene **107**, which led to formation of complex **108** as stable bright red crystals by ultrasound-promoted complexation with $Fe_2(CO)_9$.



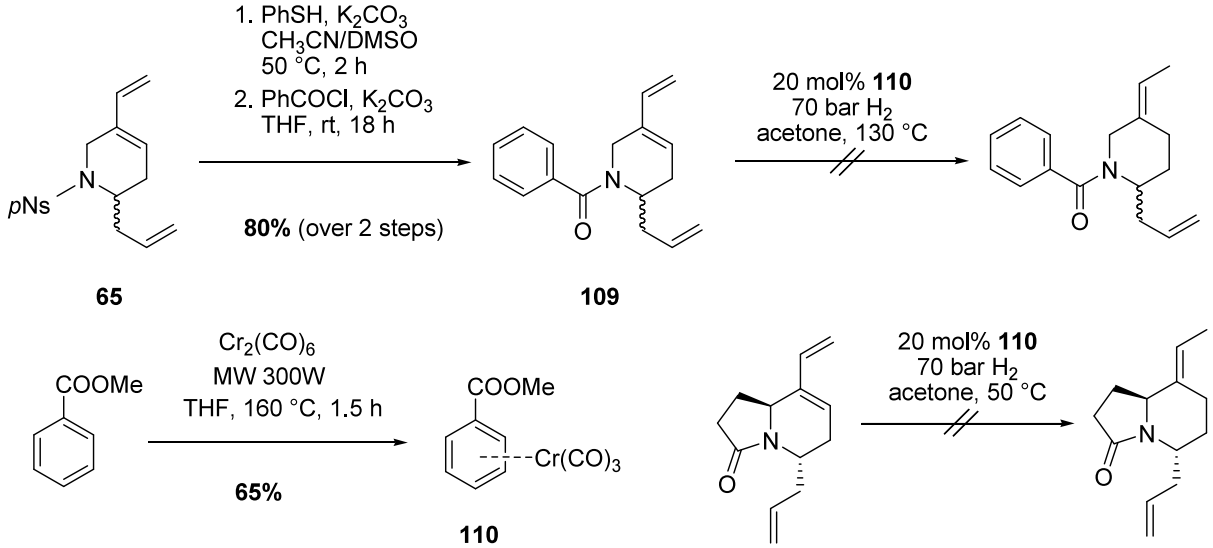
107 **108**

Scheme 53. Synthesis of transfer reagent **108**.

108 can be used in equimolar quantities or catalytically, by addition of small quantities of **107** and *in situ* generation of **108**. The azadiene-catalyzed complexation using $Fe_2(CO)_9$ proceeds best in DME at 85 °C,[129] but these conditions appeared to be still to harsh for triene **65** and decomposition of the starting material was found (entry 2). The complexation using the azadiene transfer reagent **108** in equimolar quantities is the mildest of the state-of-the-art procedures for the synthesis of trycarbonyliron diene complexes and proceeds best in THF at reflux.[130] Using this method, aprox. 50% conversion to the desired product was obtained as indicated by ESI-MS analysis (entry 3). Unfortunately both compounds **106** and the starting material **65**, presented the same R_f value and no separation of the mixture was possible.(*) The transfer reagent was thus provided in excess in order to shift the equilibrium, but under these conditions neither starting material nor **106** could be isolated from the reaction mixture (entry 4). The impracticable separation of **65** from the taget **106** reduced the prospects of using such synthetic strategy in the synthesis of indolizidine 193E and further alternatives were hence explored.

2.6.5.3 Attempts towards Selective Reduction of the Conjugated Diene

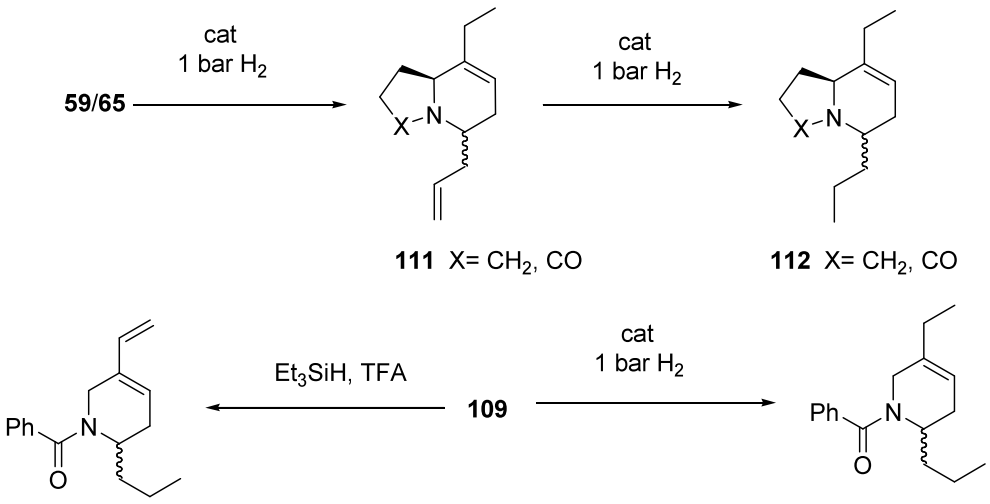
Conjugated dienes can be reduced selectively in front of other olefins by chrom-catalyzed 1,4-addition of H_2.[126] To prove if this methodology could be applied to for the preparation of 193E, a model substrate was first synthesized to gain insight into the reaction. Substrate **109** was prepared in two steps from **81**, to avoid interference of the *p*Ns group in the hydrogenation step (Scheme 54).[131]



Scheme 54. Synthesis of substrate **109** and reagent **110**, and synthetic attempts performed on the chrom-catalyzed 1,4-additon of H_2.

(*)According to Knölker, frequently protection of a diene as tricarbonyliron complex leads to no change of the polarity, compared with the free diene.

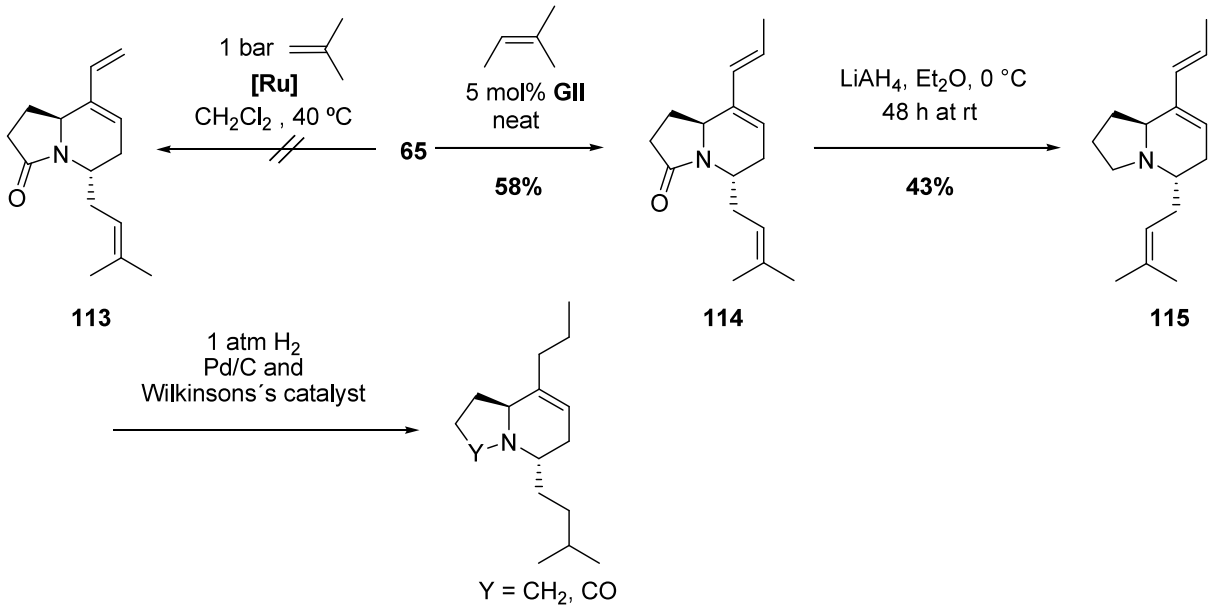
In analogy to the carbonyliron complexation, the formation of carbonylcrom-diene complexes requires high temperatures, and the subsequent hydrogenation elevated H_2 pressures. Under these conditions substrate **109** decomposed, while milder conditions resulted in the partial recovery of **109**. When the reaction was performed with the metathesis product **65**, complete conversion was achieved towards an oligomerized unstable compound which might result from LA-catalyzed intermolecular Diels-Alder reaction.With the aim of exploring if the electron rich character of the 1,3-diene or the reduction of the ring strain could favor selective reduction of the diene moiety, several hydrogenation procedures where next screened. Substrates **59**, **65** and **109**, were used as substrates and different catalysts, homogeneous and heterogeneous, were tested. (Scheme 55). In all cases, first, selective hydrogenation of the more electron rich dienic olefin took place (compound **111**) but further reaction, unfortunately, led in all attempts to the same product **112**. Ionic hydrogenation,[132] on the other hand, led to preferred reduction of the non-conjugated terminal alkene.



Scheme 55. Summarized results obtained in the selective hydrogenation of the trienes **59**, **65** and **109**.

According to the obtained results, we speculated if converting the isolated alkene in a trisubstituted olefin by CM (structures **113** and **114**), could lead to convenient differentiation between the tri-substituted almost equally sterically hindered olefins.

CM with isobutene and **65** failed to give the desired compound **113**, presumably due to the insufficient concentration of the cross-partner in solution. Metathesis in neat 2-methyl-2-butene, on the other hand, led to complete conversion, delivering **114** in a non-optimized yield of 58%. As shown in the parallel investigations towards indolizidine 209F, the cyclic endo-olefin is difficult to hydrogenate and for both compounds **114** and the amine derivate **115**, the same selectivity as for **65** was observed (Scheme 56).



Scheme 56. CM of compound **65** with isobutene and 2-methyl-2-butene and hydrogenation experiments performed with substrates **114** and its derivate **115**.

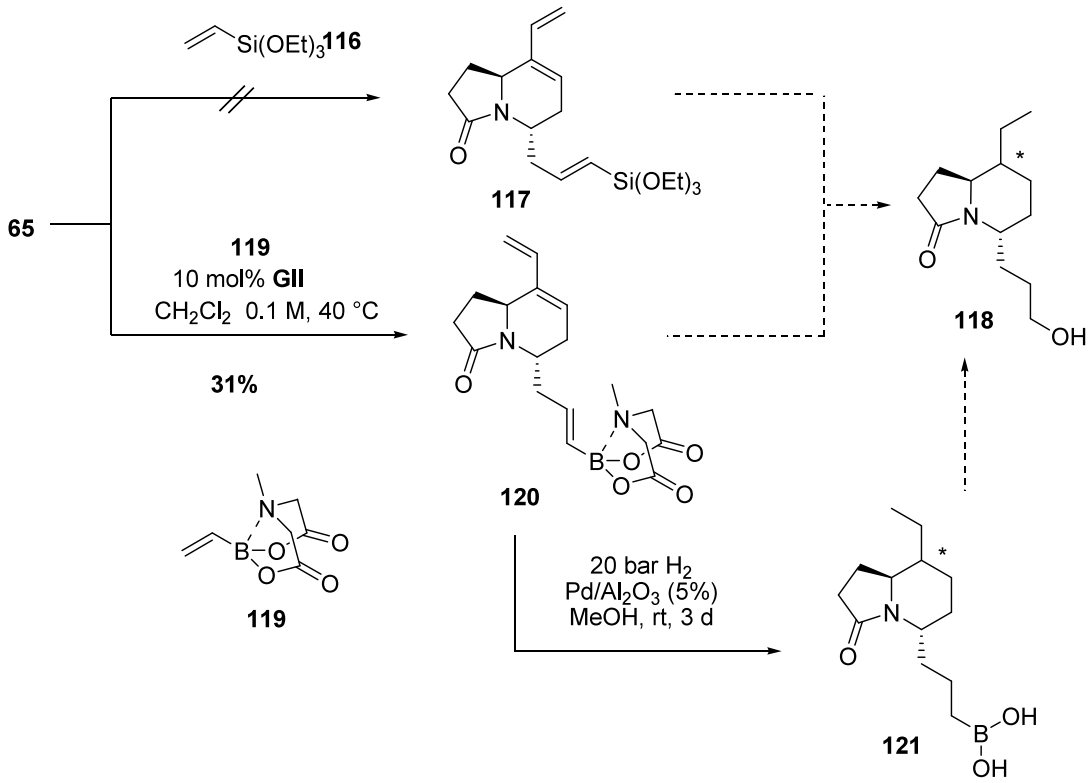
2.6.5.4 CM Srategy

Selective CM can be used to introduce functionalities that can help to re-build a double bond, once the product has been hydrogenated. For instance, double bonds can be generated, by elimination of an halogen atom[133] or dehydration of an alcohol functionality,[134] which retrosynthetically can be derived from a borane compound.[135]

Thus, we next investigated the viability of synthesizing alcohol **118** (Scheme 57), *via* CM with a convenient alkene. Vinyl derivatives **116** and **119** were chosen as promising cross-partners, since they have been used on metathesis reactions with very good yields.[136] Reaction following the protocol form Fischer and coworkers for the CM with vinylsilane **116** with **GI**,[136] resulted in no formation of the desired product **117**, and all attempts to improve the reaction with other catalysts such as **GII** and **HII** failed. On the other hand, CM with derivate **119**, a *N*-Methyliminodiacetic acid (MIDA) boronate recently developed by Burke and coworkers,[137] led to the desired compound **120** with 31% yield.

The factors responsible for the moderate isolation of **120** consisted in lack of selectivity due to formation of the self-metathesis products of both cross-partner **119** and amide **65**, and primarily, because of its difficult purification. The MIDA borane **120** presented very high polarity and could only be eluted with MeOH in the column chromatography purification, whereby other solvents such as acetone or CH_3CN presented insufficient polarity. The certain instability of MIDA boran-compounds in MeOH resulted in partial decomposition of borane **120**, which, additionally, had to be further purified by crystallization in order to remove

the ruthenium decomposition products procedents from the metathesis reactions that co-eluted under the used chromatographic conditions.



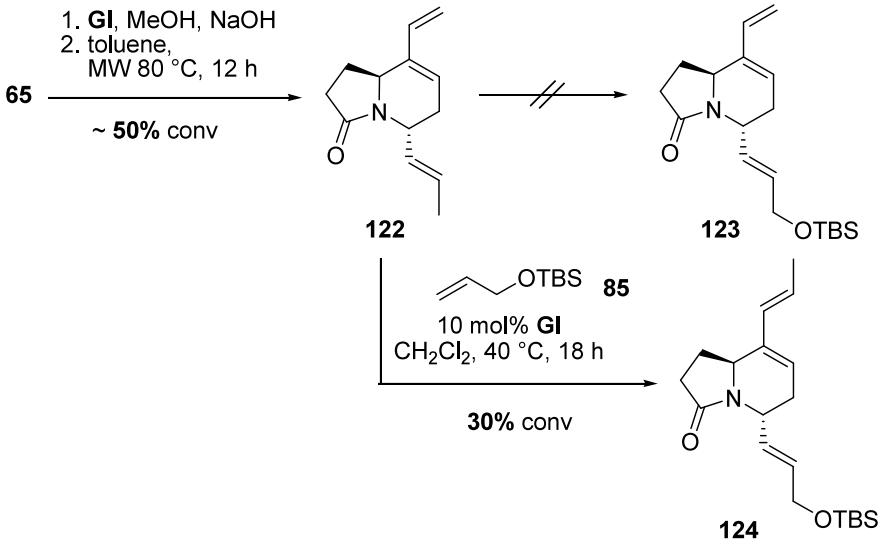
Scheme 57. Synthetic attempts to afford alcohol **118** by selective CM with **65** and alkenes **116** and **119**.

The obtained borane **102** was next hydrogenated in MeOH, since other solvents such as CH_2Cl_2 or EtOAc were unable to dissolve the substrate. Unfortunately the relative long reaction time needed to completely hydrogenate the tri-substituted olefine derived in almost fully decomposition of the substrate into a complex product mixture which included mostly the boronic acid **121**.

Since the CM strategy with C_2-OR synthons resulted unsatisfactory, the possibility of isomerizating the terminal olefin to perform a CM with a C_3-OR synthon was taken into consideration (Scheme 58).

Even though there are numerous methodologies to isomerize terminal double bonds,[138] to confirm the viability of this approach, a Ru-catalyzed procedure was chosen, envisaging the possibility of performing a one-pot procedure from amide **65** based on a *d*RRM-isomerization sequence.[30] This isomeration reaction can be catalyzed by ruthenium-hydride species derived from standard metathesis catalysts.[139] Diverse procedures unsing **GI**, **GII** and MeOH in the presence of bases such KOH and Et_3N were tested, as well as the generation of the Ru-H species by reaction with $NaBH_4$.

The best results were delivered following the procedure developed in the group by Shaudt that consists in the preparation of the Ru-H catalyst in toluene by reaction of **GI** with MeOH and NaOH, followed by the irradiation of the sample in the MW at 80 °C for 6 h. Under these conditions, analysis by GC-MS indicated the recovery of a mixture 1:1:1 including starting material, the desired product **122** and a compound or compounds with a mass of 205 g/mol (result of the mono-hydrogenation of one of the three possible double bonds).[140] Further reaction led to complete conversion of substrate **65** within 12 h, and the target **122** was isolated as inseparable mixture containing approx. 50% of the desired triene **22** (Scheme 58).



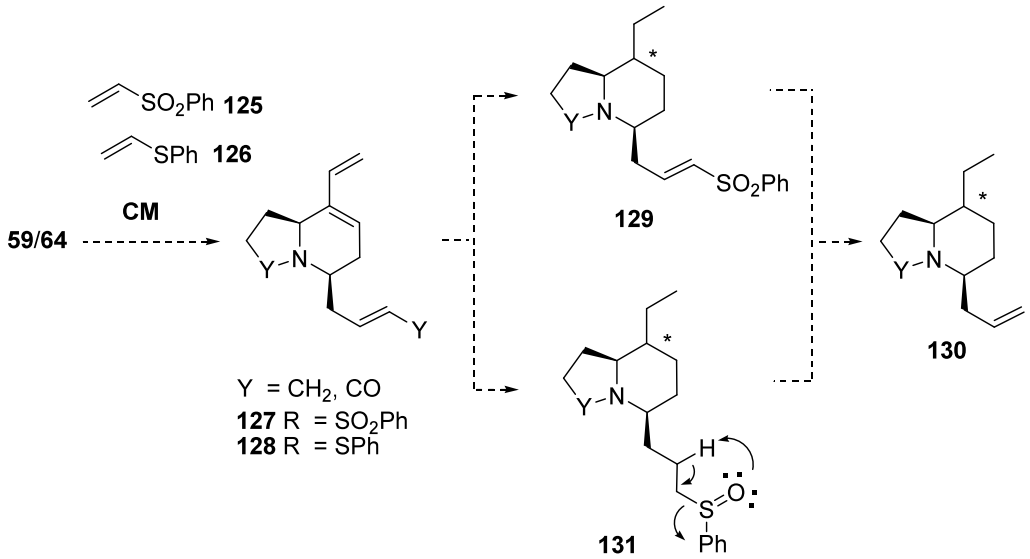
Scheme 58. Ru-catalyzed olefin isomerization followed by CM with alkene **85**.

CM reaction under the optimized conditions used for the synthesis of indolizidine 3-*epi*-209F resulted in the formation of product **124**, instead of the desired compound **123**. An additional CM step with ethylene would be thus required before performing the CM reaction with alkene **85**, reducing the step efficiency of this synthetic pathway, and therefore further investigations following this route were discarded.

Another alternative to construct double bonds consists in the reductive elimination of conjugated phenyl sulfones (desulfonylation) by treatment with sodium amalgame,[141] or by addition of tributylstannyl-lithium.[142] Compound **130** could be achieved from sulfone **127** by selective CM with **125** and subsequent selective hydrogenation of the diene moiety leading to structure **129** (Scheme 59). The corresponding fully hydrogenated sulfon could alternative serve as precursor for sulfoxide **131**, which upon heating would undergo elimination leading to the 193E indolizidine structure.[143]

Metathesis with sulfur-containing compounds is well known[144] and particularly, CM reaction with vinyl phenyl sulfides have been described within ROM-CM sequences with norbornene

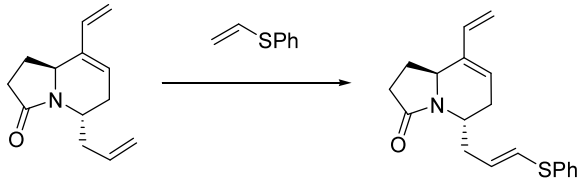
derivatives.[145] CM with **126** could likewise lead to **131** by hydrogenation of **128** followed by selective oxidation, avoiding the sulfone reduction step.



Scheme 59. Alternatives *via* CM with sulfur-containing compounds to generate the terminal double bond.

To prove this working hypothesis amide **65** was subjected to different CM conditions with commercially available ruthenium catalysts (Table 22). To our surprise, no formation of the desired CM product **128** was detected, even by using alkene **126** as solvent (entry 8) or with equimolar quantities of catalyst **HII** (entry 9).

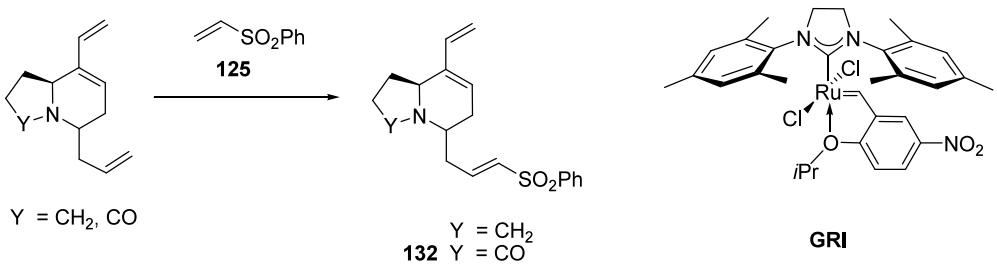
Table 22. Reaction conditions screened for the CM of amide **65** with alkene **126**.



Entry	Catalyst	Solvent	T	[mol/l]
1	10 mol% **GI**	CH_2Cl_2	40 °C	0.05
2	10 mol% **GI**			
3	10 mol% **GII**			
4	10 mol% **GII**			
5	10 mol% **HII**			
6	10 mol% **HII**			
7	10 mol% **HII**	toluene	80 °C	
8	10 mol% **HII**	-	40 °C	neat
9	100 mol% **HII**	CH_2Cl_2	40 °C	0.05

CM with vinyl sulfone **125**, on the other hand, led to encouraging results already in the first synthetic attempts. The 'second generation' ruthenium-complex **HII** was chosen as catalyst since it has shown improved performance *vs* catalysts **GI** and **GII** in CM reaction with electron-deficient olefins.[146] With 3.4 mol% catalyst loading using 3 eq of cross-partner **125**, an isolated yield of 13% was obtained with a conversion of approx. 50% according to the ^{1}H-NMR spectra of the crude material (entry 1, Table 23). An increase of the concentration and the amount of catalyst led to the improved yield of 41% *brsm* (entry 2). The low amount of isolated sulfone **132** was attributed to incomplete conversion of amide **65** and competing oligomerization of the starting material. Catalyst and reaction conditions were thus next screened to improve the course of the reaction. Qualitative analysis by ^{1}H-NMR and GC-MS verified that ruthenium-complexes **GII** and **FI** delivered significantly lower conversions, whereas catalyst **GRI**, with known efficiency in CM with electron-deficient alkenes,[147] gave improved conversions than **HII**. Optimized reaction conditions were found to be in 0.05 M in CH_2Cl_2 at 40 °C with 10 eq of alkene **125**. Rising the temperature or the concentration lead to an increase of oligomerization, whereas diluted conditions and lower temperatures delivered almost no conversions. With the new conditions and pre-catalyst **GRI**, a 40% *brsm* yield of **132** was isolated (entry 3).

Table 23. Reaction conditions screened for the optimization of the CM reaction of alkene **125** with substrates **59** and **65**.

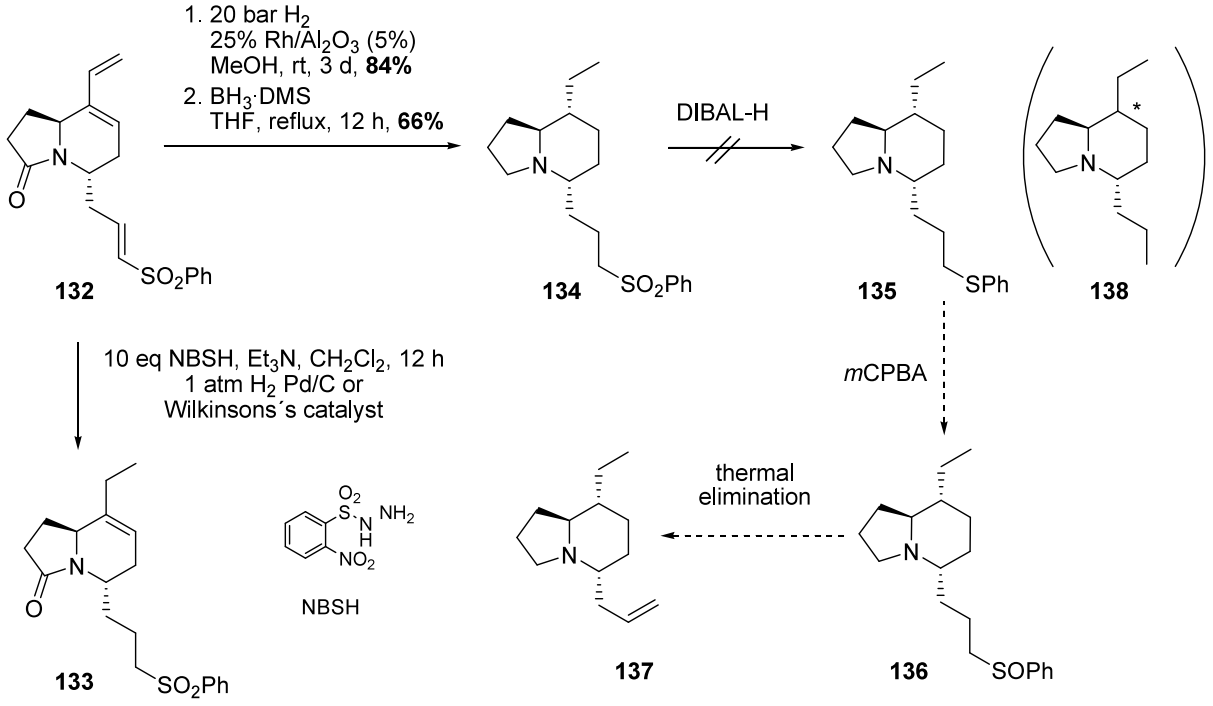


Entry	Substrate	Catalyst	Solvent	T	[mol/l]	Yield [a]	Yield *brsm*
1	**65**	3.4 mol% **HII**	$C_2H_2Cl_2$	60 °C	0.05	13%	18%
2	**65**	10 mol% **HII**			0.08	30%	42%
3	**65**	10 mol% **GRI**	CH_2Cl_2	40 °C	0.05	19%	40%
4	**65** [b]	10 mol% **HII**				41%	65%
5	**65** [b]	10 mol% **GRI**				50%	74%
6	**64**	10 mol% **HII**				53%	87%
7	**59**·*p*TSA	10 mol% **HII**				-	-
8	**65** [b]	10 mol% **GRI** [c]				55%	70%
9	**65** [b]	10 mol% **HII** [c]				56%	76%

[a] Isolated after column chromatographic purification on SiO_2. [b] Substrate **65** was distilled prior to use. [b] A solution of the catalyst was added dropwise within 12 h.

The purity of the starting material was found to be decisive and when the RRM product **65** was distilled prior to use, an improved yield of 40% and 48% was obtained, with catalysts **HII** and **GRI** respectively (entries 4 and 5). Under the same reaction conditions, isomer **64**, with the correct stereochemistry regarding 193E, gave the target compound in 53% yield (87% *brsm*), whereas reaction with the *p*TSA ammonium salt derived from **59** led to complete reisolation of the sarting material **59** (entries 6 and 7). Finally, a slight improvement was achieved by adding the catalyst dropwise to a concentrated solution of **65** and **125**. Under these conditions, the desired sulfone **132** was isolated in 56% yield (entries 8 and 9).

With vinyl sulfone **132** in our hands, the possibility of performing a selective reduction of the diene moiety was explored. The conversion of the terminal alkene in a more sterically hindered electron poor olefin, however, was not sufficient to avoid the preferred reduction *of* the trisubstituted double bond. Hydrogenation with heterogeneous, homogeneous catalysts and the chemical reduction with *in situ* generated diimide[148] with NBSH[149] as reagent led to the same partially hydrogenated compound **133** (Scheme 60).[150]



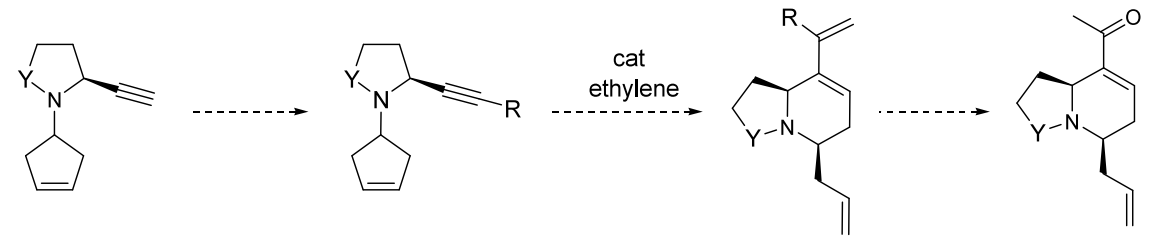
Scheme 60. Further synthetic steps from vinyl sulfone **132**.

The synthetic studies towards the structural core of indolizidine 193E continued by preparing the reduced sulfone **134**. Complete hydrogenation and reduction of the amidic carbonyl group led to the target **134** in good yields. The synthetic challenge consisted now in the reduction of the sulfone moiety to the corresponding sulfide **135**, for further selective oxidation to the corresponding sulfoxide **136** and thermal elimination to build-up the terminal alkene on **137**.

The reduction of sulfones to sulfides is a straightforward transformation for cyclic compounds, but requires more drastic conditions for aliphatic molecules.[151] Two synthetic procedures towards sulfide **135** were approached. Reduction with $LiAlH_4/TiCl_4$ led,[152] after work-up, to an intractable crude mixture containing the target compound, whereby any attempt of purification by column chromatography or by distillation failed. An alternative procedure was reported by Gardner and coworkers and described a more practicable reduction using DIBAL-H.[153] The published conditions in toluene at 110 °C resulted too harsh and tiophenol and the fully hydrogenated structure **138** were reisolated. Reduction at 30 °C was found to be sufficient for the formation of **135**, whereas at lower temperatures LRMS-ESI analysis indicated remaining sulfone **134** in the reaction mixture. Unfortunately reaction conditions at a small scale were difficult to reproduce(*) and chromatographic purification of the desired compound **135** resulted in complete decomposition. Alternative, small quantities of sulfide **135** were successfully isolated by an aqueous extraction work-up but first attempts to oxidize **135** to the sulfoxide **136** resulted again in decomposition of the starting material. Due to the difficult practicability of the sulfone reduction procedure, further synthetic alternatives towards 193E were investigated.

2.6.5.5 Enyne *d*RRM of Alkyne Derivates

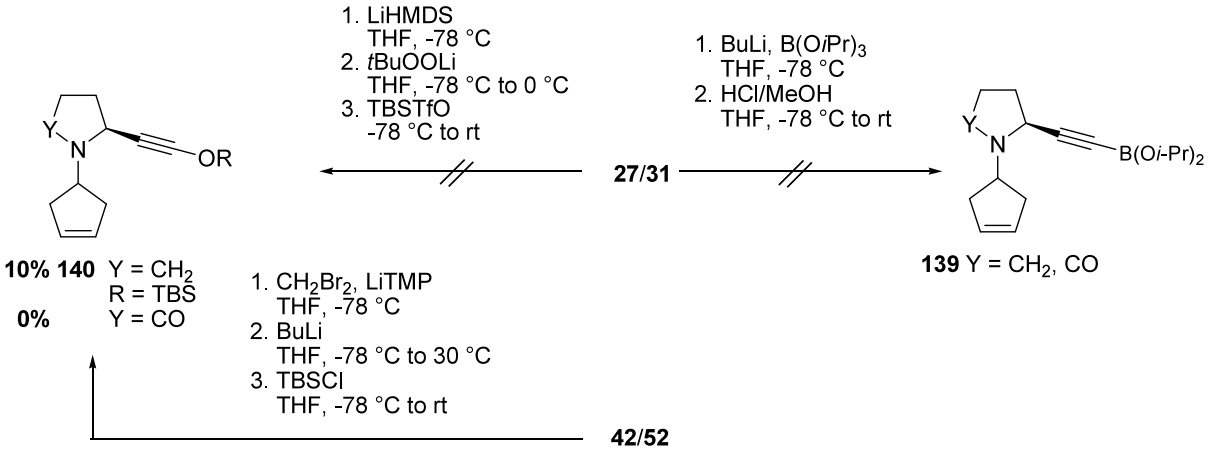
As alternative for the selective derivatization of the diene moiety, we anticipated that RRM of compounds **139** and **140** could lead to an α-unsaturated ketone **141** after oxidation[154] or deprotection[155] respectively (Scheme 61). Selective reduction of unsaturated ketones is a well known procedure and can be performed selectively with a wide range of reagents.[156]



Scheme 61. Synthesis of unsaturated ketones by enyne RRM of compounds **139** and **140**.

(*) The reduction was performed with 2.5 M DIBAL-H solution and without solvent. The quenching of the reaction had to be performed at -10 °C. Because of the exothermic character of this process, it was difficult to maintain the low temperature in such a small scale and high concentrations.

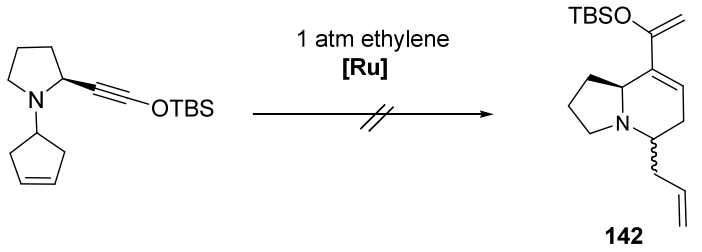
Although synthetic attempts towards alkyne **139** failed, synthesis of the protected alcohol **140** was achieved following the procedure described by Kowalski from methyl ester **52**,[157] with low yield, but leading to enough substance to prove the viability of performing the following RRM reaction (Scheme 62).



Scheme 62. Synthetic approach for metathesis substrates **139** and **140**.

Despite of all the different reaction conditions screened, *d*RRM of alkyne **140** failed to give the desired compound **142** (Table 24). Neither of the catalysts tested succeded in the transformation of **140** by using the corresponding ammonium salt, or by using Ti(*i*PrO)$_4$ as lewis acid.[158]

Table 24. Summarized results obtained when alkyne **140** was subjected to enyne *d*RRM.

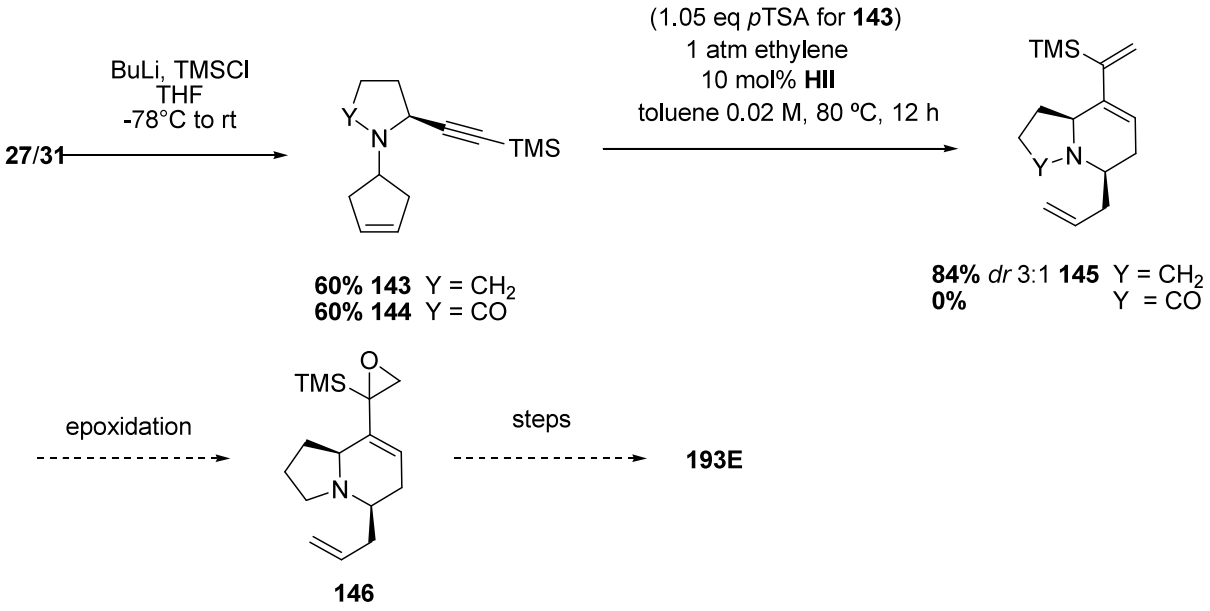


Entry	Catalyst	Solvent	T	Conv [a]
1	10 mol% **GI**	CH_2Cl_2, 20 eq Ti(*i*PrO)$_4$	40 °C	0%
2	10 mol% **GI**	$C_2H_4Cl_2$, 20 eq Ti(*i*PrO)$_4$	40 °C	0%
3	10 mol% **HII**	CH_2Cl_2, TsOH	40 °C	0%
4	10 mol% **HII**	CH_2Cl_2, TfOH	40 °C	0%
5	10 mol% **HII**	toluene, TsOH	80 °C	0%[b]
6	10 mol% **HII**	toluene, TfOH	80 °C	0%[b]

[a] Determined by ^{1}H-NMR spectroscopic analysis. [b] Starting material and decomposition products were reisolated.

2.6.5.6 Further Transformation Towards Indolizidine 193E

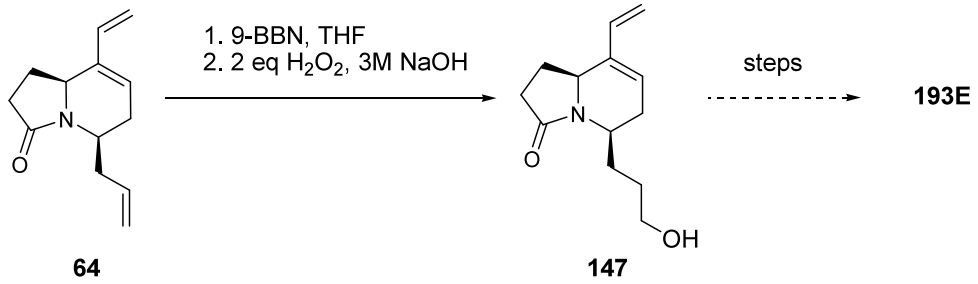
Vinylic TMS fragments are known to be ketone equivalents by conversion into epoxysilanes and subsequent acid catalyzed rearrangement.[159] With the same synthetic purpose described in Section 2.6.5.5, TMS derivates **143** and **144** were obtained from the corresponding alkynes in a non-optimized yield of 60% each (Scheme 63). Even though, the amide compound **144** was unable to undergo metathesis, the amine analogue **143** led to 84% yield with catalyst **HII** in toluene at 80 °C. The diastereoselectivity was calculated after protodesilylation of the rearranged product **145**, and was found to be 3:1 *cis*:*trans* with the use of *p*TSA as Brønsted acid. Selective epoxidation followed by treatment with TFA[160] could lead to the α-unsaturated ketone **146**, and indolizidine 193E could be obtained after two synthetic steps. Further, diastereoselectivity could be also improved by the use of other acids such as TFA[(*)] and other catalysts such as **FII**.



Scheme 63. Synthesis of triene **145** by enyne *d*RRM and proposed synthetic pathway towards indolizidine 193E.

Alternatively, the target alkaloid could be approached by a selective hydroboration-oxidation sequence of the metathesis product **65** leading to alcohol **147**. 193E should be smoothly obtained in few transformations, including hydrogenation and elimination of the alcohol functionality, which have already been studied in some extent within the synthesis of indolizidine 209F (Scheme 64).

[(*)] The use of strong acids such TfOH led to protodesilylation of the starting material.



64 **147**

Scheme 64. Synthetic approach towards indolizidine 193E by selective hydroboration of the metathesis product **64**.

First synthetic attempts were conducted with the *trans* isomer **65**,[161] and very promising results were obtained. As depicted in Figure 14, the ^{1}H-NMR spectra indicates the reaction of the terminal olefin while the diene functionality remained intact. After filtration over a pad of SiO_2, ESI-MS analysis revealed the formation of the desired product.(*)

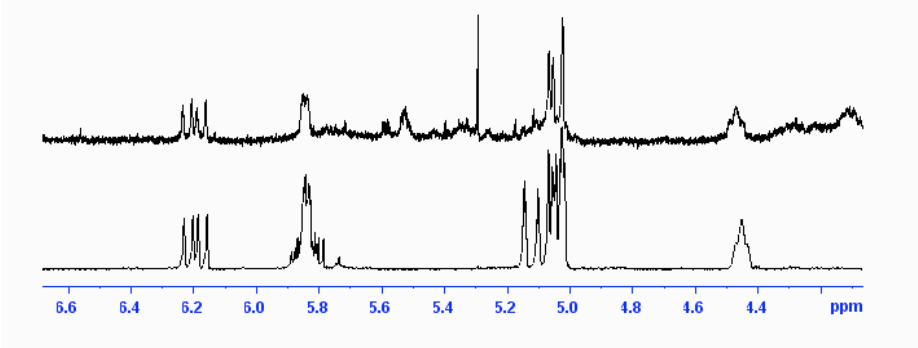


Figure 14. On the top, ^{1}H-NMR spectra from the reaction of amide **65** with 9-BBN and subsequent oxidation, on the bottom ^{1}H-NMR spectra of the starting material.

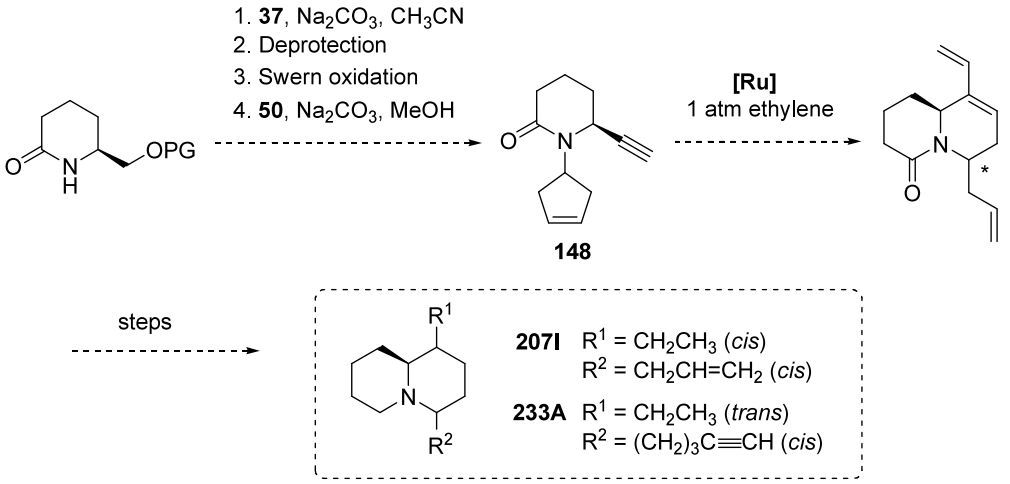
2.6.6 Synthetic Studies Towards 1,4-disubstituted Quinolizidines

Following the same synthetic strategy it should be possible to have access to other natural products families based on alkaloids structures. For instance, 1,4-disubstituted quinolizidines could be synthesized by enyne *d*RRM of alkyne **148** (Scheme 65).[37,162]

Likewise, in analogy to the synthesis of indolizidine 223AA, quinolizidine 259E could be approached from alkyne **151** (Scheme 66). Preliminary investigations began with **149**, which was synthesized from picolinic acid. Hydrogenation with PtO_2 and H_2 in the presence of (-)-tartaric acid,[163] afforded a mixture of diastereoisomeric salts which was separated by crystallization.[164] The obtained solid was then treated with $SOCl_2$, and the obtained methyl pipecolate hydrochloride **149** was separated from the crude material by recristalisation in refluxing EtOAc.(*) Alkylation with tosilate **37** under the optimized conditions found for the

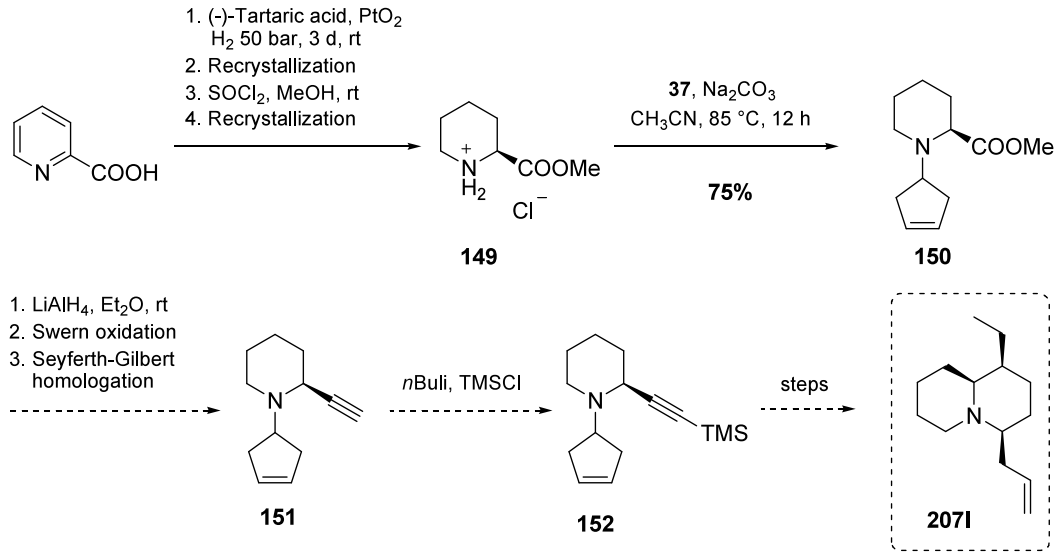
(*) About 50% product was reisolated, although the yield was not quantified due to the small reaction scale.
(*) The synthetic route to **149** was not optimized. The obtained yields were not calculated since not all crude material **149** was recristalized. According to the literature **149** should present up to 85% ee.

preparation of methyl ester **44**, led to the desired product **150** in 75% isolated yield. The enyne substrate **151** should be easily obtained with the used protocols for the preparation of alkyne **27**.



Scheme 65. Proposed synthetic approach towards natural occurring disubstituted 1,4-quinolizidines from alkyne **148**.

Alternatively, following the proposed synthesis towards 193E outlined in Section 2.6.5.6, quinolizidine 207I could be approached from TMS derivate **152** (Scheme 66). Further investigations on *d*RRM of metathesis subtrate **151** are currently being performed in the group.

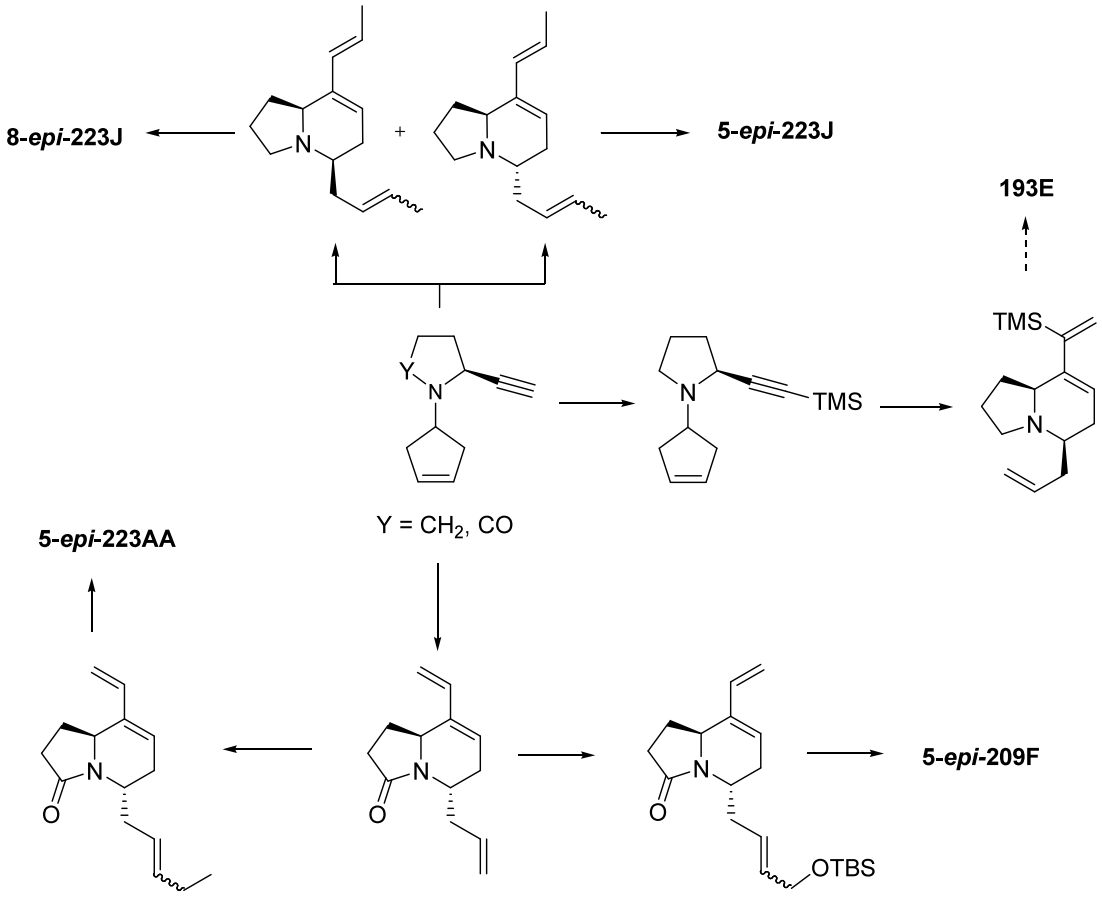


Scheme 66. Proposed synthetic pathway towards quinolizidine 259E and 207I.

2.7 Summary and Outlook

In this Chapter studies on enyne *d*RRM as applied to the synthesis of alkaloid natural products have been presented. Total syntheses of 5,8-disubstituted indolizidine alkaloids previously developed have always been focused on the generation of a single configuration of the structural core, depending on the desired target. In the presented investigations, a new synthetic concept has been developed for the divergent synthesis of different derivatives, with variable stereochemistry (Scheme 67).

Starting from cheap chiral-pool-substrates such as (*S*)-proline and (*S*)-glutamic acid, metathesis substrates **27** and **31** were synthesized in a multigram scale with 79% and 44% overall yield respectively, within very few steps and chromatographic purifications.



Scheme 67. Summarized synthetic approach for indolizidine alkaloids by enyne *d*RRM as key step.

Metathesis studies were performed with different catalyst complexes, some of them commercially available, as well as novel Ru-complexes recently developed by Blechert and coworkers. By means of catalyst choice it has been possible to control the diastereoselectivity for the investigated enyne *d*RRM with **31** from values of 1:10 (*cis*/*trans*) with **FI** to 4:1 with **BVIII**. For the particular case of the substrate **27**, the Lewis basic character

of the nitrogen atom was overcome by formation of its ammonium salt to avoid catalyst deactivation. For the first time in metathesis transformations, it has been demonstrated that the counterion of such ammonium salts play an important role in the reaction outcome. After extensive screening of substrates derived from **27** in combination with diverse ruthenium-based metathesis complexes, it has been possible to control the *dr,* obtaining values from 1:3 (*cis*/*trans*) with **27**·TfOH with **HII** to complete selectivity towards the desired *cis*-diastereoisomer with **27**·HPF_6 and catalyst **FII** (> 20:1 *cis*/*trans*).

These results were next applied in the synthesis of 5,8-indolizidines using the newly developed enyne *d*RRM as key synthetic step. C-5 and C-8 epimers of indolizidines 223J, 219F and 223AA were prepared using a concise and practical route. Further investigations towards indolizidine 193E were conducted and two synthetic pathways were envisaged for the conclusion of such an approach.

Lastly, the results obtained using ammonium salts of **27** as substrates and the use of catalyst complexes such as **FII** or the novel catalyst complex **BVIII** open up new perspectives in the field of diastereoselective metathesis reactions, and further investigations should be of great interest.

Chapter 3

Metathesis Reactions with Unprotected Tertiary Amines

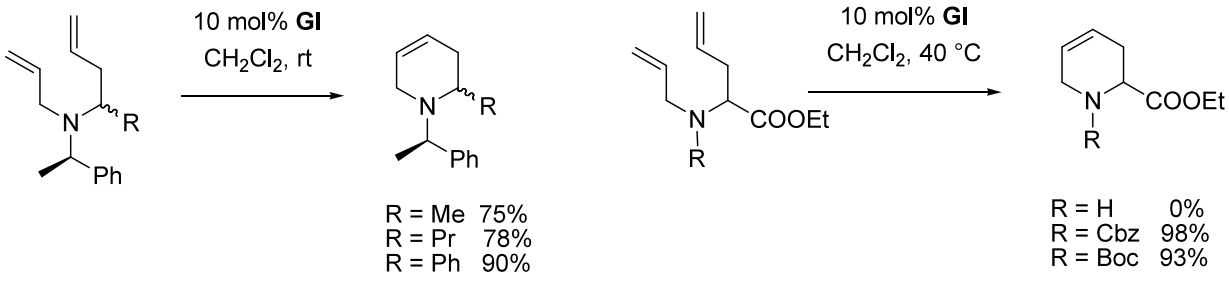
Chapter 3

Metathesis Reactions with Unprotected Tertiary Amines

3.1 Introduction and Motivation

Olefin metathesis is a particularly useful synthetic methodology for the construction of *N*-heterocyclic compounds such as pyridines, pyrrolidines and piperidines, which are usually present in the structure of biologically active molecules.[165] Despite the efficiency of metathesis transformations for the synthesis of functionalized heterocycles, a common drawback for the synthesis of amine-containing structures by metathesis is the nature of the amine itself. The lone pair of the amino group can coordinate the metal center, leading to a decrease of catalyst efficiency and activity or complete inactivation of the metal-alkylidene complex.[59]

In general three principal tactics are used in order to avoid this complexation. One of them exploits the steric hindrance around the nitrogen atom (Scheme 68).[166] Even though there are many examples in the literature of ruthenium-catalyzed RCM of sterically hindered secondary and tertiary amines, its applicability depends on the structure of the synthetic target, and does not denote a general solution.



Scheme 68. Examples on RCM reactions with amine-containing compounds. On the left steric hindrance is used to avoid coordination with the catalyst; on the right, protection of the nitrogen.

Alternatively, a protecting group can be used to decrease the nucleophilicity of the nitrogen. This constitutes the most common strategy, and is based in diminishing the Lewis basicity of the nitrogen by suitable protection of the amino group as carbamate, sulfonamide or amide (Scheme 68).[166,167] This approach, however, adds protection group manipulations and can reduce the efficiency of the synthetic sequence. Nevertheless, certain protecting groups may likewise interfere with the catalyst activity by intermolecular chelation with the metal.[168]

On the other hand, the Lewis basicity of an amine compound can be decreased by reaction with a Lewis acid. $Ti(O\textit{i}Pr)_4$ or Brønsted acids like HCl, are usually employed either by direct addition to the reaction mixture, or, in case of Brønsted acids, by previous formation of the corresponding ammonium salt.[106]

The nature of the catalyst, in terms of reactivity and functional group tolerance, also plays an important role when the reaction is performed with tertiary amines. Molybdenum-based complexes are relatively tolerant towards tertiary amines and have been used successfully in the synthesis of different alkaloids such as (+)-quebrachamine.[169] Their incompatibility with oxygen, moisture and alcohol functionalities among others, however, hampers the use of this catalyst for many academic applications, and especially for industrial processes.

Considering the ubiquity of amines in organic compounds and the synthetic power of metathesis, efficient strategies to increase amino group compatibility with metal-alkylidene complexes still have to be developed. During our studies on enyne *d*RRM of **27** we observed that diastereoselectivity and reaction rate were counterion dependant. As mentioned in Chapter 2, despite that protonation of amines is a common strategy in metathesis to avoid catalyst deactivation, there are only very few reports discussing the influence of the Brønsted acid applied.[107,108,170] Hydrochloric acid is the common choice,[106i] with some reports using *p*TSA,[106ii] and very few on the use of CSA,[106iii] HBr[107] and TFA.[106iv] On the other hand, utilization of acids such HBF_4 or TfOH has not been yet reported. In this regard, encouraged by the obtained results with **27**, we became interested in investigating the reaction outcome and the counterion effect when secondary and tertiary amines where subjected to metathesis conditions with different catalysts and Brønsted acids.

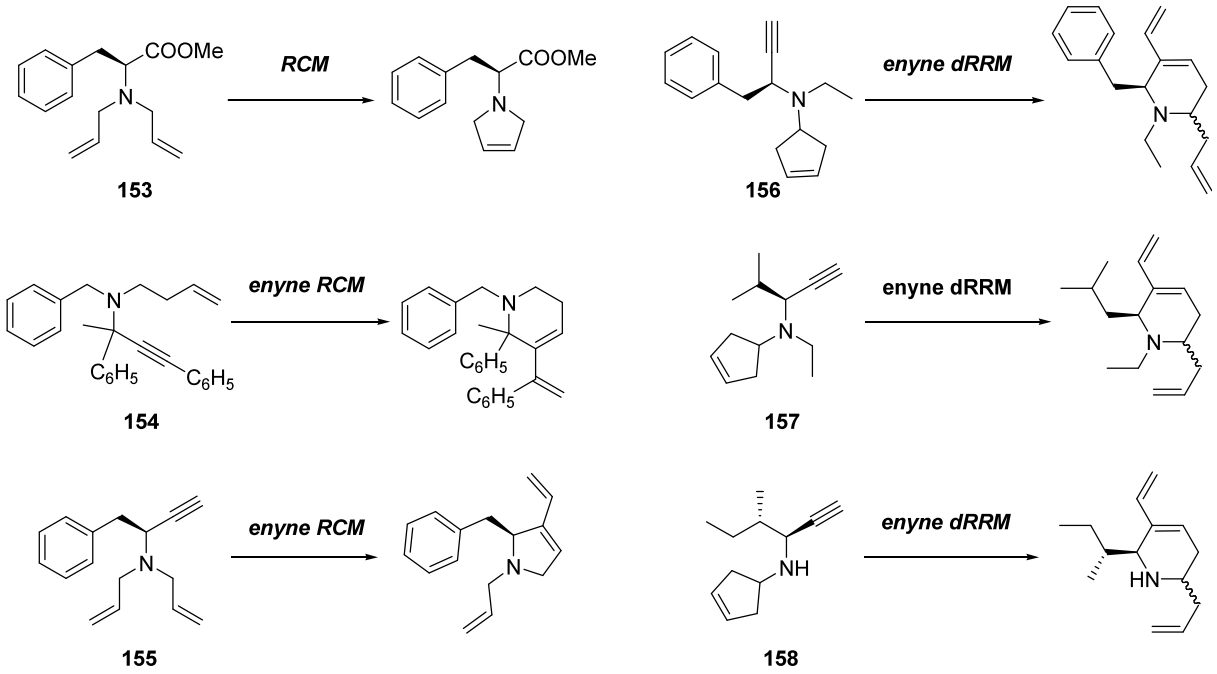
3.2 Results and Discussion

We decided to cover different type of Ru-catalyzed metathesis transformations with easily accessible compounds. RCM of **153**, enyne RCM of **154** and **155**, and enyne *d*RRM of **156**, **157** and **158**, were chosen as model reactions (Scheme 69).

We aimed to start with an easy transformation such as the ring closure of a diallyl amine, to progressively increment the synthetic challenge, and find restrictions on the applicability of Brønsted acids in metathesis with unprotected amines. We envisaged that in enyne RCM the use of ethylene would be needed, and therefore, quantitative or near to quantitative amount of active specie would be generated from the pre-catalytic complex. Due to the reduced stability of such species in comparison with the non-initiated catalyst, the achievement of good conversion may result more challenging, and thus, enhanced counterion effects may be observed. This should be considered for compound **155**, where additionally, by introducing a

competing RCM transformation, stability, reactivity and activity of the ruthenium catalyst under the different conditions may play an important role.

Studies on *d*RRM present even more challenge since they involve a cascade metathesis of ROM-enyne RCM (or enyne CM-enyne RCM-ROM if the "yne-then-en" pathway is considered), in an ethylene atmosphere (since one equivalent of CH_2=CH_2 is required) and on substrates with differently strained structures.



Scheme 69. Selected substrates for the investigations on counterion effects in metathesis reactions.

3.2.1 Substrate Synthesis

Amino acids are common starting materials in chiral pool synthesis. We decided to use this family of substances because they are cheap compounds with variable functional groups, and, synthetically, they offer the possibility of selectively modify the nitrogen functionality and subsequently use the carboxy group to introduce the alkyne moiety by homologation (Figure 15).

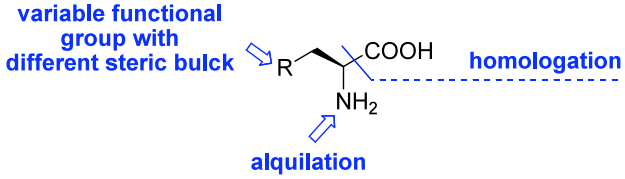
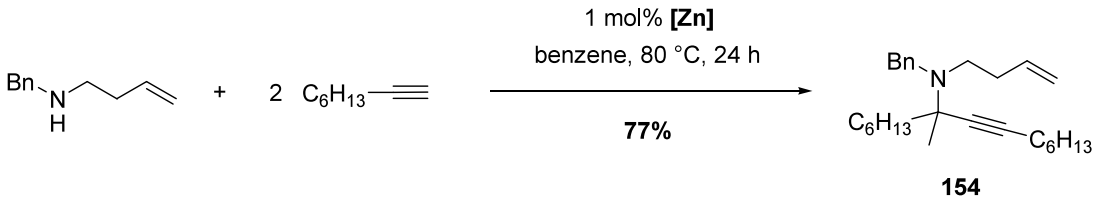


Figure 15. Planned synthetic strategy for the synthesis of the metathesis substrates.

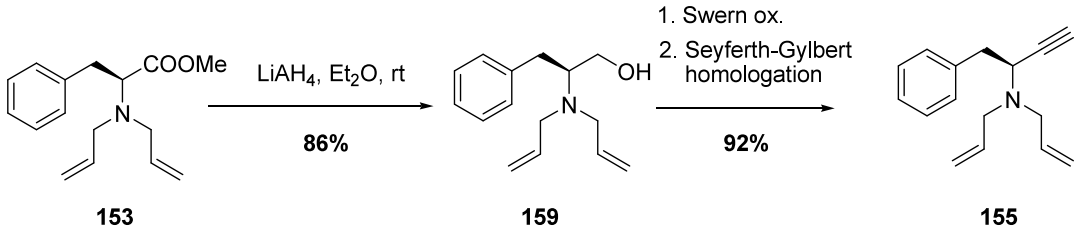
Firstly, **153** was synthesized from phenylalanine following the published protocol of Xiao and coworkers by esterification and by bis-alkylation with allyl bromide.[171]

An exception of the synthetic strategy for the preparation of metathesis substrates is compound **154**. Propargylic amine **154** was prepared by tandem hydroamination-alkyne addition within the studies on hydroamination reaction performed in Blechert's group.[172] We envisaged that enyne RCM of such a structure would furnish interesting *N*-heterocyclic compounds and could be an adequate substrate to investigate the influence of the counterion in the metathesis outcome (Scheme 71).



Scheme 71. Synthesis of substrate **154** by tandem hydroamination-alkylynation.

Derivate **155**, was easily synthesized from **153** by reduction to the alcohol **159**, oxidation to the corresponding aldehyde and subsequent Seyferth-Gilbert homologation with very good yields (Scheme 70).



Scheme 70. Synthesis of substrate **155.**

In an analogous approach to **27**, enyne compounds **156**, **157** and **158** were synthesized from benchmark amino acids, whereby alkynes **156**, **157** should serve as model for *d*RRM of tertiary amines and substrate **158** for secondary (Figure 16).

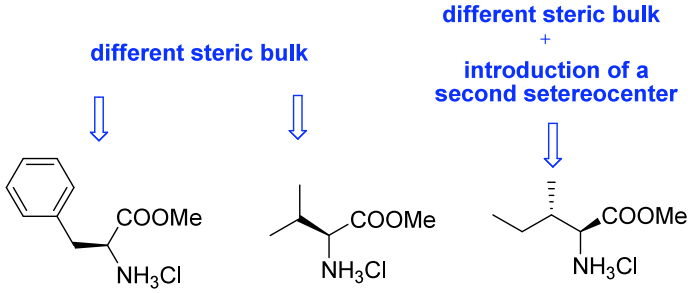
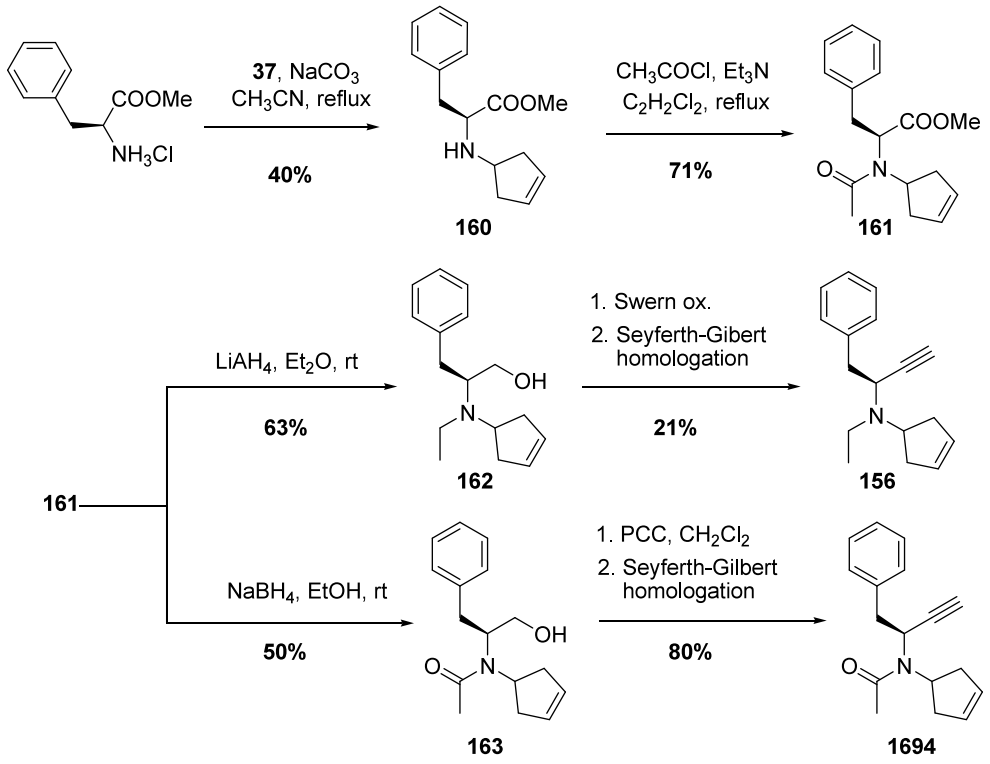


Figure 16. Starting materials for the synthesis of substrates for *d*RRM investigations.

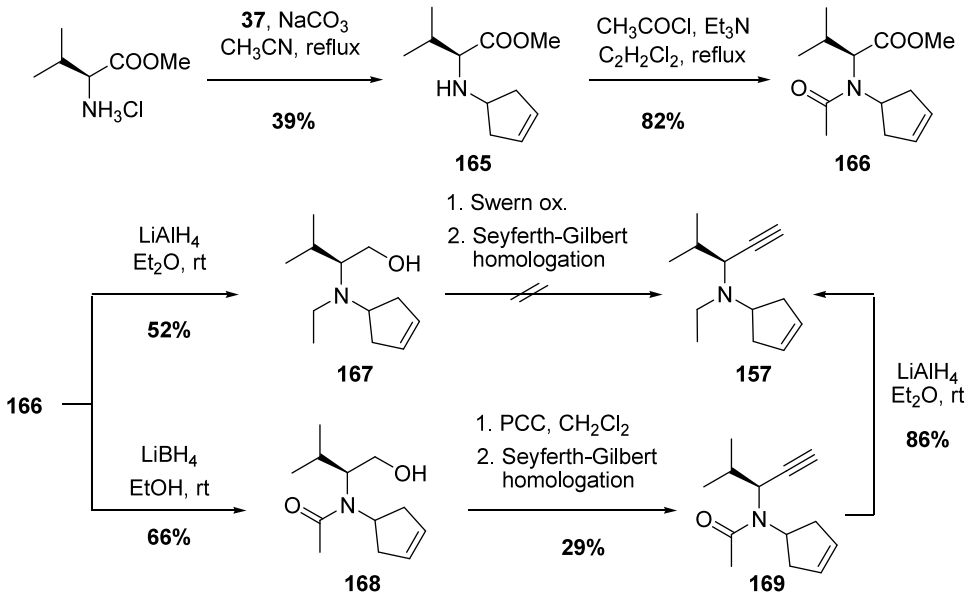
The synthesis of **156** was accomplished in five steps with a moderate yield of 4% (Scheme 72). Swern oxidation of **162** showed to be particularly problematic, and PCC oxidation failed due to the interference of the unprotected amine. Alternatively, usig amide **163** as substrate,

sequential oxidation with PCC followed by Seyferth-Gilbert homologation proceeded with an improved yield of 80%.



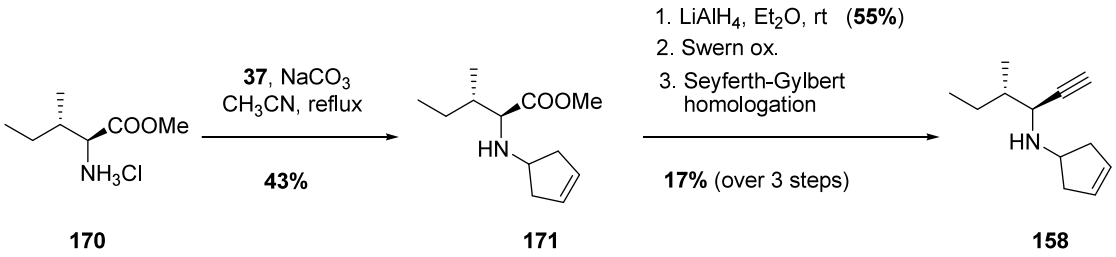
Scheme 72. Synthesis tertiary amine **156**.

The synthesis of **157** was approached in a similar manner (Scheme 73). Swern oxidation of **167** in this case failed completely and the desired aldehyde could not be isolated. Sequential PCC oxidation-Seyferth Gilbert homologation showed again to be more effective, although **169** was isolated in very low yield. The metathesis substrate **157** was synthesized in six steps with a non-optimized yield of 5%.



Scheme 73. Synthesis tertiary amine **157**.

Secondary amine 158 was likewise approached. Nuclephilic substitution on **170** by the corresponding amino ester **171**, was followed by reduction to the alcohol, Swern oxidation and Seyferth-Gilbert homologation of the formed aldehyde, furnishing **158** in an overall yield of 7% (Scheme 74).



170 **171** **158**

Scheme 74. Synthesis tertiary amine **158**.

3.2.2 Metathesis Studies

3.2.2.1 RCM Studies

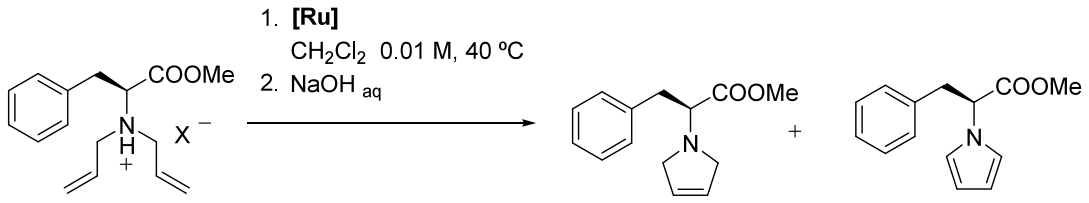
Substrate **153** had already been employed by Xiao and Yu, in RCM studies on **153** and other amino acid derivatives. The authors, reported the use of $Ti(O^iPr)_4$ to prevent coordination of the substrate with the Ru-complex and consequent catalyst deactivation.[171] When no Lewis acid was added to the reaction mixture very low yields were obtained with commercially available catalyst, even at high temperatures. Further, when the corresponding hydrochloride salt was subjected to metathesis conditions the pyrrole derivative **173** was isolated in very high yields. Compound **23**, was chosen as challenging substrate for RCM studies, with the aim of demonstrating that it is possible to avoid the use of organometallic additives and subsequent necessary chromatographic purifications, by performing the metathesis reaction with the adequate ammonium salt. Additionally, by accurate choice of the counterion, we intended to overcome the formation of the by-product **173** (Table 25).

Different ammonium salts were synthesized from **153**, by using acids with different pK_a values (Table 8, Section 2.5.2.3), and reacted under various conditions with commercially available catalysts **GI**, **GII**, **HI** and **HII**.

When metathesis was performed in CH_2Cl_2 at room temperature very low conversions were obtained with 2.5 mol% catalyst loading. Both first generation and second generation catalyst furnished very similar results (entries 1-4, 6-9, 17-20, 31-34 and 41-44) whereby the best conversions were obtained with with **153**·HBF_4 and second generation catalysts (entries 19 and 20), and with **153**·*p*TSA under the use of **HI** and **HII** (entries 32 and 34).

By raising the temperature to 40 °C similar conversions were obtained as with 2.5 mol% at rt and, therefore, the catalyst loading was increased to 5 mol%. Second generation catalyst

Table 25. Representative results in RCM reactions with compound **153**.



153·HX

X = TfO, BF_4, CF_3COO, TsO, etc.

172 **173**

	Subs.	Conditions	Catalyst	Conv [a]		Subs.	Conditions	Catalyst	Conv [a]
1			2.5 mol% **GI**	9% (0%)	26			5 mol% **GI**	27% (0%)
2		CH_2Cl_2, rt	2.5 mol% **HI**	4% (0%)	27			5 mol% **HI**	30% (3%)
3	**153**·TFA		2.5 mol% **GII**	3% (0%)	28	**153**·TFA	CH_2Cl_2, 40 °C	5 mol% **GII**	0% (0%)
4			2.5 mol% **HII**	6% (0%)	29			5 mol% **HII**	0/% (0%)
5		toluene, 80 °C	10 mol% **GI**	20% (29%)	30			10 mol% **HII**	0% (0%)
6			2.5 mol% **GI**	13% (4%)	31			2.5 mol% **GI**	10% (1%)
7		CH_2Cl_2, rt	2.5 mol% **HI**	18% (3%)	32		CH_2Cl_2, rt	2.5 mol% **HI**	20% (2%)
8			2.5 mol% **GII**	17% (6%)	33			2.5 mol% **GII**	12% (3%)
9			2.5 mol% **HII**	3% (1%)	34			2.5 mol% **HII**	22% (3%)
10			5 mol% **GI**	17% (0%)	35			5 mol% **GI**	9% (0%)
11	**153**·HCl		5 mol% **HI**	7% (0%)	36			5 mol% **HI**	28% (1%)
12		CH_2Cl_2, 40 °C	5 mol% **GII**	37% (1%)	37	**153**·*p*TSA	CH_2Cl_2, 40 °C	5 mol% **GII**	27% (0%)
13			5 mol% **HII**	23% (0%)	38			5 mol% **HII**	30% (0%)
14			10 mol% **HII**	45% (2%)	39			10 mol% **HII**	44% (0%)
15		toluene, 40 °C	10 mol% **HII**	0% (0%)	40		toluene, 80 °C	10 mol% **HII**	20% (3%)
16		toluene, 80 °C	10 mol% **HII**	2% (0%)	41			5 mol% **GI**	13% (1%)
17			2.5 mol% **GI**	4% (0%)	42		CH_2Cl_2, rt	5 mol% **HI**	15% (1%)
18		CH_2Cl_2, rt	2.5 mol% **HI**	6% (0%)	43			5 mol% **GII**	11% (2%)
19			2.5 mol% **GII**	24% (2%)	44			5 mol% **HII**	17% (1%)
20			2.5 mol% **HII**	26% (2%)	45			5 mol% **GI**	7% (0%)
21	**153**·HBF_4		5 mol% **GI**	47% (1%)	46	**153**·TfOH		5 mol% **HI**	23% (0%)
22		CH_2Cl_2, 40 °C	5 mol% **HI**	24% (0%)	47		CH_2Cl_2, 40 °C	5 mol% **GII**	19% (1%)
23			5 mol% **GII**	93% (7%)	48			5 mol% **HII**	54% (1%)
24			5 mol% **HII**	96% (4%)	49			10 mol% **HII**	86% (14%)
25		toluene, 80 °C	10 mol% **HII**	97% (3%)	50		toluene, 80 °C	10 mol% **HII**	99% (1%)

[a] Conversions were determined by ^{1}H-NMR spectroscopic analysis of the reaction mixture after basic work up. Conversion to compound **173** is indicated in brackets.

furnished under this conditions better results than the phosphine counterparts (entries 10-14, 21-24, 35-39, and 45-49), except for **153**·TFA where surprisingly only **GI** and **HI** let to the formation of the desired compound **172** (entries 26-30). The counterion effect becomes unequivocal and **153**·HBF_4 achieves complete conversion towards **172**, with significant formation of the pyrrole byproduct **173** (entries 23 and 24).

By increasing the temperature to 80 °C complete conversion was achieved with **153**·TfOH (entries 49 and 50) with lower formation of the undesired pyrrole **173** (entries 15 and 16).

In the specific case of **153**·HCl salt, possibly due to low solubility, very low formation of **172** was detected either at 40 °C or at 80 °C.

Noteworthy, Xiao and Yu report a 73% isolated yield for the by-product 173 using **153**·HCl as substrate at 40 °C and catalyst **GII**. According to a previous report from Verpoort,[173] in his investigations the purchase of pyrrole derivatives by RCM of diallyl amines could only be achieved by adding $RuCl_3 \cdot H_2O$ to the reaction mixture, promoting the formation of Ru-hydride species that catalyze the isomerization and the dehydrogenation reaction after the RCM step. Since the results from Xiao could not be reproduced, we concluded that catalyst or solvent impurities might be responsible for the formation of such hydride species.[140]

The use of $Ti(O\textit{i}Pr)_4$ is hence not necessary the best solution to avoid pyrrole formation. By forming the adequate ammonium salt and by working under inert conditions it is possible to afford compound **152** with excellent conversions, and this can be isolated without the need of chromatographic purifications by a simple aqueous work-up.

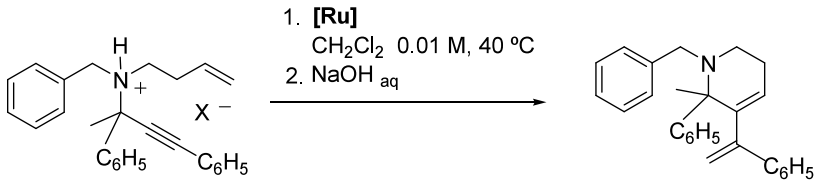
3.2.2.2 Enyne-RCM Studies

Next, we aimed to investigate whether the same tendencies were observed in enyne RCM.

The studies began with substrate **154**. Initially, due to the steric bulk around the nitrogen, we expected to observe conversion towards the cyclized product, even in the absence of acid. By performing the reaction with **HII** at 40 °C and in the presence of ethylene, 13% conversion was detected by ^{1}H-NMR spectroscopy (entry 1, Table 26).

Diverse ammonium salts were next prepared from **154** by adding 1.05 eq of the corresponding acid, to a solution of alkyne **154** in CH_2Cl_2. When ammonium salts **154**·TFA, **154**·TfOH and **154**·HCl were used in the metathesis reaction, only starting material was reisolated from the reaction mixture (entries 2-5). When these experiments were repeated with 1 eq the same result were obtained, indicating that the excess of acid was not responsible for the reaction failure. For substrates **154**·*p*TSA and **154**·HBF_4, complete conversions were observed at the same mild conditions.

Table 26. Summarized results obtained when substrate **154** was subjected to enyne-RCM.

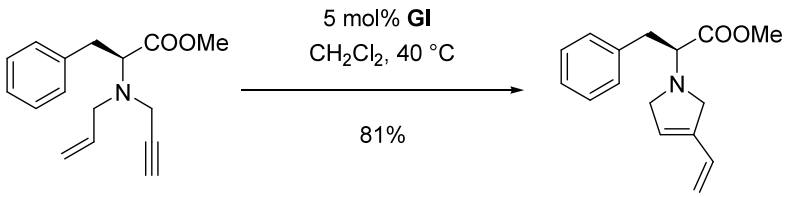


154·HX
X = TfO, BF_4, CF_3COO, TsO, etc.

Entry	Substrate	Conditions	Conv [a]
1	**154**	2.5 mol% **HII**, ethylene, CH_2Cl_2, 40 °C, 24 h	13%
2	**154**·HCl		0%
3	**154**·TFA		0%
4	**154**·TfOH		0%[b]
5	**154**·*p*TSA		100%
6	**154**·HBF_4		100%

[a] Conversions were determined *via* ^{1}H-NMR of the reaction mixture after basic work up. [b] When performed at rt the same result was obtained.

Next, we focused our attention in enyne substrate **155**, to compare the obtained results with the investigations of Xiao and coworkers with alkyne **174**. In 2007 this authors published a series of new pyrrolidine derivatives prepared by enyne RCM of substrates such **174** containing a basic nitrogen under mild reaction conditions, in absence of ethylene or other additives (Scheme 75).[174] They attributed the obtained results to preferred coordination of the **GI** catalyst to the alkyne bond instead of to the nitrogen atom. Steric hindrance around the nitrogen may also difficult coordination of the lone pair with the catalyst, although when **153** and **174** are compared, this steric bulk is not sufficient to avoid catalyst deactivation.



174

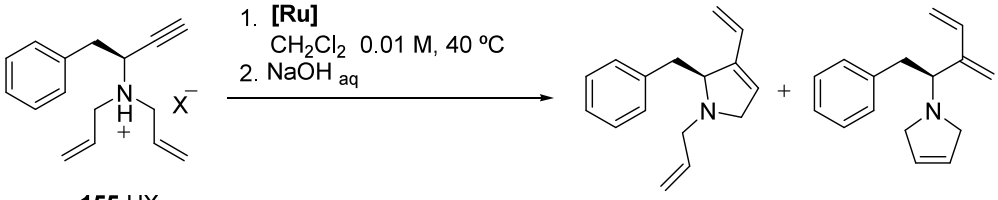
Scheme 75. Preparation of pyrrolidine derivatives by Xiao and coworkers.

In this regard, we aimed to investigate if effectively was not necessary to protect the nitrogen to perform enyne RCM, to study the influence of the counterion in the reaction outcome, and to observe the selectivity of the "en-then-yne", "yne-then-en" and alkene metathesis competing reactions.

When **155** was submitted to metathesis reaction conditions without any additives very low conversions were achieved (entries 1 and 2, Table 27). The use of ethylene improved the obtained conversion (entry 3) but was insufficient to obtain good results.

By conducting the reaction in the presence of a Brønsted acid with 5 mol% **HII** in CH_2Cl_2 at 40 °C under ethylene atmosphere, low conversions between 4-8% were obtained, whereby increasing the temperature to 80°C lead to improved results (entries 5 and 6), achieving complete conversion with **155**·TfOH (entry 7). The formation of amine hydrochloride salt (entry 4), even though is the most commonly used Brønsted acid for such transformation, showed again to be the less indicated choice.

Table 27. Summarized results obtained when substrate **155** was subjected to enyne-RCM.



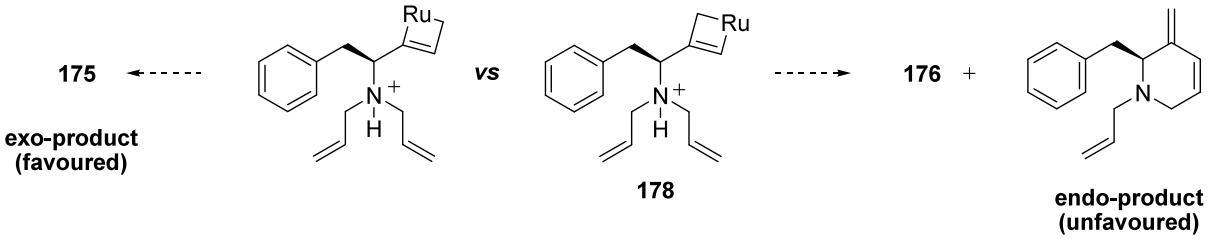
155·HX
X = TfO, BF_4, Cl, TsO

175 **176**

Entry	Substrate	Conditions [a]	Conv [b]	Ratio 175/176	
1	**155**	**GI**, CH_2Cl_2, 40 °C	14%	1	0
2	**155**	**GI**, toluene, 80 °C	9%	1	0
3	**155**	**GI**, ethylene, CH_2Cl_2, 40 °C	27%	1	0
4	**155**·HCl	**HII**, ethylene, toluene, 80 °C	19%	1	0
5	**155**·*p*TSA		82%	91	9
6	**155**·HBF_4		89%	86	24
7	**155**·TfOH		100%	77	23

[a] 0.02 M, 5 mol% catalyst, overnight. [b] Conversions were determined *via* ^{1}H-NMR of the reaction mixture after basic work up.

The formation of the desired cyclized product **175** however, was accompanied with **176** as by-product, result of the less productive addition of ethylene to the triple bond and RCM of the allylic rests. As discussed in Chapter 2, enyne metathesis can take place *via* an “en-then-yne” pathway, or/and an “yne-then-en” pathway. For this specific substrate, the formation of **176** proofs the existence of an “yne-then-en” catalytic cycle in the reaction mechanism.
Further, taking into account that the endo-cyclization in Ru-catalyzed metathesis reactions is unfavoured, the formation of **176** might result from intermediate **178** which is less able to react further towards the cyclized product, reacting with a molecule of ethylene (Scheme 76). As discussed in Chapter 2, the RCM of with the allylic rests is thermodynamically driven, due to the lost of a molecule of ethylene, and, unless high pressures of ethylene are used, it is expected to obtain **176** rather than the corresponding bis-allylic compound.



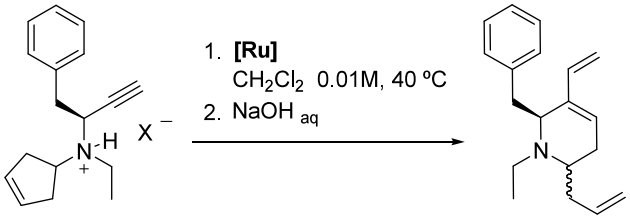
Scheme 76. Metathesis intermediates, according to an yne-en mechanism, responsible for the formation of **176**.

3.2.2.3 Enyne *d*RRM of Non-Cyclic Amino Acid Derivatives

Having demonstrated the utility of protecting amino functionalities as ammonium salts in RCM and enyne RCM, we aimed to study the counterion influence in RRM, and determine if the results obtained for **27** in terms of diasteroselectivity, were also extrapolative to other systems.

We began our experiment with **156** using acids *p*TSA and TfOH since they had shown to furnish opposite selectivities in *d*RRM with **27**. Both substrates furnished a same *dr* of 4:1, with very low conversion.(*) Unfortunately, attempts to determine the relative stereochemistry of **179** by NOE experiments with the crude material were not concluding, since no correlation between signals was observed (Table 28).

Table 28. Metathesis results obtained with substrate **156** in enyne-dRRM.



156·HX
X = TfO, TsO

179

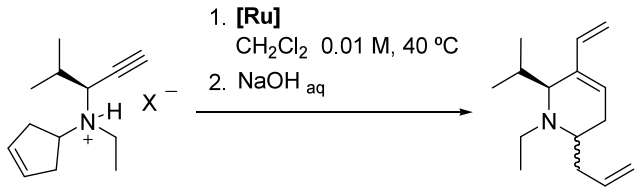
Entry	Substrate	Conditions	Conv [a]
1	**156**·*p*TSA	5 mol% **HII**, ethylene, $C_2H_2Cl_2$, 40 °C, 24 h	33%
2	**156**·TfOH		27%

[a] Conversions were determined *via* ^{1}H-NMR analysis of the reaction mixture after basic work up.

Valine derivative **157** was next investigated. In this case the desired product was only afforded with **157**·*p*TSA as substrate with a *dr* 6:1, and comparative results in terms of selectivity could not be obtained (Table 29).

(*) The *dr* was calculated from the ^{1}H-NMR using the same proton signals as for **59**/**60** and **64**/**65**.

Table 29. Metathesis results in enyne *d*RRM of tertiary amine **157**.



157•HX
X = TfO, BF_4, TsO

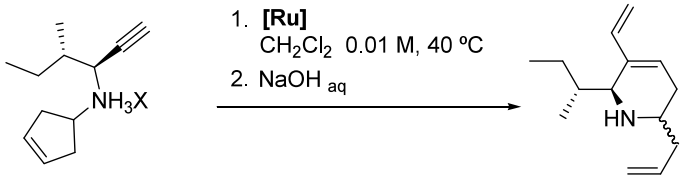
180

Entry	Substrate	Conditions	Conv [a]
1	**157**·TfOH	5 mol% **HII**, ethylene, CH_2Cl_2, 40 °C, 24 h	0%[b]
2	**157**·HBF_4		2%
3	**157**·*p*TSA		100%

[a] Conversions were determined by ^{1}H-NMR analysis of the reaction mixture after basic work up. [b] When performed at rt, and at 80 °C in toluene, the same result was obtained

Finally, we conducted metathesis experiments with compound **158** with the Brønsted acids that had furnished better results for the previous substrates (Table 30). We found complete conversion when *p*TSA, HBF_4 and HPF_6 were used (entries 2-4), but no formation of **181** was achieved with TfOH under the used reaction conditions. According to spectroscopical analysis, all three experiments with 100% conversion furnished the same product mixture, and no variation on the diastereoselectivity was observed (*dr* = 7:2). Unfortunately, attempts to determine the relative stereochemistry of **181** by NOE experiments with the crude product failed again, and purification of the combined samples by column chromatography resulted in complete decomposition of the substrate.

Table 30. Metathesis results in enyne *d*RRM with alkyne **158**.



158•HX
X = TfO, BF_4, TsO, etc.

181

Entry	Substrate	Conditions	Conv [a]
1	**158**·TfOH	5 mol% **HII**, ethylene, CH_2Cl_2, 40 °C, 24 h	0%
2	**158**·*p*TSA		100%
3	**158**·HBF_4		100%
4	**158**·HPF_6		100%

[a] Conversions were determined *via* ^{1}H-NMR analysis of the reaction mixture after basic work up.

3.3 Sumary and Outlook

From the presented results, it can be concluded that the use of Brønsted acids is a very effective methodology in avoiding catalyst deactivation when unprotected amines are used as substrates in metathesis. It has been demonstrated that this strategy is more convenient than the use of other Lewis acids such $Ti(O\textit{i}Pr)_4$, since this avoids tedious chromatographic purifications.

Further, corroborating the results in metathesis studies presented in Chapter 2, where different ammonium salts compared, the counterion plays an important role in the outcome of the metathesis reaction. With the model substrates **153**-**158** it has been clearly proven that HCl, usually used for the protection amines in metathesis reactions, is not necessarily the best choice. For the investigated reactions, HBF_4 and *p*TSA instead furnished better conversion towards the desired products.

Less predictable are salts of trifluoromethane sulfonic acid. The failure of RCM with **154**, and the enyne *d*RRM with **157** and **158**, could be attributed to faster catalyst decomposition in comparison with the metathesis reaction rate. If metathesis occurs fast enough, TfOH seems to be the acid of choice (Table 25 and Table 27). On the other hand, for slower reactions, acids such *p*TSA and HBF_4 appear to be more appropriate. As mentioned in Chapter 2, indeed the ruthenium-catalysts used have shown certain instability with TfOH ammonium salts, especially under an ethylene atmosphere. *p*TSA on the other hand, even in 0.5 eq excess, does not interfere significantly in the catalyst performance or stability, and hence, may provide better results in metathesis reactions with ammonium salts.

The different results obtained with the utilized Brønsted acids cannot be explained from their pK_a value alone or from the coordination character of the corresponding counterion. In the specific case of TfOH, we believe that the triflate anion may coordinate to ruthenium in the catalytic specie. Carboxylate and sulfoxylate ruthenium-based metathesis catalyst are known[175] and have been prepared by substitution of the chlorine atoms by the corresponding anionic ligands. Thus, such a complexation with triflate might be possible and would explain the faster reactions observed for TfOH ammonium salts, as well as the diminished stability of ruthenium catalysts with such substrates. Further investigations in this regard could be of great interest, since they may help to develop more reactive catalysts and broaden the applicability of the metathesis reactions.

Chapter 4

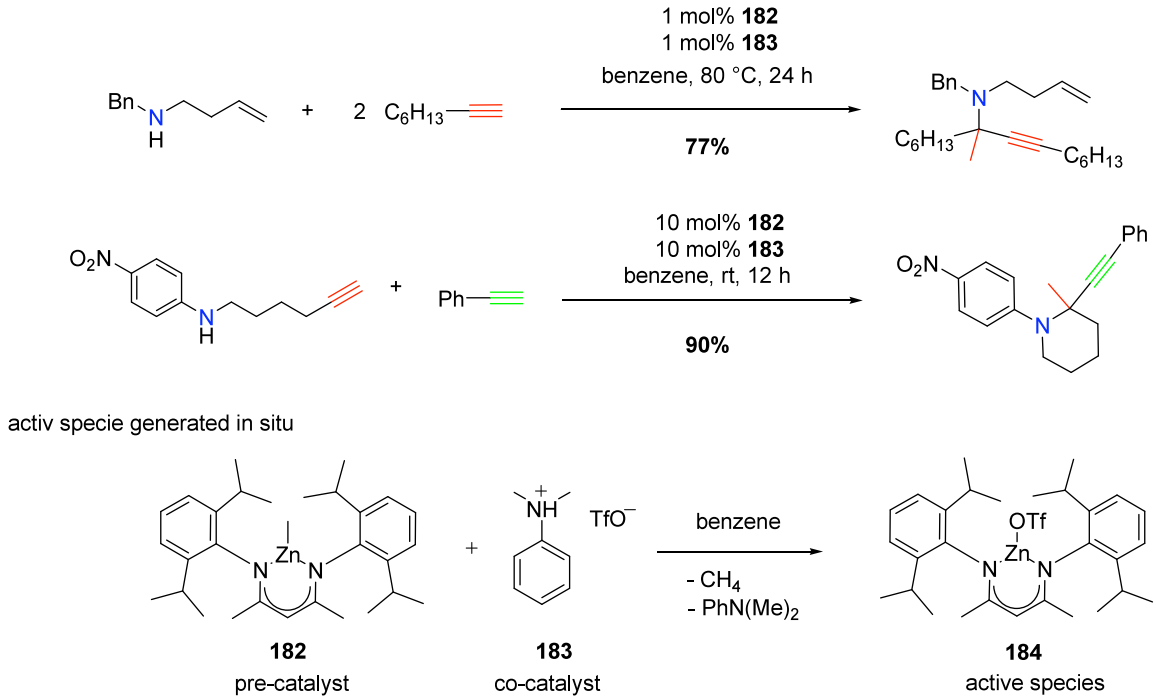
Sequential Zn-Ru Catalysis: One-pot Hydroamination-RCM

Chapter 4

Sequential Zn-Ru Catalysis: One-pot Hydroamination–RCM

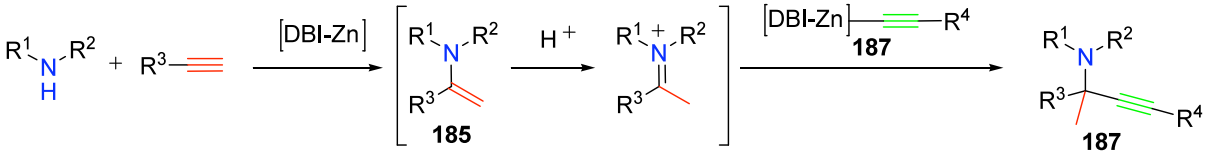
4.1 Introduction and Motivation

Blechert and colleges recently reported a one step synthesis of quaternary propargylamines with four different substituents by a Zn-catalyzed tandem amination-alkynylation (Scheme 77).[172] Such a sequence has not been described intensively in the literature and only a few cases are known. In an early report acetylene was converted to propargyl amines having a secondary carbon centre in a copper catalyzed reaction.[176] These copper-catalyzed reactions have been described recently with diverse phenylacetylenes furnishing the anti-Markovnikov product by using CuBr as a catalyst at high temperatures.[177] The same catalyst was used by Hammond and Xu for an intramolecular hydroamination-alkynylation under microwave conditions. When the same conditions were applied for intermolecular reactions, however, anti-Markovnikov addition was again observed. With a Zn/Cd-catalyst the Markovnikov addition has been observed but only propyne and dimethyl- or diethylamine were used under drastic conditions.[178] The tandem reaction reported by Blechert furnishes Markovnikov hydroamination and is catalyzed by the a zinc-BDI-complex under mild conditions, whereby the catalytic active species **184** is generated *in situ* by the reaction of **182** with **183** readily at rt.



Scheme 77. Examples of the tandem hydroamination-alkynylation reported by Blechert and coworkers.

The reaction mechanism has not been verified yet, but is probably similar to the copper-catalyzed analogue. Zn-catalyzed hydroamination to the corresponding enamine **185** must take place (Scheme **78**), followed by the addition of a second alkyne to the formed intermediate **185**, or, alternatively, to the tautomeric iminium derivative, affording propargylamine **187**. The alkynylation step proceeds likely *via* the alkyn-Zn complex **186**, already known from investigations in the Zn-catalyzed addition of alkynes to aldehydes described by Carreira.[179]



Scheme 78. Proposed mechanism for the Zn-catalyzed tandem hydroamination-alkyne addition.

Developing novel C-C and C-N bond forming-procedures, with enhanced selectivity and efficiency, remains as a major interest for organic chemists. Catalyzed reactions are a focal point of research since they provide access to reactive intermediates under milder conditions and are considered environmentally friendlier transformations in terms of atom economy.[180] One-pot procedures(*) are especially attractive for being ecologically and economically favorable since they minimize the amount of waste, cost and energy compared to stepwise reactions.[181]

Further, when mechanistically distinct catalytic complexes are used, novel reaction outcomes beyond those possible with a single catalyst can be achieved, and more readily available starting materials for the given transformation can be used. In such tandem processes, also known as "dual-catalysis" or "bi-catalyzed", the compatibility of products and catalysts of all reaction included is required. To overcome this difficulty, the second catalyst or reagent can be introduced once the previous transformation has been completed.(**)

The Zn-catalyzed cascade reported by Blechert has been performed with benzylic, allylic and homoallylic amines, as well as functionalized aniline derivatives, providing access to structurally different enyne compounds which can be further functionalized. Propargyl amine **155**, for instance, was reacted under acidic conditions with Grubbs' 'second generation' catalyst and afforded the corresponding heterocyclic compound (Chapter 3). Given the stability and functional group tolerance of the commercially available ruthenium catalysts, the

(*) One-pot procedures are defined as a transformations of an organic substrate through two or more individual elaborations with a single work-up step. This classification includes domino (or cascade) and tandem reactions. Domino processes are defined by Tietze as: "reactions involving two or more bond-forming transformations which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step".[181a]

(**) According to Fogg and coworkers "Modification of an organic moiety via two catalytic elaborations, with addition of the second catalyst only after the first catalytic transformation is complete, is not a tandem catalysis, but a one-pot (bicatalytic) reaction." Fogg defines domino and tandem catalyses, in contrast, as having all catalytic species –whether masked or apparent– present from the outset.[181c]

viability of assembling olefin metathesis with Zn-catalyzed hydroamination in a one-pot transformation, called into question.

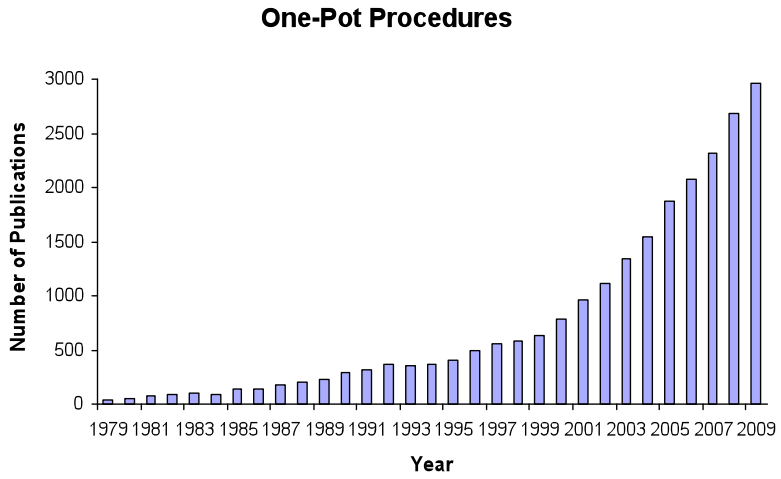


Figure 17. Number of publications (limited to journals and review articles in English) dealing with "one-pot" reactions until 2009 (SciFinder Scholar).

The amount of examples for one-pot and tandem processes in the literature increases every year (Figure 17), simultaneously with the diversity of the transformations that are combined. Ru-mediated relations,[182] particularly metathesis, and hydroaminations[183] appear frequently as key transformation in one-pot processes, since they enable the derivatization of olefins with a high level of selectivity and tolerance towards functional groups. Till to date, however, there is no report where both reactions have been combined into a single process.

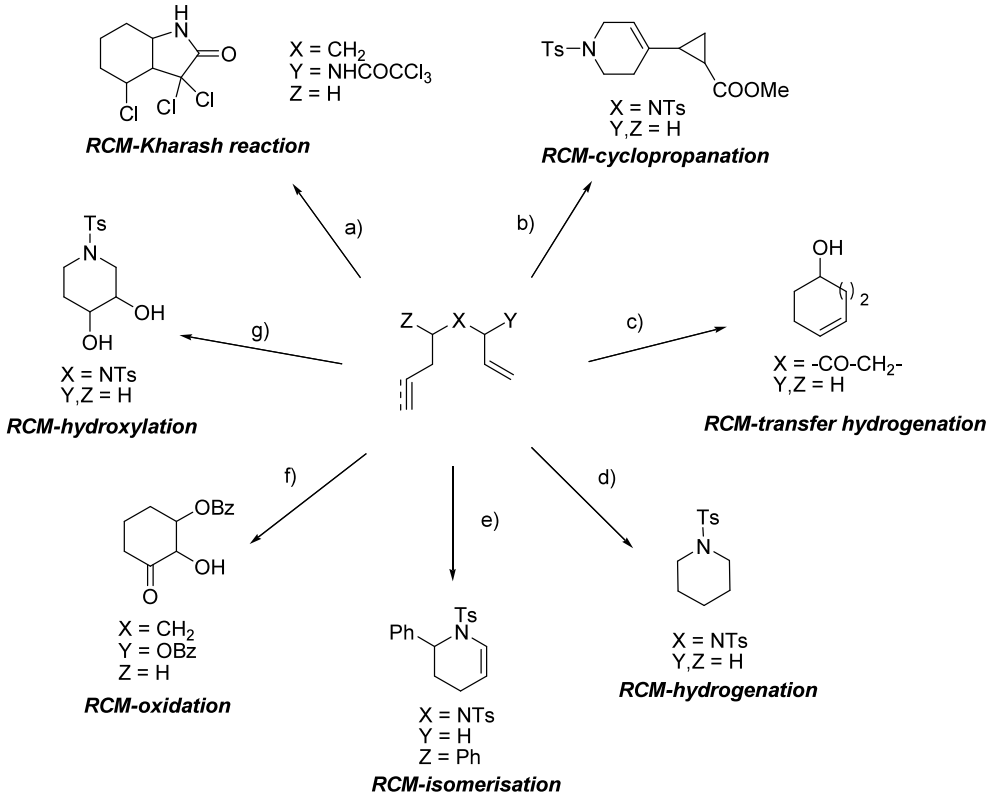
4.1.1 One-Pot Transformations Based on Ru-Catalyzed Metathesis

There are four different types of one-pot metathesis processes considering the nature of the reactions taking place:

- Sequences that include a metathesis reaction, followed by modification of the Ru-complex, which then catalyzes the next step. (Section 4.1.1.1)
- Sequences that include a metathesis reaction and a further transformation which profit from the Lewis acidity of Ru-complexes. (Section 4.1.1.2)
- Combination of a non-catalyzed transformation with a metathesis step. (Section 4.1.1.3)
- Combination of a catalyzed reaction and a metathesis reaction in a bi-catalytic process. (Section 4.1.1.4)

4.1.1.1 Ru-Catalyzed One-Pot Metathesis Reactions

Besides the conventional metathesis transformation (CM, ROM, RCM, RRM), different non-metathetic processes promoted by ruthenium-metathesis complexes have been reported. These reactions, such as the Kharasch addition,[184] cyclopropanation sequences,[185] reduction[186] and oxidation processes,[187] were first detected as side reactions, often due to decomposition of the ruthenium catalysts.[188] Nowadays, most of these non-metathetic transformations have been optimized and combined with CM, RCM and RRM in one-pot processes, broadening the synthetic potential of metathesis reactions (Scheme 79). The most widely used sequences are those which involve oxidative and reductive transformations. In 2001 Grubbs reported for the first time a RCM-hydrogenation methodology, where the products obtained after RCM were directly hydrogenated by changing the reaction conditions to an atmosphere of H_2 and slightly higher temperatures. This sequence can be mediated by both first-generation and second-generation catalysts, and has been applied as synthetic strategy for the synthesis of several natural products, for instance, the odoriferous alkaloid (*R*)-(+)-muscopyridine synthesized by Fürstner and coworkers.[189] Transfer-dehydrogenations and transfer-hydrogenations[186c] have also been assembled with metathesis, by adding protic additives such as isopropanol or ethylendiamine in the presence of a base to the reaction mixture, once the metathesis step has been completed.

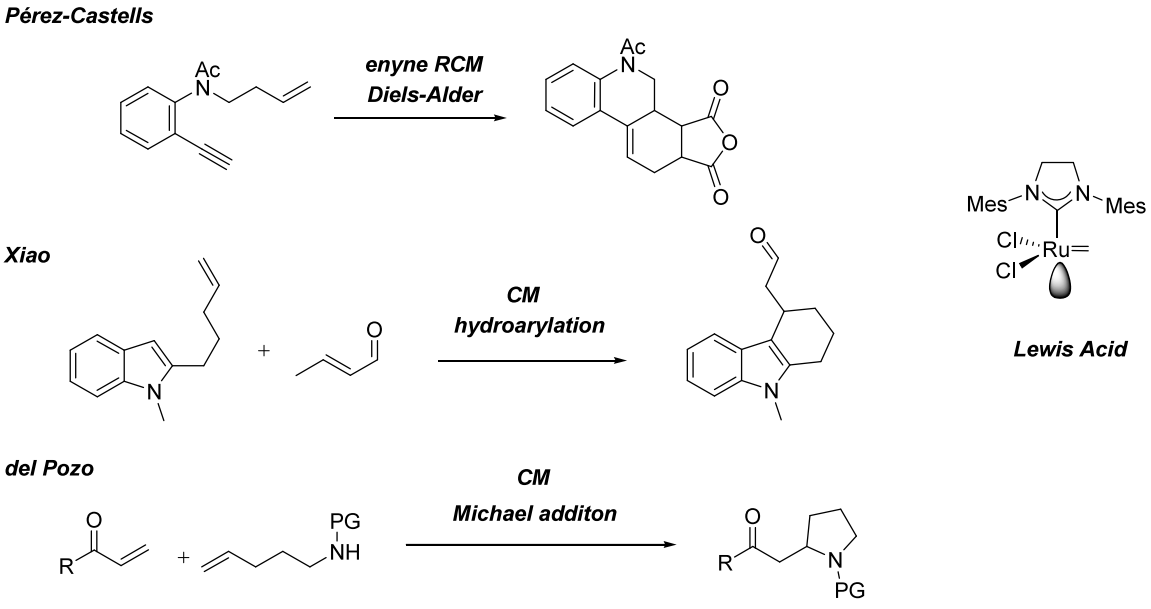


Scheme 79. Examples on combinations of metathesis with Ru-catalyzed non-metathetic transformations. a) 5 mol% ***GI***, toluene Δ. b) 10 mol% ***GI***, benzene, Δ; CHN_2CO_2Et. c) 3 mol% ***GII***, DCM, Δ; K2CO3, 2-propanol. d) 5 mol% ***GI***, Et_3SiH, DCM, Δ. e) 10 mol% ***GII***, DCM, Δ; (95:5 N_2:H_2) 70 °C. f) 5 mol% ***GII***, EtOAc, rt; oxone, $NaHCO_3$, MeCN/EtOAc/H_2O, rt. g) 1 mol% ***GI***, DCM, Δ; $NaIO_4$, $YbCl_3{\cdot}6H_2O$, MeCN/H_2O, 0 °C.

Oxidation reactions can be promoted with the use of oxidants such as $NaIO_4$ in the presence of $YbCl_3 \cdot 6H_2O$. Blechert published this methodology for the first time, for the construction of cyclic *cis*-diols *via* RCM.[190] Alternatively α-ketohydroxylation can be obtained when oxone is used as oxidation agent.[191] Metathesis-isomerization reactions have been also widely used[192] by using protic solvents, silyl enol ethylether or H_2 as an additive, subsequently to the metathesis step. A remarkable example is the application of a RRM-isomerisation reaction mediated by $NaBH_4$ in the synthesis of the antibiotic (–)-centrolobine.[31]

4.1.1.2 One-Pot Metathesis–Lewis Acid Catalyzed Reactions

One of the most described metathesis tandem reactions involving the Lewis acidity of Ru, consists of the combination of enyne RCM and cycloaddition reactions such as Diels-Alder (Scheme 80).[193] A remarkable application of this synthetic strategy has been recently published within the research in cancer treatments for the construction of natural product-based libraries.[193f] Alternatively, investigations of Xiao and coworkers embrace a tandem CM-intramolecular hydroarylation sequence leading to the synthesis of polycyclic indoles. The one-pot transformation was catalyzed by the second generation catalyst **HII**, which furnished better yields in the CM with the employed electron deficient olefins.[194] A further example exploring the Lewis acidy of the Ru-metathesis catalyst, consist of a sequence reported by del Pozo and coworkers, describing a microwave-assisted CM-intramolecular aza-Michael reaction for the construction of β-amino carbonyl derivatives.[195]

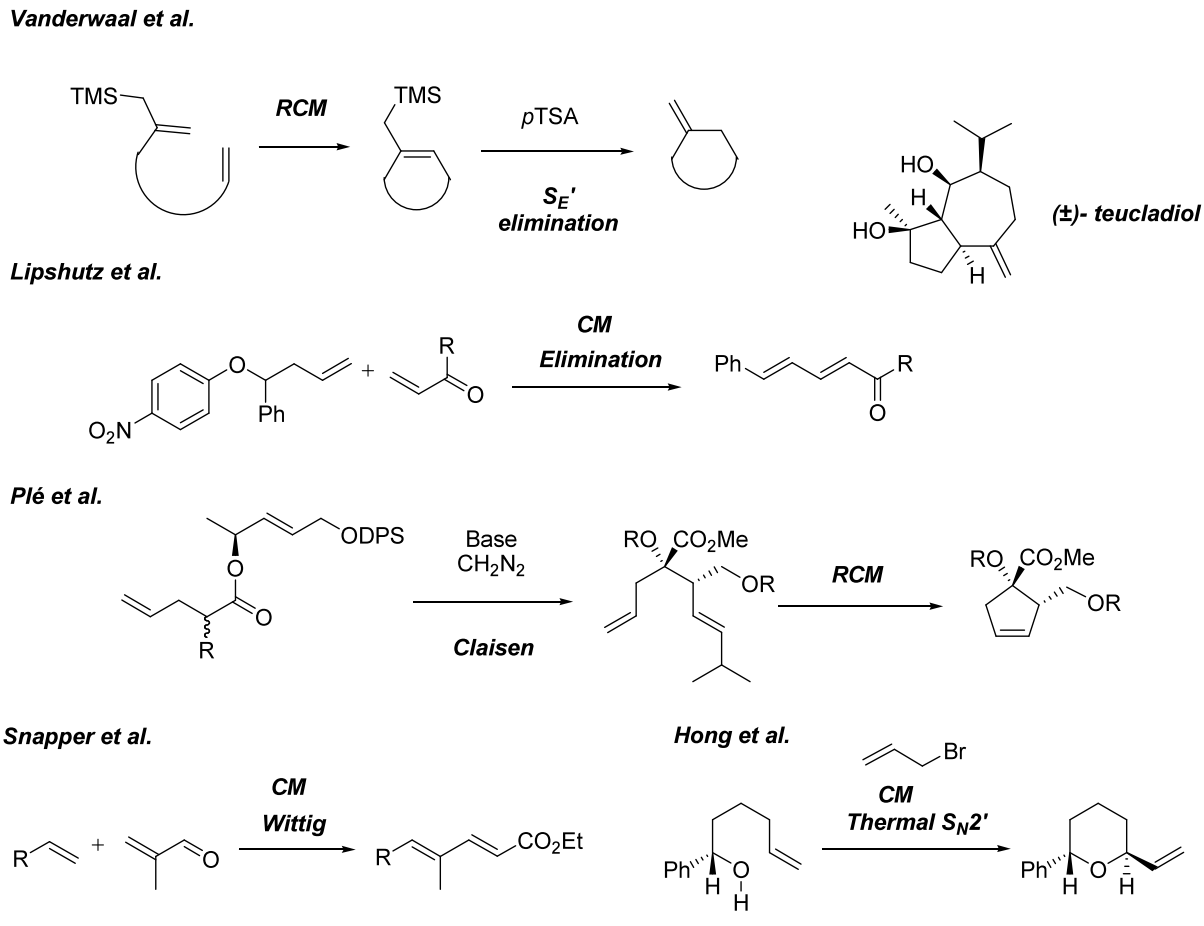


Scheme 80. One-pot metathesis-Lewis acid catalyzed reactions.

4.1.1.3 One-Pot Non-Catalyzed Transformation–Metathesis Reactions

All above described sequences involve ruthenium catalyzed transformations. Alternatively, metathesis can be combined with other non-catalyzed processes, which either modify the metathesis product furnishing more complex structures, or leads to the metathesis substrate itself.

For instance, metathesis has been often assembled with acid/base mediated transformations. One of the recent examples in the literature describes the synthesis of exocyclic methylenes by consecutive RCM-electrophilic desilylation (Scheme 81).[196] This transformation was promoted by catalyst **GII** with further treatment with *p*TSA, and was applied as a key step for the synthesis of the natural product (–)-teucladiol. Another interesting application describes the preparation of doubly unsaturated carbonyl derivatives described by Lipshutz, where a CM-elimination sequence is performed, using 4-nitrophenolate as leaving group.[197] The combination of Claisen rearrangements with RCM,[198] is often promoted by deprotonation and has been employed in the synthesis, for example, of quaternary hydroxy acid carbocycles.[199]

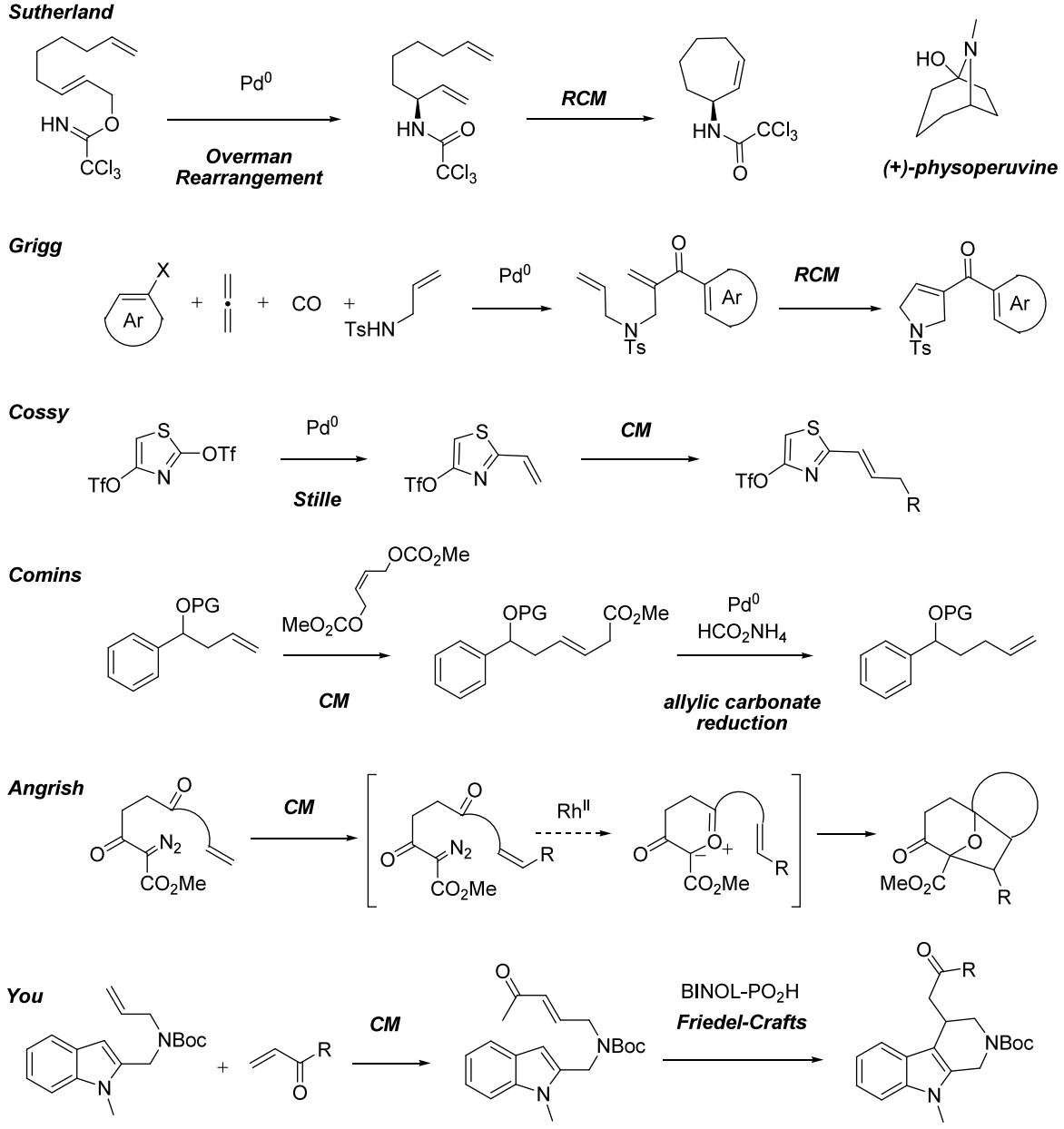


Scheme 81. One-pot metathesis–non-catalyzed reactions.

Combinations of metathesis with other non-catalyzed transformations have also been performed. In Scheme 81 are depicted remarkable examples from Snapper and Hong respectively, where CM is assembled to a Wittig olefination, to generate conjugated dienoic esters,[200] and to a thermal S_N2' reaction towards the formation of tetrahydropyran derivatives.[201]

4.1.1.4 Bi-Catalyzed One-Pot Metathesis Sequences

More interesting are one-pot processes under dual catalysis, since they broaden the spectrum of synthetically available products. In comparison with the one-pot methodologies described in Section 4.1.1.1, however, there are far less reports in this field. Most of these bi-catalyzed transformations describe combinations of metathesis and Pd-catalyzed reactions.



Scheme 82. Bi-catalyzed one-pot metathesis sequences.

The first account was published by Grigg in 2000, and explored tandem allenylation-RCM sequences (Scheme 82),[202] while more recent applications include the combination of Stille coupling with CM described by Cossy[203] or a tandem olefin cross-metathesis-allylic carbonate reduction developed by Comins within the field of one-carbon homologation reactions.[204] The combination of 3,3-sigmatropic rearrangements with metathesis has also been performed by dual Pd-Ru catalysis. A remarkable application of the described aza-Claisen-metathesis one-pot sequence comprises the combination of enantioselective Pd-catalyzed Overman rearrangement with RCM. This synthetic strategy has been explored by Shuterland and used as the key step for the synthesis of the tropan alkaloid (+)-physoperuvine.[205]

Other possible combinations involving metathesis include Rh- and Cu-catalyzed transformations. Angrisha reported in 2006 a remarkable contribution in one-pot bi-catalyzed metathesis sequences, in terms of structural complexity. A RCM with different styrene derivatives was followed by Rh-catalyzed intramolecular ylide formation and cycloaddition.[206]

A copper-catalyzed enantioselective allylation-RCM sequence was published by Alexakys and coworkers for the synthesis of enantiomerical enriched cyclopentene derivatives.[207]

Combinations of organocatalysis and metathesis have also been accomplished. Since ruthenium catalysts are rather stable in acidic conditions, metathesis has been often used in the presence of Brønsted acids. This was investigated by You and coworkers in a recently reported bi-catalyzed metathesis-Friedel-Crafts sequence.[208] Enantiomerically enriched polycyclic indoles were smoothly obtained by CM and subsequent alkylation catalyzed by chiral phosphoric acids.

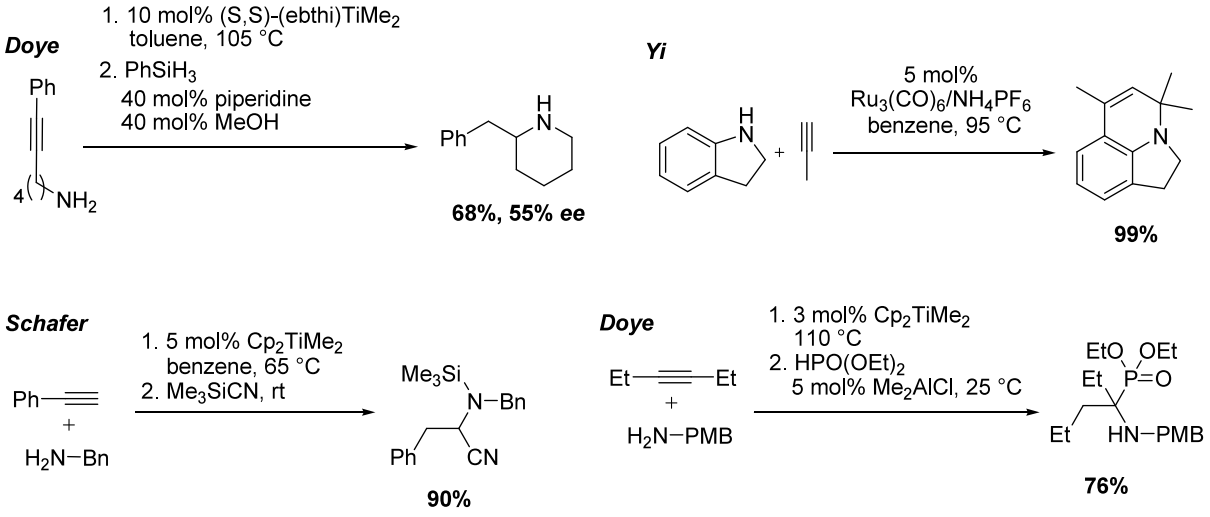
4.1.2 Hydroamination and Hydroamination-Based Tandem Transformations

One-pot sequences are an efficient method to introduce structural complexity and versatility to the hydroamination reaction, especially in the case of alkyne-hydroamination, since imines and enamines are a good target for further functionalization. Resembling metathesis tandem transformations, one-pot processes which contain hydroamination reactions can be divided into different subgroups considering if the non-hydroamination reaction is catalyzed by the same catalyst, forms part of a bi-catalytic sequence, or is a conventional non-catalyzed reaction.

4.1.2.1 Sequential Hydroamination-Metall Catalyzed Reactions

One type of reported one-pot reactions including hydroamination describes the combination of hydroamination with a hydrosilylation process, accomplished by using iridium,[209]

titanium,[210] and rare-earth[211] metal catalysts. The titanium catalysts (*S*,*S*)-(ebthi)$TiMe_2$, for instance, effectively catalyzed the intramolecular hydroamination-hydrosilylation sequence with good enantioselectivity using $PhSiH_3$ (Scheme 83).[212] Hydroaminations have been also combined in a tandem process with gold[213] or Ru-catalyzed hydroarylation,[214] and with diverse addition reactions[215] including nucleophiles such as Me_3SiCN,[216] or dialkyl phosphites towards precursors for α-amino phosphonates that can serve as building blocks for phosphorous containing peptide mimetics.[217]

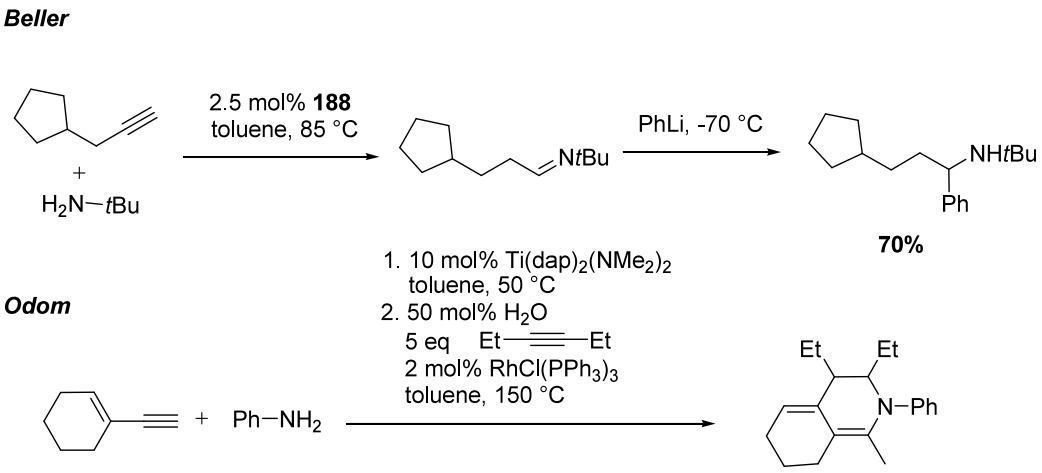


Scheme 83. Representative examples on sequential hydroamination-metal catalyzed reactions.

4.1.2.2 Other Hydroamination One-Pot Reactions

Excluding in situ reduction of unstable enamines and imines with $NaBH_4$,[218] for instance, there are very few reports on hydroamination tandem reactions including transformations that are not catalyzed by the hydroamination catalyst. One example describes the addition of organometallic reagents to the *in situ* generated aldimines, as convenient method for the preparation of secondary amines (Scheme 84). Anti-Markovnikov hydroamination with sterically demanding aliphatic amines to terminal alkynes catalyzed by $Cp_2Ti(\eta_2\text{-}Me_3SiC{\equiv}CSiMe_3)$ **188** is followed by nucleophilic addition of *n*-BuLi or PhLi, affording the desired amines in moderate to good yields.[219]

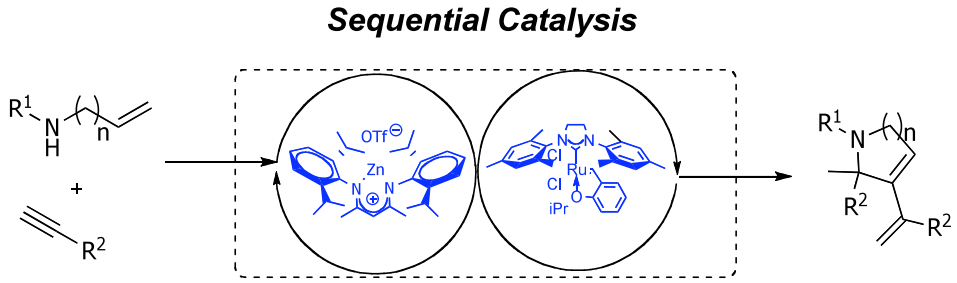
In the concrete case of bi-catalyzed transformations the only reactions described in the literature till to the date, consist in a Ti-catalyzed enyne hydroamination affording an α-unsaturated imine, which can be further functionalized by a Rh-catalyzed C-H-activation/alkyne insertion reaction to generate dihydropyridines after electrocyclic ring closure.[220] The drawback of this otherwise very elegant process, however, is that requires quenching of the titanium species to avoid interference with the rhodium catalyst.



Scheme 84. Examples on other sequential hydroamination reactions.

4.2 Objectives

There are only few examples of bi-catalyzed one-pot metathesis processes in the literature, and even less including hydroamination. In the presented work a novel one-pot transformation assembling RCM with Zn-catalyzed hydroamination tandem alkynylation will be developed (Scheme 85). This methodology should allow facile access to *N*-heterocyclic structures from secondary amines and unactivated alkynes without the need of isolating the enyne non-cyclic intermediates, minimizing costs and time consuming work up procedures.



Scheme 85. General synthetic strategy for sequential hydroamination-alkynylation-RCM.

This one-pot sequence will be performed on structurally different anilines and amine derivatives, to construct different ring-sized heterocycles and will be tested on bioactive-like molecules in order to demonstrate its synthetic potential.

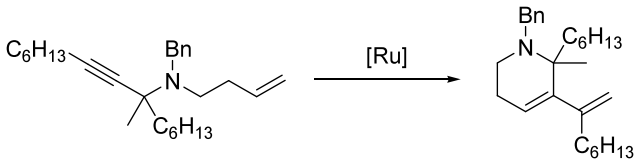
4.3 Results and Discussion

4.3.1 Preliminary Studies

To proof the viability of the proposed one-pot procedure, the feasibility of conducting enyne RCM of the enyne intermediates in presence of all by-products and decomposition products generated in the hydroamination reactions had to be addressed. Hence, even though RCM of propargyl amine **154** was already accomplished within the investigations in metathesis reactions with unprotected amines disclosed in Chapter 3, optimized reaction conditions for the RCM step had to be newly investigated on the crude material obtained from the hydroamination reaction.

The results presented in Table 31 were performed on the crude compound **154**, isolated after concentration at 50-60 °C under high vacuum, to remove the undesired excess of alkyne reagent. Alkyne **154** was then treated with different ruthenium catalysts at different temperatures (entries 1-4, Table 31), leading, as expected,[221] to no conversion towards the cyclized product. By conducting the reaction under ethylene atmosphere[222] and 1.05 eq of *p*TSA to prevent catalyst deactivation, 100% conversion towards the desired product **189** was achieved with first and second generation ruthenium catalysts (entries 5-7), showing that the employed ruthenium catalysts were compatible with the Zn-compounds and impurities present in the mixture. When octyne was still in the sample, however, catalyst inactivation or decrease in efficiency to promote the desired transformation was observed.

Table 31. Metathesis conditions screening.



154 **189**

Entry	Catalyst	Reaction Conditions	Additives	Conv [a]
1	10 mol% **GI**	DCM, 40 °C, 24 h	-	0%
2	10 mol% **GII**	DCM, 40 °C, 24 h	-	0%
3	10 mol% **HII**	DCM, 40 °C, 24 h	-	0%
4	10 mol% **HII**	toluene, 80 °C, 24 h	-	0%
5	5 mol% **GI**	DCM, 40 °C, 24 h	*p*TSA, ethylene	100%
6	5 mol% **GII**	DCM, 40 °C, 24 h	*p*TSA, ethylene	100%
7	5 mol% **HII**	DCM, 40 °C, 24 h	*p*TSA, ethylene	100%

[a] Determined by ^{1}H-NMR spectroscopy.

4.3.2 Synthesis of the Enyne Intermediates

Having ascertained the possibility of conducting the hydroamination-alkynylation-RCM one pot precedure, readily available amines were used to construct different eneyne intermediates. Olephinic anilines and benzyl amines with variations on the tether length were chosen in order to construct five-, six- and seven-membered heterocyclic compounds. Aniline derivatives are of special interest since they are present as structural unit in many herbicides, dyes and pharmaceutical compounds,[223] whereas benzyl amines can be readily deprotected under hydrogenolytic conditions to furnish the corresponding cyclic secondary amines which can be further functionalized.

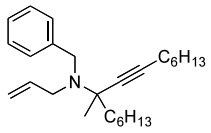
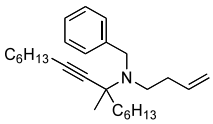
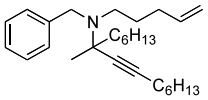
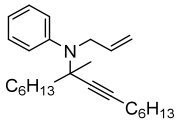
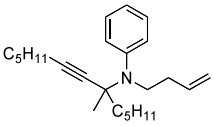
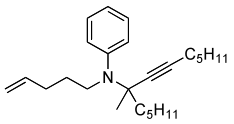
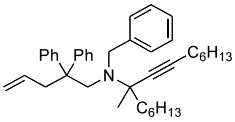
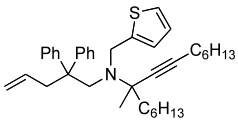
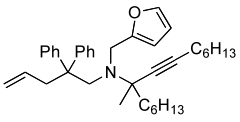
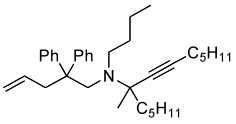
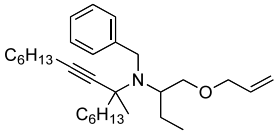
By using the reaction conditions published by Blechert and coworkers, complete conversion was successfully achieved for the benzylic amines **190a**, **190b** and **190c** (entries 1-3, Table 32). When its homologue aniline derivatives were employed, the reaction proceeded smoothly and the corresponding propargyl amines were also obtained with excellent conversions (entries 4-6).

Since the ring-closure step for seven-membered rings may be more challenging than for smaller ring sizes, **190g** was prepared with the purpose of favoring cyclization by Thorpe-Ingold-Effect (entry 7).[224,225]

With the aim of expanding molecular complexity the synthesis of compounds **190h-190k** was approached (entries 8-11). Compounds **190h** and **190i**, were smoothly obtained under the used reaction conditions, whereby, remarkably, no intramolecular hydroamination reaction was detected, indicating a high selectivity of catalyst **184** for hydroamination of triple bonds. Unfortunately, even though the formation of **190j** was detected by MS analysis of the crude material, very low conversion was achieved even after heating the reaction mixture at 120 °C for 7 days. In the case of allyl ether **190k** no conversion was detected either by NMR or Mass spectroscopy, possibly, due to a N-Zn-O quelate formation and subsequent deactivation of the catalyst.

We next investigated the possibility of conducting the hydroamination selectively with two different alkynes (Table 33). Therefore, the key step should imply one of the alkynes reacting preferently toward the enamin/imin intermediate and the other alkyne selectively performing the addition. We anticipated that a protected propargylic alcohol could be a suitable alkyne, since they have not shown to undergo hydroamination in previous reactions.[226] We first investigated the reaction of **191**, with TBS protected propargylic alcohol with heptyne under the standard procedure. Unfortunately, the silyl protecting group appeared to be unstable under the used reaction conditions, and a complicated product mixture was obtained. The corresponding benzyl protected alcohol **192**, on the other hand, showed good stability. By using 1.1 eq heptyne and 2.5 eq **192,** a mixture of products was obtained (entry 1).

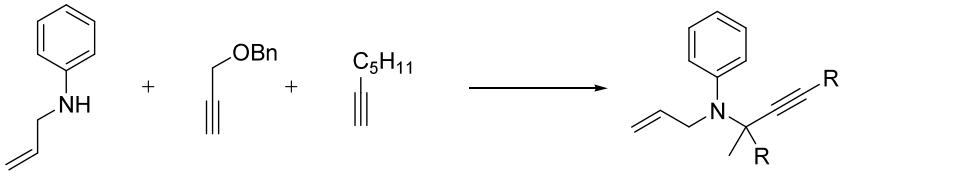
Table 32. Substrate scope on the hydroamination-alkyne addition step.

Entry	Product	Reaction Conditions [a]	Conv [b]
1		80 °C, 48 h	**190a** 100%
2		80 °C, 48 h	**190b** 100%
3		80 °C, 48 h	**190c** 100%
4		80 °C, 48 h	**190d** 100%
5		80°C, 48 h	**190e** 100%
6		80 °C, 48 h	**190f** 100%
7		80 °C, 48 h	**190g** 100%
8		80 °C, 48 h	**190h** 100%
9		80 °C, 48 h	**190i** 100%
10		80 °C, 48 h 120 °C, 168 h [c]	**190j** < 20 % [d] **190j** < 20 % [d]
11		80 °C, 96 h	**190k** 0%

[a] 1 eq amine (typically 0.3-0.38 mmol), 2.5 eq alkyne, catalyst **184** (10 mol%), toluene (typically 0.3-0.4 M). [b] Determined via ^{1}H-NMR spectroscopy. [c] In C_6D_6 in a flame-sealed NMR tube. [d] Estimated according the ESI-MS analysis of the crude material.

The obtention of **194b**, points out that **192** is indeed able to undergo hydroamination under the used catalytic conditions. By diminishing the number of equivalents of **192** added (entry 2) a good selectivity was obtained towards the desired product. Any attempts to purify the crude material, however, resulted in the isolation of inseparable product mixtures, which may well indicate the formation of both $R^1 = C_5H_{11}$, $R^2 = CH_2OBn$ and $R^1 = CH_2OBn$, $R^2 = C_5H_{11}$.

Table 33. Results obtained in mixed hydroamination-alkyne addition experiments with **192**.



191 **192** **193**

194a R^1, $R^2 = C_5H_{11}$
194b R^1, $R^2 = CH_2OBn$
194c $R^1 = C_5H_{11}$, $R^2 = CH_2OBn$
or $R^1 = CH_2OBn$, $R^2 = C_5H_{11}$

Entry	eq 192	eq 193	Reaction Outcome (192: 194a: 194b: 194c) [a]
1	2.5	1.1	0 : 1 : 24 : 38
2	1.1	1.1	1 : 19 : 18 : 121

[a] Determined by mass spectroscopy

4.3.3 Synthesis of Substrates with Potential Pharmacological Activity

In order to illustrate the utility of the Zn-Ru sequential catalysis we aimed to apply the sequential procedure in potentially pharmacologically active molecules. Natural products have always been a useful pool of molecules from which the pharmaceutical industry can find novel medicinal agents.[227] Steroids and analogue structures are of high interest in synthetic and medicinal investigations since they display a wide range of biological activities[228] such as anticonceptive,[229] anavolic, or anti-tumor for the treatment of prostate and breast cancers.[230] We envisaged that by sequential hydroamination-alkynylation-RCM very interesting steroid derivatives could be afforded from readily available precursors, delivering new compounds with potential biological properties (Figure 18).

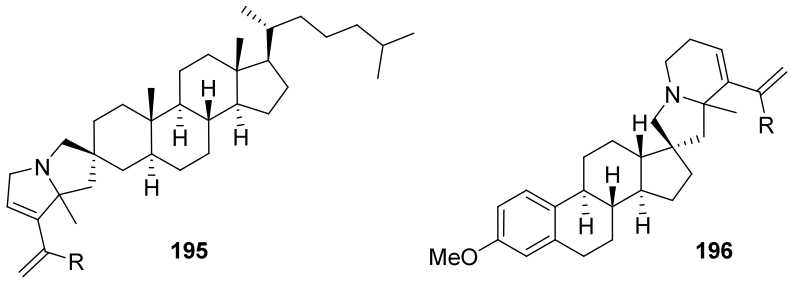
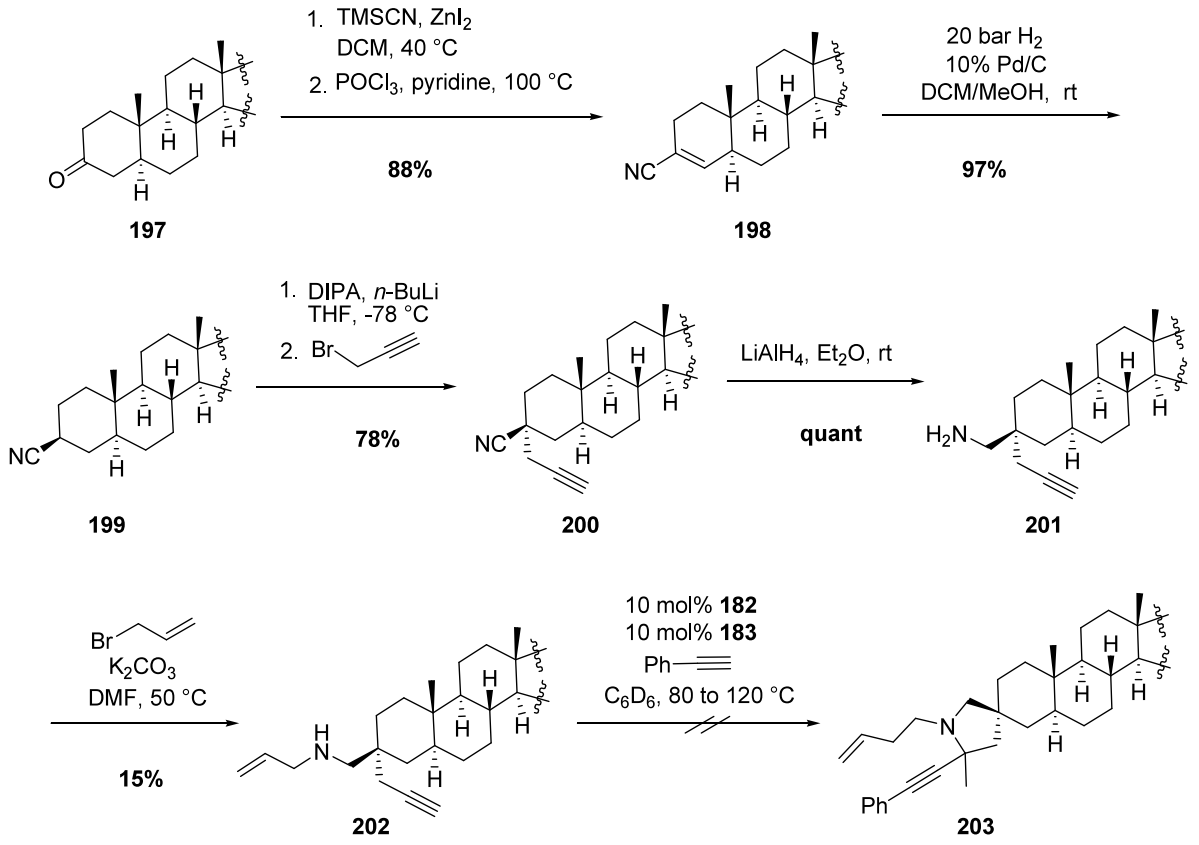


Figure 18. Proposed potentially active molecules synthesized by sequential Zn-Ru catalysis.

We first envisaged that structure **203** could afford the spiro-compound **195** by intra-molecular hydroamination followed by intermolecular alkyne additions, and subsequent metathesis (Scheme 85). The synthesis of compound **203** was afforded within five steps from commercially available cholestane **197**. Nucleophilic addition of cyanid was followed by dehydration with $POCl_3$ in pyridine. Hydrogenation under heterogeneous conditions afforded the carbonitrile derivative **199** selectively. Deprotonation and alkylation with propargyl bromide led to alkyne **200**, which was subsequently reduced to the corresponding amine and monoalkylated with allylbromide.

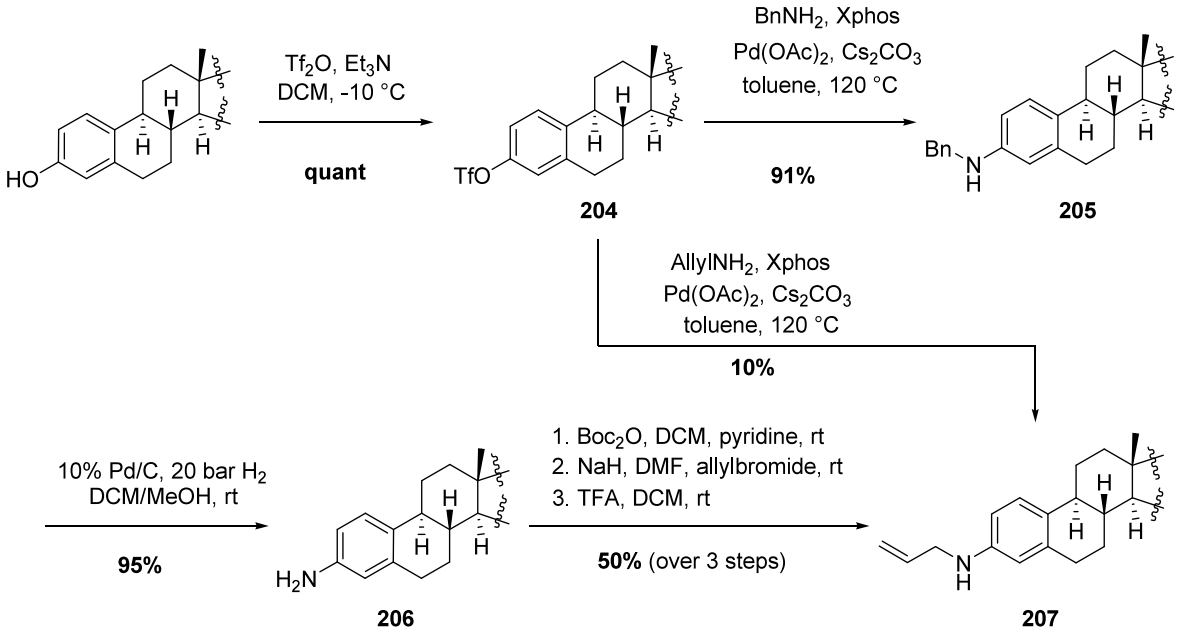


Scheme 85. Synthesis of cholestane derivative **203** and planned sequential hydroamination-alkyne addition-RCM towards **195**.

Unfortunately, attempts to obtain **203** under the usual applied reaction conditions furnished a complex mixture of products. From the obtained result it was not possible to determine the cause of the reaction failure, since many factors could be taken in account. On one hand, since no starting material was recovered, either the product, the intermediates or the starting material may present instability under the given reaction conditions. On the other hand, considering the obtained results with **190j**, amine derivative **202** may not be nucleophylic enough, or too sterically hindered to undergo the desired reaction. Further, the obtained results can be attributed to a preferred intermolecular alkyne-hydroamination *vs* intramolecular reaction, whilst the intramolecular formation of five-membered rings may be unfavoured with the used catalytic system. Synthetic studies towards **196** where therefore

not further investigated.

In order to overcome this problem, compound **207** was considered as substrate for an intermolecular Zn-Ru tandem reaction (Scheme 86). Allylamine **207** was prepared from precursor **206**, within three steps, whereby amine **206** was afforded *via* Buchwald-Hartwig Pd-catalyzed amination of estrone triflate **204**, and hydrogenation of the obtained benzylamine **205** following the published procedure of Schön and coworkers.[231] In the first step, a yield improvement was achieved by performing the reaction with triflate anhydride at lower temperatures and for a longer reaction time. The Bn deprotection was likewise optimized by carrying out an aqueous extraction, which also avoided the need of chromatographic purification. The protection and deprotection steps were conducted quantitatively, but the deprotonation and alkylation were relatively challenging due to competing α-alkylation to the cyclopentenone. To avoid all this synthetic manipulations direct Buchwald-Hartwig reaction with allyl amine was approached. Unfortunately, due to β-hydride elimination in the allylamine-Pd-estrone intermediate, a very low yield was obtained.



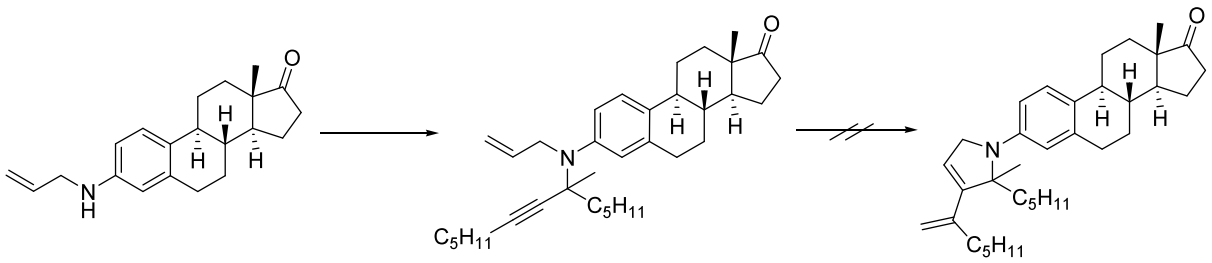
Scheme 86. Synthesis of substrate **207.**

With **207** in our hands, we performed several hydroamination-alkyne addition experiments (Table 34). Reactions were conducted in a flame-sealed NMR tube, with heptyne and catalyst **184** in C_6D_6. Temperatures between 80 and 100 °C afforded complete conversion to an intermediate compound, which furnished the desired steroid derivate **208**, upon heating at 120 °C. High concentration and high purity of compound **207** showed to be crucial for the success of the reactions. More diluted reaction conditions resulted in decomposition of the starting material, and residual silica gel caused catalyst decomposition.

Further metathesis experiments with **208** failed, due to instability of the obtained propargylic

amine **208** in the used conditions. Indeed, compound **208** decomposed in CD_2Cl_2 within less than 5 days, according to spectroscopic measurements (Table 35).

Table 34 and 35. Results in the sequential hydramination-alkyne addition-RCM with **207**.



207 **208** **209**

Entry	Conditions [a]	Conv [b]
1	80 °C, 72 h	0% [c]
2	100 °C, 72 h	0% [c]
3	120 °C, 48 h	100%

Entry	Catalyst	Conditions [d]	Conv [b]
1	10 mol% **GI**	DCM, 40 °C, 14 h	0%
2	10 mol% **GI**	DCM, *p*TSA, 40 °C, 14 h	0%
3	10 mol% **HII**	toluene, 70 °C, 14 h	0%
4	10 mol% **HII**	Toluene, *p*TSA, 70 °C, 14 h	0% [e]

[a] 1 eq amine, 2.5 eq alkyne, catalyst **184** (10 mol%), C_6D_6 (0.35 M). [b] Determined via ^{1}H-NMR spectroscopy. [c] Complete conversion towards the hydroamination intermediate. [d] 0.02 M in the indicated solvent, under ethylene atmosphere. [e] Complete decomposition was observed.

4.3.4 Studies on the Enyne RCM Step

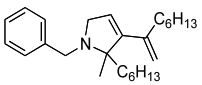
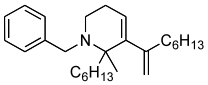
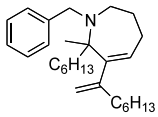
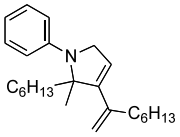
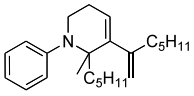
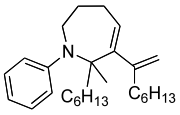
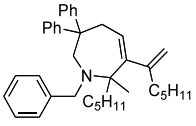
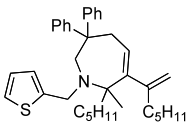
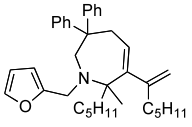
Cyclization of five, six and seven membered rings may require different conditions, therefore, the appropriate reaction conditions for the synthesis of the corresponding cyclized products *via* RCM for each compound were next investigated. In table 36 are presented the results of the optimization of the RCM of the crude en-yne intermediates.

N-benzyl dihydropyrrole **210a** was obtained with complete conversion at 80 °C in toluene with the use of 'second generation' catalyst **HII** (entry 5). For the aniline counterpart **210d** (entry 11), remarkably, complete conversion was achieved without the need of adding a Brønsted acid, and at very mild conditions. Six membered-rings were likewise smoothly afforded with **GI** at 40 °C (entries 6 and 12), whereas formation of seven membered-rings required higher temperatures and more temperature stable catalysts (entries 9, 14, 21). Propargylic amines **190g** and **190h** showed to be incompatible with the chosen reaction conditions. When no acid was used as additive, formation of the desired product was not observed, and when *p*TSA was added, decompositions occurred (entries 16-19). The furan derivate **190i** instead, showed enough stability and complete conversion towards the desired product **210i** was obtained at 80 °C in toluene (entry 21).

Concerning the catalyst loading, for reactions catalyzed with **GI**, a low mol% catalyst was sufficient to successfully afford the corresponding cyclized products with complete

conversion. For RCM proceeding at 80 °C in toluene, however, catalyst loadings of 10 mol% were needed. Initially, **HII** was the catalyst chosen, due to its improved stability at high temperatures compared with **GII** and **GI**. Nevertheless, ruthenium catalyst **GII** is also a suitable catalyst for the described one-pot procedure (entry 14).

Table 36. Substrate scope and metathesis conditions optimization.

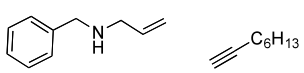
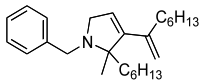
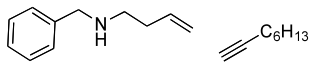
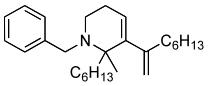
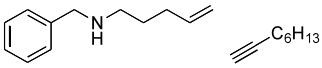
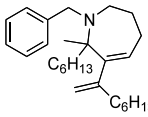
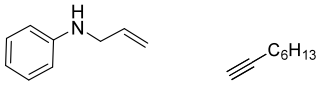
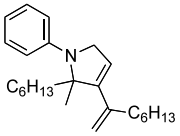
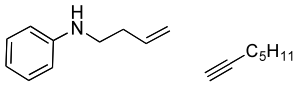
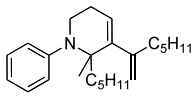
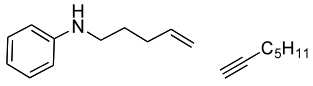
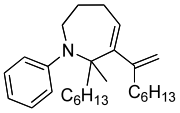
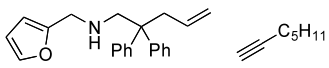
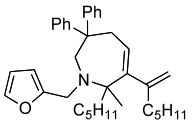
Entry	Product	[Ru]	Reaction Conditions [a]	Conv [b]
1		3 mol% **GI**	*p*TSA, DCM, 40 °C, 14 h	**210a** 0%
2		15 mol% **GI**	*p*TSA, DCM, 40 °C, 14 h	**210a** 32%
3		3 mol% **HII**	*p*TSA, DCM, 40 °C, 14 h	**210a** 12%
4		5 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210a** 50%
5		10 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210a** 100%
6		2.5 mol % **GI**	*p*TSA, DCM, 40 °C, 14 h	**210b** 100%
7		3 mol% **GI**	*p*TSA, DCM, 40 °C, 14 h	**210c** 0%
8		5 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210c** 32%
9		10 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210c** 50%
10		2 mol% **GI**	DCM, 40 °C, 14 h	**210d** 56%
11		3 mol% **GI**	DCM, 40 °C, 14 h	**210d** 100%
12		3 mol% **GI**	DCM, 40 °C, 14 h	**210e** 100%
13		10 mol% **HII**	toluene, 80 °C, 14 h	**210f** 50%
14		10 mo% **GII** [c]	toluene, 80 °C, 6 h	**210f** 100%
15		10 mol% **GI**	*p*TSA, DCM, 40 °C, 14 h	**210g** 0% [d]
16		10 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210g** 0% [e]
17		10 mol% **GI**	*p*TSA, DCM, 40 °C, 14 h	**210h** 0%
18		10 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210h** 0% [e]
19		5 mol% **HII**	toluene, 80 °C, 14 h	**210h** 0%
20		10 mol% **GI**	*p*TSA, toluene, 40 °C, 14 h	**210i** 0%
21		10 mol% **HII**	*p*TSA, toluene, 80 °C, 14 h	**210i** 100%

[a] 0.02 M in the indicated solvent, under ethylene atmosphere. [b] Determined via ^{1}H-NMR spectroscopy. [c] Added in 3 portions. [d] Partially substrate/product decomposition. [e] Complete decomposition was observed.

4.3.5 One-pot Procedures

Having optimized the reaction conditions for the hydroamination products, one-pot procedures were performed (Table 37). Benzyl amines and anilines are easily transformed to five, six and seven membered rings in a one-pot catalyzed transformation. The yields obtained lied in the range of 60-70%, which indicates that each transformation in the three step sequence proceeds with high yield. In most of the cases, complete conversions were achieved in both steps according to spectroscopical analysis, and no byproducts were formed in the metathesis reaction. Most of the presented compounds almost completely decomposed on SiO_2, hence, purification was performed with pentane (1% Et_3N) on SiO_2 or on Al_2O_3. The moderate yields obtained after purification are thus ascribed to the certain instability of the products under chromatographic purification.

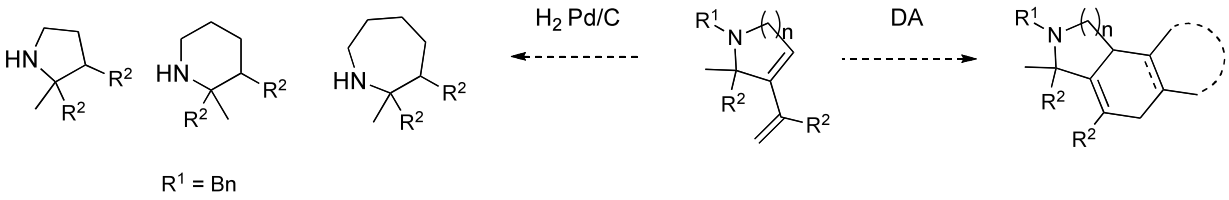
Table 37. Results of the one-pot hydroamination-alkynylation-metathesis sequence.

Entry	Substrates	Product	Reaction Conditions [a]	Yield [b]
1			Protocol A	**210a** 57%
2			Protocol B	**210b** 70%
3			Protocol A	**210c** 50% [c]
4			Protocol B	**210d** 60%
5			Protocol B	**210e** 65%
6			Protocol A [d]	**210f** 60%
7			Protocol A	**210i** 15% [e]

[a] Protocol A: i) ***1*** (10 mol%), toluene, 80 °C, 48 h. ii) **HII** (10 mol%), *p*TSA, toluene, 80 °C, 14 h. Protocol B: i) ***184*** (10 mol%), toluene, 80 °C, 48 h. ii) **GI** (10 mol%), *p*TSA, DCM, 40 °C, 14 h. [b] Obtained yields after purification by column chromatography. [c] 50% refers to the obtained conversion in the metathesis step. The yield was not quantified due to difficult separation from the hydroamination-alkyne addition product. [d] Catalyst **GII** was used in the metathesis step. [e] Decomposes easily on SiO_2.

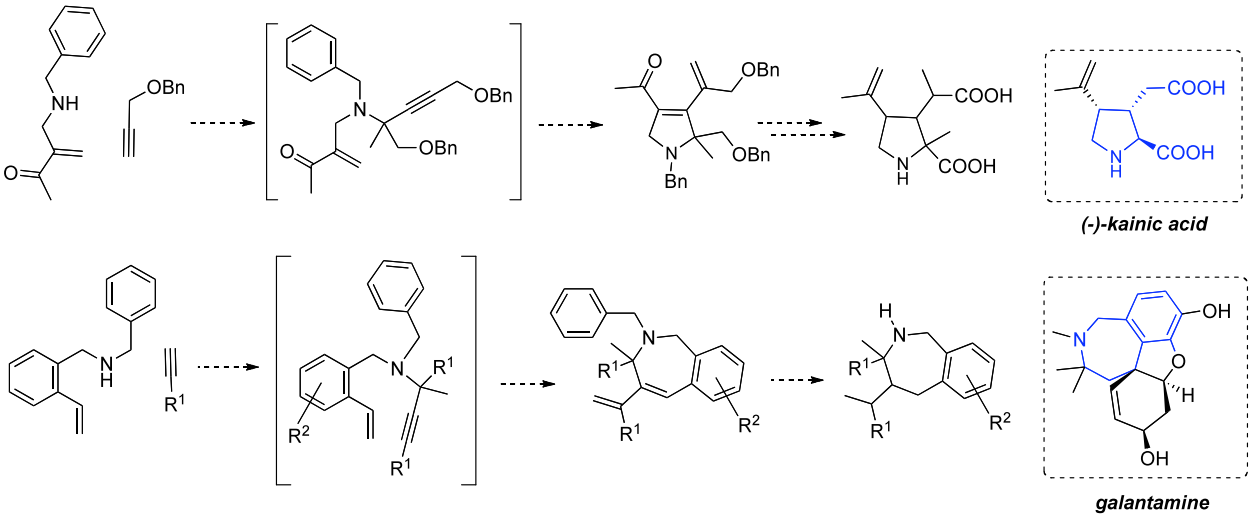
4.3.6 Synthetic Potential and Further Transformations

Very attractive structures result from the presented procedure which may easily furnish further functionalized heterocycles by simple hydrogenation. Such transformations may be especially convenient for the benzyl amine derivatives, since the protecting group cleavage occurs under hydrogenolytic conditions (Scheme 87). Alternatively the newly formed 1,3-diene units may serve as starting material to further transformations such as Diels-Alder (DA). Some preliminary experiments were performed with **210e** towards a sequential hydroamination-alkynylation-RCM-DA reaction unfortunately, following the published reactions conditions[193a-c] neither product nor starting material could be reisolated from the reaction mixture.



Scheme 87. Possible further transformation from the obtained products by one-pot hydroamination-alkynylation-RCM sequence.

Structures such as tetrahydro-pyrrolidines, piperidines and azepines are also of special interest since they are common structural features in biologically active molecules. The presented one-pot methodology, for instance, could serve as a key strategic step for the synthesis of derivatives of kainic acid[232] a marine natural product which possesses interesting biological properties and has attracted considerable attention in the scientific community (Scheme 88).



Scheme 88. Possible synthetic applications of the developed one-pot methodology in natural product-like combinatorial libraries.

The presented one-pot procedure is also a very suitable methodology for constructing combinatorial libraries. Benzazepines can be smoothly obtained in few steps with varied structural diversity, furnishing compounds that bear considerable resemblance to the structures of potent pharmacological drugs such as galantamine or fenoldopan.[233]

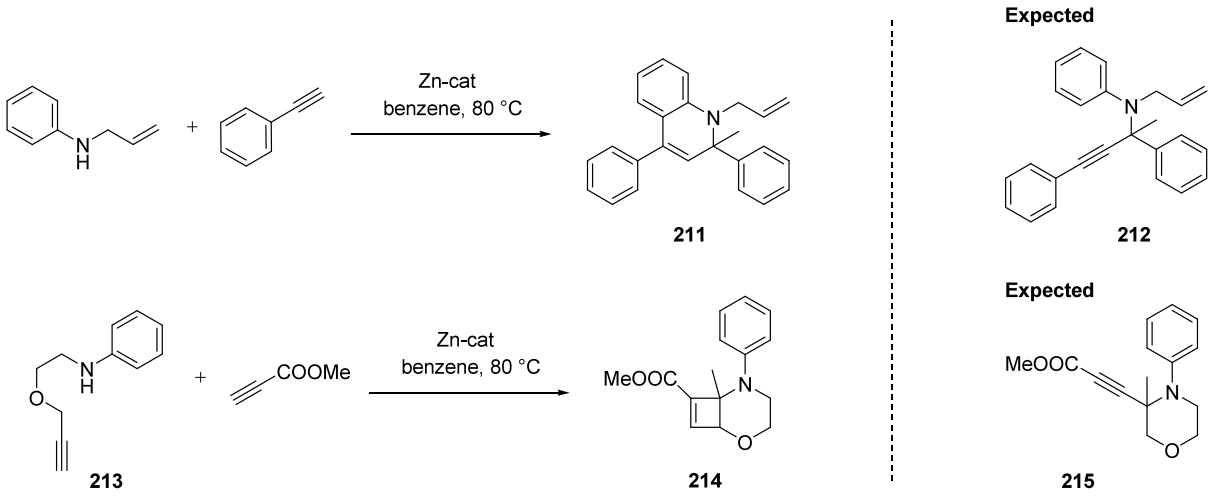
4.4 Summary and Outlook

A novel three-step hydroamination-alkylination-metathesis sequence has been presented. The combination of DBI-Zn complexes with Ru-based metathesis catalysts enables the formation of unsaturated *N*-heterocycles in a one-pot procedure, and is one of the few examples on both bi-catalyzed hydroamination and bi-catalyzed metathesis one-pot procedures, being the first report on a Zn-Ru sequential catalysis.

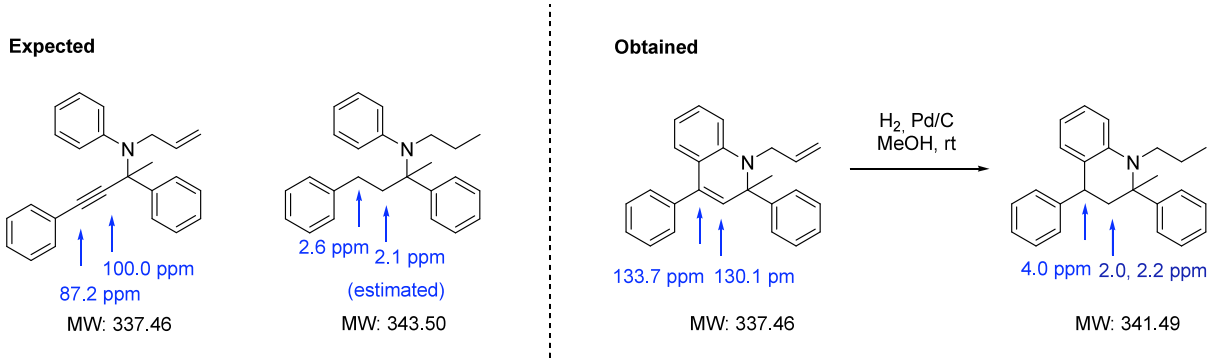
The studied transformation provides access to very complex structures in one synthetic step from readily available amines and inactivated alkynes in good yields, where tedious purification procedures, cost, labor and waste are reduced. The methodology is suitable for benzylic amines, anilines and other heterocyclic derived amines, and the products obtained, as well as further possible synthetic derivatives, are amine-containing compounds that resemble the structural core of different natural products. Furthermore, due to its easy practicability, this one-pot sequence is a suitable reaction for combinatorial chemistry, and can be interesting, for instance, for high-throughput-screening methods in pharma or agrochemical research.

4.5 Addendum

During the course of these investigations in collaboration with Biyikal unexpected products were isolated (Scheme 89). The hydroamination reaction of *N*-allyl aniline with phenylacetylene at 80 °C afforded an unknown substance **211** with **12%** yield, while the same reaction conducted at room temperature gave the desired propargyl amine **212.** ^{13}C-NMR analysis of compound **211** indicated the absence of an alkyne moiety and the non-equivalence of the hydrogens on the aniline ring. In order to verify the structure of the product isolated, **211** was hydrogenated on Pd/C (10%) at 30 bar H_2 atmosphere. By comparison of the spectroscopical data obtained with the estimated values, it was possible to confirm the tetracyclic structure of compound **211** (Scheme 90).



Scheme 89. Unexpected results obtained during hydroamination-alkynylation investigations.



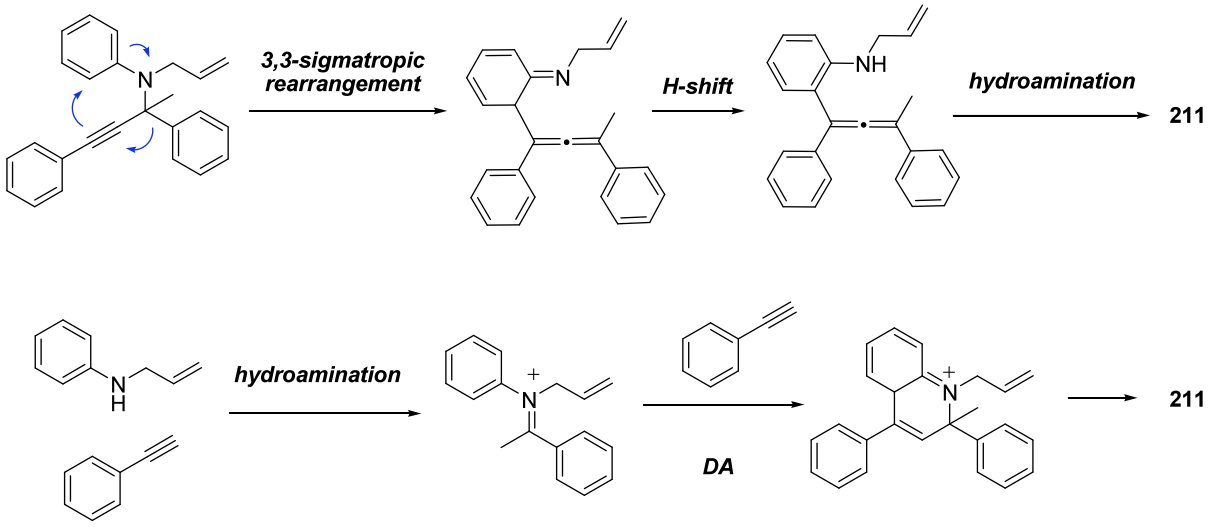
Sheme 90. Key spectroscopical data for the structure elucidation of **211**.

As a mechanistic explanation a [3,3]-sigmatropic rearrangement was proposed, followed by intramolecular hydroamination (Scheme 91). An alternative mechanistic explanation consists of a Diels-Alder (Povarov) reaction after the hydroamination step followed by

rearomatization. Different experiments were performed to verify the first hypothesis and to investigate the role of the catalyst in the reaction.

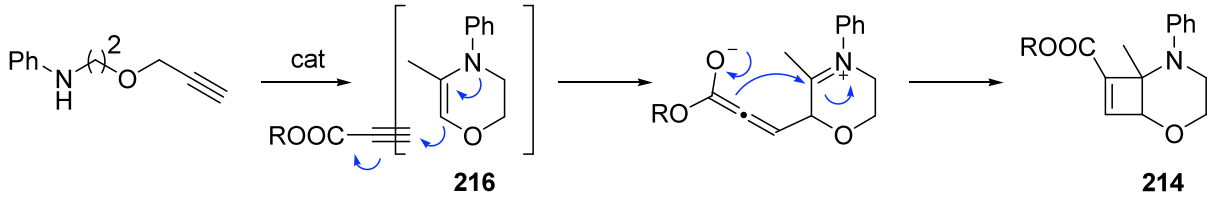
On one hand, when isolated amine **212** was heated at high temperatures only decomposition was observed, while when the same structure was heated in the presence of the pre-generated catalytic species, some product was detected via ^{1}H-NMR, along with many decompositions products. On the other hand, when product **212** was heated at 120 °C for several days, no decomposition was observed, while addition of the Zn-catalyst promoted the formation of one single product, whose structure could not be determined.

Further investigations on the mechanism, substrate scope and optimal reactions conditions are currently being performed in the group.



Sheme 91. Proposed mechanisms for the obtention of **211**.

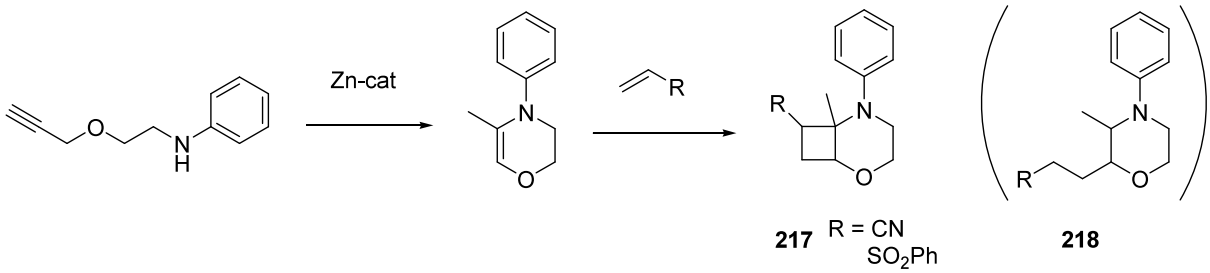
A further unexpected result was obtained in the intramolecular hydroamination reaction of aniline **213** followed by addition of methyl propionate under standard reaction conditions (Scheme 92). Again, the absence of quaternary carbons in the ^{13}C-NMR spectra corresponding to the alkyne moiety indicated the formation of a product different from the expected compound **215**. Further spectroscopical analysis and NOE experiments indicated the presence of a fused cyclobutene unit in the product structure. As a mechanistic explanation a hydroamination-Michael-Mannich cascade was proposed (Scheme 92).



Scheme 92. Proposed mechanism for the formation of **214**.

According to this hypothesis, intermediate **216** should also react with other Michael acceptors in a similar manner. In collaboration with Lenard Hussein, some preliminary experiments were performed by reacting the *in situ* generated enamine **216** with acrolein, acrylonitryl and vinylsulfone (Scheme 93). Instead of the bicyclic compounds **217**, analysis by ^{1}H-NMR spectroscopy indicated the formation of **218** with acrylonitrile and vinylsulfone, while acrolein led to a complex mixture of polymeric compounds.

Further investigation on the reaction mechanism and substrate are currently being performed in the group.



Scheme 93. Preliminary experiments on the investigation of sequential hydromination-Michael-Mannich additon sequence.

Chapter 5

Experimental Part

Chapter 5

Experimental Part

5.1 Materials and Methods

General Experimental Details. All moisture sensitive reactions and reactions involving organometallic reagents were performed in flame-dried glassware under positive pressure of nitrogen, with freshly distilled solvents.
Diethyl ether, toluene, and tetrahydrofuran were distilled over sodium, methanol over magnesium and DCM over phosphorus pentaoxide. Benzene and DMF, were distilled over calcium hydride and were stored over 4 Å MS. 1,2-dichloroethane, acetone, acetonitrile and DMSO over phosphorus pentaoxide, and stored over 3 Å MS, while benzene was stored on sodium. Pyridine was stored over KOH (20 g/l) and used without further purification.
Reactions with air labile catalysts were conducted in an inert gas box MB 120 GB from *MBraun* under nitrogen atmosphere.
The term "concentrated under reduced pressure", unless otherwise indicated, refers to the removal of solvents and other volatile materials using a rotary evaporator with the water bath temperature at 40 °C, followed by removal of residual solvent at high vacuum (< 0.2 mbar).

Materials. Unless otherwise specified, all substances were purchased from commercial suppliers and used without further purification.
Ruthenium catalyst **GII**,[234] **HI**,[93] **HII**,[235] **WI,**[120] **GRI**[147]and **BVIII**[102] were prepared according to the published procedures. Unsymmetrical catalyst **BIII** and **BIV** were kindly purchased from M. Lichtenheld and K. Velow, catalyst **BV** was prepared by D. Rost, **BVII** was synthesized by A. Giraud, catalyst **FII** and **BVI** by K. Vehlow and complexes **BI** and **BII** by P. Deshmukh from the Blechert group.

Column chromatography was performed with silica gel (40-63 µm), aluminum oxide basic grade III (6% water) from *Fluka* or silica RP C-18 (18-32 µm) from *ICN Biomedicals GmbH*.

Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} precoated plates, aluminum oxide 150 F_{254} precoated plates or RP-18 precoated plates F_{254}s from *Merck.*
The substances were detected by visualization under a UV lamp (254 nm) and revealed using permanganate reagent (2.5% $KMnO_4$ in 5% NaOH aqueous solution), vanillin (1 M

H_2SO_4 ethanolic solution of vanillin), ninhidrin (0.2 g / 100 mL EtOH) or cerium molybdate solution (40 g of ammonium pentamolybdate + 1.6 g of cerium (IV) sulfate + 800 mL of diluted sulfuric acid -1:9, with water, v/v-).

Preparative thin layer chromatography was carried out on silica-plates (F_{254}, 20 x 20 cm, 60 A) from *ICN Biomedicals* or on aluminum oxide-plates (F_{254}, 20 x 20 cm, 150 T) from *Merck*.

^{1}H-NMR were recorded on an *AM 400* (400 MHz) and *DRX 500* (500 MHz), spectrometer from *Bruker* in $CDCl_3$, CD_2Cl_2, C_6D_6, CD_3CN, or d_6-Acetone. Chemical shifts are expressed in part per million (ppm), relative to the internal solvent peak. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), or a suitable combination. Coupling constants were rounded to the nearest 0.1 Hz.

^{13}C NMR and **2D-NMR** (COSY, HMBC, HMQC) spectra were recorded an *AM 400* (100 MHz) and *DRX 500* (126 MHz) spectrometer from *Bruker*.

IR spectra were obtained as ATR (Attenuated Total Reflectance) on a *Perkin-Elmer 881* spectrometer. The bands are given in wave numbers (cm^{-1}) and the intensity is abbreviated as follows: s: strong, m: medium, w: weak.

GC-MS spectra were recorded on a *GC HP 6890* with a glass capillary column HP-1 (25 m, ID 0.25 mm, film thickness 0.3 mm) and *MSD HP 5971 A* detector from *Hewlett-Packard.*

MS and **HRMS** spectra were recorded on a *Finnigan MAT 95 SQ* or *Varian MAT 711* and measured by EI (electron ionization) method at an ionization potential of 70 eV. The vaporization temperature is given in each case. The intensities are in percent relative to the highest signal. Masses are given in ppm.

ESI-MS spectra were recorded on an *Agilent Technologies 1200 Series* (UV/Vis-Detector G1315D DAD; autosampler G1329A ALS; G1312A Bin Pump; MS Agilent Technologies 6130 Quadrupole LC/MS).

ESI-HRMS spectra were recorded on a LTQ XL FTMS autosampler (MeOH + 0.1% HCO_2H, 200µL/min flow) from *Thermo Scientific* and measured by EI (5 kV ionization potential).

Melting points were measured on a *Büchi 535* apparatus and are uncorrected.

Optical rotations were recorded on a *Perkin-Elmer 341* polarimeter at 20 °C, with sodium D line at 589 nm, and are given as a_D^{20} (concentration in gram/100mL of solvent).

Hydrogenation experiments were performed in an autoclave reactor or in a *H-Cube™ Hydrogenation reactor* HC 2-ST 1 from *THALES Nanotechnology Inc.*

Ozonolisis reactions were performed on an *Ozone Generator 500* from *Fischer technology*.

Microwave-reactions were performed in a *Discover-Microwave* from *CEM.*

The **chemical names** of the synthesized compounds were generated by Cambridge Soft Chemdraw Ultra 11.0, which is in accordance with Beilstein nomenclature. Atom numbering is given in the structural representation for each experimental data set. For clarity, the atom numbering in the figures does not always follow the IUPAC-nomenclature.

5.2 Experimental Section for Chapter 2

5.2.1 General Procedures

General procedure for the sequential Swern oxidation - Seyferth Gilbert homologation of alcohols to the corresponding alkynes.

To a solution of 3 eq DMSO in anhydrous CH_2Cl_2 at -78 °C, 1.5 eq oxalylchlorid was slowly added maintaining the temperature below -70 °C (exothermic reaction occurred). Approximately 15 min after addition was finished, a solution of the substrate in CH_2Cl_2 was added dropwise, again maintaining the solution temperature below -70 °C. The reaction was further stirred for 30 min. Finally, and still at -78 °C, 3 eq Et_3N were given *via* cannula, paying attention to the mixture temperature, and the reaction was then allowed to warm up to rt for 1 h. Work up was performed by washing once with sat. aqueous solution of $NaHCO_3$. The organic layer was then dried over $MgSO_4$ and concentrated. Without further purification, the crude material was dissolved in anhydrous MeOH with subsequently addition of 1.2 eq of **50** and 2 eq of K_2CO_3. The suspension was stirred at rt and when complete conversion was achieved, the reaction was diluted with MTBE, filtered through a pad of Celite and concentrated under reduced pressure. The obtained crude material was usually purified by column chromatography.

Typical procedure for ammonium salt formation.

7 mmol of substrate were dissolved in CH_2Cl_2 and 1.03 eq of Brønsted acid were added. The mixture was then slowly concentrated under reduced pressure and purified by column chromatography (EtOAc → MeOH, elution with EtOAc to remove impurities, and further elution with MeOH to isolate the desired salt). For *p*TSA salts, stirring at 40 °C for 30 min was needed in order to dissolve the acid. Purification on column chromatography was avoided since slight excess on *p*TSA do not interfere in the metathesis reaction. In the case of HCl salts, when prepared with 12 M HCl, several azeotropic distillations were conducted. Alternatively, salt formation was performed with anhydrous 2.5 M ethereal HCl, where the excess of HCl was removed by evaporation.

Typical procedure for enyne RRM experiments under normal ethylene pressure.

With pre-synthesized ammonium salt: typically 0.03 - 0.06 mmol of substrate were dissolved

in anhydrous solvent (CH_2Cl_2, benzene, dichloretane or toluene, 0.01 M - 0.02 M) in a 10 mL Schlenk flask. The solution was then flushed with ethylene via cannula before the catalyst was added (2 - 10 mol%). The mixture was the flushed again for 30 seconds and stirred at the desired temperature. Usual work-up procedure consisted in extracting with aqueous sat. $NaHCO_3$ solution. The organic layer was then separated and the aqueous phase was extracted once with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. In experiments for catalyst and reaction conditions screening no further purification was performed. Otherwise, the crude material was purified by column chromatography and then distilled *via* bulb-to-bulb distillation.

Ammonium salt formed prior to use: 0.03 mmol of substrate was dissolved in CH_2Cl_2 approx. 0.02 M in a 10 mL Schlenk flask and the desired Brønsted acid was added. The mixture was stirred at 40 °C for approx. 20 min and the solvent was evaporated under reduced pressure (high vacuum). CH_2Cl_2 was again added and the mixture was azeotropically evaporated. The obtained salt was dissolved in anhydrous solvent and the same procedure as indicated above was conducted.

Typical procedure for enyne RRM experiments under high ethylene pressure.

A solution of substrate was placed in a thick wall Schlenk flask and concentrated under reduced pressure (high vacuum). Anhydrous solvent was then added, flushed with H_2 *via* cannula for 5 min and filled with ethylene, directly from the gas bottle, at the desired pressure. A catalyst solution in anhydrous solvent was then injected via cannula and the resulting mixture was stirred at rt for the desired time. The same work-up procedure as described above was then applied.

Typical procedure for hydrogenations experiments under normal H_2 pressure.

Typically the substrate was dissolved in MeOH in a one-neck round-bottom flask and the hydrogenation catalyst was added. The reaction mixture was flushed with H_2 *via* cannula for 5 min and stirred for the desired time. When complete conversion was achieved, the reaction mixture was filtered through a pad of Celite, concentrated and purified by column chromatography if necessary.

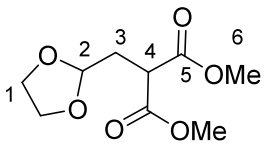
Typical procedure for hydrogenations experiments under higher hydrogen pressure.

To a solution of the substrate in MeOH in a one-neck round-bottom flask the catalyst was added. The reaction was placed in an autoclave and purged several times with argon and

subsequently with H_2 before applying the desired hydrogen pressure. After purging, the reaction was heated at the desired temperature. After the given time, the solution was filtered through a pad of Celite and concentrated *in vacuo* to afford the crude material, which was then purified by column chromatography if necessary.

5.2.2 Procedures and Spectroscopic Data

Dimethyl 2-((1,3-dioxolan-2-yl)methyl)malonate 18



$C_9H_{14}O_6$
218.20 g/mol

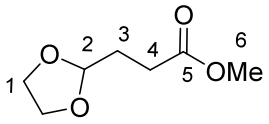
To a suspension of K_2CO_3 (32.8 g, 237 mmol) and TBAI (2.92 g, 10 mol%) in 160 mL anhydrous THF at rt, dimethylmalonate (8.6 mL, 73.4 mmol) and 2-brommethyl-1,3-dioxolane (18.6 mL, 176 mmol) were added *via* syringe. The reaction mixture was refluxed for 110 h, and after cooling down to rt, MTBE was added, the inorganic residue was filtered off, and the organic layer was concentrated. The crude material was purified by column chromatography (SiO_2, cyclohexane/EtOAc 10:1 → 4:1) to give **18** (10.0 g, 62%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.00 (t, *J* = 3.7 Hz, 1H, H-2), 3.97-3.90 (m, 2H, H-1), 3.86-3.82 (m, 2H, H-1), 3.74 (s, 6H, H-6), 3.63 (t, *J* = 6.1 Hz, 1H, H-4), 2.36 (dd, *J* = 7.1 Hz, *J* = 3.7 Hz, 2H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 169.7 (C-5), 101.9 (C-2), 65.2 (C-1), 52.7 (C-6), 46.4 (C-4), 32.5 (C-3).

R_f (SiO_2, cyclohexane/EtOAc 5:1) = 0.11.

Methyl 3-(1,3-dioxolan-2-yl)propanoate 19



$C_7H_{12}O_4$
160.17 g/mol

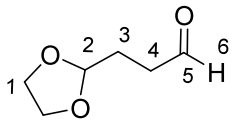
Dimethyl 2-((1,3-dioxolan-2-yl)methyl)malonate **18** (1.00 g, 4.5 mmol) and LiCl (388 mg, 9.16 mmol) were dissolved in wet DMSO and heated overnight at 160 °C. After cooling down to rt, the solution was poured into CH_2Cl_2 and washed three times with brine. The combined organic layer were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (SiO_2, cyclohexane/EtOAc 10:1 → 4:1) to afford **19** (595 mg, 83%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.95 (t, *J* = 4.4 Hz, 1H, H-2), 3.99-3.93 (m, 2H, H-1), 3.91-3.84 (m, 2H, H-1), 3.69 (s, 3H, H-6), 2.46 (t, *J* = 7.6 Hz, 2H, H-4), 2.03 (m, 2H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.7 (C-5), 103.1 (C-2), 65.1 (C-1), 51.7 (C-6), 28.8 (C-4), 28.1 (C-3).

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.21.

3-(1,3-dioxolan-2-yl)propanal 13



$C_6H_{10}O_3$
130.14 g/mol

From methyl 3-(1,3-dioxolan-2-yl)propanoate **19***:* To a solution of **19** (300 mg, 1.87 mmol) in anhydrous CH_2Cl_2 (14 mL) at -78 °C, DIBAL-H (1.4 mL, 2.06 mmol) was added dropwise over 30 min. After 8 h the reaction mixture was quenched with MeOH (2 mL) and a saturated aqueous solution of Na_2SO_4 (4 mL) and let warm up to rt. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to furnish **13** (100 mg, 41%) as a colorless oil.

From 3-(1,3-dioxolan-2-yl)propan-1-ol: the titel alcohol (200 mg, 1.53 mmol) and DMSO (435 µL, 6.14 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL) at -78 °C and oxalylchlorid (263 µL, 3.07 mmol) was added. Stirring continued at -78 °C for 60 min before Et_3N (2.16 mL, 15.3 mmol) was added and the reaction was allowed to warm up to rt. After addition of 5 mL 2 M HCl solution, the organic phase was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to provide the pure aldehyde **13** (100 mg, 50%).

From 2-(but-3-enyl)-1,3-dioxolane **21***:* A solution of 2-(but-3-enyl)-1,3-dioxolane **21** (5.1 g, 39.8 mmol) in CH_2Cl_2 (100 mL) was flushed with O_3 at -78 °C for 3 h, until a blue color persisted. The excess of ozone was removed by passing a stream of nitrogen gas through the solution. Subsequently, PPh_3 (10.5 g, 39.8 mmol) was added and the reaction mixture was allowed to warm up to rt overnight. 100 mL from a mixture Et_2O/hexane 1:1 were added and the precipitate formed was filtered off. The organic phase was evaporated and the crude material purified by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) to obtain **13** (400 mg, 8%) in poor yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 9.75 (s, 1H, H-6), 4.95 (s, 1H, H-2), 3.93 (br s, 2H, H-1), 3.84 (br s, 2H, H-1), 2.53 (t, *J* = 7.6 Hz, 2H, H-4), 2.04 (m, 2H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 201.6 (C-5), 103.0 (C-2), 65.1 (C-1), 37.6 (C-4), 26.3 (C-3).

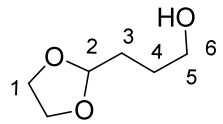
IR (ATR): ν (cm^{-1}) = 3404 (br w), 3210 (br w), 2953 (m), 2933 (m), 2888 (m), 1734 (s), 1397 (m), 1137 (s), 1070 (m), 1031 (s), 946 (m).

LRMS-ESI: *m/z* (%) = 131 (90) [MH^+], 111 (40), 102 (100), 80 (20).

HRMS-ESI (MH^+, $C_6H_{11}O_3$) = calcd: 131.0708, found: 131.0701.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.10.

3-(1,3-dioxolan-2-yl)propan-1-ol

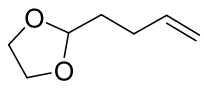


$C_6H_{12}O_3$
132.16 g/mol

Methyl 3-(1,3-dioxolan-2-yl)propanoate **19** (620 mg, 3.87 mmol) dissolved in anhydrous Et_2O (5 mL) was slowly added to a suspension of $LiAlH_4$ (88 mg, 2.32 mmol) in anhydrous Et_2O (5 mL) at 0 °C under nitrogen atmosphere. After 4 h the reaction was quenched with 1 mL of a 10% aqueous H_2SO_4 solution. The organic layer was then filtered, dried and concentrated. The title compound (250 mg, 50%) was obtained as a clear oil and was directly used in the next step.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.90 (t, *J* = 4.4 Hz, 1H, H-2), 4.01-3.85 (m, 4H, H-1), 3.67 (t, *J* = 6.0 Hz, 2H, H-5), 1.83-1.67 (m, 4H, H-3, H-4).

2-(but-3-enyl)-1,3-dioxolane 21

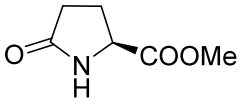


$C_7H_{12}O_2$
128.17 g/mol

Allyl vinyl ether (5.6 g, 66.3 mmol) was heated overnight at 150 °C in a sealed tube to furnish pent-4-enal **20** (5.4 g, 97%) which was used in the next step without further purification.

$RuCl_3 \cdot H_2O$ (225 mg, 10 mol%) was added to a mixture of pent-4-enal (841 mg, 10 mmol) and ethane-1,2-diol (2 mL) and the reaction mixture was stirred at rt for 10 h. After addition of 15 mL of a mixture 1:1 Et_2O/H_2O, the organic phase was separated, dried over $MgSO_4$ and concentrated to furnish almost pure 2-(but-3-enyl)-1,3-dioxolane **21** (730 mg, 57%), which was directly used in the following step.

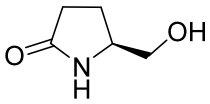
(*S*)-methyl 5-oxopyrrolidine-2-carboxylate 35



$C_6H_9NO_3$
143.14 g/mol

Was prepared according to the procedure described by Enders and coworkers: *Angew. Chem. Int. Ed.* **2006**, *45*, 1463–1467.

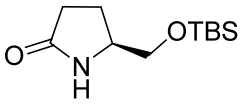
(*S*)-5-(hydroxymethyl)pyrrolidin-2-one



$C_5H_9NO_2$
115.13 g/mol

Was synthesized according to the procedure described by Enders and coworkers: *Angew. Chem. Int. Ed.* **2006**, *45*, 1463–1467.

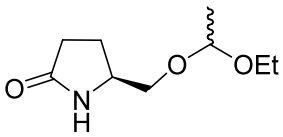
(*S*)-5-((tert-butyldimethylsilyloxy)methyl)pyrrolidin-2-one 34



$C_{11}H_{23}NO_2Si$
229.39 g/mol

Was synthesized according to the procedure described by Somfai and coworkers: *J. Org. Chem.* **2007**, *72*, 4246–4249.

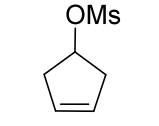
(*S*)-5-((1-ethoxyethoxy)methyl)pyrrolidin-2-one 35



$C_9H_{17}NO_3$
187.24 g/mol

Was synthesized according to the procedure described by Lee and coworkers: *J. Am. Chem. Soc.* **2000,** *122,* 4295–4303.

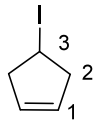
Cyclopent-3-enyl methanesulfonate 38



$C_6H_{10}O_3S$
162.21 g/mol

Was prepared from cyclopenatdiene in three steps according to the procedure described by Nelson and coworkers: *Org. Biomol. Chem.* **2004**, *2*, 2874–2883.

4-iodocyclopent-1-ene 39



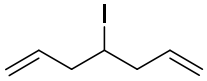
C_5H_7I
194.01 g/mol

38 (700 mg, 4.3 mmol) was dissolved in anhydrous acetone (4.3 mL, 1 M) and NaI (1.3 g, 8.6 mmol) was added. The reaction was allowed to stir at rt under light protection for 10 days. 10 mL of water were then added and the mixture was extracted with Et_2O (3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated. After bulb-to-bulb distillation the desired product **39** was obtained as a colorless liquid (416 mg, 50%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.75 (s, 1H, H-3), 4.71 (m, 1H, H-1), 4.10 (d, *J* = 4.0 Hz, 1H, H-1), 2.98-2.83 (m, 4H, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.5 (C-1), 46.6 (C-2), 22.7 (C-3).

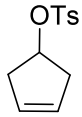
4-iodohepta-1,6-diene 41



$C_7H_{11}I$
222.07 g/mol

Was prepared according to the procedure described by Hutchison and coworkers: *J. Org. Chem.* **2006**, *71,* 9622–9627.

Cyclopent-3-enyl 4-methylbenzenesulfonate 37

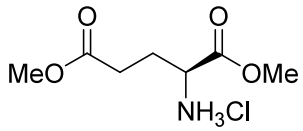


$C_{12}H_{14}O_3S$
238.30 g/mol

The published procedure was modified as follows: Alcohol **23** (14.17 g, 0.17 mol) was dissolved in pyridine (210 mL) and TsCl (48.20 g, 0.25 mol) was added at 0 °C. The reaction stirred at this temperature for 3 h and poured into ice/12 M HCl (240 g / 72 mL). Once the ice had melted, the water phase was extracted several times with EtOAc, and the combined organics were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 10:1) and tosylate **37** was obtained as a white solid (35.15 g, 88%).
The spectroscopic data are in full agreement with those published in the literature.[236]

(*S*)-glutamic acid methyl ester 43

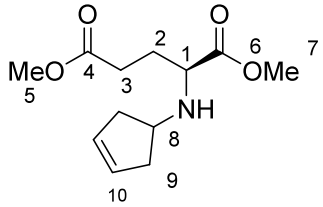
To a solution of (*S*)-glutamic acid (12.0 g, 81.6 mmol) in anhydrous MeOH (120 mL), $SOCl_2$ (14.2 mL, 196 mmol) was added dropwise at 0 °C. After stirring 2 h at rt the solvent was



$C_7H_{14}ClNO_4$
211.64 g/mol

removed under reduced pressure and the crude material was recristallized in ethyl acetate to furnish substrate **43** (16.91 g, 98%) as a white solid, which was used without further purification.

(*S*)-dimethyl 2-(cyclopent-3-enylamino)pentanedioate 44



$C_{12}H_{19}NO_4$
241.28 g/mol

Glutamic acid methyl ester hydrochloride **43** (2.57 g, 12.14 mmol), **37** (1.46 g, 6.07 mmol) and Na_2CO_3 (2.56 g, 24 mmol) were suspended in CH_3CN (15 mL, 0.8 M) and refluxed for 5 days. After cooling to rt, 50 mL MTBE were added, the inorganic residue was filtered off and the filtrate evaporated under reduce pressure. Purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 3:1) furnished the desired product **44** (700 mg, 48%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.59 (m, 2H, H-10), 3.69 (s, 3H, H-5), 3.62 (s, 3H, H-7), 3.32 (dquintet, *J* = 5.0 Hz, *J* = 2.0 Hz, 1H, H-8), 3.25 (dd, 1H, *J* = 7.9 Hz, *J* = 5.7 Hz, H-1), 2.54-2.42 (m, 2H, H-9), 2.39 (t, *J* = 7.4 Hz, 2H, H-3), 2.30 (m, 2H, H-9), 1.92 (m, 1H, H-2), 1.85-1.78 (m, 1H, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 175.8 (C-4), 173.5 (C-6), 128.8 (C-10), 128.7 (C-10), 59.0 (C-1), 56.2 (C-8), 51.9 (C-5), 51.6 (C-7), 40.3 (C-9), 39.6 (C-9), 30.5 (C-3), 28.6 (C-2).

IR (ATR): ν (cm^{-1}) = 3321 (w), 3053 (w), 2994 (w), 2951 (w), 2921 (w), 2843 (w), 1734 (s), 1435 (m), 1198 (m), 1169 (m).

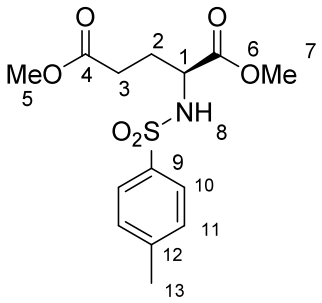
MS (EI, 70 eV): *m/z* (%) = 182 (100) [M^+-COOMe].

HRMS (M^+, $C_{12}H_{19}NO_4$) = calcd: 241.13141, found: 241.13099.

Optical rotation a_D^{20} = -26° (c = 1.45, $CHCl_3$).

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.14.

(*S*)-dimethyl 2-(4-methylphenylsulfonamido)pentanedioate 47



$C_{14}H_{19}NO_6S$
329.37 g/mol

Glutamic acid methyl ester hydrochloride salt (300 mg, 1.42 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL) and TsCl (270 mg, 2.83 mmol) and Et_3N (0.6 mL, 3.55 mmol) were added at 0 °C. The mixture was stirred at rt for 3 h, the solvent was removed under reduced pressure and the crude material was purified by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1). The the title compound **47** (452 mg, 97%) was obtained as a colorless oil, which solidifies at -20 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.70 (d, *J* = 8.3 Hz, 2H, H-10), 7.30 (d, *J* = 8.3 Hz, 2H, H-11), 5.20 (d, *J* = 9.1 Hz, 1H, H-8), 3.96 (m, 1H, H-1), 3.67 (s, 3H, H-7), 3.51 (s, 3H, H-5), 2.51-2.38 (m, 5H, H-3, H-13), 2.15-2.04 (m, 1H, H-2), 1.92-1.84 (m, 1H, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.9 (C-4), 171.7 (C-6), 143.7 (C-9), 136.5 (C-12), 129.6 (C-10), 127.3 (C-11), 54.9 (C-1), 52.6 (C-5), 51.8 (C-7), 29.4 (C-3), 28.3 (C-2), 21.5 (C-13).

IR (ATR): ν (cm^{-1}) = 3273 (br m), 2954 (w), 1737 (m), 1598 (w), 1437 (m), 1341 (m), 1207 (m), 1161 (s), 1092 (m), 984 (m), 888 (m), 816 (m), 707 (m), 666 (m).

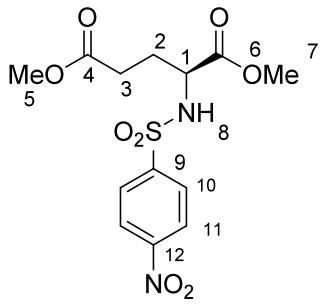
LRMS-ESI: *m/z* (%) = 330 (5) [MH^+], 298 (100).

HRMS-ESI (MH^+, $C_{14}H_{20}NO_6S$) = calcd: 330.1011, found: 330.1008.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.42.

(*S*)-dimethyl 2-(4-nitrophenylsulfonamido)pentanedioate 48

Glutamic acid methylester hydrochloride salt (300 mg, 1.4 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) and nosylchlorid (377 mg, 1.7 mmol) and Et_3N (0.6 mL, 4.2 mmol) were added at 0 °C. The reaction was stirred at rt for 3 h, the solvent removed under reduced pressure and the residue was purified by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) to give **48** as a colorless oil (400 mg, 78%), which solidifies at -20 °C.



$C_{13}H_{16}N_2O_8S$
360.34 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.34 (d, *J* = 8.9 Hz, 2H, H-11), 8.03 (d,*J* = 8.9 Hz, 2H, H-10), 5.48 (d, *J* = 9.0 Hz, 1H, H-8), 8.34 (m, 1H, H-1), 3.69 (s, 3H, H-7), 3.56 (s, 3H, H-5), 2.53-2.42 (m, 2H, H-3), 2.2-2.13 (m, 1H, H-2), 1.97-1.88 (m, 1H, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.9 (C-4), 171.3 (C-6), 150.2 (C-12), 145.5 (C-9), 128.5 (C-11), 124.3 (C-10), 55.1 (C-1), 52.9 (C-5), 51.9 (C-7), 29.4 (C-3), 28.1 (C-2).

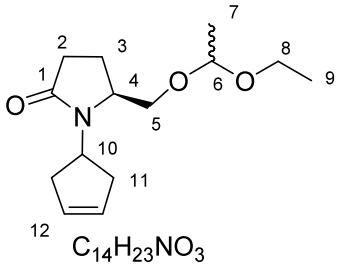
IR (ATR): ν (cm^{-1}) = 3266 (br m), 3107 (w), 2955 (w), 1735 (s), 1530 (s), 1437 (m), 1350 (s), 1164 (s), 1091 (m), 854 (m), 737 (m), 686 (m).

LRMS-ESI: *m/z* (%) = 361.18 (10) [M^+], 329.04 (100).

HRMS (MH^+, $C_{13}H_{17}N_2O_8S$) = calcd: 361.0706, found: 361.0703.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.46.

(S)-1-(cyclopent-3-enyl)-5-((1-ethoxyethoxy)methyl)pyrrolidin-2-one 51



$C_{14}H_{23}NO_3$
253.34 g/mol

36 (50 mg, 0.26 mmol), **37** (76 mg, 0.32 mmol) and Na_2CO_3 (115 mg, 1.08 mmol) were suspended in CH_3CN (0.3 mL, 0.8 M) and heated at 85°C in a MW-tube for 5 days. After cooling to rt, 10 mL CH_2Cl_2 were added, the inorganic residue was filtered off and the filtrate evaporated under reduce pressure. Purification by column chromatography (SiO_2, cyclohexane → cyclohexane/ EtOAc 1:1) furnished the desired product **51** (41 mg, 61%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.72 (m, 2H, H-12), 5.37 (m, 1H, H-4), 4.72 (m, 1H, H-6), 4.05 (m, 1H, H-10), 3.75-3.36 (m, 4H, H-5, H-8), 2.78-2.69 (m, 2H, H-11), 2.59-2.39 (m, 4H, H-2, H-11), 2.16-2.05 (m, 1H, H-3), 1.87-1.76 (m, 1H, H-3), 2.31-1.27 (m, 3H, H-7), 1.19 (dt, *J* = 1.0 Hz, *J* = 7.0 Hz, 3H, H-9).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.6 (C-1), 172.6 (C-1), 128.4 (C-12), 99.9 (C-6), 99.7 (C-6), 77.3 (C-4), 69.1 (C-5), 68.5 (C-5), 66.7 (C-10), 66.6 (C-10), 61.2 (C-8), 60.9 (C-8), 39.9 (C-11), 31.6 (C-2), 31.5 (C-2), 26.1 (C-3), 26.0 (C-3), 19.9 (C-7), 19.8 (C-7), 15.3 (C-9).

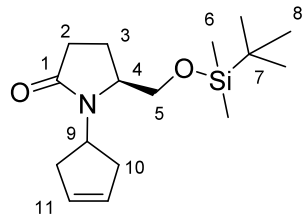
IR (ATR): ν (cm^{-1}) = 3062 (w), 2971 (m), 2927 (m), 2871 (m), 1731 (m), 1688 (s), 1642 (m), 1457 (m), 1378 (m), 1332 (s), 1177 (m), 1133 (s), 1095 (s), 1057 (s), 954 (m), 931 (m), 874 (m), 668 (m).

MS-ESI: *m/z* (%) = 254 (5) [MH^+], 208 (70), 182 (60), 142 (100).

HRMS-ESI (MH^+, $C_{14}H_{24}NO_3$) = calcd: 254.17562, found: 254.17526.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.47.

(*S*)-5-((tert-butyldimethylsilyloxy)methyl)-1-(cyclopent-3-enyl)pyrrolidin-2-one



$C_{16}H_{29}NO_2Si$
295.49 g/mol

34 (50 mg, 0.22 mmol), **37** (63 mg, 0.26 mmol) and Na_2CO_3 (115 mg, 1.08 mmol) were suspended in CH_3CN (0.3 mL, 0.8 M) and and heated at 85°C in a MW-tube for 5 days. After cooling to rt, 10 mL CH_2Cl_2 were added, the inorganic residue was filtered off and the filtrate evaporated under reduce pressure. Purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 3:1) furnished the desired product (33 mg, 49%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.71 (m, 2H, H-11), 5.37 (m, 1H, H-4), 3.99 (m, 1H, H-9), 3.74 (dd, *J* = 3.4 Hz, *J* = 10.0 Hz, 1H, H-5), 3.57 (dd, *J* = 5.4 Hz, *J* = 10.0 Hz, 1H, H-5), 2.78-2.69 (m, 2H, H-10), 2.54-2.43 (m, 3H, H-2, H-10), 2.40-2.32 (m, 1H, H-2), 2.10-2.00 (m, 1H, H-3), 1.95-1.86 (m, 1H, H-3), 0.87 (s, 9H, H-8), 0.03 (s, 6H, H-6).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.8 (C-1), 128.4 (C-11), 128.4 (C-11), 77.6 (C-4), 68.1 (C-9), 66.6 (C-5), 39.9 (C-10), 39.8 (C-10), 31.8 (C-2), 25.9 (C-8), 25.3 (C-3), 18.3 (C-7), -5.4 (C-6).

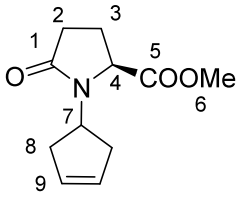
IR (ATR): ν (cm^{-1}) = 3063 (w), 2953 (m), 2928 (m), 2856 (m), 1731 (m), 1680 (m), 1644 (s), 1472 (m), 1462 (m), 1374 (m), 1333 (m), 1252 (m), 1176 (m), 1115 (m), 1098 (m), 875 (m), 873 (s), 815 (m), 776 (s), 671 (m).

MS-ESI: *m/z* (%) = 296 (5) [MH^+], 280 (10), 230 (100).

HRMS-ESI (MH^+, $C_{16}H_{30}NO_2Si$) = calcd: 296.20450, found: 296.13099.

R_f (SiO_2, cyclohexane/EtOAc 9:1) = 0.33.

(*S*)-methyl 1-(cyclopent-3-enyl)-5-oxopyrrolidine-2-carboxylate 42



$C_{11}H_{15}NO_3$
209.24 g/mol

Procedure A: **44** (1.38 g, 5.72 mmol) was dissolved in acetic acid (250 mL) and heated overnight at 110 °C. Once the reaction was cooled down to rt 250 mL of EtOAC were added and the mixture was carefully neutralized by washing several times with aqueous saturated solution of Na_2CO_3. When no more evolution of CO_2 was observed, the organic layer was dried over $MgSO_4$ and concentrated, to furnish **42** (1.15 g, 96%), which was used without further purification in the next step.

Procedure B: **44** (10 g, 41.44 mmol) and *p*TSA·H_2O (1 g, 5.80 mmol) were dissolved in toluene (200 mL) and refluxed overnight. Once the reaction was cooled to rt, the organic layer was washed with saturated solution of Na_2CO_3, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, cyclohexane/EtOAc 3:1 → 1:3) gave **42** (8 g, 92%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.70 (m, 2H, H-9), 4.73 (dquintet, *J* = 5.6 Hz, *J* = 3.5 Hz, 1H, H-7), 4.11 (dd, 1H, *J* = 9.1 Hz, *J* = 1.7 Hz, H-4), 3.69 (s, 3H, H-6), 2.62-2.45 (m, 3H, H-8, H-2), 2.32-2.16 (m, 4H, H-8, H-3, H-2,), 1.97 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 175.4 (C-1), 173.5 (C-5), 136.9 (C-9), 135.8 (C-9), 58.2 (C-4), 52.3 (C-6), 51.6 (C-7), 36.4 (C-8), 36.4 (C-8), 29.8 (C-2), 24.5 (C-3).

IR (ATR): ν (cm^{-1}) = 3056 (w), 2952 (w), 2925 (w), 2850 (w), 1742 (s), 1691 (s), 1436 (m), 1411 (m), 1281 (m), 1204 (s), 1176 (m).

MS (EI, 70 eV): *m/z* (%) = 209 (20) [M^+], 150 (60) [M^+-COOMe], 144 (100) [M-$C_5H_6^+$], 84 (15) [$C_4H_5NO^+$].

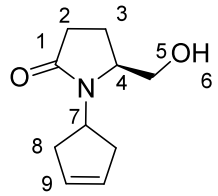
HRMS (M^+, $C_{11}H_{15}NO_3$) = calcd: 209.10519, found: 209.10481.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.16.

Optical rotation a_D^{20} = -54° (c = 3, $CHCl_3$).

(*S*)-1-(cyclopent-3-enyl)-5-(hydroxymethyl)pyrrolidin-2-one 49

Methyl ester **42** (10 g, 48 mmol) was dissolved in EtOH (150 mL) and cooled to 0 °C before $NaBH_4$ (3.34 g, 88 mmol) was added in portions. The reaction mixture was stirred at rt overnight and when complete conversion was achieved, the mixture as quenched with 10 mL



$C_{10}H_{15}NO_2$
181.23 g/mol

acetic acid and stirred for a further hour at rt. The solvent was then removed under reduced pressure and 150 mL ethyl acetate and 150 mL of a saturated aqueous NH_4Cl were added. The water phase was extracted once with EtOAc and the combined organic phases were dried over $MgSO_4$ and evaporated. After column chromatography (SiO_2, EtOAc → EtOAc/MeOH to 4:1) the product was furnished as clear oil (8.4 g, 97%) which became a white solid by storing at -20 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.73 (s, 2H, H-9), 4.68 (m, 1H, H-7), 3.73-3.57 (m, 3H, H-5, H-4), 2.69 (m, 1H, H-8), 2.62-2.38 (m, 4H, H-2, H-8), 2.31-2.23 (m, 1H, H-2), 2.15-1.96 (m, 2H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 176.1 (C-1), 129.4 (C-9), 129.2 (C-9), 64.1 (C-5), 59.2 (C-4), 51.4 (C-7), 37.9 (C-8), 35.7 (C-8), 30.8 (C-2), 22.4 (C-3).

IR (ATR): ν (cm^{-1}) = 3367 (m), 3056 (w), 2942 (m), 2858 (w), 1657 (s), 1419 (s), 1285 (m), 1059 (m).

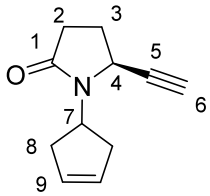
MS (EI, 70 eV): *m/z* (%) = 181 (10) [M^+], 150 (45) [M^+-CH_2OH], 116 (55) [M-$C_5H_6^+$], 84 (100) [$C_4H_5NO^+$], 67 (40) [$C_5H_7^+$], 60 (90).

HRMS (M^+, $C_{10}H_{15}NO_2$) = calcd: 181.11028, found: 181.11028.

R_f (SiO_2, EtOAc/MeOH 4:1) = 0.17.

Optical rotation a_D^{20} = -44° (c = 1.2, $CHCl_3$).

(*S*)-1-(cyclopent-3-enyl)-5-ethynylpyrrolidin-2-one 31



$C_{11}H_{13}NO$
175.23 g/mol

Following the general procedure for the synthesis of triple bonds from the corresponding alcohols, **49** (800 mg, 4.41 mmol) was oxidized via Swern oxidation (DMSO (1.00 mL, 13.23 mmol), oxalylchloride (0.6 mL, 6.62 mmol), and Et_3N (2.00 mL) in 24 mL CH_2Cl_2). Seyferth Gilbert homologation followed (**50** (1.02 g, 5.29 mmol) and K_2CO_3 (1.22 g, 8.83 mmol) in 40 ml MeOH). After addition of MTBE (40 mL), the reaction mixture was filtered over a

pad of Celite, concentrated, and the crude material was purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1 to 1:1) to obtain alkyne **31** (745 mg, 96%) as colorless oil.[1]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.75 (s, 2H, H-9), 4.79 (dquintet, *J* = 7.0 Hz, *J* = 3.0 Hz, 1H, H-7), 4.27 (dt, 1H, *J* = 5.7 Hz, *J* = 2.3 Hz, H-4), 2.86-2.80 (m, 1H, H-8), 2.64-2.55 (m, 3H, H-2, H-8), 2.41-2.23 (m, 5H, H-8, H-6, H-3, H-2), 2.14-2.06 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 174.4 (C-1), 129.9 (C-9), 128.5 (C-9), 83.2 (C-5), 72.5 (C-6), 51.5 (C-7), 47.5 (C-4), 36.4 (C-8), 36.3 (C-8), 30.2 (C-2), 27.9 (C-3).

IR (ATR): ν (cm^{-1}) = 3229 (w), 2947 (w), 2857 (w), 2111 (w), 1685 (s), 1413 (s), 1281 (m), 1253 (m), 1172 (w), 689 (m).

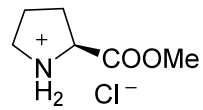
LRMS-ESI: *m/z* (%) = 176 (25) [MH^+], 110 (100) [$M-C_5H_6^+$].

HRMS-ESI (MH^+, $C_{11}H_{14}NO$) = calcd: 176.1075, found: 176.1069.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.13, (SiO_2, cyclohexane/EtOAc 1:1) = 0.25.

Optical rotation a_D^{20} = -41° (c = 1.2, CH_2Cl_2).

(*S*)-Proline methyl ester hydrochloride



$C_6H_{12}ClNO_2$
165.62 g/mol

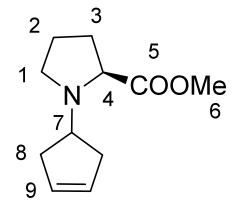
To a solution of (*S*)-proline (6 g, 51 mmol) in anhydrous MeOH (60 mL), $SOCl_2$ (4.2 mL, 58 mmol) was added dropwise at 0 °C. Stirring continued for approx. 2 h at rt before the solvent was removed in vacuo. The crude material obtained was used without further purification.

(*S*)-methyl 1-(cyclopent-3-enyl)pyrrolidine-2-carboxylate 52

(*S*)-proline methyl ester hydrochloride (281 mg, 1.69 mmol), tosilate **37** (450 mg, 1.87 mmol) and K_2CO_3 (750 mg, 5.42 mmol) were suspended in CH_3CN (4 mL, 0.4 M) and refluxed for 3 days. When the mixture was cooled down to ambient temperature, 50 mL CH_2Cl_2 were added. The inorganic residue was filtered off and the filtrate concentrated. Purification by

[1] Swern oxidation showed to be sensitive to scale. For reactions on less than 200 - 100 mg of **49** the obtained yields where often considerably lower.

column chromatography (SiO_2, cyclohexane/EtOAc 20:1 to 3:1) afforded the desired product **42** (313 mg, 95%) as a clear light orange oil.



$C_{11}H_{17}NO_2$
195.26 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.66 (s, 2H, H-9), 3.71 (s, 3H, H-6), 3.33 (m, 2H, H-4, H-7), 3.10 (m, 1H, H-1), 2.51-2.29 (m, 5H, H-1, H-8), 2.12 (m, 1H, H-3), 1.98-1.90 (m, 2H, H-3, H-2), 1.82 (m, 1H, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 175.4 (C-5),[2] 129.3 (C-9), 129.0 (C-9), 69.0 (C-4), 62.9 (C-7), 51.9 (C-6) 51.5 (C-1), 37.3 (C-8), 36.2 (C-8), 30.2 (C-3), 23.5 (C-2).

IR (ATR): ν (cm^{-1}) = 3053 (w), 2949 (m), 2930 (m), 2843 (m), 1751 (s), 1732 (s), 1434 (m), 1339 (m), 1277 (m), 1193 (s), 1164 (s), 691 (m).

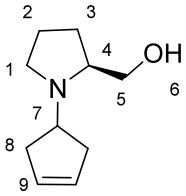
MS (EI, 70 eV): *m/z* (%) = 195 (5) [M^+], 136 (100) [M^+-COOMe], 70 (50) [$C_4H_8N^+$], 67 (30) [$C_5H_7^+$].

HRMS (M^+, $C_{11}H_{17}NO_2$) = calcd: 195.125928, found 195.125929.

R_f (SiO_2, cyclohexane/EtOAc 13:1) = 0.42.

Optical rotation a_D^{20} = -90° (c = 1.65, $CHCl_3$).

(*S*)-(1-(cyclopent-3-enyl)pyrrolidin-2-yl)methanol 53



$C_{10}H_{17}NO$
167.25 g/mol

52 (3 g, 15.36 mmol) was slowly added to a suspension of $LiAlH_4$ (1.72 g, 45.32 mmol) in anhydrous Et_2O (100 mL) at 0 °C. After stirring 1 h at rt, the reaction was heated to 40 °C and refluxed overnight. 100 mL wet EtOAc were then slowly added at rt over 2 h, until no evolution of H_2 was observed, and, subsequently, 5 mL wet MeOH were carefully added dropwise. The solution was decantated from the fine powder formed, which was washed three times with 50 mL EtOAc. The combined organic fractions were concentrated under reduced pressure and the pure alcohol **53** (2.52 g, 99%) was obtained as a clear light orange oil, which was directly used in the next step.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.68 (s, 2H, H-9), 3.70 (dd, 1H, *J* = 10.5 Hz, *J* = 4.2 Hz, H-5), 3.36 (m, 1H, H-7), 3.35 (dd, 1H, *J* = 7.6 Hz, *J* = 1.9 Hz H-5), 3.2-2.8 (br s,

[2] C-5 was identified *via* HMBC correlation

1H, H-6), 2.94 (m, 1H, H-1), 2.84 (m, 1H, H-4), 2.27-2.51 (m, 5H, H-1, H-8), 1.88 (m, 1H, H-3), 1.75-1.68 (m, 3H, H-3, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.3 (C-9), 129.1 (C-9), 62.9 (C-5), 62.0 (C-4), 60.7 (C-7), 50.2 (C-1), 38.1 (C-8), 34.6 (C-8), 29.1 (C-3), 24.1 (C-2).

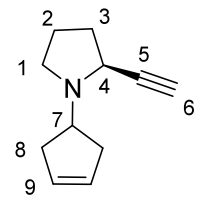
IR (ATR): ν (cm^{-1}) = 3388 (m), 3053 (m), 2925 (s), 2849 (s), 1727 (w), 1532 (w), 1457 (m), 1339 (m), 1219 (m), 1039 (s), 688 (s).

MS (EI, 70 eV): *m/z* (%) = 136 (100) [M^+-CH_2OH], 70 (100) [$C_4H_8N^+$], 67 (50) [$C_5H_7^+$].

HRMS (M^+, $C_{10}H_{16}NO$) = calcd: 166.1239, found: 166.1239.

Optical rotation a_D^{20} = -51° (c = 2.05, $CHCl_3$).

(*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidine 27



$C_{11}H_{15}N$
161.24 g/mol

Following the general procedure for the synthesis of triple bonds from the corresponding alcohols, **53** (1.1 g, 6.57 mmol) was oxidized via Swern oxidation (DMSO (1.4 mL, 19.71 mmol), oxalylchloride (0.85 mL, 9.85 mmol), and Et_3N (2.87 mL) in 24 mL CH_2Cl_2). Seyferth Gilbert homologation followed (**50** (1.51 g, 7.87 mmol) and K_2CO_3 (1.81 g, 13.15 mmol) in 54 ml MeOH). After purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) **27** (880 mg, 83%) was obtained as light orange oil. By bulb-to-bulb distillation under nitrogen atmosphere was possible to obtain as a colorless oil.[3]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.65 (s, 2H, H-9), 3.70 (dt, 1H, *J* = 7.6 Hz, *J* = 1.9 Hz, H-4), 3.36 (quintet, *J* = 7.8 Hz, 1H, H-7), 2.76 (m, 1H, H-1), 2.60-2.46 (m, 3H, H-1, H-8), 2.38-2.25 (m, 2H, H-8), 2.24 (d, *J* = 2.13 Hz, 1H, H-6), 2.15-2.07 (m, 1H, H-3), 1.96-1.79 (m, 3H, H-3, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.3 (C-9), 129.1 (C-9), 82.8 (C-5), 72.3 (C-6), 61.3 (C-7), 52.8 (C-4), 49.7 (C-1), 38.3 (C-8), 36.8 (C-8), 31.9 (C-3), 22.2 (C-2).

IR (ATR): ν (cm^{-1}) = 3308 (w), 2924 (s), 2853 (m), 1737 (w), 1611 (w), 1457 (w), 1162 (w), 1122 (w).

[3] Swern oxidation showed to be sensitive to scale. For reactions with less than 200 - 100 mg of **53**, the obtained yields where considerably lower.

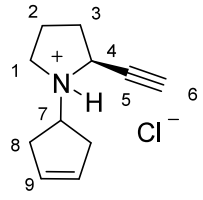
MS (EI, 70 eV): *m/z* (%) = 161 (30) [M^+], 160 (80) [M^+-1H], 120 (100), 67 (70) [$C_5H_7^+$], 55 (60) [$C_4H_7^+$].

HRMS (M^+, $C_{11}H_{14}N$) = calcd: 160.11262, found: 160.11151.

Optical rotation a_D^{20} = -98° (c = 1.55, CH_2Cl_2).

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.24.

(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium chloride



$C_{11}H_{16}ClN$
197.70 g/mol

27·HCl salt was prepared following the general procedure earlier described in Section 5.2.1.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.72 (s, 2H, H-9), 4.58 (m, H-4), 3.95 (quintet, *J* = 8.6 Hz, 1H, H-7), 3.77-3.68 (m, 1H, H-1), 3.08-2.94 (m, 3H, H-1, H-8), 2.80-2.71 (m, 2H, H-8), 2.66 (d, *J* = 2.4 Hz, 1H, H-6), 2.65-2.58 (m, 1H, H-3), 1.36-1.17 (m, 3H, H-3, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 128.5 (C-9), 128.2 (C-9), 78.6 (C-5), 75.5 (C-6), 62.6 (C-7), 55.3 (C-4), 50.6 (C-1), 35.2 (C-8), 31.2 (C-3), 21.6 (C-2).

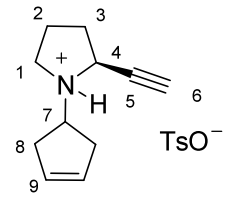
IR (ATR): ν (cm^{-1}) = 3416 (m), 3174 (s), 2940 (s), 2852 (m), 2523 (s), 2435 (s), 2115 (m), 1617 (w), 1453 (s), 1443 (s), 1345 (m), 1026 (m), 708 (s).

MS (EI, 70 eV): *m/z* (%) = 160 (75) [M^+-H_2Cl], 120 (100).

HRMS (M^+, $C_{11}H_{14}N$) = calcd: 160.11262, found: 160.1130.

Optical rotation a_D^{20} = -4° (c = 1.5, CH_2Cl_2).

(2S)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium 4-methylbenzenesulfonate



$C_{18}H_{23}NO_3S$
333.44 g/mol

27·*p*TSA salt was prepared following the general procedure earlier described.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.69 (d, *J* = 8.0 Hz, 2H, CH_{Ar}), 7.14 (d, *J* = 8.0 Hz, 2H, CH_{Ar}), 5.63 (s, 2H, H-9), 4.73 (m, H-4), 3.94 (app sextet, *J* = 8.6 Hz, 1H, H-7), 3.85-3.76 (m, 1H, H-1), 3.07-2.97

(m, 1H, H-1), 2.87-2.58 (m, 5H, H-3, H-8), 2.70 (d, *J* = 2.4 Hz, 1H, H-6), 2.33 (s, 3H, CH_3-Ar), 1.31-1.16 (m, 3H, H-3, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 140.9 (C_{qAr}), 140.7 (C_{qAr}), 128.9 (2 x CH_{Ar}), 128.3 (C-9), 128.0 (C-9), 126.1 (2 x CH_{Ar}), 78.6 (C-5), 75.2 (C-6), 62.7 (C-7), 56.0 (C-4), 51.5 (C-1), 35.4 (C-8), 35.4 (C-8), 31.1 (C-3), 21.5 (CH_3-Ar), 21.4 (C-2).

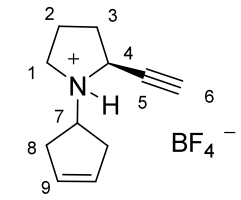
IR (ATR): ν (cm^{-1}) = 3447 (w), 3209 (m), 2963 (m), 2604 (m), 2120 (w), 1455 (m), 1226 (s), 1162 (s), 1121 (s), 1032 (s), 1009 (s), 818 (m), 681 (s).

MS (EI, 70 eV): *m/z* (%) = 160 (45) [$C_{11}H_{14}N$], 120 (60), 86 (60), 84 (100).

HRMS (M^+, $C_{11}H_{14}N$) = calcd: 160.1126, found: 160.1126.

Optical rotation a_D^{20} = -46° (c = 0.18, CH_2Cl_2).

(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium tetrafluoroborate



$C_{11}H_{16}BF_4N$
249.05 g/mol

27·HBF_4 salt was prepared following the general procedure earlier described and purified by column chromatography.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.73 (s, 2H, H-9), 4.51 (br s, 1H, H-4), 3.95 (quintet, *J* = 8.1 Hz, 1H, H-7), 3.65 (br s, 1H, H-1), 3.02 (br s, 1H, H-1), 2.84-2.70 (m, 4H, H-8), 2.72 (d, *J* = 2.3 Hz, 1H, H-6), 2.65-2.56 (m, 1H, H-3), 1.34-1.23 (m, 3H, H-3, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 128.3 (C-9), 128.2 (C-9), 79.1 (C-5), 75.1 (C-6), 63.0 (C-7), 56.5 (C-4), 51.8 (C-1), 35.7 (C-8), 35.3 (C-8), 31.1 (C-3), 21.6 (C-2).

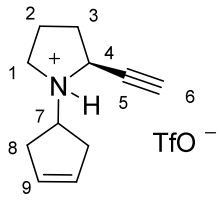
IR (ATR): ν (cm^{-1}) = 3566 (w), 3267 (m), 3120 (w), 2954 (w), 2856 (w), 2685 (w), 2589 (w), 2491 (w), 2127 (w), 1641 (w), 1456 (m), 1442 (m), 1286 (m), 1062 (s), 708 (m).

MS (EI, 70 eV): *m/z* (%) = 161 (25) [M^+], 160 (65) [M^+-H], 120 (100).

HRMS (M^+, $C_{11}H_{14}N$) = calcd: 160.1126, found: 160.1129.

Optical rotation a_D^{20} = -52° (c = 1.05, CH_2Cl_2).

(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium triflate



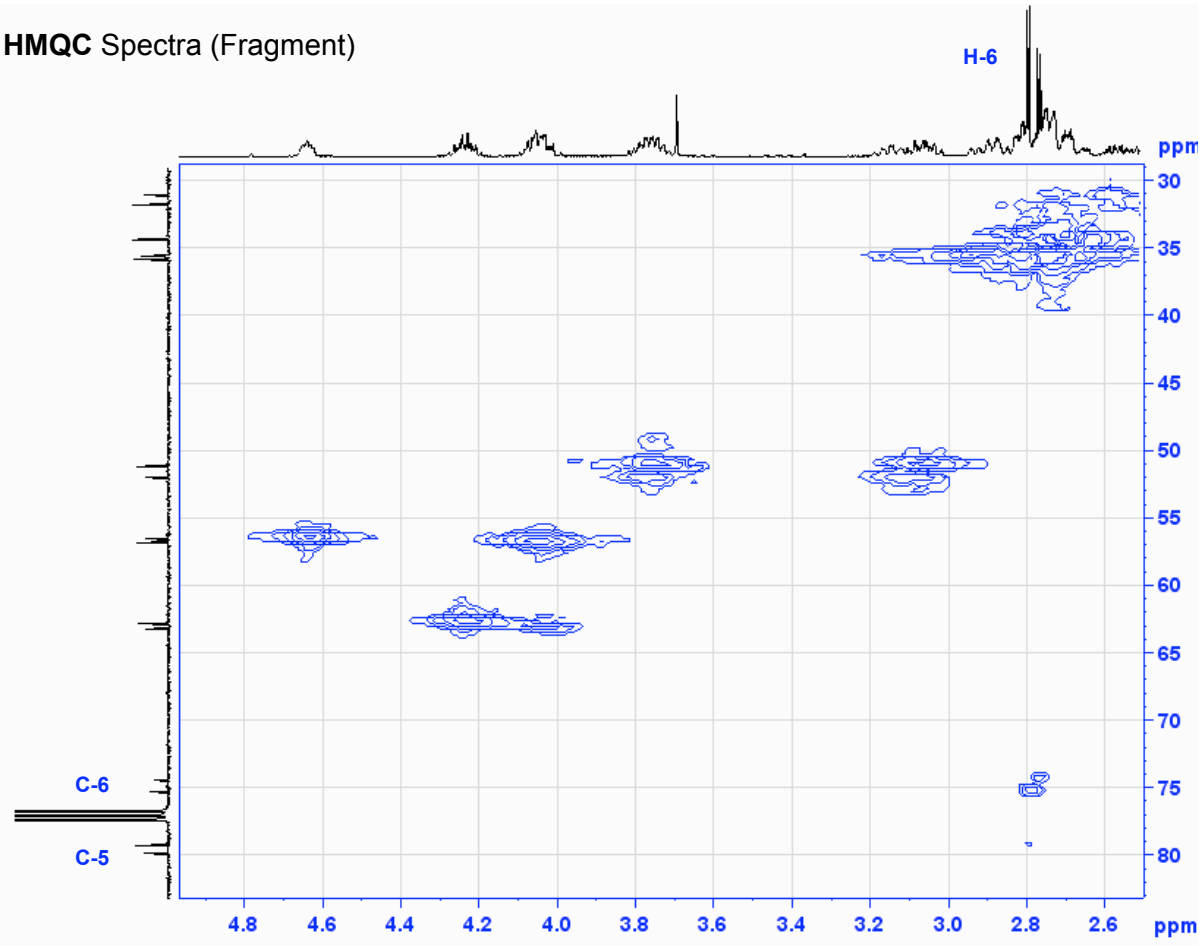
$C_{12}H_{16}F_3NO_3S$
311.32 g/mol

27·TfOH salt was prepared following the general procedure earlier described, purified by column chromatography and obtained as a diastereoisomeric mixture.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.77-5.69 (m, 2H, H-9), 4.64 (m, 0.4H, H-4), 4.24 (m, 0.6H, H-7), 4.05 (m, 1H, H-4, H-7), 3.76 (m, 1H, H-1), 3.19-3.09 (m, 1H, H-1), 2.95-2.63 (m, 4H, H-8), 2.79 (d, *J* = 2.4 Hz, H-6), 2.76 (d, *J* = 2.4 Hz, H-6), 2.61-2.43 (m, 1H, H-2), 2.37-2.19 (m, 2.5H, H-3, H-2), 2.17-2.06 (m, 0.6H, H-3).[4]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 128.7 (C-9), 128.1 (C-9), 127.9 (C-9), 79.7 (C-5), 79.3 (C-5), 75.3 (C-6), 74.4 (C-6), 63.2 (C-7), 62.8 (C-7), 56.8 (C-4), 56.5 (C-4), 51.9 (C-1), 51.1 (C-1), 35.7 (C-8), 35.5 (C-8), 35.5 (C-8), 34.3 (C-8), 31.7 (C-2), 30.9 (C-2), 22.2 (C-3), 21.4 (C-3).[5] Counterion signals: 121.6, 118.4.

HMQC Spectra (Fragment)

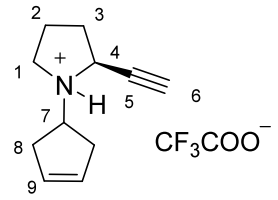


[4] The resonances corresponding to the proton on the double bond integrate 2, and the integration of the other signals corresponds to the diastereoisomeric ratio.
[5] Signals for both diastereoisomers are included.

IR (ATR): ν (cm^{-1}) = 3308 (w), 3250 (w), 3021 (w), 2737 (w), 2127 (w), 1457 (w), 1289 (s), 1236 (s), 1225 (s), 1166 (s), 1028 (s), 707 (w).

Optical rotation a_D^{20} = -38° (c = 1.8, $CHCl_3$).

(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium trifluoroacetate



$C_{13}H_{16}F_3NO_2$
275.27 g/mol

27·TFA salt was prepared following the general procedure earlier described and purified by column chromatography.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.70 (s, 2H, H-9), 4.83 (d, 1H, *J* = 6.8 Hz, H-4), 4.01 (m, 1H, H-7), 3.90 (m, 1H, H-1), 3.06 (m, 1H, H-1), 2.83-2.65 (m, 4H, H-8), 2.69 (d, *J* = 2.2 Hz, 1H, H-6), 2.46-2.16 (m, 4H, H-2, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 128.2 (C-9), 127.9 (C-9), 79.0 (C-5), 75.1 (C-6), 62.8 (C-7), 55.8 (C-4), 51.3 (C-1), 35.5 (C-8), 35.5 (C-8), 30.9 (C-2), 21.4 (C-3). Counterion signals: 161.5, 161.2, 160.8, 160.4.

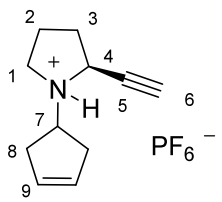
IR (ATR): ν (cm^{-1}) = 3441 (w), 3306 (w), 3230 (w), 2962 (w), 2939 (w), 2596 (w), 2550 (w), 2125 (w), 1777 (w), 1671 (s), 1416 (w), 1198 (s), 1136 (s), 799 (m), 721 (m).

MS (EI, 70 eV): *m/z* (%) = 161.1 (25) [M^+], 160.1 (65) [M^+-H], 120 (100), 69.0 (60).

HRMS (M^+, $C_{11}H_{14}N$) = calcd: 160.1126, found: 160.1129.

Optical rotation a_D^{20} = -35° (c = 1.1, CH_2Cl_2).

(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium hexafluorophosphate



$C_{11}H_{16}F_6NP$
307.22 g/mol

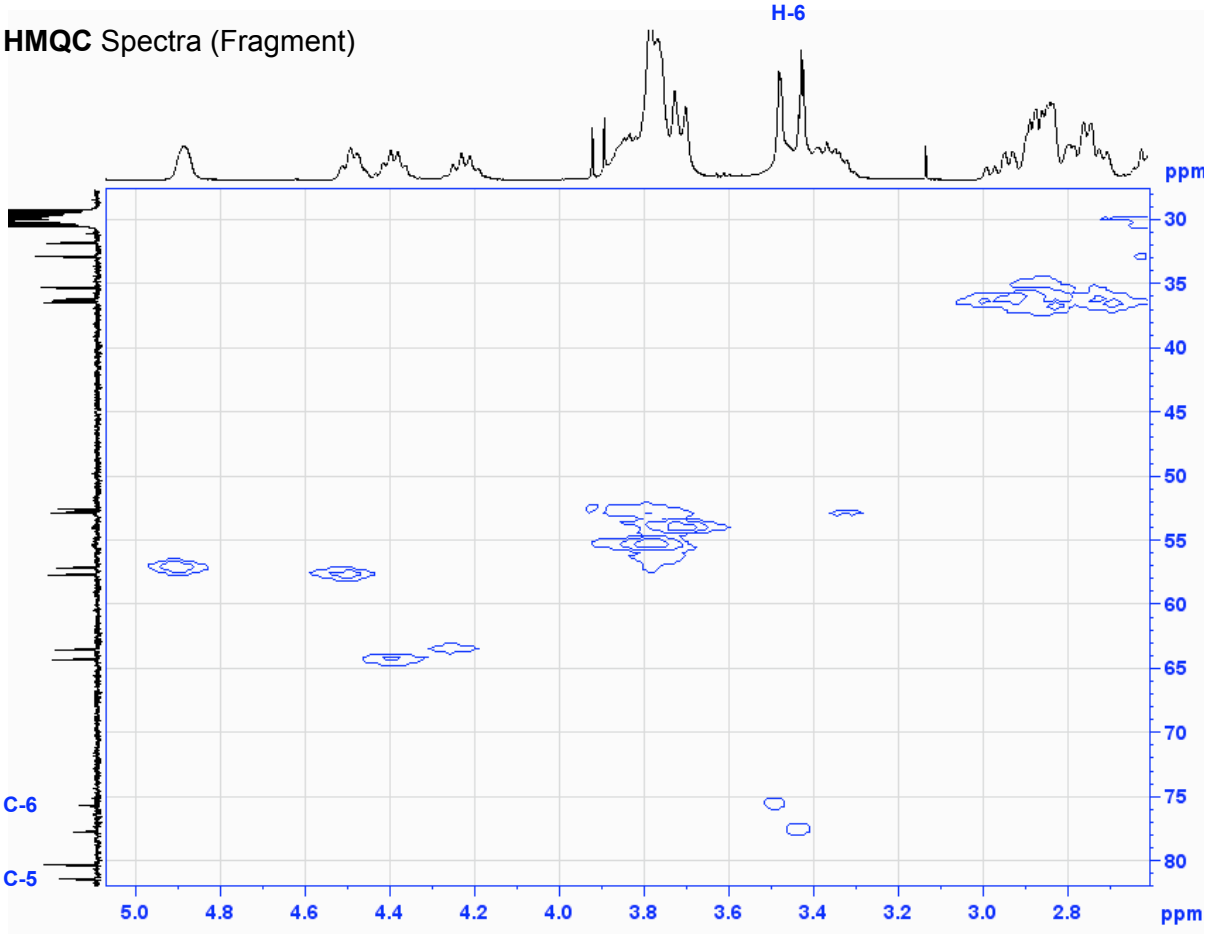
27·HPF_6 salt was prepared following the general procedure described in Section 5.2.1, purified by column chromatography and obtained as a diastereoisomeric mixture.

^{1}H-NMR (d_6-Acetone, 400 MHz): δ (ppm) = 5.80-5.71 (m, 2H, H-9), 4.88 (br s, 0.5H, H-4), 4.49 (m, 0.5H, H-4), 4.39 (m, 0.5H, H-7), 4.22 (m, 0.5H, H-7), 3.79 (m, H-1), 3.48 (m, H-6), 3.42 (m, H-6), 3.36 (m, 1H, H-1), 3.00-2.17 (m, H-2, H-3, H-8).[d]

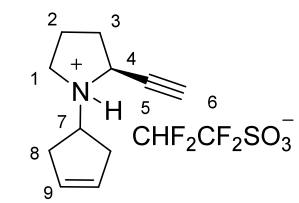
^{13}C-NMR (d_6-Acetone, 100 MHz): δ (ppm) = 129.3 (C-9), 129.2 (C-9), 129.1 (C-9), 128.9 (C-9), 81.3 (C-5), 80.2 (C-5), 77.7 (C-6), 75.7 (C-6), 64.3 (C-7), 63.6 (C-7), 57. (C-4), 57.1 (C-4), 52.8 (C-1), 52. (C-1), 36. (C-8), 36.3 (C-8), 36.2 (C-8), 35.3 (C-8), 32.9 (C-2), 31.8 (C-2), 23.3 (C-3), 22.1 (C-3).[e]

IR (ATR): ν (cm^{-1}) = 3292 (br m), 2861 (br m), 2333 (br m), 2134 (w), 1684 (br w), 1458 (w), 1191 (br s), 1019 (br s), 861 (br m).

Optical rotation a_D^{20} = -16° (c = 0.22, MeOH).



(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium 1,1,2,2-tetrafluoroethane-sulfonat



$C_{13}H_{17}F_4NO_3S$
343.34 g/mol

27·$C_2HF_4SO_3H$ salt was prepared following the general procedure earlier described, purified by column chromatography and obtained as a diastereoisomeric mixture.

^{1}H-NMR (d_6-Acetone , 400 MHz): δ (ppm) = 5.80-5.71 (m, 2H, H-9), 4.91 (m, 0.5H, H-4), 4.53 (m, 0.5H, H-4), 4.41 (quintet,

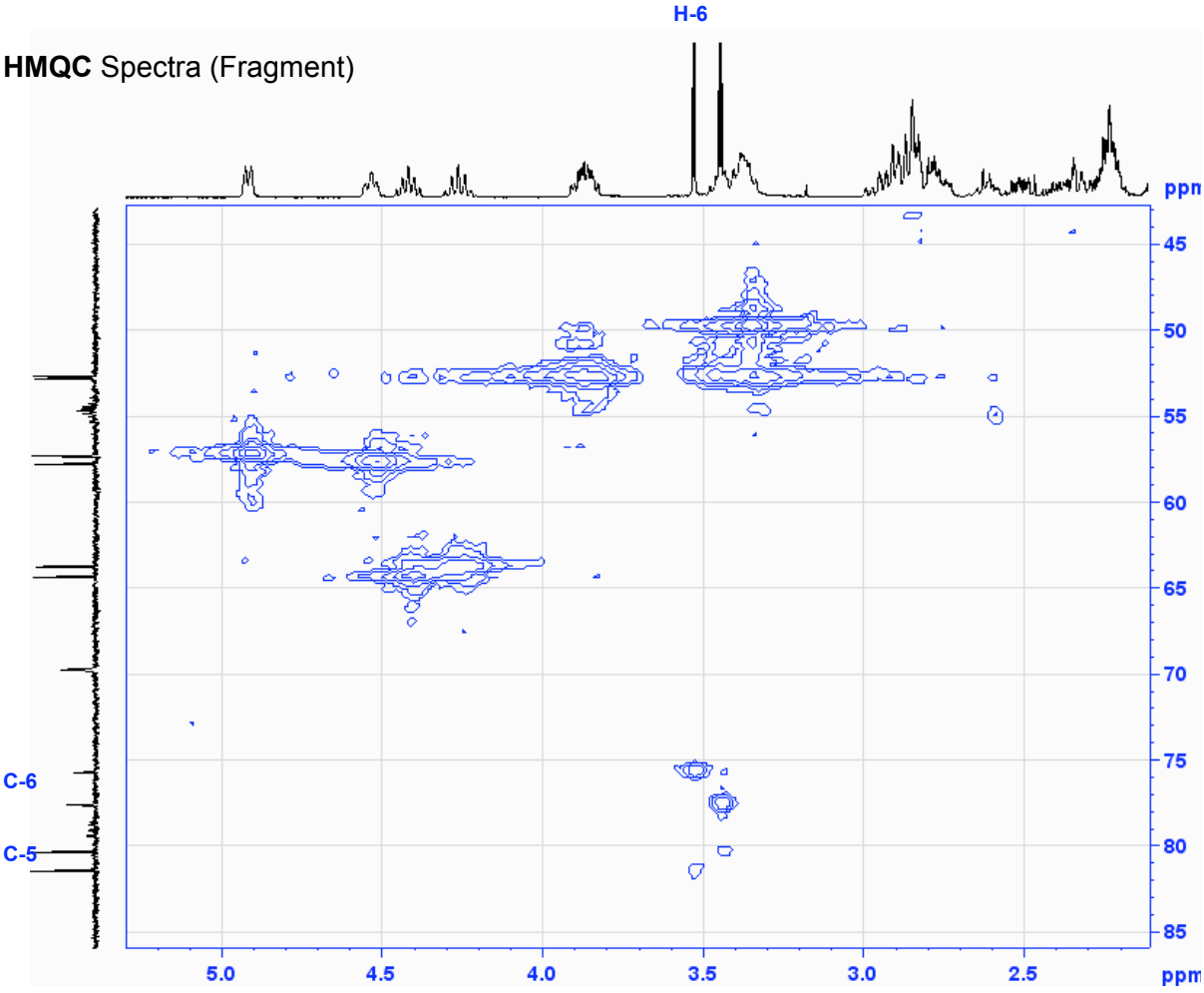
J = 7.0 Hz, 0.5H, H-7), 4.26 (quintet, *J* = 7.0 Hz, 0.5H, H-7), 3.87 (m, 1H, H-1), 3.53 (d, *J* = 2.4 Hz, 0.45H, H-6), 3.44 (d, *J* = 2.4 Hz, H-6), 3.37 (m, 1H, H-1), 3.09-2.18 (m, H-2, H-3, H-8).[d] Counterion signals: 6.44 (t, *J* = 6.2 Hz, C*H*F_2-), 6.30 (t, *J* = 6.2 Hz, C*H*F_2-), 2.17 (t, *J* = 6.2 Hz, C*H*F_2-).

^{13}C-NMR (d_6-Acetone, 100 MHz): δ (ppm) = 129.3 (C-9), 129.2 (C-9), 129.01 (C-9), 128.9 (C-9), 81.4 (C-5), 80.3 (C-5), 77.5 (C-6), 75.7 (C-6), 64.3 (C-8), 63.7 (C-8), 57.7 (C-4), 57.2 (C-4), 52.7 (C-1), 52.6 (C-1), 36.4 (C-8), 36.3 (C-8), 36.1 (C-8), 35.2 (C-8), 32.8 (C-2), 31.8 (C-2), 23.1 (C-3), 22.2 (C-3). Counterion signals: 113.1, 112.8, 112.5, 110.6, 110.3, 110.0, 108.1, 107.8, 107.5.[e]

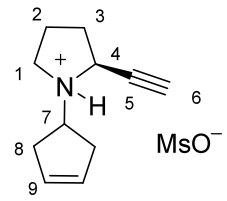
IR (ATR): ν (cm^{-1}) = 3305 (w), 3253 (w), 3019 (w), 2735 (w), 2128 (w), 1735 (w), 1457 (w), 1391 (w), 1277 (s), 1239 (s), 1142 (s), 1111 (s), 995 (s), 821 (m), 655 (s).

Optical rotation a_D^{20} = -24° (c = 0.13, MeOH).

HMQC Spectra (Fragment)



(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium methanesulfate



$C_{12}H_{19}NO_3S$
257.35 g/mol

27·MsOH salt was prepared following the general procedure described in Section 5.2.1, purified by column chromatography and obtained as a diastereoisomeric mixture.

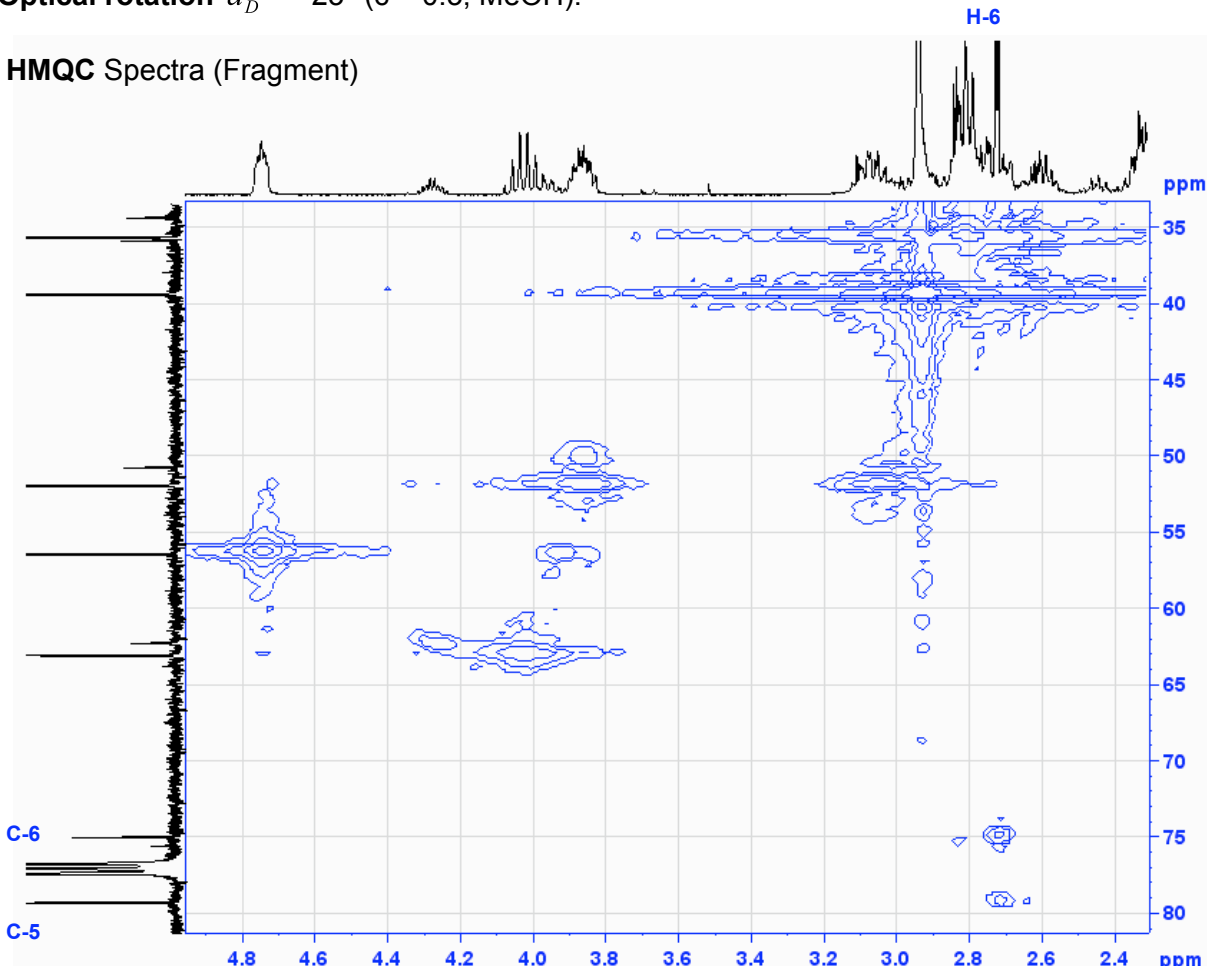
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.80-5.71 (m, 2H, H-9), 4.75 (m, 0.75H, H-4), 4.27 (m, 0.24H, H-7), 4.08-3.92 (m, 1H, H-4, H-7), 3.86 (m, 0.88H, H-1, H-4), 3.07 (m, H-1), 2.76 (s, -C*H*$_3$SO$_3$-), 2.85-2.55 (m, H-2, H-6, H-8), 2.50-2.02 (m, 3.6H, H-2, H-3).[d]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.0 (C-9), 128.3 (C-9), 128.1 (C-9), 128.0 (C-9), 79.3 (C-5), 79.2 (C-5), 75.5 (C-6), 7.0 (C-6), 63.0 (C-7), 62.2 (C-7), 56.3 (C-4), 51.9 (C-1), 50.7 (C-1), 39.3 (C-8), 35.8 (C-8), 35.7 (C-8), 35.6 (C-8), 34.3 (C-8), 31.8 (C-2), 31.0 (C-2), 22.5 (C-3), 21.5 (C-3).[e]

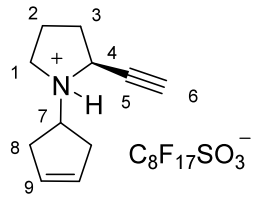
IR (ATR): ν (cm^{-1}) = 3257 (br w), 3022 (br w), 2939 (br w), 2854 (br w), 2727 (br w), 2398 (br w), 2126 (w), 1733 (w), 1709 (w), 1444 (w), 1335 (s), 1169 (s), 1125 (s), 1040 (s), 978 (s), 894 (s), 763 (m).

Optical rotation a_D^{20} = -23° (c = 0.3, MeOH).

HMQC Spectra (Fragment)



(2*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidinium 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluorooctane-1-sulfonate



$C_{19}H_{16}F_{17}NO_3S$
661.37 g/mol

27·$C_8F_{17}SO_3H$ salt was prepared following the general procedure described in Section 5.2.1 and purified by column chromatography.

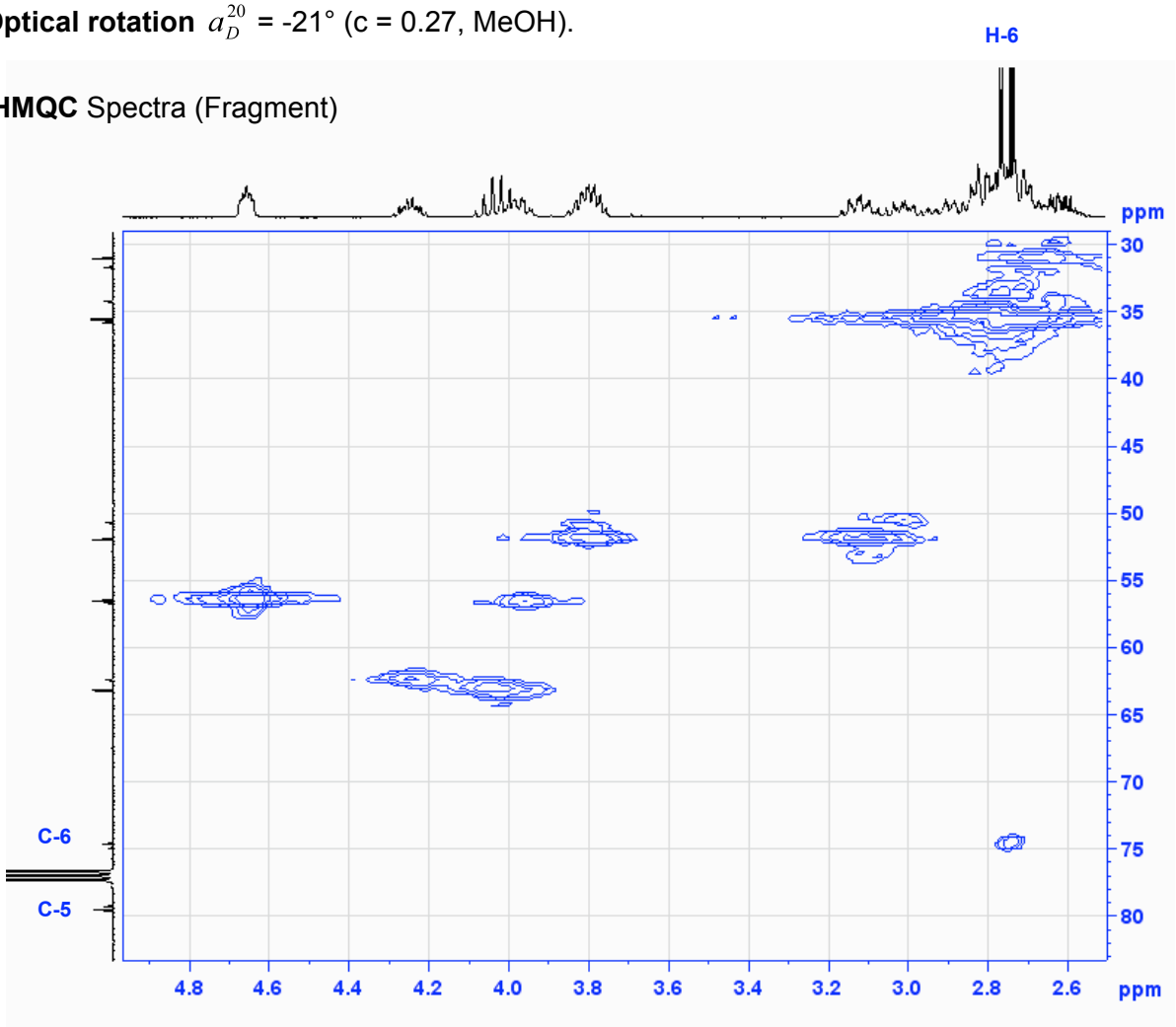
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.78-5.69 (m, 2H, H-9), 4.65 (m, 0.5H, H-4), 4.24 (m, 0.36H, H-7), 4.08-3.94 (m, 0.88H, H-4, H-7), 3.81 (m, 0.88H, H-1), 3.17-2.55 (m, H-1, H-2, H-8), 2.76 (d, *J* = 2.3 Hz, H-6), 2.74 (d, *J* = 2.3 Hz, H-6), 2.50-2.02 (m, 3H, H-2, H-3).[d]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 128.9 (C-9), 128.1 (C-9), 128.0 (C-9), 127.9 (C-9), 79.5 (C-5), 79.3 (C-5), 75.0 (C-6), 74.6 (C-6), 63.2 (C-7), 62.4 (C-7), 56.6 (C-4), 56.5 (C-4), 51.9 (C-1), 50.6 (C-1), 35.7 (C-8), 35.5 (C-8), 35.4 (C-8), 34.1 (C-8), 31.6 (C-2), 30.9 (C-2), 22.2 (C-3), 21.4 (C-3).[e]

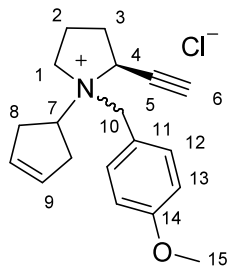
IR (ATR): ν (cm^{-1}) = 3316 (w), 3248 (w), 2736 (w), 2127 (w), 1457 (w), 1281 (s), 1236 (s), 1205 (s), 1152 (s), 1054 (w), 985 (w), 707 (w).

Optical rotation a_D^{20} = -21° (c = 0.27, MeOH).

HMQC Spectra (Fragment)



(*S*)-1-(cyclopent-3-enyl)-2-ethynyl-1-(4-methoxybenzyl)pyrrolidinium chloride 61



$C_{19}H_{24}ClNO$
317.85 g/mol

Amine **27** (100 mg, 0.62 mmol) was dissolved in CH_3CN (0.5 mL) and *p*-methoxybenzyl chloride (97 mg, 0.62 mmol) was added. After refluxing overnight the solvent was removed under reduced pressure. Analysis of the crude material by ^{1}H-NMR indicated a 80% conversion. The desired product was isolated after recristalization of the crude material in EtOAc as a white solid (mixture of stereoisomers). [6]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.8-7.78 (d, 1.3H, *J* = 8.7 Hz, H-12), 7.55-7.53 (d, 0.6H, *J* = 8.7 Hz, H-12), 6.96-6.94 (d, 0.6H, *J* = 8.7 Hz, H-13), 6.92-6.90 (d, 1.3H, *J* = 8.7 Hz, H-13), 5.84-5.67 (m, 2.6H, H-7, H-9), 5.61-5.56 (d, 0.9H, *J* = 13.1 Hz, H-10), 4.65-4.60 (d, 0.6H, *J* = 13.1 Hz, H-10), 4.54 (m, 1.34H, H-1, H-7, H-10), 4.27-4.21 (m, 0.9H, H-1), 3.94-3.87 (m, 0.3H, H-1), 3.83 (s, 0.9H, H-15), 3.81 (s, 2.1H, H-15), 3.67-3.59 (m, 0.6H, H-1), 3.30-3.21 (m, 0.95H, H-8), 3.08 (d, *J* = 2.3 Hz, H-6), 3.10-2.59 (m, H-2, H-3, H-8), 2.57 (d, *J* = 2.3 Hz, 0.62H, H-6), 2.15-2.03 (m, 1.77H, H-2, H-3).[7]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 161.3 (C-14), 134.4 (C-12), 134.0 (C-12), 128.7 (C-9), 128.4 (C-9), 127.9 (C-9), 119.8 (C-11), 114.8 (C-13), 114.5 (C-13), 82.4 (C-5), 80.7 (C-5), 77.2 (C-6), 68.3 (C-4), 67.0 (C-10), 65.5 (C-7), 59.5 (C-1), 55.5 (C-15), 55.4 (C-15), 36.1 (C-8), 35.8 (C-8), 35.5 (C-8), 34.2 (C-2), 33.5 (C-2), 22.7 (C-3).[e]

IR (ATR): ν (cm^{-1}) = 3364 (w), 3291 (w), 3130 (w), 3069 (w), 2996 (w), 2965 (w), 2932 (w), 2838 (w), 2109 (w), 1698 (m), 1610 (s), 1516 (s), 1463 (m), 1254 (s), 1184 (s), 1027 (s), 839 (m).

LRMS-ESI: *m/z* (%) = 282 (10) [MH^+], 216 (5), 160 (40), 121 (100).

HRMS-ESI (MH^+, $C_{19}H_{24}NO$) = calcd: 282.1852, found: 282.1844.

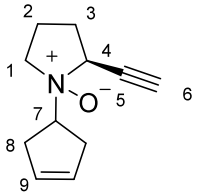
(*S*)-1-(cyclopent-3-enyl)-2-ethynylpyrrolidine *N*-oxide 62

Amine **27** (83 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (2.6 mL, 0.2 M) and *m*CPBA (154 mg, 70%, 0.69 mmol) was added. After 2 h of stirring at rt the solvent was removed in vacuo and

[6] The yield was not exactly determined since several crystallizations were needed, which afforded mainly crude material fractions. 10 mg were obtained as clean white solid and the rest of the crude material was not further purified (approx. 80% yield).

[7] Equivalent aromatic signals integrate 2, and the integration of the other signals corresponds to the diastereoisomeric ratio.

the product purified on a short pad of silica. With EtOAc unreacted starting material and byproducts were washed out, and the desired compound **62** was isolated by eluting with MeOH as a bright red oil (65 mg, 71%).



$C_{11}H_{15}NO$
177.24 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.63 (s, 2H, H-9), 4.06 (quintet, *J* = 7.6 Hz, 1H, H-7), 4.23 (d, *J* = 6.9 Hz, 1H, H-4), 3.65 (m, 2H, H-1), 3.21-2.92 (m, 3H, H-8), 2.68 (d, *J* = 2.3 Hz, 1H, H-6), 2.61 (m, 1H, H-8), 2.53-2.43 (m, 2H, H-2), 2.11 (m, 2H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 128.1 (C-9), 128.1 (C-9), 78.8 (C-5), 77.8 (C-6), 72.1 (C-7), 69.9 (C-4), 65.3 (C-1), 33.3 (C-8), 33.1 (C-8), 30.1 (C-3), 21.1 (C-2).

IR (ATR): ν (cm^{-1}) = 3123 (br s), 3061 (m), 2961 (s), 2929 (s), 2853 (m), 2102 (w), 1720 (m), 1621 (s), 1576 (s), 1441 (m), 1256 (m), 950 (m), 703 (m).

LRMS-ESI: *m/z* (%) = 178 (30) [MH^+], 112 (100).

HRMS-ESI (MH^+, $C_{11}H_{16}NO$) = calcd: 178.1232, found: 178.1226.

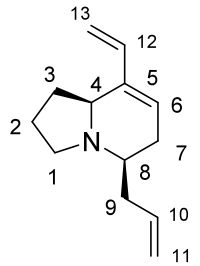
Optical rotation α_D^{20} = -47° (c = 0.19, CH_2Cl_2).

(5*R*,8a*S*)-5-allyl-8-vinyl-1,2,3,5,6,8a-hexahydroindolizine 59 and (5*S*,8a*S*)-5-allyl-8-vinyl-1,2,3,5,6,8a-hexahydroindolizine 60

A solution of **27**·TfOH (200 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (0.02 M) was flushed with ethylene for 5 min before catalyst **HII** (20 mg, 5 mol%) was added. The reaction was heated at 40 °C overnight under ethylene atmosphere. The reaction mixture was then washed with sat. aqueous Na_2CO_3 solution, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (SiO_2, MTBE → MTBE/acetone 2:3) and the title copounds (117 mg, 97%) were furnished as a 1:3 *cis*:*trans* diastereoisomeric mixture.

Following the same procedure of **27**·HPF_6 (50 mg, 0.64 mmol) and **59** (26 mg, 85%) was obtained as > 20:1 *cis:trans* mixture.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.18 (dd, *J* = 17.9 Hz, *J* = 11.2 Hz, 1H, H-12), 5.81 (m, 1H, H-10), 5.75 (br s, 1H, H-6), 5.11-4.92 (m, 4H, H-11, H-13), 3.62 (br s, 1H, H-4), 2.76 (m, 2H, H-1, H-8), 2.57 (m, 1H, H-1), 2.42 (m, 1H, H-9), 2.31-2.01 (m, 4H, H-3, H-7, H-9), 1.78 (m, 2H, H-2), 1.58 (m, 1H, H-7).



$C_{13}H_{19}N$
189.30 g/mol

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 139.2 (C-5), 137.4 (C-12), 135.8 (C-10), 126.0 (C-6), 116.6 (C-13), 112.0 (C-11), 60.4 (C-4), 55.5 (C-8), 45.3 (C-1), 39.4 (C-9), 30.0 (C-7), 27.9 (C-3), 22.8 (C-2).

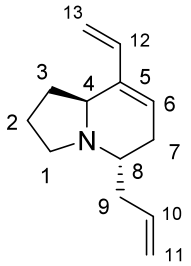
IR (ATR): ν (cm^{-1}) = 3304 (br w), 3052 (w), 2957 (s), 2926 (s), 2853 (m), 2800 (w), 1954 (w), 1736 (m), 1688 (m), 1639 (m), 1459 (m), 1443 (m), 1373 (m), 1366 (m), 1202 (m), 1130 (m), 990 (m), 911 (m).

LRMS-ESI: *m/z* (%) = 190 (100) [MH^+], 148 (90), 120 (30).

HRMS-ESI (MH^+, $C_{13}H_{20}N$) = calcd: 190.1596, found: 190.1585.

R_f (SiO_2, MTBE/acetone 3:2) = 0.22.

Optical rotation a_D^{20} = -100° (c = 1.1, CH_2Cl_2).



$C_{13}H_{19}N$
189.30 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.19 (dd, *J* = 17.9 Hz, *J* = 11.1 Hz, 1H, H-12), 5.80 (m, 1H, H-10), 5.68 (m, 1H, H-6), 5.06-4.94 (m, 4H, H-11, H-13), 3.78 (t, *J* = 7.1 Hz, 1H, H-4), 2.93 (m, app septet, *J* = 3.8 Hz, 1H, H-8), 2.88 (t, *J* = 6.9 Hz, 2H, H-1), 2.41-2.22 (m, 3H, H-3, H-7, H-9), 2.15 (m, 1H, H-9), 1.98 (m, 1H, H-3), 1.78 (m, 2H, H-2), 1.56 (m, 1H, H-7).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.5 (C-5), 137.7 (C-12), 1136.3 (C-10), 124.4 (C-6), 116.5 (C-13), 111.8 (C-11), 54.5 (C-4), 52.2 (C-8), 50.4 (C-1), 37.2 (C-9), 30.4 (C-7), 25.0 (C-3), 22.9 (C-2).

IR (ATR): ν (cm^{-1}) = 3307 (br w), 3075 (w), 2953 (m), 2925 (s), 2854 (m), 1737 (m), 1640 (m), 1442 (m), 1375 (m), 1263 (m), 1067 (m), 913 (m).

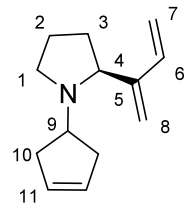
LRMS-ESI: *m/z* (%) = 190 (50) [MH^+], 148 (100).

HRMS-ESI (MH^+, $C_{13}H_{20}N$) = calcd: 190.1596, found: 190.1587.

R_f (SiO_2, MTBE/acetone 3:2) = 0.09.

Optical rotation a_D^{20} = -6° (c = 0.12, MeOH).

When the combined crude material obtained in the metathesis test was purified by column chromatography an appreciable amount of **X** was also isolated.



$C_{13}H_{19}N$
189.30 g/mol

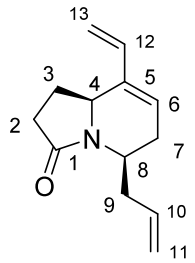
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.40 (dd, *J* = 17.7 Hz, *J* = 11.2 Hz, 1H, H-6), 5.66 (s, 2H, H-11), 5.37 (d, *J* = 17.7 Hz, 1H, H-7), 5.30 (s, 1H, H-8), 5.11 (s, 1H, H-8), 5.05 (d, *J* = 11.2 Hz, 1H, H-7), 3.42 (m, 1H, H-9), 3.29 (m, 1H, H-4), 2.98 (m, 1H, H-1), 2.45-2.21 (m, 6H, H-1, H-3, H-10), 2.00 (m, 1H, H-3), 1.71 (m, 2H, H-2).

IR (ATR): ν (cm^{-1}) = 2955 (m), 2924 (s), 2853 (m), 1738 (w), 1463 (w), 1348 (w), 1261 (w), 1124 (w), 1074 (w).

HRMS (MH^+, $C_{13}H_{20}N$) = calcd: 190.1596, found 190.1587.

(5*R*,8a*S*)-5-allyl-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one 64 and (5*S*,8a*S*)-5-allyl-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one 65

A solution of freshly distilled alkyne **31** (190 mg, 1.0838 mmol) in anhydrous degassed CH_2Cl_2 (36 mL, 0.03 M) was flushed with ethylene for 5 min before catalyst **FI** (50 mg, 5 mol%) was added. The reaction was stirred at rt overnight under ethylene atmosphere. After evaporating the solvent, the residue was purified by column chromatography (SiO_2, cyclohexane → EtOAc), the title compounds (205 mg, 93%) were furnished as a 1:10 *cis*:*trans* diastereoisomeric mixture.



$C_{13}H_{17}NO$
203.28 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.19 (dd, *J* = 17.9 Hz, *J* = 11.4 Hz, 1H, H-12), 5.89-5.78 (m, 2H, H-6, H-10), 5.16-5.01 (m, 4H, H-11, H-13), 4.45 (br s, 1H, H-4), 3.32-3.20 (m, 2H, H-8, H-9), 2.69-2.60 (m, 1H, H-9) 2.53-2.27 (m, 4H, H-2, H-3, H-7), 2.22-2.15 (m, 1H, H-7), 1.84-1.73 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 174.4 (C-1), 139.4 (C-5), 136.3 (C-12), 135.5 (C-10), 127.3 (C-6), 116.8 (C-13), 113.0 (C-11), 59.2 (C-4), 54.9 (C-8), 36.1 (C-9), 32.4 (C-7), 31.4 (C-2), 25.3 (C-3).

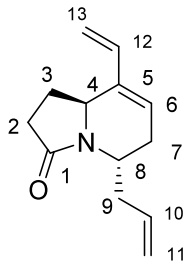
IR (ATR): ν (cm^{-1}) = 3361 (br w), 3075 (w), 2927 (m), 2854 (m), 1933 (w), 1690 (s), 1640 (m), 1417 (m), 1348 (m), 1264 (w), 993 (m), 914 (m).

LRMS-ESI: *m/z* (%) = 204.14 (20) [MH^+], 190.16 (100) [M^+-CH_2], 162.97 (20) [M^+-allyl], 149.01 (30), 129.03 (30), 116.98 (30).

HRMS (MH^+, $C_{13}H_{18}NO$) = calcd: 204.1383, found: 204.1381.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.37.

Optical rotation a_D^{20} = -102° (c = 1.03, CH_2Cl_2), -85° (c = 0.75, MeOH).



$C_{13}H_{17}NO$
203.28 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.22 (dd, *J* = 17.9 Hz, *J* = 11.4 Hz, 1H, H-12), 5.80-5.70 (m, 2H, H-6, H-10), 5.11-5.02 (m, 4H, H-11, H-13), 4.48 (m, 1H, H-8), 4.34 (br s, 1H, H-4), 2.58-2.34 (m, 4H, H-2, H-3, H-7), 2.32-2.16 (m, 2H, H-9), 2.15-2.06 (m, 1H, H-7), 1.70-1.61 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.1 (C-1), 136.8 (C-5), 135.9 (C-12), 134.8 (C-10), 124.8 (C-6), 117.4 (C-13), 112.8 (C-11), 52.3 (C-4), 44.5 (C-8), 35.9 (C-9), 31.5 (C-7), 28.7 (C-2), 26.8 (C-3).

IR (ATR): ν (cm^{-1}) = 3419 (w), 3258 (w), 3075 (w), 3004 (w), 2974 (w), 2920 (w), 2841 (w), 1689 (s), 1412 (m), 1266 (w), 993 (w), 914 (w).

LRMS-ESI: *m/z* (%) = 204 (20) [MH^+], 190 (100) [M^+-CH_2], 162 (20) [M^+-allyl], 149 (30), 129 (30), 116 (30).

HRMS-ESI (MH^+, $C_{13}H_{18}NO$) = calcd: 204.1383, found: 204.1382.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.21.

Optical rotation a_D^{20} = -101° (c = 1.14, CH_2Cl_2), -38° (c = 1.2, MeOH).

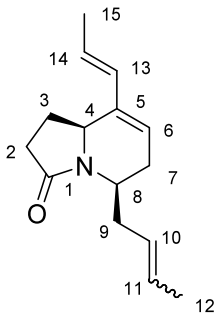
(5*R*,8a*S*)-5-(but-2-enyl)-8-(prop-1-enyl)-1,2,5,6-tetrahydroindolizin-3(8aH)-one 69 and (5*S*,8a*S*)-5-(but-2-enyl)-8-(prop-1-enyl)-1,2,5,6-tetrahydroindolizin-3(8aH)-one 70

A solution of **31** (10 mg, 0.049 mmol) in CH_2Cl_2 (1 mL) was flushed with 2-butene for 1 min before catalyst **HII** (1.5 mg, 5 mol%) was added. The mixture was heated at 40 °C overnight and concentrated. Analysis per ^{1}H-NMR showed a mixture 1:2 *cis:trans* diastereoisomers. The crude material was purified on a preparative TLC plate to obtain an analytical sample.[8]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.89 (d, *J* = 16.2 Hz, 1H, H-13), 5.70 (s, 1H, H-6), 5.60-5.49 (m, 2H, H-11, H-14), 5.48-5.37 (m, 1H, H-10), 4.38 (br s, 1H, H-4), 3.24-3.04 (m,

[8] *Cis*:*trans* ratio at C-11 was not determined.

2H, H-8, H-9), 2.61-2.10 (series of m, 7H, H-2, H-3, H-7, H-9), 1.76 (d, *J* = 6.6 Hz ,3H, H-15), 1.65 (d, *J* = 5.5 Hz, 3H, H-12).[9]



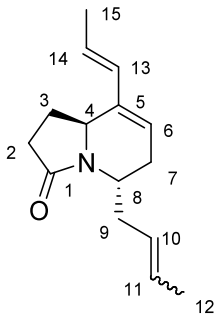
$C_{15}H_{21}NO$
231.33 g/mol

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 174.6 (C-1), 138.8 (C-5), 130.3 (C-13), 129.3 (C-14), 127.8 (C-10), 124.6 (C-6, C-11), 59.7 (C-4), 55.6 (C-8), 35.2 (C-9), 32.8 (C-7), 31.3 (C-2), 25.7 (C-3), 18.9 (C-15), 18.1 (C-12).[i]

IR (ATR): ν (cm^{-1}) = 3286 (br m), 3018 (w), 2918 (m), 2853 (m), 2729 (w), 1688 (s), 1669 (s), 1436 (m), 1420 (m), 1355 (m), 1261 (m), 967 (m).

HRMS-ESI (MH^+, $C_{15}H_{22}NO$) = calcd: 232.1701, found: 232.1689.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.39.



$C_{15}H_{21}NO$
231.33 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.74-5.62 (m ,3H, H-6, H-11, H-13), 5.60-5.36 (m, 2H, H-10, H-14), 4.16 (m, 1H, H-4), 3.46 (m, 1H, H-8), 3.02-2.90 (m, 1H, H-9), 2.42-2.10 (series of m, 7H, H-2, H-3, H-7, H-9), 1.77 (m, 3H, H-15), 1.65 (m ,3H, H-12).[i]

HRMS-ESI (MH^+, $C_{15}H_{22}NO$) = calcd: 232.1701, found: 232.1697.

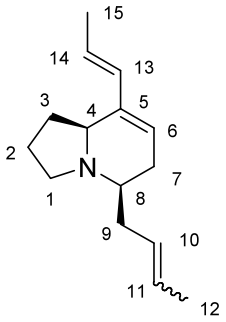
R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.26.

(5R,8aS,E)-5-(but-2-enyl)-8-(prop-1-enyl)-1,2,3,5,6,8a-hexahydroindolizine 67 and (5*S*,8a*S*,*E*)-5-(but-2-enyl)-8-(prop-1-enyl)-1,2,3,5,6,8a-hexahydroindolizine 68

Ammonium salt **27**·TFA (32 mg, 0.15 mmol) was dissolved in anhydrous CH_2Cl_2 (8 ml) and the solution was flushed for 1 - 2 min with 2-butene before catalyst **WI** (10 mg, 10 mol%) was added. The reaction was stirred overnight at 40 °C under 1 atm 2-butene atmosphere. After evaporating the solvent, analysis of the crude material indicated complete conversion towards **67**. Purification by column chromatography (Al_2O_3, EtOAc → EtOAc/MeOH 4:1) afforded **67** (30 mg, 90%) as a brown oil.

[9] Analytical data for the *trans* isomer.

Alternatively when **27**·TfOH (50 mg, 0.16 mmol) was reacted with **HII** (10 mg, 5 mol%), mixture *cis:trans* 5:7 with 86% yield (30 mg) was obtained.



$C_{15}H_{23}N$
217.35 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.88 (d, *J* = 16.2 Hz, 1H, H-13), 5.61 (s, 1H, H-6), 5.58-5.38 (m, 3H, H-10, H-11, H-14), 3.52 (bs, 1H, H-4), 2.85-2.75 (m, 1H, H-1), 2.71-2.62 (m, 1H, H-8), 2.57-2.49 (m, 1H, H-1), 2.41-2.31 (m, 1H, H-9), 2.27-2.17 (m, 1H, H-7), 2.13-2.00 (m, 3H, H-3, H-9), 1.76 (m, 5H, H-2, H-15), 1.65 (m, 3H, H-12), 1.60-1.49 (m, 1H, H-7).[i]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.8 (C-5), 131.7 (C-13), 128.1 (C-14), 127.0 (C-10), 123.30, 123.2 (C-6, C-11), 61.0 (C-4), 56.1 (C-8), 45.6 (C-1), 38.3 (C-9), 30.1 (C-7), 28.1 (C-3), 22.7 (C-2), 18.6 (C-15), 18.0 (C-12).[10]

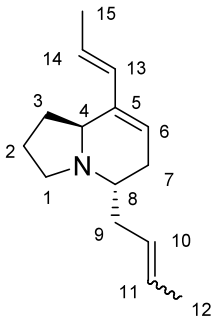
IR (ATR): ν (cm^{-1}) = 3022 (m), 2961 (s), 2913 (s), 2875 (m), 2781 (m), 1938 (w), 1448 (m), 1438 (m), 1357 (m), 1191 (m), 1141 (m), 964 (s).

LRMS-ESI: *m/z* (%) = 218 (45) [MH^+], 162 (100), 98 (75).

HRMS-ESI (MH^+, $C_{15}H_{22}NO$) = calcd: 218.1909, found: 218.1903.

R_f (SiO_2, MeOH/EtOAc 1:4) = 0.11 (SiO_2, MeOH/ CH_2Cl_2 1:10) = 0.13.

Optical rotation a_D^{20} = -35° (c = 0.12, MeOH), -50° (c = 0.25, MeOH), -73° (c = 0.2, CH_2Cl_2).



$C_{15}H_{23}N$
217.35 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.89 (d, *J* = 18.8 Hz, 1H, H-13), 5.52 (m, 1H, H-6), 5.51-5.36 (m, 3H, H-10, H-11, H-14), 3.71 (m, 1H, H-4), 2.92-2.78 (m, 3H, H-1, H-8), 2.39-2.26 (m, 1H, H-9), 2.26-2.17 (m, 2H, H-3), 2.11-2.03 (m, 1H, H-7), 1.99-1.79 (m, 1H, H-9), 1.74 (m, 5H, H-2, H-15), 1.66-1.57 (m, 3H, H-12), 1.55-1.46 (m, 1H, H-7).[i]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.2 (C-5), 132.3 (C-13), 128.7 (C-14), 126.8 (C-10), 122.9 (C-11), 121.4 (C-6), 55.2 (C-4), 52.6 (C-8), 50.4 (C-1), 36.0 (C-9), 30.5 (C-7), 25.1 (C-3), 22.9 (C-2), 18.5 (C-15), 18.1 (C-12).[j]

[10] Analytical data correspond to the *trans* isomer. In ^{13}C-NMR spectra *cis:trans* signals (C-10 - C-11 olefine) from C-1, C-3, C-10 and C-14 appear at a ratio 1:3 approx.

IR (ATR): ν (cm^{-1}) = 3023 (m), 2960 (m), 2914 (m), 2878 (m), 2853 (m), 2796 (m), 1437 (m), 1375 (m), 1336 (m), 1132 (m), 964 (s).

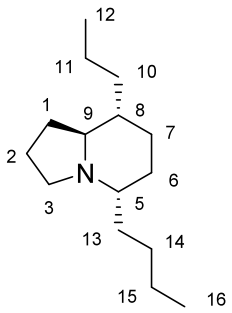
LRMS-ESI: *m/z* (%) = 218 (45) [MH$^+$], 162 (100), 98 (20).

HRMS-ESI (MH$^+$, $C_{15}H_{22}NO$) = calcd: 218.1909, found: 218.1905.

R_f (SiO_2, MeOH/EtOAc 1:4) = 0.03, (SiO_2, MeOH/DCM 1:10) = 0.05.

Optical rotation a_D^{20} = +17.6° (c = 0.044, CH_2Cl_2), -12° (c = 0.075, MeOH), -27° (c = 0.03, CH_2Cl_2).[11]

Indolizidine 5-*epi*-223J



$C_{15}H_{29}N$
223.40 g/mol

Following the standard hydrogenation procedure described previously, RRM product **68** (150 mg, 0.69 mmol) in MeOH (3 mL) were hydrogenated for 48 h at 3 bar hydrogen at rt with Rh/Al_2O_3 10%. After column chromatography (SiO_2, EtOAc → EtOAc/MeOH 4:1) a mixture of *syn:anti* (C-5/C-8) diastereoisomers (130 mg, 84%) was isolated as clear yellowish oil.[12] An analytical sample **68** was obtained by evaporating the latest fractions collected in the chromatography.

A IR band at 2509 cm^{-1} reveals the presence of an impurity. ^{1}H-NMR presents some very broad signals around 3 ppm, although the title compound showed to be spectroscopically pure by ^{13}C-NMR analysis. Several purifications on column chromatography resulted unsuccessful and aqueous work up (sat aqueous Na_2CO_3 solution) or distillation resulted in decomposition (possibly epimerization).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.72 (app quintet, *J* = 6.1 Hz, 1H, H-5), 3.51-3.33 (m, 2H, H-3), 2.56 (m, 1H, H-9), 2.37 (m, 1H, H-8), 2.11-1.09 (series of m, 18H, H-1, H-2, H-6, H-7, H-10, H-11, H-13, H-14, H-15), 0.91 (t, *J* = 6.97 Hz, 6H, H-12, H-16).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 66.0 (C-5), 57.9 (C-9), 50.0 (C-3), 34.5 (C-8), 35.4, 31.4 (C-10, C-13), 28.8, 28.2 (C-1, C-6), 23.2, 22.4 (C-7, C-14), 20.3 (C-2), 19.8 (C-15), 19.3 (C-11), 14.2 (C-12), 13.9 (C-16).

[11] Unfortunately, due to ruthenium rests, dark brown solutions were obtained and very low concentrated solutions were needed to measure the optical rotation, and the results were not reproducible.
[12] In ^{13}C-NMR spectra *syn:anti* ratio appears to be 3:1 approx. from C-1, C-4, and C-5 signals.

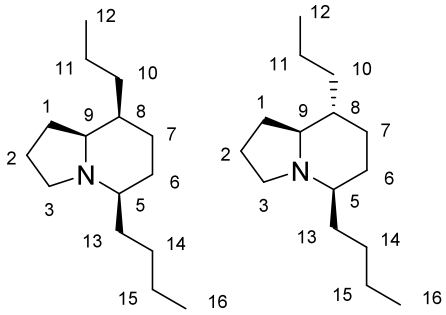
IR (ATR): ν (cm^{-1}) = 3428 (br m), 2955 (s), 2931 (s), 2871 (s), 2509 (br m), 2456 (br m), 1701 (w), 1630 (w), 1466 (m), 1457 (m), 1380 (w), 1039 (w).

HRMS-ESI (MH^+, $C_{15}H_{22}NO$) = calcd: 218.1909, found: 218.1905.

R_f (SiO_2, MTBE/MeOH 5:2) = 0.46 and 0.18.

Optical rotation a_D^{20} = -12° (c = 0.075, MeOH).

Indolizidines 8-*epi*-223J and 223J



8-*epi*-223*J* **223*J***

$C_{15}H_{29}N$
223.40 g/mol

Following the standard hydrogenation procedure described previously, RRM product **67** (95 mg, 0.44 mmol) in MeOH (1 mL) was hydrogenated for 48 h at 30 bar hydrogen pressure at rt with Pd/Al_2O_3 5%. After column chromatography (Al_2O_3, EtOAc → EtOAc/ MeOH 4:1) a mixture of *cis:trans* (C-5/C-8) diastereoisomers (60 mg, 61%) was isolated as clear yellowish oil.[l]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.26 (m, 1H, H-5), 2.06-0.99 (series of m, 22H, H-1, H-2, H-3, H-6, H-7, H-8, H-9, H-10, H-11, H-13, H-14 H-15), 0.88 (m, 6H, H-12, H-16).[13]

Literature data for **223J ^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) = 0.81-0.93 (m, 7H), 0.98-1.10 (m, 1H), 1.14-1.49 (m, 11H), 1.53-2.00 (m, 9H), 3.27 (ddd, J = 8.7, 8.7, 2.1 Hz, 1H).[14]

Found for **223J ^{13}C-NMR** ($CDCl_3$, 100 MHz): δ (ppm) = 70.3 (CH), 63.6 (CH), 51.9 (CH_2), 41.1 (CH_2), 35.63 (CH_2), 34.4 (CH), 31.2 (CH_2), 30.5 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 23.1 (CH_2), 20.4 (CH_2), 19.6 (CH_2), 14.4 (CH_3), 14.0 (CH_3).

Literature data: **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ (ppm) = 14.0, 14.4, 19.6, 20.3, 23.1, 28.0, 29.1, 30.4, 31.1, 34.2, 35.6, 41.2, 51.8, 63.5, 70.2.[n]

Found for **8-*epi*-223*J* ^{13}C-NMR** ($CDCl_3$, 100 MHz): δ (ppm) = 68.3 (CH), 65.2 (CH), 52.5 (CH_2), 34.9 (CH), 30.5 (CH_2), 28.5 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 26.0 (CH_2), 23.1 (CH_2), 21.6 (CH_2), 20.5 (CH_2), 14.3 (CH_3), 14.0 (CH_3).

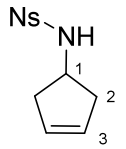
[13] For the diastereoisomeric mixture
[14] P. Michel, A. Rassat, *J. Org. Chem.* **2000**, *65*, 8908-8918.

IR (ATR): ν (cm^{-1}) = 3324 (br w), 2957 (s), 2930 (s), 2871 (m), 2861 (m), 1685 (m), 1499 (w), 1465 (m), 1457 (m), 1358 (m), 1285 (m), 1264 (m), 1173 (w), 1039 (w).[m]

HRMS-ESI (MH^+, $C_{15}H_{30}N$) = calcd: 224.2378, found: 224.2369.

R_f (SiO_2, MTBE/MeOH 5:2) = 0.4, (SiO_2, MTBE/MeOH 1:1) = 0.94 and 0.77, (SiO_2, CH_2Cl_2/MeOH 10:1) = 0.32 and 0.5.

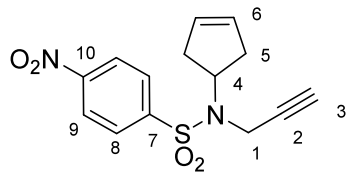
N-(cyclopent-3-enyl)-4-nitrobenzenesulfonamide 80



$C_{11}H_{12}N_2O_4S$
268.29 g/mol

Was prepared from cyclopentadiene in 6 steps according to the procedure applied by J. Neidhofer (PhD thesis).[237]

N-(cyclopent-3-enyl)-4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide



$C_{14}H_{14}N_2O_4S$
306.34

Amine **80** (3 g, 11.2 mmol) and propargyl bromide (2.5 mL, 29.4 mmol) were added to a suspension of K_2CO_3 (10 g, 72.3 mmol) in anhydrous DMF (150 mL), which was then heated at 60 °C for 10 h. After adding 150 mL CH_2Cl_2 and 80 mL brine, the organic phase was washed five times with brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 10:1) furnished the title compound as a colorless oil (2.61 mg, 76%), which solidifies at -20 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.33 (d, *J* = 8.0 Hz, 2H, H-9), 8.12 (d, *J* = 8.0 Hz, 2H, H-8), 5.69 (m, 2H, H-6), 4.71 (ddt, app septet, *J* = 4.7 Hz, 1H, H-4), 4.10 (d, *J* = 4.0 Hz, 2H, H-1), 2.60 (dd, *J* = 11.0 Hz, *J* = 8.0 Hz, 2H, H-5), 2.45 (dd, *J* = 11.0 Hz, *J* = 4.0 Hz, 2H, H-5), 2.12 (t, *J* = 1.0 Hz, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 33.1 (C-1), 37.1 (C-5), 56.8 (C-4), 73.2 (C-3), 78.9 (C-2), 124.1 (C-8), 128.8 (C-6), 129.1 (C-9), 146.3 (C-10), 150.0 (C-7).

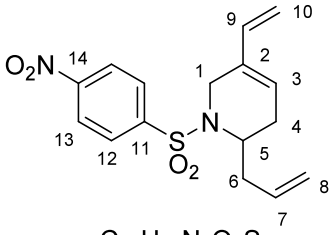
IR (ATR): ν (cm^{-1}) = 3286 (w), 3105 (w), 2923 (w), 2856 (w), 1606 (w), 1529 (s), 1349 (s), 1309 (m), 1162 (s), 1093 (m), 850 (m), 685 (m).

LRMS-ESI: *m/z* (%) = 307 (15) [MH^+], 265 (50), 241 (55) [$MH\text{-}C_5H_6^+$], 229 (100), 185 (45), 121 (60).

HRMS-ESI (MH^+, $C_{14}H_{15}N_2O_4S$) = calcd: 307.0753, found: 307.0745.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.25.

2-allyl-1-(4-nitrophenylsulfonyl)-5-vinyl-1,2,3,6-tetrahydropyridine 81



$C_{16}H_{18}N_2O_4S$
334.39

A solution of the previous alkyne (1.10 g, 3.76 mmol) in anhydrous CH_2Cl_2 (40 mL, 0.1 M) was flushed with ethylene for 2 min before catalyst **GI** (160 mg, 2 mol%) was added and the reaction mixture was stirred at rt under ethylene atmosphere overnight. After evaporating the solvent under reduced pressure the crude material was purified by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 10:1) to obtain **81** as a colorless oil (829 mg, 66%), which solidifies at -20 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.32 (d, *J* = 8.7 Hz, 2H, H-13), 7.97 (d, *J* = 8.7 Hz, 2H, H-12), 6.23 (dd, *J* = 17.9 Hz, *J* = 10.9 Hz, 1H, H-9), 5.70 (m, 1H, H-7), 5.60 (br s, 1H, H-3), 5.07 (m, 4H, H-8, H-10), 4.40 (d, *J* = 17.5 Hz, 1H, H-1), 4.22 (m, 1H, H-5), 3.74 (d, *J* = 17.7 Hz, 1H, H-1), 2.14-2.27 (m, 3H, H-4, H-6), 2.00 (dd, *J* = 17.7, *J* = 5.0 Hz, 1H, H-4).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 149.9 (C-14), 146.9 (C-11), 136.1 (C-9), 133.97 (C-7), 131.4 (C-2), 128.0 (C-12), 124.6 (C-3), 124.3 (C-13), 118.1 (C-10), 111.9 (C-8), 50.7 (C-5), 39.9 (C-1), 36.1 (C-6), 27.6 (C-4).

IR (ATR): ν (cm^{-1}) = 3103 (w), 3081 (w), 2971 (w), 2918 (w), 2849 (w), 1607 (m), 1529 (s), 1350 (s), 1310 (m), 1166 (s), 1093 (m), 855 (m), 736 (m).

LRMS-ESI: *m/z* (%) = 335 (10) [MH^+], 253 (100), 171 (20).

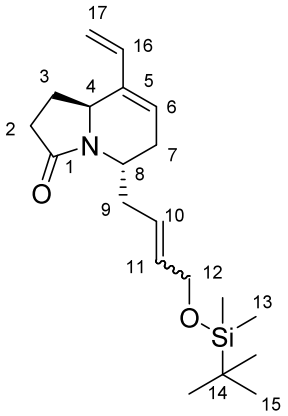
HRMS-ESI (MH^+, $C_{17}H_{19}N_2O_4S$) = calcd: 335.1066, found: 335.1057.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.50.

(5*S*, 8a*S*)-5-(4-(tert-butyldimethylsilyloxy)but-2-enyl)-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one 88

TBS protected allyl alcohol (372 mg, 1.97 mmol) and **65** (100 mg, 0.49 mmol) were dissolved in anhydrous CH_2Cl_2 (8 mL) and, after degassing *via* 3 freeze-pump-thaw cycles, the mixture

was heated at 40 °C overnight. Catalyst **GI** (40 mg, 10 mol%) was then added in 10 portions (4 mg every 60 min approx.). Stirring continued overnight. After concentrating the crude material was purified by column chromatography (SiO_2, cyclohexan → cyclohexane/EtOAc 1:1) and **88** (146 mg, 85%) was afforded as a *E/Z* mixture (7.1:1) light brown oil. [15]



$C_{20}H_{33}NO_2Si$
347.57 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.21 (dd, *J* = 17.9 Hz, 11.2 Hz, 1H, H-16), 5.73 (d, *J* = 6.1 Hz, 1H, H-6), 5.58 (m, 2H, H-10, H-11), 5.12-5.01 (m, 2H, H-17), 4.44 (m, 1H, H-8), 4.34 (br s, 1H, H-4), 4.10 (m, 2H, -12), 2.57-2.04 (series of m, 7H, H-2, H-3, H-7, H-9), 1.65 (m, 1H, H-3), 0.89 (s, 9H, H-15), 0.05 (s, 6H, H-13).[i]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.9 (C-1), 136.9 (C-5), 135.9 (C-16), 132.4 (C-11), 126.7 (C-10), 124.8 (C-6), 112.7 (C-17), 63.7 (C-12), 52.3 (C-4), 44.7 (C-8), 34.2 (C-9), 31.5 (C-2), 28.6 (C-7), 26.8 (C-3), 25.9 (C-15), 18.4 (C-14), -5.2 (C-13).[i]

IR (ATR): ν (cm^{-1}) = 3352 (br m), 2929 (m), 2854 (m), 2050 (w), 1978 (w), 1942 (w), 1672 (s), 1416 (m), 1267 (m), 1076 (m), 837 (m).

LRMS-ESI: *m/z* (%) = 348 (45) [MH^+], 316 (50), 288 (40), 266 (25), 216 (100) [M^+-TBS], 162 (25).

HRMS-ESI (MH^+, $C_{20}H_{34}NO_2Si$) = calcd: 348.2359, found: 348.2355.

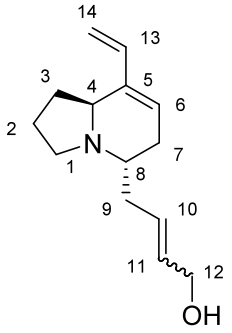
R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.36.

Optical rotation a_D^{20} = -42° (c = 0.055, MeOH).

4-((5S,8aS)-8-vinyl-1,2,3,5,6,8a-hexahydroindolizin-5-yl)but-2-en-1-ol 89

To a solution of **88** (50 mg, 0.14 mmol) in Et_2O (3 mL), $LiAlH_4$ (11 mg,0.28 mmol) was added at 0 °C. The reaction mixture was stirred at rt overnight and quenched at 0 °C with wet EtOAC. Purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) afforded the desired product **89** (30 mg, 95%) as clear oil.

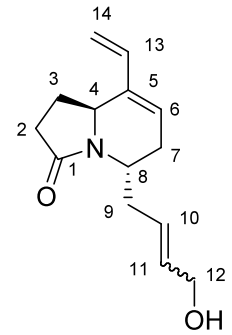
[15] Ratio determined *via* integration of C-12 signals in ^{1}H-NMR data.



$C_{14}H_{21}NO$
219.32 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.19 (dd, *J* = 17.8 Hz, *J* = 11.1 Hz, 1H, H-13), 5.78 (m, 1H, H-10), 5.69 (s, 1H, H-6), 5.59 (m, 1H, H-11), 8.98 (m, 2H, H-14), 4.59 (d, *J* = 6.6 Hz, 0.3H, H12) 4.51 (d, *J* = 6.4 Hz, 1.7H, H12), 4.12 (m, H-8), 4.05 (m, 1H combined, H-8), 3.78 (br s, 1H, H-4).[16]

(5*S*,8a*S*)-5-(4-hydroxybut-2-enyl)-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one 90



$C_{14}H_{19}NO_2$
233.31 g/mol

To a solution of **88** (191 mg, 0.549 mmol) in THF (1.5 mL) TBAF·H_2O (260 mg, 0.824 mmol) was added at 0 °C. Stirring continued overnight before the mixture was concentrated and purified by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) obtaining **90** (100 mg, 78%) as a clear oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.21 (dd, *J* = 18.2 Hz, *J* = 11.5 Hz, 1H, H-13), 5.76-5.59 (m, 3H, H-6, H-10, H-11), 5.12-5.03 (m, 2H, H-14), 4.43 (m, 1H, H-8), 4.34 (br s, 1H, H-4), 4.06 (d, *J* = 5.1 Hz, 2H, H-12), 2.58-2.05 (series of m, 7H, H-2, H-3, H-7, H-9), 1.65 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.3 (C-1), 136.66 (C-5), 135.8 (C-13), 132.2 (C-11), 128.5 (C-10), 124.7 (C-6), 112.9 (C-14), 63.3 (C-12), 52.3 (C-4), 44.9 (C-8), 34.3 (C-9), 31.5 (C-2), 29.1 (C-7), 28.9 (C-3).

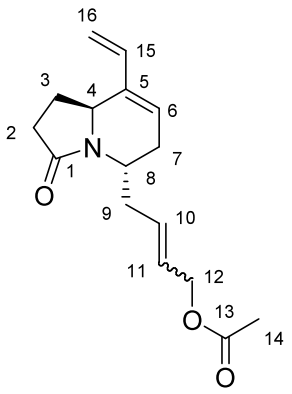
IR (ATR): ν (cm^{-1}) = 3354 (br w), 2957 (m), 2925 (s), 2854 (m), 2024 (w), 1971 (w), 1671 (m), 1457 (m), 1415 (m), 1267 (w), 1187 (w), 1081 (w), 971 (w).

HRMS-ESI (MH^+, $C_{14}H_{20}NO_2$) = calcd: 234.1494, found: 234.1493.

R_f (SiO_2, EtOAc/MeOH 4:1) = 0.22.

[16] 5.7:1 *E/Z* ratio determined *via* integration of C-12 signals in 1H-NMR data.

4-((5S,8aS)-3-oxo-8-vinyl-1,2,3,5,6,8a-hexahydroindolizin-5-yl)but-2-enyl acetate 97



$C_{16}H_{21}NO_3$
275.34 g/mol

To a solution of substrate **88** (100 mg, 0.49 mmol) in CH_2Cl_2 (8 mL), (*Z*)-but-2-ene-1,4-diyl diacetate (120 mg, 0.54 mmol) and **GI** (20 mg, 5 mol%) were subsequently added. The reaction mixture was stirred at 40 °C overnight and concentrated. Purification by column chromatography (SiO_2, cyclohexan → cyclohexane/EtOAc 1:1) afforded **97** (50 mg, 37%) as a light brown oil 5.7:1 *E/Z* mixture.[17]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.20 (dd, *J* = 18.0 Hz, 11.0 Hz, 1H, H-15), 5.72 (m, 1H, H-6), 5.70-5.57 (m, 2H, H-10, H-11), 5.11-5.03 (m, 2H, H-16), 4.58-4.42 (m, 3H, H-8, H-12), 4.31 (br s, 1H, H-4), 2.57-2.02 (series of m, 7H, H-2, H-3, H-7, H-9), 2.04 (s, 3H, H-14), 1.64 (m, 1H, H-3).[i]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.1 (C-1), 170.7 (C-13), 136.8 (C-5), 135.7 (C-15), 131.6 (C-11), 126.9 (C-10), 124.5 (C-6), 112.9 (C-16), 64.6 (C-12), 52.3 (C-4), 44.5 (C-8), 34.3
(C-9), 31.4 (C-7), 28.7 (C-2), 26.9 (C-3), 20.9 (C-14).[i]

IR (ATR): ν (cm^{-1}) =3350 (br m), 3077 (m), 2929 (m), 2854 (m), 2048 (w), 1994 (w), 1738 (s), 1686 (s), 1414 (m), 1371 (m), 1232 (s), 1028 (m).

LRMS-ESI: *m/z* (%) = 276 (57) [MH^+], 276 (59), 116 (100), 262 (43).

HRMS-ESI (MH^+, $C_{16}H_{22}NO_3$) = calcd: 276.1600, found: 276.1592.

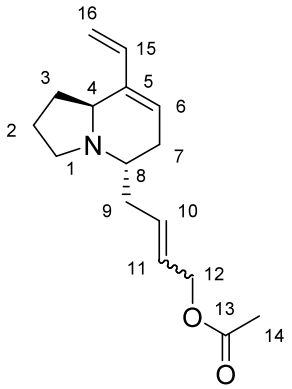
R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.11.

Optical rotation a_D^{20} = -11° (c = 0.11, CH_2Cl_2).

4-((5S,8aS)-8-vinyl-1,2,3,5,6,8a-hexahydroindolizin-5-yl)but-2-enyl acetate 99

To a solution of **97** (29 mg, 0.0968 mmol) in Et_2O (2 mL), a solution of $LiAlH_4$ in Et_2O (0.15 mL, 4 M) was added at rt. The reaction mixture was heated at 40 °C overnight and quenched at 0 °C with wet EtOAC. Purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) afforded the desired product **99** (14 mg, 55%) along with the corresponding unprotected alcohol **89** (8 mg, 38%), both as clear oil.

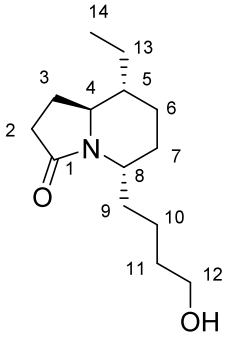
[17] *E/Z* ratio determined *via* integration of C-12 signals in ^{1}H-NMR data.



$C_{16}H_{23}NO_2$
261.36 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.20 (dd, *J* = 17.6 Hz, *J* = 11.2 Hz, 1H, H-13), 5.77 (m, 1H, H-10), 5.69 (s, 1H, H-6), 5.60 (m, 1H, H-11), 5.04-4.94 (m, 2H, H-16), 4.60-4.49 (m, 2H, H-12), 3.78 (br s, 1H, H-4), 2.96-2.78 (m, 3H, H-1, H-8), 2.05 (m, 3H, H-14).

(5S,8R,8aS)-8-ethyl-5-(4-hydroxybutyl)-hexahydroindolizin-3(5H)-one 91



$C_{14}H_{25}NO_2$
239.35 g/mol

Compound **88** (71 mg, 0.204 mmol) were dissolved in 7 ml MeOH and hydrogenated at 30 °C in the H-CUBE at 15 bar, first with Pd/C 10%, and subsequently with Rh/C 5%. The desired product **91** (23 mg, 47%) was obtained after purification by column chromatography, and 20 mg of a mixture of dehydroxylated product and dehydroformilated derivative.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.20 (m, 1H, H-4), 3.62 m, 2H, H-12), 3.18 (m, 1H, H-8), 2.33 (m, 2H, H-2), 2.21 (sextet, *J* = 6.8 Hz, 1H, H-10), 2.05-1.17 (series of m, 15H, H-2, H-3, H-5, H-6, H-7, H-9, H-10, H-11, OH), 1.13-0.96 (m, 1H, H-5), 0.90 (m, 3H, H-14).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.9 (C-1), 62.6 (C-12), 57.7 (C-8), 47.4 (C-4), 45.6 (C-5), 32.4 (C-9), 30.5 (C-2), 29.9, 27.6, 24.6, 24.3, 24.1 (C-3, C-6, C-7, C-11, C-13), 22.4 (C-10), 10.9 (C-14).

IR (ATR): ν (cm^{-1}) = 3410 (br m), 2933 (s), 2861 (m), 2095 (w), 1681 (s), 1664 (s), 1445 (m), 1421 (m), 1278 (m), 1072 (m), 1057 (m).

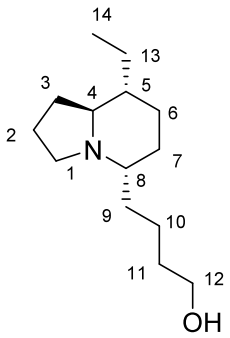
LRMS-ESI: *m/z* (%) = 240 (25) [MH^+], 222 (65), 166 (100).

HRMS-ESI (MH^+, $C_{14}H_{26}NO_2$) = calcd: 240.1964, found: 240.1954.

HRMS (MNa^+, $C_{14}H_{25}NO_2Na$) = calcd: 262.1783, found: 262.1774.

R_f (SiO_2, EtOAc/MeOH 4:1) = 0.2.

4-((5*S*,8*R*,8a*S*)-8-ethyl-octahydroindolizin-5-yl)butan-1-ol 100



$C_{14}H_{27}NO$
225.37 g/mol

Amide **91** (7 mg, 29 µmol) was dissolved in freshly distilled THF (3 mL) and $BH_3{\cdot}SMe_2$ (100 µL, 0.58 mmol) was added *via* syringe and the reaction mixture was then refluxed overnight. After cooling down to rt the reaction flask was placed in a ice/water bath and anhydrous MeOH was slowly added over 2 h until no further H_2 evolution was observed. Subsequently 1 mL of methanolic HCl was slowly added at 0 °C and the reaction was stirred 3 h further. After evaporating the volatiles the crude was dissolved in CH_2Cl_2 and washed once with 2 M Na_2CO_3 aq. solution. The organic layer was dried over $MgSO_4$, evaporated, and the crude mixture was isolated as a clear oil (5 mg, 76%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.66 (m, 3H, H-12), 3.07-2.94 (m, 1H), 2.91-2.78 (m, 1H), 2.51-2.69 (m, 1H), 2.31-1.00 (series of m), 0.96-0.85 (m, 3H, H-14).[m]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 68.4 (C-4), 65.4 (C-8), 52.6, 52.0, 35.7, 35.5, 35.0, 34.5, 29.8, 29.2, 28.5, 28.1, 27.8, 26.5, 26.2, 23.2, 21.7, 20.5, 14.5, 14.2 (C-14), 14.1 (C-14).[m]

HRMS-ESI (MH^+, $C_{14}H_{28}NO$) = calcd: 226.2171, found: 226.2159.

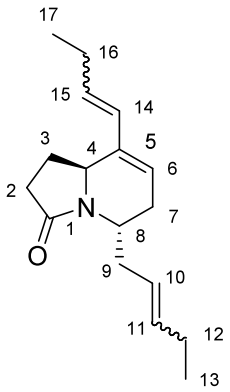
R_f(SiO_2, MeOH/EtOAc 1:4) = 0.23.

(5S,8aS)-8-(but-1-enyl)-5-(pent-2-enyl)-1,2,5,6-tetrahydroindolizin-3(8aH)-one

Amide **65** (4 mg, 24.5 µmol) and 3-hexene (1.36 µL, 11.1 µmol) were dissolved in anhydrous CH_2Cl_2 (1.2 mL) under N_2 atmosphere. Catalyst **GII** (1 mg, 4.8 mol%) was then added and the mixture was heated overnight at 40 °C. After concentration under reduced pressure, analysis *via* ^{1}H-NMR showed complete conversion, and the crude material was purified by flash column chromatography (SiO_2, cyclohexane → EtOAc) to furnish the title compound (4 mg, 63%) as brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.89 (d, *J* = 16.2 Hz, 1H, H-14), 5.65-5.30 (m, 4H, H-6, H-10, H-11, H-15), 4.38 (m, 1H, H-8), 4.29 (br s, 1H, H-4), 2.54-1.95 (series of m, 11H, H-2,

H-3, H-7, H-9, H-12, H-16), 1.61 (m, 1H, H-3), 1.03 (t, *J* = 7.7 Hz, 3H, H-17), 0.94 (t, *J* = 7.3 Hz, 3H, H-13).



$C_{17}H_{25}NO$
259.39 g/mol

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.9 (C-1), 136.4 (C-5), 135.1 (C-10), 131.1 (C-15), 128.0 (C-14), 125.2 (C-11), 121.9 (C-6), 52.8 (C-4), 45.0 (C-8), 34.6 (C-9), 31.5 (C-7), 28.5 (C-2), 27.0 (C-3), 26.1 (C-16), 25.6 (C-12), 13.9 (C-17), 13.6 (C-13).

IR (ATR): ν (cm^{-1}) = 3363 (br m), 2963 (m), 2933 (m), 2875 (m), 1671 (s), 1410 (m), 970 (m).

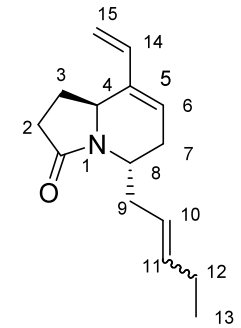
LRMS-ESI: *m/z* (%) = 260.20 (20) [MH^+], 190.13 (100).

HRMS (MH^+, $C_{17}H_{26}NO$) = calcd: 260.2014, found: 260.2010.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.33.

Optical rotation a_D^{20} = -10° (c = 0.105, CH_2Cl_2).

(5S,8aS)-5-(pent-2-enyl)-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one 104



$C_{15}H_{21}NO$
231.33 g/mol

Amide **65** (60 mg, 0.29 mmol) and 3-hexene (0.17 mL, 14 mmol) were dissolved in anhydrous CH_2Cl_2 (7 mL) under N_2 atmosphere. Catalyst **GII** (12 mg, 4.8 mol%) was then added and the mixture was stirred overnight at rt. After concentration under reduced pressure at ambient temperature, analysis *via* ^{1}H-NMR showed 80% conversion. The crude material was purified by flash column chromatography (SiO_2, cyclohexane → EtOAc) to furnish product **104** (36 mg, 57% brsm) as brown oil.[18]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.22 (dd, *J* = 17.9 Hz, *J* = 11.1 Hz, 1H, H-14), 5.73 (d, *J* = 6.5 Hz, 1H, H-6), 5.49 (m, 1H, H-10), 5.35 (m, 1H, H-11), 5.12-5.02 (m, 2H, H-15), 4.40 (m, 1H, H-8), 4.33 (br s, 1H, H-4), 2.57-1.95 (series of m, 9H, H-2, H-3, H-7, H-9, H-12), 1.64 (m, 1H, H-3), 0.95 (t, *J* = 7.4 Hz, 3H, H-13).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.9 (C-1), 136.8 (C-5), 135.9 (C-14), 135.2 (C-10), 125.1 (C-6), 124.9 (C-11), 112.6 (C-15), 52.4 (C-4), 44.9 (C-8), 34.7 (C-9), 31.5 (C-7), 28.6 (C-2), 26.8 (C-12), 25.6 (C-3), 13.9 (C-13).

[18] *E/Z* ratio at C-11 not determined

IR (ATR): ν (cm^{-1}) = 3363 (br m), 2961 (m), 2932 (m), 1668 (s), 1413 (m), 1266 (m), 969 (m).

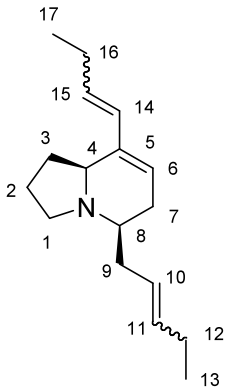
LRMS-ESI: *m/z* (%) = 232 (20) [MH^+], 162 (100).

HRMS-ESI (MH^+, $C_{15}H_{22}NO$) = calcd: 232.1701, found: 232.1697.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.21.

Optical rotation a_D^{20} = -35° (c = 0.6, CH_2Cl_2).

(5*R*,8a*S*)-8-(but-1-enyl)-5-(pent-2-enyl)-1,2,3,5,6,8a-hexahydroindolizine 103



$C_{17}H_{27}N$
245.40 g/mol

Amine **59** (5 mg, 0.026 mmol) was dissolved in CH_2Cl_2 and *p*TSA (6 mg, 1.2 eq) was added. The mixture was stirred at 40 °C for 30 min and evaporated under reduced pressure. Anhydrous CH_2Cl_2 was then added, and subsequently *cis*-3-hexene (0.45 eq) and catalyst **GII** (5 mol%). The reaction mixture was then stirred at 40°C overnight. After concentrating under vacuo at 0 °C, ^{1}H-NMR of the crude product showed complete conversion towards **103**.[19]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.95-5.83 (m, 1H, H-14), 5.62-5.32 (m, 4H, H-6, H-10, H-11, H-15), 3.78 (br s, 1H, H-4), 2.89 (m, 3H, H-1, H-8), 2.36-1.08 (series of m; H-2, H-3, H-7, H-9, H-12, H-16), 1.03-0.83 (m, 6H, H-13, H-17).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 135.4 (C-14), 131.4 (C-15), 128.9 (C-10), 125.0 (C-11), 120.8 (C-6), 55.7 (C-4), 53.4 (C-8), 50.7 (C-1), 34.8 (C-9), 30.3, 26.1 (C-3, C-7), 25.6 (C-12, C-16), 22.5 (C-2),13.8, 13.6 (C-13, C-17).[20]

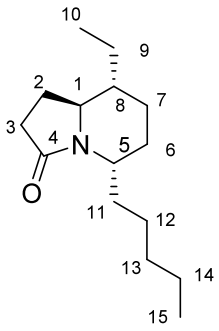
IR (ATR): ν (cm^{-1}) = 3312 (br m), 3020 (w), 2959 (m), 2927 (s), 2853 (m), 2038 (w), 1924 (w), 1738 (w), 1630 (m), 1447 (m), 1377 (w), 1261 (m), 1033 (m), 1013 (m), 965 (m), 851 (w), 802 (m), 680 (w).

LRMS-ESI: *m/z* (%) = 246.22 (24) [MH^+], 190.16 (10), 176.14 (100), 162.13 (14).

HRMS-ESI (MH^+, $C_{17}H_{28}N$) = calcd: 246.2222, found: 246.2213.

[19] *E/Z* ratio at C-15 and C-11 not determined.
[20] C-5 not detected.

(5S,8R,8aS)-8-ethyl-5-pentyl-hexahydroindolizin-3(5H)-one 105



$C_{15}H_{27}NO$
237.38 g/mol

Compound **104** (30 mg, 0.129 mmol) was dissolved in 1 mL MeOH and 30 mg Pd/Al_2O_3 10% were added. Hydrogenation at 30 bar was performed following the general procedure described earlier in Section 5.2.1. Amide **105** (30 mg, 98%) was isolated after filtration over Celite as clear oil (C-5/C-8 *cis:trans* mixture 3:2).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 4.17 (m, 1H, H-1), 3.82 (m, 0.4H, H-5), 3.17 (m, 0.6H, H-5), 2.33 (m, 2H, H-3), 2.20 (m, 0.7 H, H-2), 2.01 (m, 0.5 H, H-2), 1.86-0.96 (series of m, 16H, H-2, H-6, H-7, H-8, H-9, H-11, H-12, H-13, H-14), 1.13-0.88 (m, 6H, H-10, H-15).[21]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.7 (C-4), 173.5 (C-4), 57.7 (C-5), 56.6 (C-5), 47.7 (C-1), 47.7 (C-1), 45.6 (C-8), 39.0 (C-8), 31.8 (CH_2), 31.8 (CH_2), 30.6 (CH_2), 30.6 (CH_2), 30.3 (CH_2), 30.0 (CH_2), 27.3 (CH_2), 26.0 (CH_2), 24.6 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 21.5 (CH_2), 21.3 (CH_2), 20.4 (CH_2), 16.1 (CH_2), 14.1 (C-15), 11.7 (C-10), 10.9 (C-10).[22]

IR (ATR): ν (cm^{-1}) = 2956 (s), 2930 (s), 2859 (m), 1734 (w), 1686 (s), 1457 (m), 1419 (m), 1379 (w), 1275 (m), 1156 (w), 1032 (m), 803 (w).

LRMS-ESI: *m/z* (%) = 238 (100) [MH^+], 84 (80).

HRMS-ESI (MH^+, $C_{15}H_{28}NO$) = calcd: 238.2171, found: 238.2159.

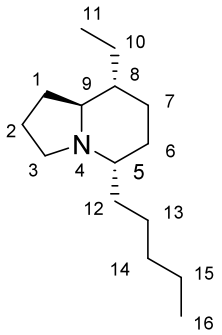
R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.41.

Indolizidine 5-*epi*-223AA

Amide **105** (30 mg, 0.13 mmol) was dissolved in freshly distilled THF (2 mL) and $BH_3{\cdot}SMe_2$ (0.23 mL, 2.52 mmol) was added *via* syringe and the reaction mixture was then refluxed overnight. After cooling down to rt the reaction flask was placed in a ice/water bath and anhydrous MeOH was slowly added over 2 h until no further H_2 evolution was observed. Subsequently 1 mL of methanolic HCl was slowly added at 0 °C and the reaction was stirred 3 h further. After evaporating the volatiles the crude was dissolved in CH_2Cl_2 and washed once with 2 M Na_2CO_3 aq. solution. The organic layer was dried over $MgSO_4$, evaporated,

[21] Signal corresponding to H-1 integrates to 1, and the integration of the other signals corresponds to the diastereoisomeric ratio.
[22] Both diastereoisomers are indicated.

and the crude mixture was isolated as a clear oil (26 mg, 93%).



$C_{15}H_{29}N$
223.40 g/mol

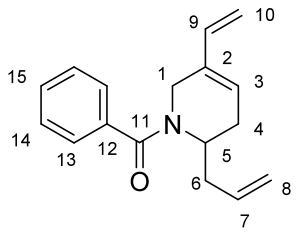
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 3.69-2.78 (series of m), 2.11-1.00 (series of m), 0.96-0.82 (m, H-11, H-16).[m]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 64.0 (C-9), 60.1 (C-5), 55.2, 54.3 (C-3), 50.4, 48.9, 44.2, 38.8, 34.8, 32.3, 32.3, 31.3, 29.7, 27.9, 27.5, 26.5, 26.1, 25.7, 24.9, 24.3, 22.7, 21.9, 21.2, 20.9, 20.7, 14.1 (C-16) , 11.9, 11.3 (C-11).[m]

HRMS-ESI (MH^+, $C_{15}H_{30}N$) = calcd: 224.2378, found: 224.2366.

R_f (C_{18}-SiO_2, MeOH) = 0.5.

(6-allyl-3-vinyl-5,6-dihydropyridin-1(2H)-yl)(phenyl)methanone 109



$C_{17}H_{19}NO$
253.34 g/mol

Amine **65** (1.1 g, 3.4 mmol) was dissolved in 65 mL of a mixture of CH_3CN/DMSO (4:0.1) and thiophenol (1.7 mL, 17.2 mmol) and K_2CO_3 (1.9 g, 13.5 mmol) was subsequently added. The reaction was heated at 50 °C overnight. After cooling down to ambient temperature 50 mL aqueous sat. NH_4Cl solution was added, and the organic layer was separated, dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (CH_2Cl_2/MeOH 10:0 → 10:1) to obtain the deprotected amine as a light orange oil. This secondary amine was directly dissolved in 20 mL THF/H_2O 1:1 and benzoylchlorid (0.4 mL) and K_2CO_3 (1.9 g, 13.7 mmol) were subsequently added. The reaction mixture was stirred overnight at rt, and when complete conversion was achieved, the organic phase was then separated, dried over $MgSO_4$ and the solvent was removed *in vacuo*. After purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 10:1), the title compound **109** (728 mg, 84% - over 2 steps -) was provided as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.40 (m, 5H, H-13, H-14, H-15), 6.40-6.20 (m, 1H, H-9), 5.80 (s, 1H, H-3), 5.90-5.50 (m, 1H, H-7), 5.30-4.90 (m, 4H, H-8, H-10), 4.05 (m, 1H, H-5), 3.85-3.30 (m, 1H, H-1), 2.70-2.00 (m, 5H, H-1, H-4, H-6).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 171.3 (C-11), 136.8 (C-2), 136.4 (C-9), 134.06 (C-12), 129.5 (C-15), 128.5 (C-13, C-14), 126.7 (C-7), 124.0 (C-3), 118.3 (C-10), 112.0 (C-8), 52.3 (C-5), 38.1 (C-1), 36.3 (C-6), 29.5 (C-4).

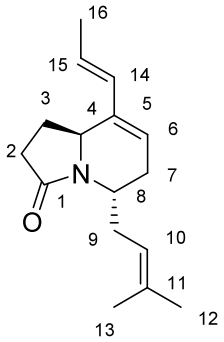
IR (ATR): ν (cm^{-1}) = 3256 (br m), 3078 (w), 2921 (w), 2846 (w), 1629 (s), 1577 (m), 1422 (s), 1361 (m), 1248 (m), 988 (m), 916 (m), 727 (m), 701 (s).

LRMS-ESI: *m/z* (%) = 254 (30) [MH^+], 212 (100), 105 (60).

HRMS-ESI (MH^+, $C_{17}H_{20}NO$) = calcd: 254.1545, found: 254.1536.

R_f (SiO_2, cyclohexane/MTBE 4:1) = 0.21.

(5*S*,8a*S*,*E*)-5-(3-methylbut-2-enyl)-8-(prop-1-enyl)-1,2,5,6-tetrahydroindolizin-3(8aH)-one 114



$C_{16}H_{23}NO$
245.36 g/mol

To a solution of substrate **65** (100 mg, 0.49 mmol) in 2-methyl-2-butene (2.5 mL) catalyst **GII** (20.7 mg, 5 mol%) was added under inert conditions. The mixture was stirred at rt overnight and concentrated. The crude oil was purified by column chromatography (SiO_2, cyclohexane/EtOAc 1:1) to yield 70 mg the metathesis product **114** (58%, >95:5 *E/Z*).[23]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.92 (d, *J* = 16.0 Hz, 1H, H-14), 5.58 (m, 2H, H-6, H-15), 5.06 (m, 1H, H-10), 4.34 (m, 1H, H-8), 4.28 (br s, 1H, H-4), 2.53-2.31 (m, 4H, H-2, H-3, H-7), 2.16 (m, 2H, H-9), 2.04 (m, 1H, H-7), 1.77 (d, *J* = 16.6 Hz, 3H, H-16), 1.68 (s, 3H, H-12), 1.62 (m, 1H, H-3), 1.57 (s, 3H, H-13).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.9 (C-1), 136.6 (C-5), 134.0 (C-11), 130.4 (C-14), 124.0 (C-15), 121.8 (C-6), 120.4 (C-10), 52.8 (C-4), 45.3 (C-8), 31.5 (C-2), 29.9 (C-9), 28.5 (C-7), 27.0 (C-3), 25.7 (C-12), 18.5 (C-16), 18.0 (C-13).

IR (ATR): ν (cm^{-1}) = 3354 (br m), 2972 (m), 2929 (m), 2857 (m), 1666 (s), 1436 (m), 1416 (m), 1377 (m), 1267 (m), 967 (m).

LRMS-ESI: *m/z* (%) = 246 (30) [MH^+], 176. (100).

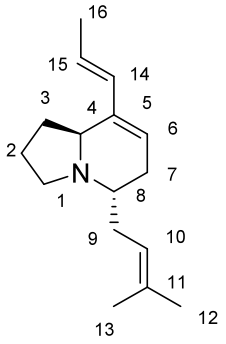
HRMS-ESI (MH^+, $C_{16}H_{24}NO$) = calcd: 246.1858, found: 248.1847 and 268.1667 (MNa^+, $C_{16}H_{23}NONa$).

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.28.

Optical rotation a_D^{20} = -32° (c = 0.06, MeOH).

[23] *E/Z* ratio determined via ^{1}H-NMR spectroscopy.

(5*S*,8a*S*,*E*)-5-(3-methylbut-2-enyl)-8-(prop-1-enyl)-1,2,3,5,6,8a-hexahydroindolizine 115



$C_{16}H_{25}N$
231.38 g/mol

Amide **114** (50 mg, 0.203 mmol) was dissolved in Et_2O (1 mL) and added to a suspension of $LiAlH_4$ (15 mg, 0.406 mmol) in Et_2O (3 mL) at 0 °C. The reaction was allowed to warm up to rt and stirred at 40 °C overnight. After cooling down to 0 °C the mixture was quenched with wet EtOA, filtrated over Celite and concentrated under reduced pressure. The title compound **115** (20 mg, 43%) was obtained as a colorless oil and was used without further purification.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.89 (d, *J* = 15.8 Hz, 1H, H-14), 5.50 (m, 2H, H-6, H-15), 5.13 (m, 1H, H-10), 3.75 (br t, 1H, H-4), 2.86 (m, 3H, H-1, H-8), 2.32 (br d, *J* = 18.8 Hz, 1H, H-7), 2.27-2.08 (m, 3H, H-3, H-9), 1.91 (br d, *J* = 18.8 Hz, 1H, H-7), 1.80-1.67 (m, 8H, H-2, H-12, H-16), 1.58 (s, 3H, H-13), 1.53 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.1 (C-5), 132.2 (C-11), 132.9 (C-14), 122.9 (C-15), 121.8 (C-10), 121.5 (C-6), 55.4 (C-4), 52.9 (C-8), 50.4 (C-1), 31.3 (C-3, C-9), 30.6 (C-3, C-9), 25.8 (C-12), 25.3 (C-7), 22.9 (C-2), 18.5 (C-16), 17.9 (C-13).

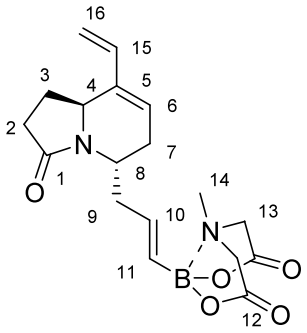
IR (ATR): ν (cm^{-1}) = 3362 (br w), 3025 (w), 2963 (s), 2925 (s), 2854 (m), 1671 (w), 1448 (m), 1376 (m), 1128 (w), 1103 (w), 965 (m), 846 (w).

HRMS-ESI (MH^+, $C_{16}H_{26}N$) = calcd: 232.2065, found: 232.2054.

(*E*)-3-((5*S*,8a*S*)-3-oxo-8-vinyl-1,2,3,5,6,8a-hexahydroindolizin-5-yl)prop-1-enyl MIDA boronate 120

Amide **65** (90 mg, 0.44 mmol) and alkene **119** (122 mg, 0.65 mmol) were dissolved in CH_2Cl_2 (4.5 mL) and catalyst **GII** (36 mg, 10%) was added under N_2 atmosphere. The reaction mixture was stirred at 40 °C overnight. After concentrating under reduced pressure, the crude material was purified by column chromatography (SiO_2, CH_2Cl_2 → CH_3CN) obtaining the boronate **121** (50 mg, 32%) as a clear oil.[24]

[24] >95:5 *E/Z* ratio identified via ^{1}H-NMR spectroscopy.



$C_{18}H_{23}BN_2O_5$
358.20 g/mol

^{1}H-NMR (CD_3CN, 400 MHz): δ (ppm) = 6.29 (dd, *J* = 18.0 Hz, 11.3 Hz, 1H, H-15), 5.98 (dt, *J* = 17.7 Hz, *J* = 7.0 Hz, 1H, H-10), 5.80 (d, *J* = 5.7 Hz, 1H, H-6), 5.53 (d, *J* = 7.6 Hz, 1H, H-11), 5.18 (d, *J* = 17.6 Hz, 1H, H-16), 5.06 (d, *J* = 11.0 Hz, 1H, H-16), 4.41 (br s, 1H, H-4), 4.35 (m, 1H, H-8), 3.96-3.72 (m, 4H, H-13), 2.77 (m, 3H, H-14), 2.59 (m, 1H, H-3), 2.43 (m, 1H, H-7), 2.38-2.19 (m, 4H, H-2, H-9), 2.05 (m, 1H, H-7), 1.55 (m, 1H, H-3).

^{13}C-NMR (CD_3CN, 100 MHz): δ (ppm) = 171.7 (C-1), 167.5 (C-12), 141.3 (C-10), 136.00 (C-11), 135.1 (C-5), 123.9 (C-6), 111.7 (C-16), 60.3 (C-13), 60.1 (C-13), 51.1 (C-4), 45.5 (C-14), 44.3 (C-8), 36.1 (C-9), 30.2 (C-2), 28.3 (C-7), 25.9 (C-3).[25]

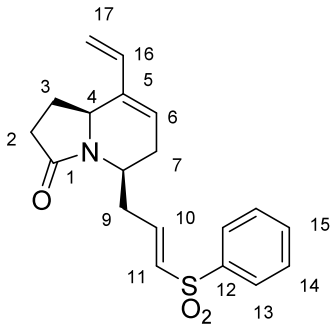
IR (ATR): ν (cm^{-1}) = 3430 (br w), 3003 (w), 2952 (m), 2926 (m), 2854 (w), 1761 (s), 1670 (s), 1416 (m), 1293 (m), 1118 (m), 1025 (m), 995 (m), 957 (m), 894 (m), 864 (m).

HRMS-ESI (MH^+, $C_{18}H_{23}BN_2O_5$) = calcd: 359.1778, found: 359.1759.

R_f (SiO_2, CH_2Cl_2/CH_3CN 1:1) = 0.15.

Optical rotation a_D^{20} = -43° (c = 0.675, MeOH).

(5S,8aS,E)-5-(3-(phenylsulfonyl)allyl)-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one



$C_{19}H_{21}NO_3S$
343.44 g/mol

To a solution of *cis*-isomer **64** (20 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (2 mL, 48 mM), vinyl sulfone **125** (165 mg, 0.98 mmol) was added followed by catalyst **HII** (6.5 mg, 10 mol%). The reaction was stirred at 40 °C overnight and, after removing the solvent under reduced pressure, the mixture was purified by column chromatography (SiO_2, cyclohexane → EtOAc). The desired compound (17 mg, 53%) was isolated along with 8 mg of starting material (87% yield *brsm,* >95:5 *E/Z*).[26]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.87 (m, 2H, H-13), 7.60 (m, 1H, H-15), 7.53 (m, 2H, H-14), 7.04 (m, 1H, H-10), 6.43 (dt, *J* = 15.0 Hz, *J* = 1.4 Hz,

[25] C-11 was not observed due to quadrupole broadening caused by the ^{11}B nucleus.
[26] >95:5 *E/Z* ratio determined *via* ^{1}H-NMR spectroscopy

1H, H-11), 6.19 (dd, *J* = 18.0 Hz, *J* = 11.3 Hz, 1H, H-16), 5.81 (d, *J* = 6.0 Hz, 1H, H-6), 5.06 (m, 2H, H-17), 4.44 (br s, 1H, H-4), 3.59 (m, 1H, H-2), 3.35 (m, 1H, H-8), 2.72 (m, 1H, H-2), 2.46-2.24 (m, 4H, H-3, H-7, H-9), 2.14 (m, 1H, H-7), 1.80 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 174.8 (C-1), 144.3 (C-10), 140.6 (C-5), 139.2 (C-12), 135.2 (C-16), 133.3 (C-15), 132.0 (C-11), 129.2 (2 x C-14), 127.6 (2 x C-13), 126.4 (C-6), 113.5 (C-17), 59.1 (C-4), 53.6 (C-8), 33.6 (C-9), 32.1 (C-2), 31.6 (C-7), 25.1 (C-3).

IR (ATR): ν (cm^{-1}) = 2925 (w), 2854 (w), 1683 (s), 1446 (m), 1306 (m), 1145 (m), 1086 (m), 826 (w), 754 (w), 689 (w).

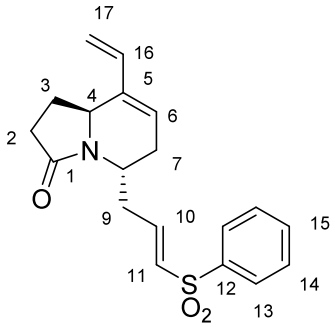
LRMS-ESI: *m/z* (%) = 344 (20) [MH^+], 316 (75), 202 (100), 162 (30).

HRMS-ESI (MH^+, $C_{19}H_{22}NO_3S$) = calcd: 344.1320, found: 344.1321 and 366.1136 ($C_{19}H_{21}NO_3SNa$).

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.18.

Optical rotation α_D^{20} = -67° (c = 0.075, MeOH).

(5*R*,8a*S*,*E*)-5-(3-(phenylsulfonyl)allyl)-8-vinyl-1,2,5,6-tetrahydroindolizin-3(8aH)-one 132



$C_{19}H_{21}NO_3S$
343.44 g/mol

<u>*Procedure A:*</u> To a solution of the *trans*-isomer **65** (118 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (12 mL, 0.05 M) was added alkene **125** (1 g, 5.80 mmol) followed by catalyst **GRI** (40 mg, 10 mol%). The reaction was stirred at 40 °C overnight and, after removing the solvent, the crude material was purified by column chromatography (SiO_2, cyclohexane → EtOAc). **132** (100 mg, 50%) was isolated as a brown oil, as well as a 38 mg of starting material (74% yield *brsm,* >95:*5 E/Z*).[27]

<u>*Procedure B:*</u> To a solution of amide **65** (180 mg, 0.88 mmol) and cross-partner **125** (1.5 g, 8.9 mmol) in anhydrous CH_2Cl_2 (5 mL), catalyst **HII** (55 mg, 10 mol%) dissolved in 15 mL anhydrous CH_2Cl_2 was slowly added over a period of 12 h. The reaction was stirred at 40 °C during this time. After concentrating *in vacuo*, the mixture was purified by column chromatography (SiO_2, cyclohexane → EtOAc) to obtain the target compound **132** (170 mg, 56%) and 47 mg of reisolated starting material (76% yield *brsm,* >95:5 *E/Z*).

[27] >95:5 *E/Z* ratio determined *via* ^{1}H-NMR spectroscopy.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.87 (m, 2H, H-13), 7.72 (m, 1H, H-15), 7.54 (m, 2H, H-14), 6.87 (dt, *J* = 15.2 Hz, *J* = 6.8 Hz, 1H, H-10), 6.56 (dt, *J* = 15.2 Hz, *J* = 1.8 Hz, 1H, H-11), 6.19 (dd, *J* = 17.9 Hz, *J* = 11.2 Hz, 1H, H-16), 5.71 (d, *J* = 5.8 Hz, 1H, H-6), 5.09-5.03 (m, 2H, H-17), 4.55 (m, 1H, H-8), 4.21 (br s, 1H, H-4), 2.57-2.21 (series of m, 6H, H-2, H-3, H-7, H-9), 2.05 (m, 1H, H-7), 1.62 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.1 (C-1), 142.2 (C-10), 140.3 (C-5), 136.7 (C-12), 135.5 (C-16), 133.4 (C-15), 132.8 (C-11), 129.3 (2 x C-14), 127.7 (2 x C-13), 123.9 (C-6), 113.4 (C-17), 52.0 (C-4), 43.4 (C-8), 33.3 (C-9), 31.2 (C-2), 29.0 (C-7), 26.9 (C-3).

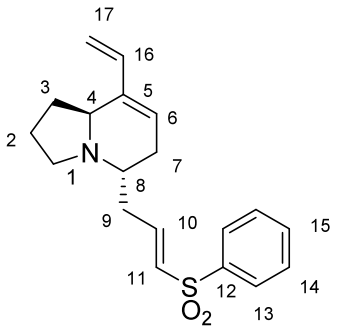
IR (ATR): ν (cm^{-1}) = 2957 (m), 2924 (s), 2854 (m), 1740 (m), 1672 (m), 1462 (m), 1447 (m), 1378 (m), 1260 (m), 1086 (m), 1031 (m), 803 (m), 690 (w).

LRMS-ESI: *m/z* (%) = 344 (23) [MH^+], 312 (49), 326 (49), 312 (45), 284 (33), 159 (100).

HRMS-ESI (MH^+, $C_{19}H_{22}NO_3S$) = calcd: 344.1322, found: 344.1310.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.04.

(5*R*,8a*S*)-5-(3-(phenylsulfonyl)propyl)-8-vinyl-1,2,3,5,6,8a-hexahydroindolizine



$C_{19}H_{25}NO_2S$
329.46 g/mol

The cross-metathesis product **132** (50 mg, 0.145 mmol) was dissolved in anhydrous Et_2O (1 mL) and added to a suspension of $LiAlH_4$ (11 mg, 0.290 mmol) in Et_2O (3 mL) at 0 °C. The reaction was allowed to warm up to rt and subsequently stirred at 40 °C overnight. After cooling to 0 °C the mixture was quenched with wet EtOAc, filtrated over Celite and concentrated under reduced pressure the title compound (35 mg, 73%) was obtained as a colorless oil and was used without further purification.

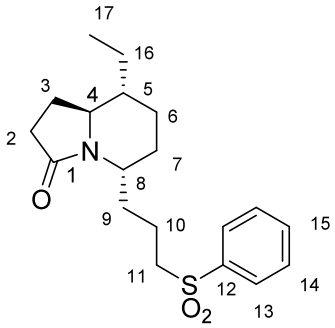
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.89 (m, 2H, H-13), 7.64 (m, 1H, H-15), 7.56 (m, 2H, H-14), 6.14 (dd, *J* = 17.7 Hz, *J* = 11.2 Hz, 1H, H-16), 6.56 (dt, *J* = 15.2 Hz, *J* = 1.8 Hz, 1H, H-16), 5.63 (m, 1H, H-6), 4.94 (m, 2H, H-17), 3.68 (br s, 1H, H-4), 3.11-2.68 (m, 5H, H-1, H-8, H-11), 2.49-0.79 (series of m, 10H, H-2, H-3, H-7, H-9, H-10).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 139.3 (C-5), 138.9 (C-12), 137.7 (C-16), 133.5 (C-15), 129.2 (2 x C-14), 128.0 (2 x C-13), 123.8 (C-6), 111.8 (C-17), 56.3 (C-11), 53.1 (C-4), 52.1 (C-8), 50.8 (C-1), 31.2, 31.0, 24.6, 23.3, 20.0 (C-2, C-3, C-7, C-9, C-10).

IR (ATR): ν (cm^{-1}) = 3500 (w), 3372 (w), 3087 (w), 3064 (w), 2956 (m), 2926 (m), 2872 (m), 1638 (w), 1585 (w), 1446 (m), 1304 (s), 1147 (s), 1086 (m), 729 (m), 690 (m).

HRMS-ESI (MH^+, $C_{19}H_{26}NO_2S$) = calcd: 332.1684, found: 332.1668.

(5*R*,8*R*,8a*S*)-8-ethyl-5-(3-(phenylsulfonyl)propyl)-hexahydroindolizin-3(5H)-one



$C_{19}H_{27}NO_3S$
349.49 g/mol

Following the general hydrogenation procedure, amide **132** (336 mg, 1.02 mmol) was dissolved in 3 mL MeOH hydrogenated at 30 bar H_2 pressure at rt for 3 days. After the previously indicated work-up, the crude product was purified by column chromatography (SiO_2, cyclohexane → EtOAc) to obtain the title compound as diastereoisomeric mixture (C-5/C-8) 5:1 *cis:trans* (286 mg, 80%) as a colorless oil.[28]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.89 (d, *J* = 7.4 Hz, 2H, H-13), 7.63 (t, *J* = 7.6 Hz, 1H, H-15), 7.55 (d, *J* = 7.6 Hz, 2H, H-14), 4.12 (m, 1H, H-4), 3.27 (m, 1H, H-11), 3.08 (m, 2H, H-8, H-11), 2.35-0.95 (series of m, 15H, H-2, H-3, H-5, H-6, H-7, H-9, H-10, H-16), 0.90 (m, 3H, H-17).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 173.7 (C-1), 139.1 (C-12), 133.6 (C-15), 129.3 (2 x C-14), 128.1 (2 x C-13), 57.6 (C-8), 55.3 (C-11), 46.4 (C-4), 45.4 (C-5), 30.3 (C-9), 28.5 (C-2), 27.5 (C-7), 24.5, 24.2, 24.0 (C-3, C-6, C-16), 19.6 (C-10), 10.9 (C-17).

IR (ATR): ν (cm^{-1}) = 3445 (br w), 3061 (w), 2956 (m), 2930 (m), 2861 (m), 1673 (s), 1446 (m), 1419 (m), 1303 (s), 1289 (s), 1146 (s), 1086 (m), 731 (m), 690 (m).

LRMS-ESI: *m/z* (%) = 350 (70) [MH^+], 208 (100), 166 (90).

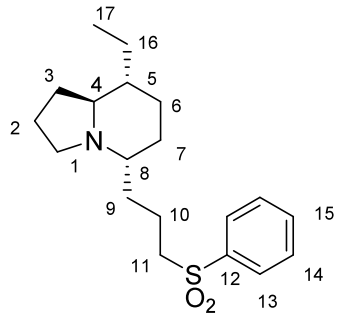
HRMS-ESI (MH^+, $C_{19}H_{28}NO_3S$) = calcd: 350.1790, found: 350.179.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.08.

Optical rotation a_D^{20} = -22° (c = 0.5, CH_2Cl_2).

[28] *cis/trans* ratio determined *via* integration of C-4 signals in ^{1}H-NMR data. Analytical data for the C-5/C-8 *cis* isomer.

(5R,8R,8aS)-8-ethyl-5-(3-(phenylsulfonyl)propyl)-octahydroindolizine 134



$C_{19}H_{29}NO_2S$
335.50 g/mol

The previous compound (100 mg, 0.5 mmol) was dissolved in freshly distilled THF (12 mL) and $BH_3 \cdot SMe_2$ (0.96 mL, 10 mmol) was added *via* syringe and the reaction mixture was then refluxed overnight. After cooling down to rt the reaction flask was placed in a ice/water bath and anhydrous MeOH was slowly added over 2 h until no further H_2 evolution was observed. Subsequently 4.3 mL of methanolic HCl were slowly added at 0 °C and the reaction was stirred 3 h further. After evaporating the volatiles the crude was dissolved in CH_2Cl_2 and washed once with 2 M Na_2CO_3 aq. solution. The organic layer was dried over $MgSO_4$, evaporated, and after purification by column chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) the desired amine **134** was isolated as a clear oil (110 mg, 66%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.89 (m, 2H, H-13), 7.66 (m, 1H, H-15), 7.57 (m, 2H, H-14), 3.10 (m, 2H, H-11), 3.00 (br s, 1H, H-8), 2.87 (b s, 1H, H-1), 2.66 (br s, 1H, H-1), 2.23 (br s, 1H, H-4), 1.94 (br s, 1H, H-9), 1.86-1.39 (series of m, 11H, H-2, H-6, H-7, H-9, H-10, H-16), 1.19 (m, 1H, H-5), 1.03 (m, 2H, H-3), 0.86 (t, *J* = 7.4 Hz, 3H, H-17).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 139.1 (C-12), 133.8 (C-15), 129.4 (C-14), 128.0 (2 x C-13), 60.7 (2 x C-4), 56.2 (C-11), 55.0 (C-8), 49.1 (C-1), 42.6 (C-5), 29.1 (C-9), 26.6, 25.8 (C-3, C-7), 23.7 (C-6), 22.1, 20.7, 20.6 (C-2, C-10, C-16), 11.0 (C-17).

IR (ATR): ν (cm^{-1}) = 3385 (br w), 3060 (w), 2958 (m), 2932 (m), 2873 (m), 2808 (m), 2507 (m), 1675 (w), 1447 (m), 1305 (m), 1148 (s), 1087 (m), 690 (m).

LRMS-ESI: *m/z* (%) = 337 (100) [MH^+], 194 (75) 152 (30).

HRMS-ESI (MH^+, $C_{19}H_{30}NO_2S$) = calcd: 336.1997, found: 336.2007.

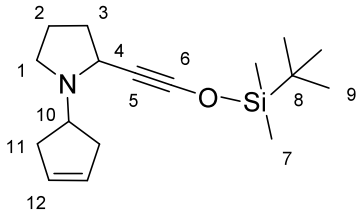
Optical rotation a_D^{20} = -8° (c = 0.85, CH_2Cl_2).

(*S*)-2-((*tert*-butyldimethylsilyloxy)ethynyl)-1-(cyclopent-3-enyl)pyrrolidine 140

To a solution of CH_2Br_2 (312 µL, 4.4 mmol) in anhydrous THF (6 mL) at -78 °C a freshly prepared solution of LiTMP (4.4 mmol) in THF (6 mL) was slowly added. After 5 min stirring a solution of amine **52** (390 mg, 2 mmol) in THF (5 mL) was slowly added and approx. 10 min

later *n*-BuLi (4 mL, 10.0 mmol) was added via syringe to the mixture still at -78 °C. The reaction vessel was then placed into a water bath and stirred at 30 °C for 30 min. At this point the reaction was again cooled to -78 °C and $SiMe_2$*t*-BuCl (1.5 g, 10 mmol) was then added dropwise. After 10 min stirring the reaction was stirred overnight at 0 °C (cryostat). The solvent was removed under reduced pressure and the crude purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1 → 1:1) to furnish the desired product (60 mg, 10%) as a light brown oil.

LiTMP was prepared as following: to a solution of TMP (315 µL, 4.8 mmol) in anhydrous THF (6 mL) at 0 °C *n*-BuLi (1.76 mL, 4.4 mmol) was slowly added. Stirring continued for 30 min at this temperature and was then cooled down to -78 °C prior to use.



$C_{17}H_{29}NOSi$
291.50 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.73-5.63 (m, 2H, H-12), 3.74 (quintet, *J* = 7.4 Hz, 1H, H-10), 2.90 (dd, *J* = 7.3 Hz, *J* = 5.00 Hz, 1H, H-4), 2.83-2.67 (m, 2H, H-1), 2.60-1.41 (series of m, 8H, H-2, H-3, H-11), 0.91 (m, 9H, H-9).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.5 (C-12), 129.4 (C-12), 77.2 (C-5), 75.2 (C-6), 68.4 (C-4), 63.3 (C-10), 48.4 (C-1), 38.3 (C-2), 37.6 (C-2), 34.3 (C-11), 33.0 (C-11), 26.0 (C-3), 22.7 (C-8), 14.2 (C-9).

IR (ATR): ν (cm^{-1}) = 3460 (w), 3052 (w), 2954 (s), 2931 (s), 2857 (m), 2860 (m), 1747 (m), 1466 (m), 1459 (m), 1378 (m), 1219 (m), 1105 (m), 695 (m).

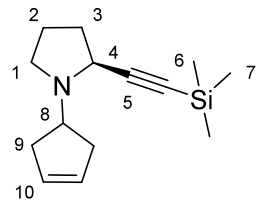
HRMS-ESI (MH^+, $C_{17}H_{30}NOSi$) = calcd: 292.2097, found: 292.2106.

Optical rotation a_D^{20} = -31° (c = 1, CH_2Cl_2).

(*S*)-1-(cyclopent-3-enyl)-2-((trimethylsilyl)ethynyl)pyrrolidine 143

To a solution of **27** (70 mg, 0.43 mmol) in anhydrous THF (16 mL) BuLi (189 µL, 0.47 mmol, 2.5 M in hexane) was slowly added at -78 °C. Stirring continued for 30 min before $SiMe_3Cl$ (60.7 µL, 0.48 mmol) was added. The reaction was allowed to warm up to rt and stirred at this temperature overnight. 5 mL aqueous 1 M HCl solution and 15 mL CH_2Cl_2 were added, and the organic phase washed once with 10 mL aqueous 1 M HCl solution. The combined aqueous layers were basified with solid Na_2CO_3 and extracted with CH_2Cl_2 (3 x 15 mL). The

organics were then dried over $MgSO_4$, concentrated and purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to obtain **143** (60 mg, 60%) as a colorless oil.



$C_{14}H_{23}NSi$
233.42 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.67 (s, 2H, H-10), 3.67-6.50 (m, 1H, H-4), 3.38 (quintet, *J* = 7.9 Hz, 1H, H-8), 2.77-1.77 (series of m, 10H, H-1, H-2, H-3, H-9), 1.79 (s, 9H, H-7).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.3 (C-10), 129.1 (C-10), 77.2 (C-5), 61.4 (C-6), 53.7 (C-8), 52.8 (C-4), 49.8 (C-1), 38.2 (C-9), 36.6 (C-9), 32.0 (C-3), 22.2 (C-2), 0.1 (C-7).

IR (ATR): ν (cm^{-1}) = 3054 (w), 2957 (s), 2928 (s), 2856 (m), 2806 (w), 2157 (w), 1738 (w), 1458 (w), 1338 (w), 1250 (s), 1149 (w), 1129 (w), 994 (w), 873 (s), 842 (s), 760 (m), 700 (m).

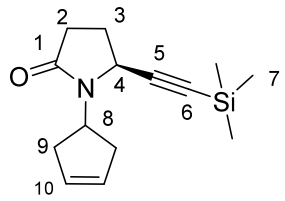
LRMS-ESI: *m/z* (%) = 234 (5) [MH^+], 218 (30), 206 (30), 168 (70), 160 (100) [M^+-TMS].

HRMS-ESI (MH^+, $C_{14}H_{24}NSi$) = calcd: 234.1678, found: 234.1677.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.33.

Optical rotation a_D^{20} = -125° (c = 0.12, CH_2Cl_2).

(*S*)-1-(cyclopent-3-enyl)-5-((trimethylsilyl)ethynyl)pyrrolidin-2-one 144



$C_{14}H_{21}NOSi$
247.41g/mol

To a solution of **31** (188 mg, 0.93 mmol) in anhydrous THF (40 mL) *n*-BuLi (370 µL, 0.93 mmol, 2.5 M in hexane) was slowly added at -78 °C via syringe. Stirring continued for 30 min before $SiMe_3Cl$ (175 µL, 1.38 mmol) was added dropwise. The reaction was allowed to warm up to rt and was stirred overnight. 10 mL aqueous 1 M HCl solution and 30 mL CH_2Cl_2 were added and the organic layer was washed once with 15 mL aqueous 1 M HCl solution. The combined aqueous layers were basified with solid Na_2CO_3 and extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was then dried over $MgSO_4$, concentrated and purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to obtain **144** (130 mg, 60%) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.74 (s, 2H, H-10), 4.80 (dquintet, *J* = 7.0 Hz, *J* = 3.0 Hz, 1H, H-8), 4.28 (dd, 1H, *J* = 7.8 Hz, *J* = 3.14 Hz, H-4), 2.90-2.80 (m, 1H, H-9),

2.64-2.53 (m, 3H, H-2, H-9), 2.46-2.37 (m, 1H, H-9), 2.35-2.16 (m, 2H, H-3, H-2), 2.12-2.03 (m, 1H, H-3), 0.15 (s, 9H, H-7).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 174.4 (C-1), 129.8 (C-10), 128.4 (C-10), 104.9 (C-6), 89.4 (C-5), 51.6 (C-8), 48.3 (C-4), 36.5 (C-9), 36.1 (C-9), 30.3 (C-2), 27.7 (C-3), -0.33 (C-7).

IR (ATR): ν (cm^{-1}) = 3210 (br w), 3058 (w), 2958 (m), 2856 (w), 2172 (w), 1693 (s), 1668 (s), 1413 (m), 1250 (m), 1059 (w), 844 (s), 761 (m), 676 (m).

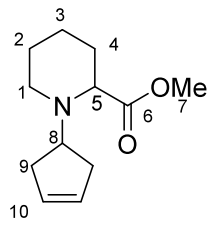
LRMS-ESI: *m/z* (%) = 248 (30) [MH^+], 182 (100) [$M\text{-}C_5H_6^+$].

HRMS-ESI (MH^+, $C_{14}H_{22}NOSi$) = calcd: 248.1471, found: 248.1461.

R_f (SiO_2, cyclohexane/EtOAc 1:1) = 0.43.

Optical rotation a_D^{20} = -27° (c = 1.15, CH_2Cl_2).

1-(cyclopent-3-enyl)-2-ethynylpiperidine 150



$C_{12}H_{19}NO_2$
209.28 g/mol

Picolinic acid methyl ester hydrochloride **149** (400 mg, 2.23 mmol), tosylate **37** (580 mg, 2.41 mmol), and Na_2CO_3 (500 mg, 4.72 mmol) were suspended in CH_3CN (2.5 mL, 0.8 M) and the reaction mixture was heated at 80 °C overnight. The CH_3CN was evaporated at the same temperature under reduced pressure and analysis with ^{1}H-NMR showed complete conversion. The crude material was then dissolved in MTBE and filtrated over a silica gel pad. After concentration, **150** (350 mg, 75%) was furnished as slightly unpurified oil. No further purification was conducted.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 35.62 (m, 2H, H-1), 3.68 (s, 3H, H-7), 3.47 (m, 1H, H-8), 3.35 (dd, *J* = 6.6 Hz, *J* = 4.8 Hz, 1H, H-5), 2.84 (m, 1H, H-1), 2.50 (m, 1H, H-9), 2.36-2.16 (m, 4H, H-1, H-9), 1.79 (m, 2H, H-4), 1.59 (m, 3H, H-2, H-3), 1.37 (m, 1H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 174.2 (C-6), 129.3 (C-10), 62.4 (C-5), 61.9 (C-8), 51.5 (C-7), 44.9 (C-1), 37.2 (C-9), 32.7 (C-9), 29.5 (C-4), 25.3 (C-2), 22.1 (C-3).

IR (ATR): ν (cm^{-1}) = 3054 (w), 2933 (m), 2853 (w), 1737 (s), 1445 (m), 1351 (m), 1196 (m), 1175 (s), 1159 (s), 1126 (w), 1096 (w), 945 (w), 888 (w), 816 (w), 703 (w), 673 (w).

LRMS-ESI: *m/z* (%) = 210 (12) [MH^+], 150 (22), 144 (100), 84 (27).

HRMS-ESI (MH^+, $C_{12}H_{20}NO_2$) = calcd: 210.1494, found: 210.1489.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.43.

5.3 Experimental Section for Chapter 3

5.3.1 General Procedures

General procedure for the sequential Swern oxidation - Seyferth Gilbert homologation of alcohols to the corresponding alkynes.

To a solution of 3 eq DMSO in anhydrous CH_2Cl_2 at -78 °C, 1.5 eq oxalylchlorid was slowly added maintaining the temperature below -70 °C (exothermic reaction occurred). Approximately 15 min after addition was finished, a solution of the substrate in CH_2Cl_2 was added dropwise, again maintaining the solution temperature below -70 °C. The reaction was further stirred for 30 min. Finally, and still at -78 °C, 3 eq Et_3N were given *via* cannula, paying attention to the mixture temperature, and the reaction was then allowed to warm up to rt for 1 h. Work up was performed by washing once with sat. aqueous solution of $NaHCO_3$. The organic layer was then dried over $MgSO_4$ and concentrated. Without further purification, the crude material was dissolved in anhydrous MeOH with subsequently addition of 1.2 eq of **50** and 2 eq of K_2CO_3. The suspension was stirred at rt and when complete conversion was achieved, the reaction was diluted with MTBE or CH_2Cl_2, filtered through a pad of Celite and concentrated under reduced pressure. The obtained crude material was usually purified by column chromatography.

Typical procedure for ammonium salt formation.

7 mmol of substrate were dissolved in CH_2Cl_2 and 1.03 eq of Brønsted acid were added. The mixture was then slowly concentrated under reduced pressure and purified by column chromatography (EtOAc → MeOH, elution with EtOAc to remove impurities, and further elution with MeOH to isolate the desired salt). For *p*TSA salts, stirring at 40 °C for 30 min was needed in order to dissolve the acid. Purification on column chromatography was avoided since slight excess on *p*TSA do not interfere in the metathesis reaction. In the case of HCl salts, when prepared with 12 M HCl, several azeotropic distillations were conducted. Alternatively, salt formation was performed with anhydrous 2.5 M ethereal HCl, where the excess of HCl was removed by evaporation.

Typical procedure for alkene RCM

With pre-synthesized ammonium salt: typically 0.03 - 0.06 mmol of substrate were dissolved in anhydrous solvent (CH_2Cl_2, benzene, dichloretane or toluene, 0.01 M - 0.02 M) in a 10 mL

Schlenk flask and heated for the indicated time. Usual work-up procedure consisted in extracting with aqueous sat. $NaHCO_3$ solution. The organic layer was then separated and the aqueous phase was extracted once with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure.

Ammonium salt formed prior to use: 0.03 mmol of substrate was dissolved in CH_2Cl_2 approx. 0.02 M in a 10 mL Schlenk flask and the desired Brønsted acid was added. The mixture was stirred at 40 °C for approx. 20 min and the solvent was evaporated under reduced pressure (high vacuum). CH_2Cl_2 was again added and the mixture was azeotropically evaporated. The obtained salt was dissolved in anhydrous solvent and the same procedure as indicated above was conducted.

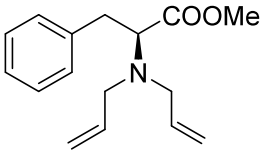
Typical procedure for enyne RCM and enyne RRM experiments.

With pre-synthesized ammonium salt: typically 0.03 - 0.06 mmol of substrate were dissolved in anhydrous solvent (CH_2Cl_2, benzene, dichloretane or toluene, 0.01 M - 0.02 M) in a 10 mL Schlenk flask. The solution was then flushed with ethylene via cannula before the catalyst was added (2 - 10 mol%). The mixture was the flushed again for 30 seconds and stirred at the desired temperature. Usual work-up procedure consisted in extracting with aqueous sat. $NaHCO_3$ solution. The organic layer was then separated and the aqueous phase was extracted once with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure.

Ammonium salt formed prior to use: 0.03 mmol of substrate was dissolved in CH_2Cl_2 approx. 0.02 M in a 10 mL Schlenk flask and the desired Brønsted acid was added. The mixture was stirred at 40 °C for approx. 20 min and the solvent was evaporated under reduced pressure (high vacuum). CH_2Cl_2 was again added and the mixture was azeotropically evaporated. The obtained salt was dissolved in anhydrous solvent and the same procedure as indicated above was conducted.

5.3.2 Procedures and Spectroscopic Data

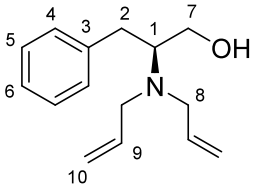
(*S*)-methyl 2-(diallylamino)-3-phenylpropanoate 153



$C_{16}H_{21}NO_2$
259.34 g/mol

Was synthesized from phenyl alanine according to the procedure described by Yu *et al.*: *Org. Lett.* **2005**, *7*, 871-874.

(*S*)-2-(diallylamino)-3-phenylpropanol 159



$C_{15}H_{21}NO$
231.33 g/mol

To a suspension of $LiAlH_4$ (145 mg, 3.82 mmol) in 15 mL anhydrous Et_2O phenylalanine derivate **153** (1.78 g, 6.95 mmol) was added at 0 °C and stirred overnight at rt. The reaction mixture was quenched dropwise with wet MeOH at 0 °C until evolution of H_2 ceased. The suspension was stirred for 1h and the inorganic residue was filtered off. Evaporation of the solvent followed by bulb to bulb distillation (210 °C), allowed to isolate the desired product **159** (1.55 g, 86%) as clear colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.29-7.09 (m, 5H, H-4, H-5, H-6), 5.80 (m, 2H, H-10), 5.17 (m, 4H, H-11), 3.39 (m, 4H, H-7, H-9), 3.20 (m, 1H, H-1), 3.02-2.91 (m, 3H, H-2, H-9), 2.31 (dd, 1H, *J* = 9.7 Hz, *J* = 3.7 Hz, 1H, H-2).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 139.2 (C-3), 136.6 (C-10), 129.0 (2 x C-5), 128.5 (2 x C-4), 126.3 (C-6), 117.4 (C-11), 61.6 (C-1), 60.4 (C-7), 52.3 (C-9), 32.0 (C-2).

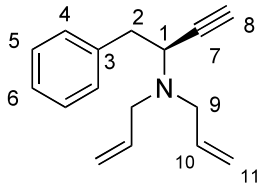
IR (ATR): ν (cm^{-1}) =3429 (br m), 3080 (m), 3026 (m), 2973 (m), 2928 (m), 2856 (m), 2815 (m), 1947 (w), 1871 (w), 1844 (w), 1694 (w), 1642 (m), 1603 (m),1584 (m), 1495 (m),1454 (m), 1416 (m), 1147 (m), 1123 (m), 1039 (s), 992 (m), 919 (m), 795 (w), 745 (m), 700 (s).

LRMS-ESI: *m/z* (%) = 232 (5) [MH^+], 190 (100), 117 (39).

HRMS-ESI (MH^+, $C_{15}H_{22}NO$) = calcd: 232.1701, found: 232.1693.

Optical rotation a_D^{20} = +42° (c = 1.13, CH_2Cl_2).

(*S*)-*N*,*N*-diallyl-1-phenylbut-3-yn-2-amine 155



$C_{16}H_{19}NO_2$
225.33 g/mol

Following the general procedure for the synthesis of alkynes from the corresponding alcohols, **159** (780 mg, 3.38 mmol) was oxidized *via* Swern oxidation (DMSO (0.36 mL, 5.07 mmol), oxalylchloride (0.22 mL, 2.54 mmol) and Et_3N (0.94 mL, 6.76 mmol) in 17 mL CH_2Cl_2). Seyferth Gilbert homologation followed (**50** (0.89 g, 4.63 mmol) and K_2CO_3 (0.95 g, 6.76 mmol) in 28 mL MeOH). After addition of CH_2Cl_2 (20 mL), the reaction mixture was filtered over a pad of Celite, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated and the crude material obtained was purified by column chromatography (SiO_2, cyclohexane/EtOAc 40:1) to afford alkyne **155** (700 mg, 92%) as yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.30-7.21 (m, 5H, H-4, H-5, H-6), 5.77 (m, 2H, H-10), 5.18 (d, *J* = 17.1 Hz, 2H, H-11), 5.10 (d, *J* = 10.3 Hz, 2H, H-11), 3.77 (m, 1H, H-1), 3.36-3.31 (m, 2H, H-2), 3.00-2.90 (m, 4H, H-9), 2.25 (d, 1H, *J* = 2.2 Hz, H-8).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.4 (C-3), 136.3 (C-10), 129.4 (2 x C-5), 128.1 (2 x C-4), 126.4 (C-6), 117.2 (C-11), 81.7 (C-7), 73.1 (C-8), 54.3 (C-1), 53.9 (C-9), 40.2 (C-2).

IR (ATR): ν (cm^{-1}) = 3302 (m), 3080 (w), 3066 (w), 3028 (w), 3006 (w), 2977 (w), 2954 (m), 2929 (m), 2857 (w), 2817 (m), 1642 (m), 1604 (w), 1497 (m), 1453 (m), 1418 (m), 1401 (w), 1356 (w),1339 (w), 1292 (w), 1261 (w), 1155 (w), 1114 (m), 1078 (w), 996 (m), 980 (w), 921 (s), 744 (m), 698 (s).

LRMS-ESI: *m/z* (%) = 226 (100) [MH^+], 184 (80), 129 (45), 96 (45).

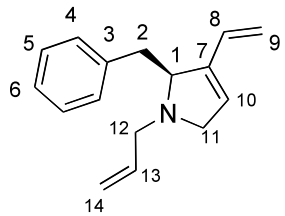
HRMS-ESI (MH^+, $C_{16}H_{20}NO_2$) = calcd: 226.1596, found: 226.1584.

R_f (SiO_2, cyclohexane / ethylacetate 10:1) = 0.52.

Optical rotation a_D^{20} = -33° (c = 0.65, CH_2Cl_2).

(*S*)-1-allyl-2-benzyl-3-vinyl-2,5-dihydro-1H-pyrrole 172

From the combined crude material of the different metathesis test (see general procedure for enyne RCM reactions), the product **172** was isolated after purification on column chromatography (SiO_2, cyclohexane→ cyclohexane/EtOAc 1:1)



$C_{16}H_{19}NO_2$
225.33 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.30-7.21 (m, 5H, H-4. H-5, H-6), 6.42 (dd, *J* = 16.7 Hz, *J* = 10.9 Hz, 1H, H-8), 5.78-5.67 (m, 2H, H-10, H-13), 5.23-4.99 (m, 4H, H-9, H-14), 4.01 (m, 1H, H-1), 3.68 (br d, *J* = 17.2 Hz, 1H, H-11), 3.24 (br d, *J* = 16.4 Hz, 1H, H-11), 3.12 (dd, *J* = 14.1 Hz, *J* = 5.5 Hz 1H, H-12), 3.01 (m, 2H, H-2, H-12), 2.72 (dd, *J* = 14.1 Hz, *J* = 7.0 Hz, 1H, H-2).

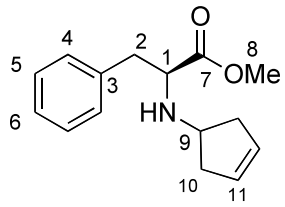
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 142.0 (C-7), 139.7 (C-3), 136.4 (C-13), 131.4 (C-8), 129.9 (2 x C-5), 127.7 (2 x C-4), 127.3 (C-10), 125.8 (C-6), 116.4 (C-14), 114.9 (C-9), 70.6 (C-1), 59.2 (C-11), 59.0 (C-12), 40.4 (C-2).

LRMS-ESI: *m/z* (%) = 226 (100) [MH^+], 184 (100), 129 (50), 96 (50).

HRMS-ESI (MH^+, $C_{16}H_{20}NO_2$) = calcd: 226.1596, found: 226.1588.

R_f (SiO_2, cyclohexane / ethylacetate 10:1) = 0.52.

(*S*)-methyl 2-(cyclopent-3-enylamino)-3-phenylpropanoate 160



$C_{15}H_{19}NO_2$
245.32 g/mol

(*S*)-phenyl alanine methyl ester hydrochloride (2.68 g, 12.43 mmol), tosylate **37** (2.96 g, 12.42 mmol) and Na_2CO_3 (4 g, 37.74 mmol) were suspended in a mixture of 30 mL CH_3CN and 20 mL DMF and heated at 90 °C for 5 days. After addition of 30 mL CH_2Cl_2, the obtained slurry was filtrated and concentrated. Purification by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) afforded the desired product **160** (1.21 g, 40%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.29-7.15 (m, 5H, H-4, H-5, H-6), 5.61 (m, 2H, H-11), 3.60 (s, 3H, H-8), 3.56 (t, 1H, *J* = 7.3 Hz, H-1), 3.38 (m, 1H, H-9), 2.58-2.43 (m, 2H, H-10), 2.12-2.00 (m, 2H, H-10).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 175.4 (C-7), 129.8 (C-3), 129.1 (2 x C-5), 128.9 (C-11), 128.8 (C-11), 128.4 (2 x C-4), 126.7 (C-6), 61.8 (C-1), 56.3 (C-9), 51.6 (C-8), 40.3 (C-10), 40.1 (C-2), 39.3 (C-10).

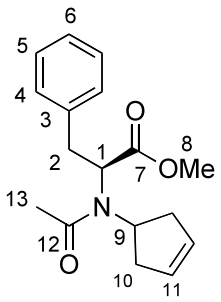
IR (ATR): ν (cm^{-1}) = 3320 (w), 3086 (w), 3061 (w), 3029 (w) 3001 (w), 2949 (m), 2927 (m), 2844 (m), 1953 (w), 1736 (s), 1604 (w), 1496 (w), 1454 (m), 1434 (m), 1352 (w), 1272 (w) 1200 (m), 1170 (m), 1135 (w), 1077 (w), 1031 (w), 1018 (w), 983 (w), 787 (w), 751 (w), 700 (w).

LRMS-ESI: *m/z* (%) = 246 (75) [MH^+], 186 (100) [M^+-1H], 180 (85), 120 (65).

HRMS-ESI (MH^+, $C_{15}H_{20}NO_2$) = calcd: 246.1494, found: 246.1489.

R_f (SiO_2, cyclohexane/EtOAc 5:1) = 0.25.

(*S*)-methyl 2-(*N*-(cyclopent-3-enyl)acetamido)-3-phenylpropanoate 161



$C_{17}H_{21}NO_3$
287.35 g/mol

To a solution of amine **160** (0.52 g, 2.12 mmol) in 15 mL $C_2H_2Cl_2$ acetylchloride (3.83 mL, 53.70 mmol) was added and the mixture refluxed for 3 h. After cooling to rt, the reaction was quenched with the addition of 8 mL sat. aqueous Na_2CO_3 solution. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to isolate acetamide **161** (430 mg, 71%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.32-7.11 (m, 5H, H-4, H-5, H-6), 5.65-5.45 (m, 2H, H-11), 4.38 (m, 1H, H-9), 3.97 (dd, *J* = 8.2 Hz, *J* = 5.4 Hz, 1H, H-1), 3.71 (s, 3H, H-8), 3.51 (dd, *J* = 14.3 Hz, *J* = 5.4 Hz, 1H, H-2), 3.28 (dd, *J* = 14.3 Hz, *J* = 8.5 Hz, 2H, H-2), 2.56 (m, 2H, H-10), 2.1-2.06 (m, 4H, H-13, H-10), 1.54-1.47 (m, 1H, H-10).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 171.6 (C-7), 170.7 (C-12), 139.0 (C-3), 129.7 (2 x C-5), 129.3 (C-11), 129.2 (C-11), 128.3 (2 x C-4), 126.5 (C-6), 59.1 (C-1), 57.5 (C-9), 52.3 (C-8), 37.0 (C-10), 36.8 (C-10), 35.8 (C-2), 22.5 (C-13).

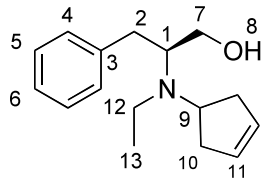
IR (ATR): ν (cm^{-1}) = 3341 (br w), 3218 (br w), 3085 (w), 3060 (w), 3027 (w), 3002 (w), 2949 (m), 2931 (w), 2855 (w), 1955 (w), 1739 (s), 1646 (s), 1584 (w), 1496 (m), 1454 (s), 1428 (s), 1362 (m), 1326 (m), 1275 (m), 1231 (s), 1209 (s), 1179 (m), 1109 (w), 1092 (w), 1079 (w), 1046 (w), 1030 (w), 1014 (m), 996 (m), 947 (w), 901 (w), 772 (w), 752 (m), 702 (s), 679 (m).

LRMS-ESI: *m/z* (%) = 288 (5) [MH^+], 246 (100).

HRMS-ESI (MH^+, $C_{17}H_{22}NO_3$) = calcd: 288.1600, found: 288.1587.

R_f (SiO_2, cyclohexane/EtOAc 3:2) = 0.17.

(*S*)-2-(cyclopent-3-enyl-ethyl-amino)-3-phenyl-1-propanol 162



$C_{16}H_{23}NO$
245.36 g/mol

To a suspension of $LiAlH_4$ (240 mg, 6.43 mmol) in 10 mL Et_2O, acetamide **161** (0.37 g, 1.29 mmol) was added dropwise at 0 °C and stirred overnight at rt. The reaction mixture was quenched with wet MeOH at 0 °C until no further evolution of H_2 was observed. The suspension was stirred for 1 h and the inorganic residue was filtered off. Evaporation of the solvent followed by purification on column chromatography (SiO_2, MTBE/cyclohexane 2:1) allowed isolating the desired product **162** (200 mg, 63%) as a clear yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.29-7.24 (m, 2H, H-5), 7.22-7.16 (m, 1H, H6), 7.13-7.09 (m, 2H, H-4), 5.72 (s, 2H, H-11), 3.78 (m, 1H, H-9), 3.30 (d, *J* = 7.8 Hz, 2H, H-7), 3.09 (m, 1H, H-1), 2.96 (dd, *J* = 13.2 Hz, *J* = 3.7 Hz, 1H, H-2), 2.68-2.25 (series of m, 7H, H-2, H-10, H-12), 1.11 (t, *J* = 7.1 Hz, 3H, H-13).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 139.2 (C-3), 129.7 (C-11), 129.5 (C-11), 128.9 (2 x C-5), 128.5 (2 x C-4), 126.2 (C-6), 62.0 (C-1), 60.3 (C-7), 57.0 (C-9), 39.6 (C-10), 39.2 (C-10), 35.6 (C-12), 34.5 (C-2), 15.6 (C-13).

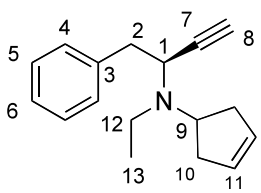
IR (ATR): ν (cm^{-1}) = 3431 (br m), 3084 (w), 3058 (w), 3026 (w), 2964 (s), 2929 (s), 2851 (m), 1943 (w), 1873 (w), 1740 (w), 1617 (w), 1602 (w), 1584 (w), 1495 (m), 1465 (w), 1454 (m), 1411 (m), 1384 (m), 1348 (w), 1326 (w), 1310 (w), 1288 (w), 1234 (m), 1211 (m), 1175 (m), 1132 (m), 1090 (m), 1062 (m), 1040 (s), 1031 (s), 948 (w), 868 (w), 797 (w), 743 (m), 700 (s).

LRMS-ESI: *m/z* (%) = 246 (90) [MH^+], 180 (100), 117 (60), 112 (35) [$M\text{-}C_5H_6^+$].

HRMS-ESI (MH^+, $C_{16}H_{23}NO$) = calcd: 246.1848, found: 246.1844.

R_f (SiO_2, cyclohexane/MTBE 1:1) = 0.19.

(*S*)-*N*-ethyl-*N*-(1-phenylbut-3-yn-2-yl)cyclopent-3-enamine 156



$C_{17}H_{21}N$
239.36 g/mol

Following the general procedure for the synthesis of alkynes from the corresponding alcohols, **162** (198 mg, 0.81 mmol) was oxidized via Swern oxidation (DMSO (169 µL, 2.34 mmol), oxalylchloride (107 µL, 1.25 mmol), and Et_3N (0.6 mL, 4.16 mmol) in 8 mL CH_2Cl_2). Seyferth Gilbert homologation followed (**50** (212 mg,

1.10 mmol) and K_2CO_3 (0.22 g, 1.60 mmol) in 6.5 mL MeOH). After addition of CH_2Cl_2 (10 mL), the reaction mixture was filtered over a pad of Celite, washed with sat. aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated. The crude material obtained was purified on column chromatography (SiO_2, cyclohexane/EtOAc 10:1) to obtain the alkyne **156** (40 mg, 21%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.31-7.20 (m, 5H, H-4, H-5, H-6), 5.67 (s, 2H, H-11), 3.76-3.72 (m, 2H, H-1, H-9), 2.97 (m, 1H, H-2), 2.87 (m, 1H, H-2), 2.76 (m, 1H, H-12), 2.61 (m, 1H, H-12), 2.51-2.42 (m, 3H, H-10), 2.21 (d, *J* = 2.2 Hz, 1H, H-8), 2.20-2.13 (m, 1H, H-10), 1.09 (t, *J* = 7.2 Hz, 3H, H-13).

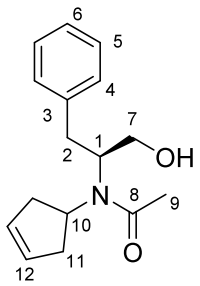
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 138.8 (C-3), 129.7 (C-11), 129.5 (C-5), 129.3 (C-11), 128.1 (C-4), 126.3 (C-6), 83.8 (C-7), 73.0 (C-8), 60.3, 54.2 (C-1, C-9), 42.3 (C-10), 41.7 (C-10), 42.3 (C-12), 41.7 (C-2), 15.2 (C-13).

LRMS-ESI: *m/z* (%) = 240 (30) [MH^+], 174 (50), 129 (40), 110 (100).

HRMS-ESI (MH^+, $C_{17}H_{22}N$) = calcd: 240.1752, found: 240.1738.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.66.

(S)-*N*-(cyclopent-3-enyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)acetamide 163



$C_{16}H_{21}NO_2$
259.34 g/mol

To a solution of substrate **161** (336 mg, 1.17 mmol) in EtOH, $NaBH_4$ (132 mg, 3.5 mmol) was added at 0 °C. The mixture was stirred for 48 h at rt. After quenchig with CH_3COOH at 0 °C the solvent was evaporated under reduced presure and the crude material was disolved in CH_2Cl_2 and extracted twice with NH_4Cl sat. solution, dried over $MgSO_4$ and evaporated. The crude material obtained was purified on column chromatography (SiO_2, cyclohexane → MTBE) to obtain the title compound **163** (150 mg, 50%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.30-7.18 (m, 5H, H-4, H-5, H-6), 5.64 (m, 2H, H-12), 4.77 (br s, OH), 4.45 (m, 1H, H-10), 3.76 (m, 2H, H-7), 3.47 (br s, 1H, H-1), 3.34-3.31 (m, 1H, H-2), 3.08-3.02 (m, 1H, H-2), 2.62-2.53 (m, 1H, H-11), 2.38-2.28 (m, 2H, H-11), 2.17 (s, 3H, H-9), 1.98-1.90 (m, 1H, H-11).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 172.7 (C-8), 139.3 (C-3), 129.5 (C-12), 129.5 (C-5), 129.0 (C-12), 128.5 (C-4), 126.5 (C-6), 65.2 (C-7), 60.3 (C-1), 58.1 (C-10), 37.2 (C-11), 36.5 (C-11), 34.5 (C-2), 23.4 (C-9).

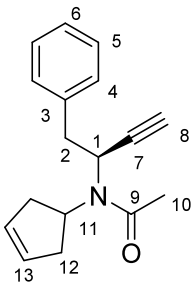
IR (ATR): ν (cm^{-1}) = 3357 (br m), 3059 (w), 2925 (m), 2855 (m), 1737 (w), 1622 (s), 1613 (s), 1495 (m), 1454 (s), 1434 (s), 1365 (m), 1345 (m), 1070 (m), 1032 (m), 1013 (m), 948 (w), 749 (m), 700 (s).

LRMS-ESI: *m/z* (%) = 260 (20) [MH^+], 242 (60) [M^+-OH], 218 (60) [MH_2^+-COMe], 200 (100), 117 (70) [$C_5H_6^+$].

HRMS-ESI (MH^+, $C_{16}H_{21}NO_2$) = calcd: 260.1651, found 260.1645.

R_f (SiO_2, MTBE) = 0.26.

(*S*)-*N*-(cyclopent-3-enyl)-*N*-(1-phenylbut-3-yn-2-yl)acetamide 164



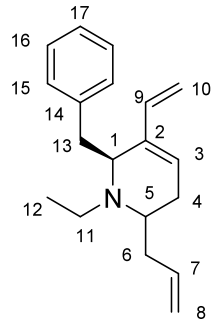
$C_{17}H_{19}NO$
253.34 g/mol

Alcohol **163** (114 mg, 0.44 mmol) was dissolved in freshly distilled CH_2Cl_2 (22 mL) and PCC (228 mg, 1.59 mmol) was added in one portion under N_2 atmosphere. After 3 h stirring at rt 20 mL Et_2O were added, and the suspension formed was filtrated through Celite. After evaporating, the isolated crude material was dissolved in MeOH (30 mL) and **50** (123 mg, 0.64 mmol) and K_2CO_3 (150 mg, 1.08 mmol) were added. Seyferth Gilbert homologation was performed following the procedure described in Section 5.3.1. The desired product **164** (100 mg, 80%) was obtained as clear oil after column chromatography (SiO_2, cyclohexane → EtOAc).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34-7.20 (m, 5H, H-4, H-5, H-6), 5.73 (m, 2H, H-13), 5.65 (m, 1H-H-1), 4.42 (m, 1H, H-11), 3.15-2.51 (m, 6H, H-2, H-12), 2.29 (d, *J* = 2.2 Hz, 1H, H-8), 2.06 (s, 3H, H-10).

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.38.

(6*S*)-2-allyl-6-benzyl-1-ethyl-5-vinyl-1,2,3,6-tetrahydropyridine 179



$C_{19}H_{25}N$
267.41 g/mol

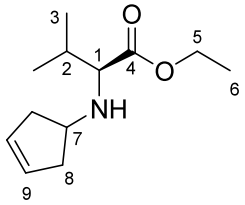
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = characteristic signals 6.30 (dd, *J* = 17.6 Hz, *J* = 11.1 Hz, 1H, H-9), 5.95-5.83 (m, 2H, H-3, H-7), 5.08 (m, 4H, H-8, H-10), 3.48 (br d, *J* = 9.5 Hz, 1H, H-1), 3.25 (m, 1H, H-5).

LRMS-ESI: *m/z* (%) = 268 (50) [MH^+], 98 (100).

HRMS-ESI (MH^+, $C_{19}H_{26}N$) = calcd: 268.2065, found: 268.2052.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.66.

(*S*)-ethyl 2-(cyclopent-3-enylamino)-3-methylbutanoate 157



$C_{12}H_{21}NO_2$
211.30 g/mol

(*S*)-valin ethyl ester hydrochloride (1.2 g, 6.6 mmol), tosilate **37** (1.88 g, 7.9 mmol) and K_2CO_3 (2 g, 14.52 mmol) were suspended in CH_3CN (8 mL) and heated to reflux for five days. After evaporating the solvent, the crude material was purified by column chromatography (SiO_2, cyclohexane → EtOAc) and the desired product **157** (540 mg, 39%) was obtained as brown oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.64 (s, 2H, H-9), 4.19 (m, 2H, H-5), 3.32 (m, 1H, H-7), 2.99 (d, *J* = 6.2 Hz, 1H, H-1), 2.60-2.45 (m, 2H, H-8), 2.14-2.05 (m, 2H, H-8), 1.88 (m, 1H, H-2), 1.66 (br s, 1H, NH), 1.28 (t, *J* = 7.2 Hz, 3H, H-6), 0.93 (dd, *J* = 6.9 Hz, *J* = 2.5 Hz, 6H, H-3).

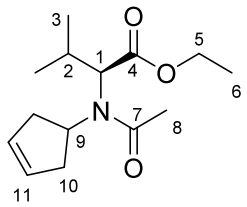
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 175.7 (C-4), 128.9 (C-9), 128.8 (C-9), 65.9 (C-1), 60.4 (C-5), 56.65(C-7), 40.4 (C-8), 39.6 (C-8), 31.8 (C-2), 19.1 (C-3), 18.8 (C-3), 14.4 (C-6).

IR (ATR): ν (cm^{-1}) = 3325 (br w), 3054 (w), 2959 (s), 2926 (s), 2854 (m), 1732 (s), 1466 (m), 1368 (m), 1261 (m), 1179 (m), 1026 (m), 799 (m).

LRMS-ESI: *m/z* (%) = 121 (20) [MH^+], 146 (20) [$MH\text{-}C_5H_6^+$], 138 (100).

HRMS-ESI (MH^+, $C_{12}H_{22}NO_2$) = calcd: 212.1651, found: 212.1645.

(*S*)-ethyl 2-(*N*-(cyclopent-3-enyl)acetamido)-3-methylbutanoate 166



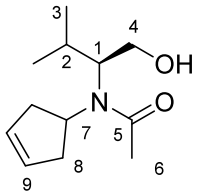
$C_{14}H_{23}NO_3$
253.34 g/mol

Amino ester **165** (340 mg, 1.61 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and acetylchloride (1.80 mL) and Et_3N (2 mL) were subsequently added. The reaction mixture was heated at 40 °C overnight, washed with sat. $NaHCO_3$ solution and concentrated under reduced pressure. Purification by column chromatography (SiO_2, cyclohexane → EtOAc) afforded the desired product **166** (364 mg, 89%) as colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) =5.75-5.63 (m, 2H, H-11), 4.52-3.76 (m, 4H, H-1, H-5, H-9), 2.93-2.21 (m, 5H, H-2, H-10), 2.16, 2.07 (2 x s, combined 3H, H-8), 1.31-1.23 (m, 3H, H-6), 1.06-0.84 (m, 6H, H-3).[29]

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.16.

(*S*)-*N*-(cyclopent-3-enyl)-*N*-(1-hydroxy-3-methylbutan-2-yl)acetamide 168



$C_{12}H_{21}NO_2$
211.3 g/mol

Acetamide **166** (364 mg, 1.44 mmol) was dissolved in EtOH (6mL) and $NaBH_4$ (164 mg, 4.32 mmol) was added in 3 portions at 0 °C. Stirring continued for 48 h at rt before the reaction was quenched with 0.3 mL acetic acid. The suspension was concentrated, dissolved in MTBE and extracted with sat. aqueous NH_4Cl solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Since analysis via ^{1}H-NMR of the crude material showed very low conversion (approx. 20%), the product obtained was again dissolved in EtOH (5 mL) and $NaBH_4$ (164 mg, 4.32 mmol) and LiCl (184 mg, 4.32 mmol) were subsequently added at 0 °C. After 48 h stirring at rt, the same work up was performed, and the product isolated **167** (200 mg, 66%) was used in the next synthetic step without further purification.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.71 (m, 2H, H-9), 3.90-3.39 (m, 4H, H-1, H-4, H-7), 3.03-2.35 (m, 5H, H-2, H-8), 2.15, 2.13 (2 x s, combined 3H, H-6), 1.02-0.85 (m, 6H, H-3).[cc]

HRMS-ESI (MH^+, $C_{12}H_{22}NO_2$) = calcd: 512.1651, found: 512.1640 and 534.1457 ($C_{12}H_{21}NaNO_2^+$).

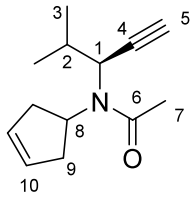
R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.10.

(*S*)-*N*-(cyclopent-3-enyl)-*N*-(4-methylpent-1-yn-3-yl)acetamide 169

Alcohol **168** (180 mg, 0.85 mmol) was dissolved in freshly distilled CH_2Cl_2 (44 mL) and PCC (437 mg, 2.03 mmol) was added in one portion under N_2 atmosphere. After 3 h stirring at rt 20 mL Et_2O were added, and the suspension formed was filtrated through Celite. After evaporating, the isolated crude material was dissolved in MeOH (22 mL) and **51** (233 mg, 1.21 mmol) and K_2CO_3 (250 mg, 1.81 mmol) were added. Seyferth Gilbert homologation was

[29] The title compound showed a mixture of conformational isomers and/or rotamers evidenced by doubling of ^{1}H and ^{13}C resonances for many protons and carbons.

performed following the procedure described in Section 5.3.1. The desired product **169** (50 mg, 29%) was obtained as clear oil after column chromatography (SiO_2, cyclohexane → EtOAc).



$C_{13}H_{19}NO$
205.3 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.79-5.64 (m, 2H, H-10), 5.08-3.94 (m, 2H, H-1, H-8), 2.96-1.92 (m, 5H, H-2, H-9), 2.38, 2.26 (2 x d, *J* = 2.1 Hz, combined 1H, H-5), 2.10, 2.03 (2 x s, combined 3H, H-7), 0.92 (t, *J* = 7.4 Hz, 3H, H-5), 0.85 (d, *J* = 6.9 Hz, 3H, H-3).[cc]

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.8, 129.5, 128.9 (C-10), 82.8 (C-4), 73.3, 72.0 (C-5), 58.4, 55.6, 53.6, 53.3 (C-8, C-1), 40.2, 39.8, 36.3 (C-9), 32.8, 32.1 (C-2), 23.6, 22.5 (C-7), 19.9, 19.6, 19.1, 19.0 (C-3).

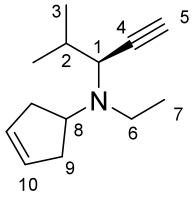
IR (ATR): ν (cm^{-1}) = 3305 (m), 3233 (m), 3054 (m), 2965 (m), 2928 (m), 2872 (m), 2110 (w), 1739 (m), 1638 (s), 1448 (m), 1433 (m), 1369 (m), 1300 (m), 1286 (m), 1172 (m), 1010 (m), 996 (m), 948 (m), 696 (m), 670 (m).

LRMS-ESI: *m/z* (%) = 206 (10) [MH^+], 164 (25), 140 (100) [$MH\text{-}C_5H_6^+$], 126 (30).

HRMS-ESI (MH^+, $C_{13}H_{20}NO$) = calcd: 206.1545, found: 206.1535 and 228.1352 ($C_{13}H_{19}NNaO^+$).

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.17.

(*S*)-*N*-ethyl-*N*-(4-methylpent-1-yn-3-yl)cyclopent-3-enamine 157



$C_{13}H_{21}N$
191.31 g/mol

Acetamide **169** (50 mg, 0.24 mmol) was dissolved in freshly distilled Et_2O (0.5 mL) and $LiAlH_4$ (30 mg, 0.81 mmol) was added at 0 °C. The reaction mixture was stirred at rt over night under N_2 atmosphere. Quenching was performed by subsequent addition of wet EtOAc and wet MeOH until a white precipitate was formed and evolution of hydrogen ceased. After filtration (twice) through a pad of Celite, the crude material **157** was concentrated and used without further purification (40 mg, 86%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.68 (m, 2H, H-10), 3.66 (m, 1H, H-8), 2.95 (dd, *J* = 9.9 Hz, *J* = 2.3 Hz, 1H, H-1), 2.62 (m, 1H, H-6), 2.55-2.43 (m, 3H, H-9, H-6), 2.39-2.20

(m, 2H, H-9), 2.18 (d, *J* = 2.2 Hz, 1H, H-5), 1.76 (m, 2H, H-2), 0.92 (t, *J* = 7.4 Hz, 3H, H-7), 0.85 (d, *J* = 7.0 Hz, 6H, H-3).[30]

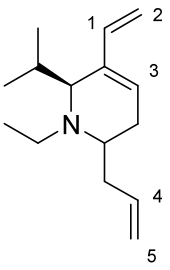
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.9 (C-10), 129.3 (C-10), 84.3 (C-4), 72.4 (C-5), 60.1 (C-1), 58.9 (C-8), 42.3 (C-6), 38.3 (C-9), 34.3 (C-9), 31.8 (C-2), 20.4 (C-3), 20.2 (C-3), 15.1 (C-7).[31]

IR (ATR): ν (cm^{-1}) = 3307 (br w), 3052 (w), 2955 (m), 2924 (s), 2853 (m), 1644 (w), 1466 (m), 1378 (m), 1056 (w), 698 (w).

LRMS-ESI: *m/z* (%) = 192 (10) [MH^+], 126 (15) [MH^+-$C_5H_6^+$], 110 (100).

HRMS-ESI (MH^+, $C_{13}H_{22}N$) = calcd: 192.1742, found 192.1743.

(6*S*)-2-allyl-1-ethyl-6-isopropyl-5-vinyl-1,2,3,6-tetrahydropyridine 180

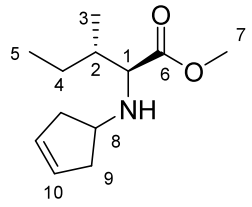


$C_{15}H_{25}N$
219.37 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = characteristic signals 6.28 (dd, *J* = 18.3 Hz, *J* = 11.3 Hz, 1H, H-1), 5.91 (m, 1H, H-4), 5.86 (m, 1H, H-3), 5.08-4.87 (m, 4H, H-2, H-5).

LRMS-ESI: *m/z* (%) = 220 [MH^+].

(2*S*,3*S*)-methyl 2-(cyclopent-3-enylamino)-3-methylpentanoate 171



$C_{12}H_{21}NO_2$
211.3 g/mol

(*S*)-isoleucin methyl ester hydrochloride **170** (1.85 g, 10.2 mmol), tosylate **37** (2.70 g, 11.23 mmol) and Na_2CO_3 (5.60 g, 53 mmol) were suspended in acetonitril (40 mL) and refluxed for 5 days. 30 mL CH_2Cl_2 were then added, the reaction mixture was filtrated and the solvent evaporated. Purification by column chromatography (SiO_2, cyclohexane/EtOAc 3:1) afforded the desired product **171** (1.15 g, 53%) as a yellow oil.

[30] At 1.3 and 0.85 ppm appears an impurity which could not be separated via column chromatography.
[31] At 29.69 ppm appears the signal corresponding to the mentioned impurity.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.63 (s, 2H, H-10), 3.71 (s, 3H, H-7), 3.32 (ddt, *J* = 12.5 Hz, *J* = 7.4 Hz, *J* = 5.2 Hz, 1H, H-8), 3.11 (d, *J* = 6.1 Hz, 1H, H-1), 2.60-2.45 (m, 2H, H-9), 2.14-2.05 (m, 2H, H-9), 1.68-1.49 (m, 3H, OH, H-2, H-4), 1.21-1.12 (m, 1H, H-4), 0.88 (m, 6H, H-3, H-5).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 176.1 (C-6), 128.9 (C-10), 64.6 (C-1), 56.6 (C-8), 51.4 (C-7), 40.4 (C-9), 39.6 (C-9), 38.5 (C-2), 25.7 (C-4), 15.4 (C-3), 11.4 (C-5).

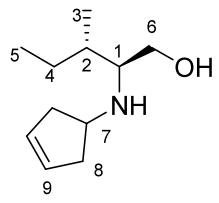
IR (ATR): ν (cm^{-1}) = 3357 (br m), 3340 (w), 2963 (s), 2924 (s), 2852 (m), 1738 (s), 1678 (m), 1363 (m), 1189 (m), 1177 (m), 1363 (m), 1189 (m), 1177 (s).

LRMS-ESI: *m/z* (%) = 212 (10) [MH^+], 152 (100), 146 (20), [$MH\text{-}C_5H_7^+$].

HRMS-ESI (MH^+, $C_{12}H_{22}NO_2$) = calcd: 212.1651, found: 212.1646.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.56.

(2*S*,3*S*)-2-(cyclopent-3-enylamino)-3-methylpentan-1-ol



$C_{11}H_{21}NO$
183.29 g/mol

To a suspension of $LiAlH_4$ (538 mg, 14.5 mmol) in 30 mL Et_2O, **171** (1 g, 4.73 mmol) was added at 0 °C and stirred overnight at rt. The reaction mixture was quenched with wet MeOH at 0 °C until evolution of H_2 ceased. The suspension was stirred for 1 h and the inorganic residue was filtered off. Evaporation of the solvent followed by purification by column chromatography (SiO_2, cyclohexane/EtOAc 1:1 → EtOAc) allowed the isolation of the title compound (527 mg, 61%) as a clear yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.67 (s, 2H, H-9), 3.56 (m, 2H, H-6, H-7), 3.27 (dd, *J* = 10.4 Hz, *J* = 7.2 Hz, 1H, H-6), 2.56 (m, 3H, H-1, H-8), 2.20-1.98 (m, 3H, H-8, NH), 1.60 (m, 1H, H-2), 1.43 (m, 1H, H-4), 1.19 (m, 1H, H-4), 0.92 (t, *J* = 7.4 Hz, 3H, H-5), 0.85 (d, *J* = 6.9 Hz, 3H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.1 (C-9), 128.7 (C-9), 60.5 (C-6), 60.1 (C-1), 55.2 (C-7), 40.5 (C-8), 40.3 (C-8), 35.8 (C-2), 26.5 (C-4), 14.4 (C-3), 12.0 (C-5).

IR (ATR): ν (cm^{-1}) = 3372 (br m), 3055 (w), 2961 (s), 2929 (s), 2857 (s), 1714 (w), 1613 (w), 1463 (m), 1378 (w), 1050 (m), 989 (w), 695 (m).

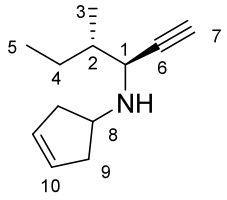
LRMS-ESI: *m/z* (%) = 161 (30) [M^+], 160 (80) [M^+-1H], 120 (100), 67 (70) [$C_5H_7^+$].

HRMS-ESI (MH^+, $C_{11}H_{22}NO$) = calcd: 184.1619, found: 184.1690.

R_f (SiO_2, EtOAc) = 0.2.

Optical rotation a_D^{20} = +21° (c = 1.27, CH_2Cl_2).

***N*-((3*S*,4*S*)-4-methylhex-1-yn-3-yl)cyclopent-3-enamine 158**



$C_{12}H_{19}N$
177.29 g/mol

Following the general procedure for the synthesis of alkynes from the corresponding alcohols the previous compound (258 mg, 0.71 mmol) was oxidized *via* Swern oxidation (DMSO (258 µL, 2.13 mmol), oxalylchloride (120 µL, 1.06 mmol), and Et_3N (0.5 mL, 2.13 mmol) in 7 mL CH_2Cl_2). Seyferth Gilbert homologation followed (**50** (280 mg, 1.45 mmol) and K_2CO_3 (337 mg, 2.44 mmol) in 9 mL MeOH). After addition of CH_2Cl_2 (10 mL), the reaction mixture was filtered over a pad of Celite, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated. The crude material obtained was purified on column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to obtain alkyne **158** (51 mg, 23%) as a yellowish oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.67 (m, 2H, H-10), 3.78 (m, 1H, H-8), 3.36 (dd, *J* = 4.7 Hz, *J* = 2.2 Hz, 1H, H-1), 2.70-2.49 (m, 2H, H-1, H-9), 2.22 (d, *J* = 2.2 Hz, 1H, H-7), 2.20-2.09 (m, 2H, H-9), 1.60 (m, 1H, H-2), 1.51 (m, 1H, H-4), 1.28 (m, 1H, H-4), 0.96 (d, *J* = 6.6 Hz, 3H, H-3), 0.91 (t, *J* = 7.3 Hz, 3H, H-5).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 129.0 (C-10), 128.9 (C-10), 84.0 (C-6), 71.9 (C-7), 55.5 (C-8), 52.9 (C-1), 40.6 (C-2), 39.4 (C-9), 39.3 (C-9), 26.8 (C-4), 14.4 (C-3), 11.7 (C-5).

HRMS-ESI (MH^+, $C_{12}H_{20}N$) = calcd: 178.1596, found: 178.1590.

R_f (SiO_2, cyclohexane/EtOAc 3:1) = 0.60.

5.4 Experimental Section for Chapter 4

5.4.1 General Procedures

Typical procedure for hydroamination experiments

Hydroamination reactions were prepared in a glovebox by adding 1 eq of amine and 2.5 eq of alkyne to a solution of 10 mol% catalyst **182** and 10 mol% activator **183** in deuterated benzene. The reaction mixture was placed in a NMR tube, which was flame-sealed under vacuum outside the glovebox, and heated at 80 °C, unless otherwise indicated. Analysis of reaction progress was conducted *via* ^{1}H-NMR. When 100% conversion was achieved, removal of the solvent in vacuo followed by column chromatographic purification afforded the pure product with the indicated yield.

General procedure for consecutive hydroamination-enyne RCM experiments

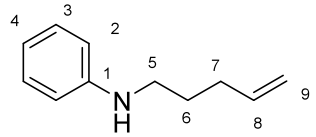
Hydroamination reactions were prepared in a glovebox where 1 eq of amine and 2.5 eq of alkyne were added to a solution of 10 mol% catalyst **182** and 10 mol% activator **183** in deuterated benzene in a 10 mL Schlenk flask. The reaction mixture was usually heated at 80 °C for 48 h. Analysis of reaction progress was conducted *via* ^{1}H-NMR. When 100% conversion was achieved, solvent and excess of alkyne were removed under reduced pressure at 80 °C (high vacuum pump). The afforded crude oil was used directly in the next step without further purification.

For aniline derivates: A solution of the hydroamination product in anhydrous CH_2Cl_2 or toluene (0.02 M) was flushed with ethylene *via* cannula for approx. 2 min before the corresponding ruthenium catalyst was added. The reaction was then stirred 16 hours at the given temperature under ethylene atmosphere. The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (SiO_2, pentane (1 vol% Et_3N) or Al_2O_3, pentane).

For benzylamine derivates: A solution of the hydroamination product with 1.05 eq of *p*TSA was stirred at 40 °C for 30 min in a Schlenk flask. After removal of the CH_2Cl_2 under reduced pressure (high vacuum pump), anhydrous CH_2Cl_2 or toluene (0.02 M) was added and flushed with ethylene *via* cannula for approx. 2 min before the catalyst was added. The reaction was then stirred 16 hours at the given temperature under ethylene atmosphere. Before chromatographic purification the reaction mixture was extred with an aqueous 2 M NaOH solution.

5.4.2 Procedures and Spectroscopic Data

_N_-(pent-4-enyl)aniline



$C_{11}H_{15}N$
161.24 g/mol

Oxalylchlorid (0.23 mL, 2.68 mmol) was slowly added under nitrogen atmosphere to a solution of pentenoic acid (0.28 g, 2.24 mmol) in 2 mL of anhydrous CH_2Cl_2 at rt. After 2 h the solvent was removed under reduced pressure. The crude material was dissolved in 3 mL anhydrous CH_2Cl_2, and a solution of aniline (0.25 g, 2.68 mmol) in 1 mL anhydrous CH_2Cl_2 followed by pyridine (0.45 mL, 5.38 mmol) were added at 0 °C. The reaction mixture was allowed to warm up to rt and stirred overnight. After addition of 20 mL of CH_2Cl_2, the organic phase was washed subsequently with an aqueous sat. solution of $NaHCO_3$ (1 x 20 mL) and a 5% HCl aqueous solution (1 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (SiO_2, hexane/EtOAc 7:1), *N*-phenyl-4-pentenamid was obtained in 68% yield (0.32 g, 1.83 mmol) as white solid. The spectroscopic data are in agreement with those reported in the literature.[238]
A solution of *N*-phenyl-4-pentenamid (0.32 g, 1.84 mmol) in 20 mL anhydrous Et_2O was added dropwise to a suspension of $LiAlH_4$ (0.21 g, 5.48 mmol) in 30 mL anhydrous Et_2O at 0 °C under N_2 atmosphere. After 3 h, complete conversion was achieved and the reaction mixture was quenched with 10 mL of wet EtOAc and 10 mL of wet MeOH. After filtration through a pad of Celite and purification by column chromatography (SiO_2, CH_2Cl_2/MeOH 20:1), the title compund was isolated as a clear colorless oil in 63% yield (0.47 g, 2.92 mmol).[239]

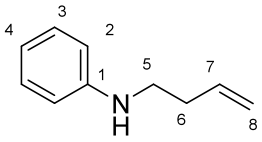
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.18 (t, *J* = 7.7 Hz, 2H, H-3), 6.70 (d, *J* = 7.7 Hz, 1H, H-4), 6.61 (m, 2H, H-2), 5.83 (m, 1H, H-7), 5.18-5.09 (m, 2H, H-8), 3.19 (t, *J* = 6.7 Hz, 2H, H-5), 2.39 (q, *J* = 6.7 Hz, 2H, H-6).

_N_-(but-3-enyl)anilin

Under nitrogen atmosphere, to a solution of butenoic acid (2.50 g, 29.04 mmol) in 50 mL CH_2Cl_2 were subsequently added DMAP (89 mg, 0.73 mmol), aniline (5.34 mL, 58.1 mmol) and DCC (5.99 g, 29 mmol) at 0 °C. The reaction mixture was stirred over night at rt. After addition of 120 mL of CH_2Cl_2, the formed precipitate was filtered and the organic phase was

extracted with 10% aqueous HCl solution (1 x 120 mL), sat. solution of $NaHCO_3$ (1 x 120 mL) and concentrated The crude material was purified by column chromatography (SiO_2, hexane/EtOAc 7:1) and the collected fractions were concentrated, diluted with 200 mL ethyl acetate, washed with 200 mL of a 2 M HCl aqueous solution, dried over $MgSO_4$ and concentrated under reduced pressure. The desired *N*-phenyl-4-butenamid was obtained in 84% yield (3.94 g, 24.44 mmol) in form of a colorless solid. The spectroscopic data are in agreement with those reported in the literature.[240]

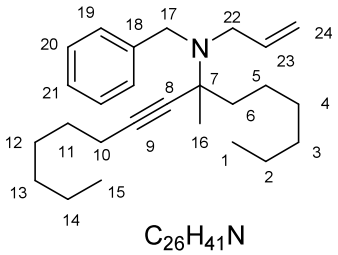
The obtained amid (3.94 g, 24.44 mmol) was dissolved in 30 mL anhydrous Et_2O was added dropwise to a suspension of $LiAlH_4$ (2.78 g, 73.3 mmol) in 60 mL anhydrous Et_2O at 0 °C. After 3 hours the reaction had reached complete conversion and the mixture was quenched with 20 mL of wet EtOAc and 20 mL of wet MeOH. Filtration through a pad of Celite was followed by purification by flash column chromatography. The title compound was isolated as a clear colorless oil in 80% yield (2.84 g, 19.29 mmol).



$C_{10}H_{13}N$
147.22 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.18 (t, *J* = 7.7 Hz, 2H, H-3), 6.69 (d, *J* = 7.7 Hz, 1H, H-4), 6.61 (t, *J* = 7.7 Hz, 2H, H-2), 5.84 (m, 1H, H-8), 5.09-4.97 (m, 2H, H-9), 3.14 (t, *J* = 7.1 Hz, 2H, H-5), 2.17 (q, *J* = 7.1 Hz, 2H, H-6), 1.72 (m, 1H, H-7).

_N_-allyl-_N_-benzyl-7-methylpentadec-8-in-7-amine 190a

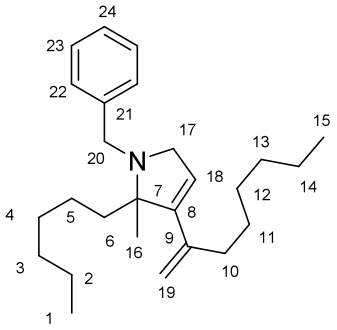


$C_{26}H_{41}N$
367.61g/mol

Following the typical procedure described for hydroamination reactions, the reaction between benzyl allyl amine (500 mg, 3.40 mmol), octyne (936 mg, 8.49 mmol), 10 mol% catalyst **182** (169 mg, 0.34 mmol) and 10 mol% activator **183** (92.1 mg, 0.34 mmol) in 1 mL C_6D_6 afforded the desired product **190a** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.37-7.33 (m, 2H, H-20), 7.29-7.24 (m, 2H, H-19), 7.20-7.15 (m, 1H, H-21), 5.89 (ddt, *J* = 16.8 Hz, *J* = 10.1 Hz, *J* = 6.5 Hz, 1H, H-23), 4.99 (d, *J* = 17.2 Hz, 1H, H-24), 4.91 (d, *J* = 10.1 Hz, 1H, H-24), 3.81 (d, *J* = 15.1 Hz, 1H, H-17), 3.71 (d, *J* = 15.1 Hz, 1H, H-17), 3.23 (m, 2H, H-22), 2.20 (t, *J* = 6.8 Hz, 2H, H-10), 1.68-1.09 (series of m, 21H, H-2, H-3, H-4, H-5, H-6, H-11, H-12, H-13, H-14, H-16), 0.89 (m, 6H, H-1, H-15).

1-benzyl-2-hexyl-2-methyl-3-(oct-1-en-2-yl)-2,5-dihydro-1H-pyrrol 210a



$C_{26}H_{41}N$
367.61 g/mol

Following the typical procedure described for consecutive hydroamination-RCM reactions, **190a** (100 mg, 0.27 mmol) was treated with 10 mol% catalyst **HII** (17.1 mg, 27.2 µmol) in 14 mL toluene at 80 °C in the presence of *p*TSA (54.3 mg, 0.29 mmol). After chromatographic purification (SiO_2, pentane/Et_2O (1 vol% Et_3N), 100:1 → 40:1), the desired product **210a** (13.9 mg, 37.8 µmol) was afforded as a colorless oil in 57% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.36-7.19 (m, 5H, H-22, H-23, H-24), 5.77 (m, 1H, H-18), 5.11 (s, 1H, H-19), 4.91 (s, 1H, H-19), 3.89 (d, *J* = 13.4 Hz, 1H, H-20), 3.55 (d, *J* = 13.4 Hz, 1H, H-20), 3.46 (dd, *J* = 14.8 Hz, *J* = 2.8 Hz, 1H, H-17), 3.17 (dd, *J* = 14.8 Hz, *J* = 2.8 Hz, 1H, H-17), 2.30-2.18 (m, 2H, H-10), 1.81-1.08 (series of m, 21H, alkyl chain and C-16), 0.88 (m, 6H, H-1, H-15).

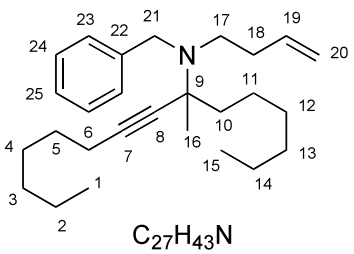
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 146.6 (C-8), 142.7 (C-9), 140.9 (C-21), 128.4, 128.2 (2 x C-22, 2 x C-23), 126.5 (C-18), 124.5 (C-24), 110.8 (C-19), 70.4 (C-7), 56.3 (C-17), 52.2 (C-20), 37.7 (C-6), 36.3 (C-10), 31.9 (C-3), 31.8 (C-13), 30.0 (C-4), 29.3 (C-12), 28.9 (C-11), 24.5 (C-5), 22.7, 22.6 (C-2, C-14), 21.4 (C-16), 14.1 (C-1, C-15).

IR (ATR): ν (cm^{-1}) = 3260 (br w), 3063 (w), 2957 (m), 2927 (s), 2856 (m), 1734 (m), 1688 (m), 1603 (w), 1533 (w), 1465 (m), 1380 (w), 1362 (w), 1268 (w), 714 (w), 698 (w).

LRMS-ESI: *m/z* (%) = 368 (70) [MH^+], 276 (100), 261 (80), 220 (40), 192 (70).

HRMS-ESI (MH^+, $C_{26}H_{42}N$) = calcd: 368.3317, found: 368.3308.

***N*-benzyl-*N*-(but-3-enyl)-7-methylpentadec-8-yn-7-amine 190b**

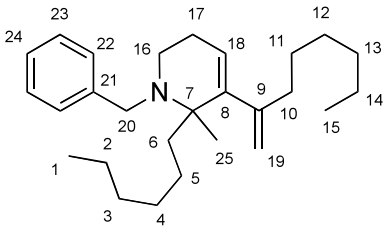


$C_{27}H_{43}N$
381.64 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between benzyl homoallyl amine (53 mg, 0.36 mmol), octyne (113.6 mg, 0.9 mmol), 10 mol% catalyst **182** (18 mg, 0.036 mmol) and 10 mol% activator **183** (10 mg, 0.036 mmol) in 1 mL C_6D_6 afforded the desired product **190b** as a light orange oil. The spectrospical data of the crude material are in full agreement with those described in the literature.[172]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.38 (m, 2H, H-23), 7.28 (m, 2H, H-24), 7.19 (m, 1H, H-25), 5.66 (m, 1H, H-19), 4.89 (m, 2H, H-20), 3.78 (m, 2H, H-21), 2.65 (m, 2H, H-17), 2.18 (t, *J* = 6.8 Hz, 2H, H-6), 2.07 (q, *J* = 7.5 Hz, 2H, H-18), 1.28 (s, 3H, H-16), 1.64-1.23 (series of m, 18H, H-2, H-3, H-4, H-5, H-10, H-11, H-12, H-13, H-14), 0.89 (m, 6H, H-1, H-15).

1-benzyl-2-hexyl-2-methyl-3-(oct-1-en-2-yl)-1,2,3,6-tetrahydropyridine 210b



$C_{27}H_{43}N$
381.64 g/mol

Following the typical procedure described for consecutive hydroamination-RCM reactions, **190b** (150 mg, 0.39 mmol) was treated with 2 mol% catalyst **GI** (9.71 mg, 11.8 µmol) in 20 mL CH_2Cl_2 at 40 °C in the presence of *p*TSA (78.5 mg, 0.41 mmol). After chromatographic purification (SiO_2, pentane/Et_2O (1 vol% Et_3N), 100:1 → 40:1), the desired product **210b** (59.7 mg, 157 µmol) was isolated as a colorless oil in 70% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.41-7.38 (m, 2H, H-21), 7.31-7.27 (m, 2H, H-22), 7.23-7.18 (m, 1H, H-23), 5.54 (m, 1H, H-18), 4.86 (m, 1H, H-19), 4.78 (d, *J* = 2.5 Hz, 1H, H-19), 3.95 (d, *J* = 13.8 Hz, 1H, H-20), 3.27 (d, *J* = 14.4 Hz, 1H, H-20), 2.61-2.45 (m, 2H, H-16), 2.23-2.07 (m, 3H, H-10, H-17), 1.91-1.81 (m, 1H, H-17), 1.67-1.15 (series of m, 18H, H-2, H-3, H-4, H-5, H-6, H-11, H-12, H-13, H-14), 1.20 (s, 3H, H-25), 0.92-0.82 (m, 6H, H-1, H-15).

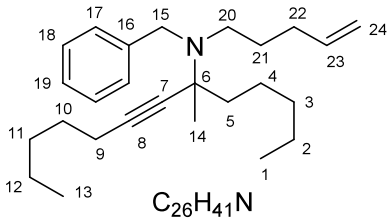
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 151.6 (C-8), 146.3 (C-9), 141.4 (C-21), 128.2 (4 x CH_{Ar}), 126.3 (C-24), 125.0 (C-18), 113.2 (C-19), 59.9 (C-7), 52.3 (C-20), 42.0 (C-16), 32.1 (C-10), 31.8 (C-3, C-13), 29.8 (C-6), 29.0 (C-11), 28.3 (C-4, C-12), 25.4 (C-17), 23.9 (C-5), 22.8, 22.7 (C-2, C-14), 20.2 (C-25), 14.1 (C-1, C-15).

IR (ATR): ν (cm^{-1}) = 3084 (w), 3063 (w), 3025 (w), 2954 (s), 2928 (s), 2871 (s), 2876 (s), 1744 (w), 1619 (w), 1494 (m), 1466 (m), 1378 (m), 1365 (m), 1028 (m), 900 (m), 730 (m), 697 (m).

LRMS-ESI: *m/z* (%) = 382 (10) [MH^+], 275 (100), 146 (20), 120 (100).

HRMS-ESI (MH^+, $C_{27}H_{44}N$) = calcd: 382.3474, found: 382.3459.

_N_-benzyl-6-methyl-_N_-(pent-4-enyl)tridec-7-yn-6-amine 190c

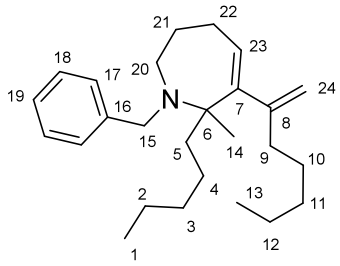


$C_{26}H_{41}N$
367.61 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between the corresponding amine (500 mg, 2.85 mmol), heptyne (686 mg, 7.13 mmol), 10 mol% catalyst **182** (142 mg, 0.29 mmol) and 10 mol% activator **183** (77.4 mg, 0.29 mmol) in 1 mL C_6D_6, afforded the desired product **190c** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.38-7.35 (m, 2H, H-18), 7.29-7.24 (m, 2H, H-17), 7.20-7.15 (m, 1H, H-19), 5.67 (ddt, *J* = 16.8 Hz, *J* = 10.2 Hz, *J* = 6.6 Hz, 1H, H-23), 4.88 (d, *J* = 17.2 Hz, 1H, H-24), 4.84 (d, *J* = 10.4 Hz, 1H, H-24), 3.79 (d, *J* = 15.4 Hz, 1H, H-15), 3.72 (d, *J* = 15.3 Hz, 1H, H-15), 2.57 (m, 2H, H-20), 2.17 (t, *J* = 7.1 Hz, 2H, H-9), 1.89 (m, 2H, H-22), 1.69-1.10 (series of m, 19H, H-2, H-3, H-4, H-5, H-10, H-11, H-12, H-14, H-21), 0.89 (m, 6H, H-1, H-13).

(_Z_)-1-benzyl-3-(hept-1-en-2-yl)-2-methyl-2-pentyl-2,5,6,7-tetrahydro-1H-azepine 210c



$C_{26}H_{41}N$
367.61 g/mol

Following the typical procedure described for consecutive hydroamination-RCM reactions, **190c** (100 mg, 0.25 mmol) was treated with 5 mol% catalyst **HII** (7.9 mg, 12.6 µmol) in 13 mL toluene at 80 °C in the presence of *p*TSA (50.5 mg, 0.27 mmol). After 6 h 5 mol% catalyst **HII** (7.9 mg, 12.6 µmol) were additionally added, and the reaction mixture was allowed to stir at 80 °C overnight. Analysis by ^{1}H-NMR spectroscopy indicated 50% conversion.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.38-7.35 (m, 2H, H-18), 7.31-7.27 (m, 2H, H-17), 7.22-7.17 (m, 1H, H-19), 5.43 (dd, *J* = 16.8 Hz, *J* = 10.2 Hz, 1H, H-23), 4.79 (m, 1H, H-24), 4.84 (d, *J* = 2.5 Hz, 1H, H-24), 3.86 (d, *J* = 14.4 Hz, 1H, H-15), 3.57 (d, *J* = 14.4 Hz, 1H, H-15), 2.95-2.86 (m, 1H, H-20), 2.80-2.72 (m, 1H, H-20), 2.63-2.53 (m, 1H, H-9), 2.10-2.04 (m, 2H, H-9, H-22), 1.63-1.24 (series of m, 17H, H-2, H-3, H-4, H-5, H-10, H-11, H-12, H-21, H-22), 1.23 (s, 3H-, H-14) 0.90 (m, 6H, H-1, H-13).

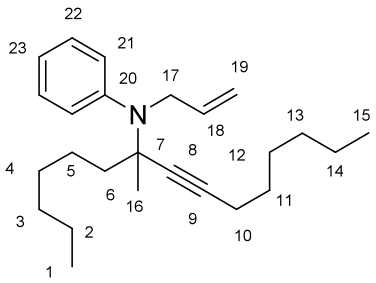
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 153.6 (C-7), 150.5 (C-8), 142.3 (C-16), 128.4 (2 x C-18), 128.1 (2 x C-17), 126.5 (C-19), 126.3 (C-23), 111.8 (C-24), 64.8 (C-6), 51.5 (C-15), 46.3 (C-20), 38.6 (C-9), 38.3 (C-5 and C-21), 32.7, 31.8 (C-3, C-11), 27.7 (C-10), 26.3

(C-22), 22.9, 22.6 (C-2, C-12), 22.6 (C-14), 22.6 (C-4), 14.2, 14.1 (C-1, C-13).

IR (ATR): ν (cm^{-1}) = 3083 (w), 3064 (w), 2954 (s), 2929 (s), 2870 (m), 2857 (m), 1738 (w), 1620 (w), 1494 (m), 1465 (m), 1453 (m), 1377 (m), 895 (m), 731 (m), 698 (m).

HRMS-ESI (MH^+, $C_{26}H_{42}N$) = calcd: 368.3317, found: 368.3301.

N-allyl-*N*-(7-methylpentadec-8-yn-7-yl)aniline 190d

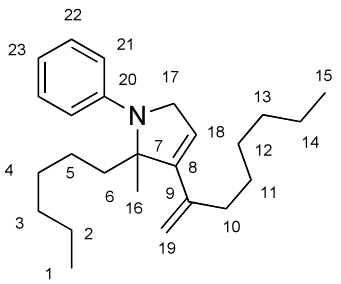


$C_{25}H_{39}N$
353.58 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between allyl aniline (500 mg, 3.75 mmol), octyne (1.03 mg, 9.39 mmol), 10 mol% catalyst **182** (187 mg, 0.38 mmol) and 10 mol% activator **183** (102 mg, 0.38 mmol) in 1 mL C_6D_6 afforded the desired product **210d** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.32-7.28 (m, 2H, H-21), 7.25-7.21 (m, 2H, H-22), 7.13-7.07 (m, 1H, H-23), 5.72 (ddt, *J* = 17.0 Hz, *J* = 10.4 Hz, *J* = 6.0 Hz, 1H, H-18), 5.01 (dd, *J* = 17.4 Hz, *J* = 1.6 Hz, 1H, H-19), 4.88 (dd, *J* = 10.4 Hz, *J* = 1.2 Hz, 1H, H-19), 3.85-3.73 (m, 2H, H-17), 2.24 (t, *J* = 6.9 Hz, 2H, H-10), 1.62-1.10 (series of m, 19H, H-2, H-3, H-4, H-5, H-6, H-11, H-12, H-13, H-14, H-16), 0.92-0.85 (m, 6H, H-1, H-15), 0.87 (t, *J* = 7.3 Hz, 3H).

2-hexyl-2-methyl-3-(oct-1-en-2-yl)-1-phenyl-2,5-dihydro-1H-pyrrol 210d



$C_{25}H_{39}N$
353.58 g/mol

Following the typical procedure described for consecutive hydroamination-RCM reactions, **190d** (300 mg, 0.85 mmol) was treated with 3 mol% catalyst **GI** (20.9 mg, 25.5 µmol) in 43 mL CH_2Cl_2 at 40 °C. After chromatographic purification (SiO_2, pentane/Et_2O (1 vol% Et_3N), 100:1 → 40:1), the desired product **210d** (60.2 mg, 169 µmol) was afforded as a colorless oil in 60% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.26-7.19 (m, 2H, H-22), 6.77-6.73 (m, 2H, H-21), 6.8-6.62 (m, 1H, H-23), 5.87 (t, *J* = 2.2 Hz, 1H, H-18), 5.12 (m, 1H, H-19), 5.04 (m, 1H, H-19), 4.14 (dd, *J* = 15.0 Hz, *J* = 2.2 Hz 1H, H-17), 4.05 (dd,

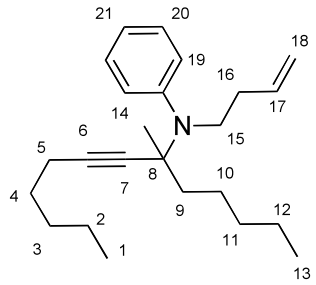
J = 15.0 Hz, *J* = 2.2 Hz, 1H, H-17), 2.39 (m, 1H, H-6), 2.26 (m, 2H, H-10), 1.85 (m, 1H, H-6), 1.67 (s, 3H, H-16), 1.51-1.46 (m, 2H, H-11) 1.38-1.09 (series of m, 12H, H-2, H-3, H-4, H-12, H-13, H-14), 1.06-0.96 (m, 2H, H-5), 0.90 (m, 3H, CH_3), 0.79 (t, *J* = 6.7 Hz, 3H, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 146.5 (C-20), 145.3 (C-8), 142.0 (C-9), 128.9 (2 x C-22), 121.5 (C-18), 115.0 (C-23), 112.9 (C-19), 112.5 (2 x C-21), 71.8 (C-7), 55.0 (C-17), 36.8 (C-10), 36.3 (C-6), 31.8, 31.7 (C-3, C-13), 29.3, 29.28 (C-4, C-12), 28.8 (C-11), 24.6 (C-16), 24.0 (C-5), 22.7, 22.6 (C-2, C-14), 14.1, 14.0 (C-1, C-15).

IR (ATR): ν (cm^{-1}) = 3105 (w), 3060 (w), 2955 (s), 2925 (s), 2855 (m), 1701 (w), 1597 (m), 1504 (s), 1467 (m), 1358 (m), 1344 (m), 1187 (w), 897 (w), 744 (m), 692 (m).

HRMS-ESI (MH^+, $C_{25}H_{40}N$) = calcd: 354.3160, found: 354.3153.

N-(but-3-enyl)-*N*-(6-methyltridec-7-yn-6-yl)aniline 190e



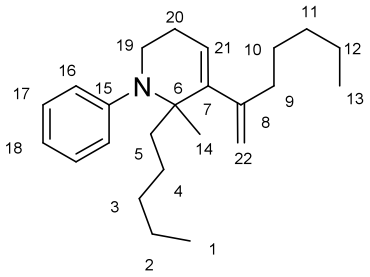
$C_{24}H_{37}N$
339.56 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between homoallyl aniline (200 mg, 1.36 mmol), heptyne (327 mg, 3.40 mmol), 10 mol% catalyst **182** (67.70 mg, 0.14 mmol) and 10 mol% activator **183** (36.90 mg, 0.14 mmol) in 0.5 mL C_6D_6 afforded the desired product **190e** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.36-7.09 (m, 5H, H-19, H-20, H-21), 5.79 (ddt, *J* = 17.0 Hz, *J* = 10.4 Hz, *J* = 6.5 Hz, 1H, H-17), 4.98-4.89 (m, 2H, H-18), 3.16 (t, *J* = 7.3 Hz, 2H, H-15), 2.23 (t, *J* = 6.9 Hz, 2H, H-5), 1.97 (m, 2H, H-16), 1.15 (s, 3H, H-14), 1.59-1.09 (series of m, 14H, H-2, H-3, H-4, H-9, H-10. H-11, H-12), 0.89 (m, 6H, H-13, H-1).

3-(hept-1-en-2-yl)-2-methyl-2-pentyl-1-phenyl-1,2,5,6-tetrahydropyridine 210e

Following the typical procedure described for consecutive hydroamination-RCM reactions, **190e** (100 mg, 0.29 mmol) was treated with 3 mol% catalyst **GI** (7.28 mg, 8.84 µmol) in 15 mL CH_2Cl_2 at 40 °C. After chromatographic purification (SiO_2, pentane/Et_2O (1 vol% Et_3N) 100:1 → 40:1), the desired product **210e** (65 mg, 19 µmol) was isolated as a colourles oil in 65% yield.



$C_{24}H_{37}N$
339.56 g/mol

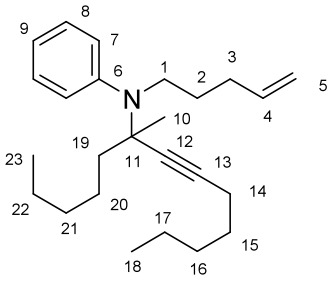
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.25-7.21 (m, 2H, H-17), 7.19-7.15 (m, 2H, H-16), 7.07-7.02 (m, 1H, H-8), 5.62 (dd, *J* = 5.1 Hz, *J* = 3.3 Hz, 1H, H-21), 4.88 (m, 1H, H-22), 4.81 (s, 1H, H-22), 3.33-3.26 (m, 1H, H-19), 3.22-3.16 (m, 1H, H-19), 2.16 (m, 2H, H-20), 2.10-2.01 (m, 1H, H-9), 1.70-1.10 (series of m, 14H, H-2, H-3, H-4, H-5, H-10. H-11, H-12), 1.07 (s, 3H, H-14), 0.88 (m, 6H, H-1, H-13).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 151.3 (C-7) 150.9 (C-8), 147.2 (C-15), 128.0 (2 x C-17), 127.5 (2 x C-16), 124.9 (C-21), 123.5 (C-18), 113.3 (C-22), 60.6 (C-6), 46.7 (C-19), 39.1 (C-5), 38.2 (C-9), 32.1 (C-11), 31.6 (C-3), 28.0 (C-10), 25.1 (C-20), 23.5 (C-4), 23.1 (C-14), 22.8 (C-12), 22.6 (C-2), 14.2 (C-13), 14.1 (C-1).

IR (ATR): ν (cm^{-1}) = 3079 (w), 3057 (w), 2954 (s), 2928 (s), 2871 (m),2858 (m),1734 (w), 1596 (m), 1491 (s), 1466 (m), 1457 (m), 1376 (m), 1029 (m), 899 (m), 768 (m), 701 (s).

HRMS-ESI (MH^+, $C_{24}H_{38}N$) = calcd: 340.3004, found 340.2990.

N-(6-methyltridec-7-yn-6-yl)-*N*-(pent-4-enyl)aniline 190f



$C_{25}H_{39}N$
353.58 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between the corresponding aniline (60 mg, 0.37 mmol), heptyne (89.50 mg, 0.93 mmol), 10 mol% catalyst **182** (18.50 mg, 0.04 mmol) and 10 mol% activator **183** (10.1 mg, 0.04 mmol) in 0.5 mL C_6D_6 afforded the desired product **190f** as a light orange oil.

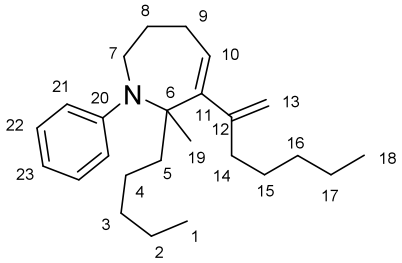
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.34-7.10 (m, 5H, C-7, C-8, C-9), 5.75 (m, 1H, H-4), 5.04-4.86 (m, 2H, H-5), 3.11 (m, 2H, H-1), 2.38-1.11 (series of m, 16H, H-2, H-3, H-14, H-15, H-16, H-17, H-19, H-20, H-21, H-22), 0.90 (m, 6H, C-18, C-23).

3-(hept-1-en-2-yl)-2-methyl-2-pentyl-1-phenyl-2,5,6,7-tetrahydro-1H-azepin 210f

Procedure A: Following the typical procedure described for consecutive hydroamination-RCM reactions, **190f** (10 mg, 0.028 mmol) was reacted with 10 mol% catalyst **HII** (1.77 mg,

2.83 µmol) in 1.40 mL toluene at 80 °C. ^{1}H-NMR of the crude product showed 50% conversion.

Procedure B: Following the typical procedure described for consecutive hydroamination-RCM reactions, **190f** (38 mg, 0.11 mmol) was treated with 10 mol % catalyst **GII** in three portions (6.45 mg, 11 µmol) in 6 mL toluene at 80 °C for 6 h. ^{1}H-NMR of the crude material showed complete conversion, and after chromatographic purification (SiO_2, pentane) the desired product **210f** (23 mg, 65.05 µmol) was isolated as a colorless oil in 60% yield.



$C_{25}H_{39}N$
353.58 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.19-7.12 (m, 4H, H-21, H-22), 6.87 (m, 1H, H-23), 5.45 (m, 1H, H-10), 4.82 (m, 1H, H-19), 4.79 (d, *J* = 2.3 Hz, 1H, H-19), 3.65-3.49 (m, 2H, H-7), 2.32 (m, 1H, H-9), 2.16 (m, 3H, H-9, H-10), 1.96 (m, 1H, H-8), 1.68-1.08 (series of m, 15H, H-2, H-3, H-4, H-5, H-8, H-14, H-15, H-16, H-17), 1.28 (s, 3H, H-19), 0.91, 0.83 (2 x t, *J* = 7.0 Hz, 3H, C-1, C-18).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 153.9 (C-20), 152.4 (C-11), 151.6 (C-12), 128.0 (2 x C-22), 127.5 (C-10), 125.4 (2 x C-21), 120.9 (C-23), 112.5 (C-13), 63.2 (C-6), 52.2 (C-7), 38.6 (C-10), 38.2 (C-8), 32.5, 31.7, 27.8 (C-3, C-5, C-15, C-16), 26.8 (C-9), 24.9 (C-19), 22.8, 22.7, 22.7 (C-2, C-4, C-17), 14.2 (C-1, C-18).

IR (ATR): ν (cm^{-1}) = 3071 (w), 2954 (s), 2929 (s), 2871 (m), 2857 (m), 1596 (m), 1491 (s), 1465 (m), 1458 (m), 1378 (w), 1260 (w), 1177 (w), 1028 (w), 894 (m), 758 (m), 702 (s).

LRMS-ESI: *m/z* (%) = 3.54 (10) [MH^+], 261 (80), 146 (100).

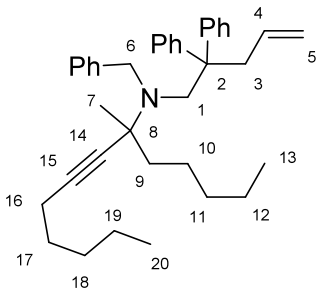
HRMS-ESI (MH^+,$C_{25}H_{40}N$) = calcd: 354.3161, found: 354.3150.

N-benzyl-*N*-(2,2-diphenylpent-4-enyl)-6-methyltridec-7-yn-6-amine 190g

Following the typical procedure described for hydroamination reactions, the reaction between the corresponding amine (100 mg, 0.3 mmol), heptyne (73 mg, 0.76 mmol), 10 mol% catalyst **182** (15 mg, 0.03 mmol) and 10 mol% activator **183** (8 mg, 0.03 mmol) in 1 mL C_6D_6 afforded the desired product **190g** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.28-7.05 (m, 15H, CH_{Ar}), 5.45 (ddt, *J* = 17.0 Hz, *J* = 10.5 Hz, *J* = 6.6 Hz, 1H, H-4), 4.83-4.75 (m, 2H, H-5), 3.75 (d, *J* = 17.8 Hz, 1H, H-6), 3.64

(d, *J* = 17.8 Hz, 1H, H-6), 3.56 (d, *J* = 13.7 Hz, 1H, H-1), 3.47 (d, *J* = 13.7 Hz, 1H, H-1), 3.03 (t, *J* = 7.4 Hz, 2H, H-3), 2.16 (m, 2H, H-16), 1.79-0.97 (series of m, 14H, H-9, H-10, H-11, H-12, H-17, H-18, H-19), 0.95 (s, 3H, H-7), 0.92, 0.82 (2 x t, *J* = 7.0 Hz, 6H, H-13, H-20).



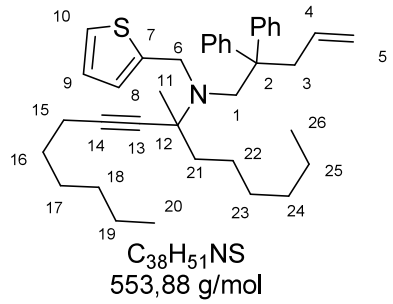
$C_{38}H_{49}N$
519.8 g/mol

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 148.0 (C_q), 147.8 (C_q), 144.0 (C_q), 135.7 (C-4), 128.9 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 127.4 (2 x CH_{Ar}), 127.4 (2 x CH_{Ar}), 127.3 (2 x CH_{Ar}), 126.9 (2 x CH_{Ar}), 125.6 (2 x CH_{Ar}), 125.3 (CH_{Ar}), 116.8 (C-5), 83.3 (C-15), 83.2 (C-14), 61.7 (C-1), 61.5 (C-8), 57.5 (C-6), 50.8 (C-2), 40.8 (C-3), 40.4 (C-9), 32.2 (C-11), 31.1 (C-18), 28.8 (C-17), 26.0 (C-7), 25.1 (C-12), 22.6 (C-19), 22.3 (C-10), 18.7 (C-16), 14.1, 14.0 (C-13, C-20).

IR (ATR): ν (cm^{-1}) = 3085 (w), 3059 (w), 3025 (w), 2956 (s), 2929 (s), 2871 (m), 2858 (m), 1602 (w), 1494 (m), 1450 (m), 1444 (m), 1377 (w), 755 (m), 729 (m), 698 (s).

HRMS (MH^+, $C_{38}H_{50}N$) = calcd: 520.3943, found: 520.3921.

N-(2,2-diphenylpent-4-enyl)-7-methyl-*N*-(thiophen-2-ylmethyl)pentadec-8-yn-7-amine 190h



$C_{38}H_{51}NS$
553,88 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between the corresponding amine (500 mg, 1.50 mmol), octyne (413 mg, 3.75 mmol), 10 mol% catalyst **182** (74.7 mg, 0.15 mmol) and 10 mol% activator **183** (40.7 mg, 0.15 mmol) in 1 mL C_6D_6 afforded the desired product **190h** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.26-7.08 (m, 11H, 10 x CH_{Ar}, H-10), 6.85 (m, 1H, H-9), 6.72 (m, 1H, H-8), 5.46 (ddt, *J* = 16.9 Hz, *J* = 10.2 Hz, *J* = 6.4 Hz, 1H, H-4), 4.88 (d, *J* = 17.4 Hz, 1H, H-5), 4.83 (d, *J* = 10.6 Hz, 1H, H-5), 3.82 (d, *J* = 17.6 Hz, 1H, H-6), 3.69 (d, *J* = 17.7 Hz, 1H, H-6), 3.54 (d, *J* = 14.0 Hz, 1H, H-1), 3.44 (d, *J* = 14.0 Hz, 1H, H-1), 3.24-3.07 (m, 2H, H-3), 2.18 (t, *J* = 6.9 Hz, 2H, H-15), 1.55 (s, 3H, H-11), 1.52-0.94 (series of m, 18H, H-16, H-17, H-18, H-19, H-21, H-22, H-23, H-24, H-25), 0.93-0.82 (m, 6H, H-20, H-26).

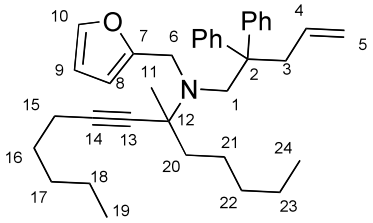
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 148.4 (C-7), 147.7 (C_{qAr}), 147.6 (C_{qAr}), 135.8 (C-4),

129.0 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 127.6 (2 x CH_{Ar}), 127.5 (2 x CH_{Ar}), 127.5 (CH_{Ar}), 125.9 (C-9), 125.7 (CH_{Ar}), 123.1 (C-8), 122.6 (C-10), 116.9 (C-5), 83.6 (C-14), 83.2 (C-13), 61.4 (C-12), 61.1 (C-1), 52.4 (C-6), 50.8 (C-2), 40.9 (C-3), 40.5 (C-21), 31.8 (C-24), 31.4 (C-18), 29.6 (C-16), 29.1 (C-23), 28.6 (C-17), 25.9 (C-11), 25.2 (C-22), 22.6 (C-19, C-25), 18.7 (C-15), 14.1 (C-20, C-26).

IR (ATR): ν (cm^{-1}) = 3086 (w), 3058 (w), 3021 (w), 2955 (s), 2927 (s), 2871 (s), 2856 (s), 1637 (w), 1600 (w), 1496 (m), 1457 (m), 1444 (m), 1377 (w), 915 (w), 755, 698 (s).

HRMS-ESI (MH^+, $C_{38}H_{52}NS$) = calcd: 554.3820, found: 554.3812.

***N*-(2,2-diphenylpent-4-enyl)-*N*-(furan-2-ylmethyl)-6-methyltridec-7-yn-6-amine 190i**



$C_{38}H_{51}NO$
537.82 g/mol

Following the typical procedure described for hydroamination reactions, the reaction between the corresponding amine (60 mg, 0.37 mmol), heptyne (89.50 mg, 0.93 mmol), 10 mol% catalyst **182** (18.50 mg, 37 µmol) and 10 mol% activator **183** (10 mg, 37 µmol) in 0.5 mL C_6D_6 afforded the desired product **190i** as a light orange oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.26-7.11 (m, 11H, H-10, 10 x CH_{Ar}), 6.24 (m, 1H, H-8), 6.04 (m, 1H, H-9), 5.52 (ddt, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, 1H, H-4), 4.85 (m, 2H, H-5), 3.54 (m, 2H, H-6), 3.33 (m, 2H, H-1), 3.14 (d, *J* = 6.4 Hz, 2H, H-3), 2.15 (t, *J* = 6.7 Hz, 2H, H-15), 1.50-1.05 (series of m, 14H, H-16, H-17, H-18, H-20, H-21. H-22, H-23), 0.93 (s, 3H, H-11), 0.91, 0.86 (t, *J* = 7.2 Hz, 3H, C-19, C-24).

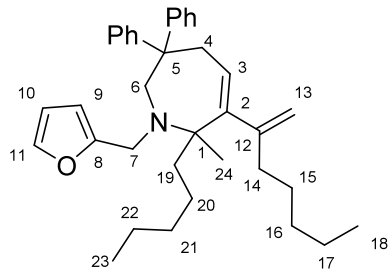
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 156.0 (C_{qAr}), 147.6 (C_{qAr}), 147.5 (C_{qAr}), 140.2 (CH_{Ar}), 136.0 (C-4), 129.1 (2 x CH_{Ar}), 129.0 (2 x CH_{Ar}), 127.4 (4 x CH_{Ar}), 125.7 (CH_{Ar}), 125.7 (CH_{Ar}), 116.8 (C-5), 109.9 (C-8), 107.1 (C-9), 83.7 (C-14), 83.2 (C-13), 60.2 (C-12), 59.7 (C-6), 51.0 (C-2), 48.2 (C-1), 41.2 (C-3), 40.3 (C-20), 32.2 (C-23), 31.1 (C-17), 28.8 (C-16), 25.6 (C-11), 24.6 (C-24), 22.6 (C-18), 22.2 (C-21), 18.7 (C-15), 14.0 (C-19, C-25).

IR (ATR): ν (cm^{-1}) = 3087 (w), 3058 (w), 3021 (w), 2956 (s), 2929 (s), 2858 (m), 1599 (w), 1496 (m), 1466 (m), 1444 (m), 1377 (w), 1148 (m), 1012 (m), 912 (m), 755 (m), 727 (m), 699 (s).

LRMS-ESI: *m/z* (%) = 510.37 (50) [MH^+], 469.33 (100), 396.25 (50), 290.25 (60).

HRMS (MH^+, $C_{36}H_{48}NO$) = calcd: 510.3736, found: 510.3724.

(*Z*)-1-(furan-2-ylmethyl)-2-pentyl-2-methyl-3-(hept-1-en-2-yl)-6,6-diphenyl-2,5,6,7–tetra-hydro-1H-azepine 210i



Following the typical procedure described for consecutive hydroamination-RCM reactions, **190i** (100 mg, 196 µmol) was reacted with 10 mol% catalyst **HII** (12.3 mg, 19.6 µmol) in 10 mL toluene at 80 °C. After chromatographic purification (SiO_2, pentane/Et_2O (1 vol% Et_3N), 100:1 → 40:1), the desired product **210i** (15 mg, 29.4 µmol) was afforded as a colourles oil in 15% yield.[32]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.26-7.00 (m, 11H, H-11, CH_{Ar}), 6.02 (s, 1H, H-10), 5.78 (s, 1H, H-9), 5.33 (dd, *J* = 8.5 Hz, *J* = 6.2 Hz, 1H, H-3), 4.77 (s, 1H, H-13), 4.55 (s, 1H, H-13), 3.85-3.66 (m, 3H, H-4, H-6, H-7), 3.54 (m, 2H, H-6, H-7), 2.51 (m, 1H, H-4), 2.00 (m, 2H, H-14), 1.83-1.10 (series of m, 14H, H-15, H-16, H-17, H-19, H-20, H-21, H-22), 1.55 (s, 3H, H-24), 0.86-0.83 (m, 6H, H-18, H-23).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 154.9 (C_q), 152.8 (C_q), 149.7 (C_q), 148.5 (C_q), 141.1 (C-11), 127.8 (2 x CH_{Ar}), 127.8 (2 x CH_{Ar}), 127.5 (2 x CH_{Ar}), 127.4 (2 x CH_{Ar}), 125.8 (C-3), 125.5 (CH_{Ar}), 125.1 (CH_{Ar}), 113.0 (C-13), 110.0 (C-9), 107.4 (C-10), 68.0 (C-5), 59.5 (C-6), 52.3 (C-1), 46.4 (C-7), 38.7 (C-14,C-24), 34.7 (C-4), 32.4 (C-16, C-21), 31.6 (C-19), 27.8 (C-15), 23.1 (C-20), 22.8, 22.5 (C-17, C-22), 14.3, 14.12 (C-18, C-23).

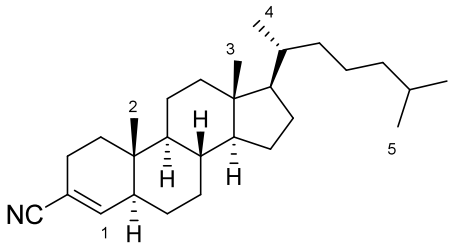
IR (ATR): ν (cm^{-1}) = 3086 (w), 3057 (w), 3022 (w), 2954 (s), 2931 (s), 2870 (m), 2859 (m), 1756 (w), 1599 (m), 1494 (m), 1466 (m), 1445 (m), 1378 (m), 1149 (m), 1011 (m), 899 (m), 727 (m), 698 (s).

LRMS-ESI: *m/z* (%) = 510.37 (70) [MH^+], 302.15 (100), 167.08 (55).

HRMS (MH^+, $C_{36}H_{48}NO$) = calcd: 510.3736, found: 510.3727.

[32] 100% conversion was indicated via ^{1}H-NMR spectroscopy. After the first purification 50 mg (50%) of almost clean product was obtained. **210i** seems to decompose in SiO_2 and Al_2O_3, and only 15 mg were isolated after 3 purifications on column chromatography and subsequent purification on a preparative Al_2O_3-TLC plate.

(5*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,5,6,7,8,9,10, 11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[α] phenanthrene-3-carbonitrile 198



$C_{28}H_{45}N$
395.66 g/mol

A solution of the starting material **197** (486 mg, 1.257 mol) and zinc iodide (15 mg, 0.047 mmol) in CH_2Cl_2 (3 mL) was treated at rt with trimethylsilyl cyanide (400 μL, 0.051 mol). The mixture was heated at reflux for 1 h, cooled to rt, and trimethylsilyl cyanide (150 μL, 0.019 mol) was added continuing heating at reflux for further 2 h. After cooling to rt, the solution was quenched with 12 M HCl (0.5 mL) and was heated to reflux for 2 h. Additional CH_2Cl_2 (5 mL) and water (5 mL) were added, and the heating was continued for a further hour. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated. The crude material, in form of a white solid, was used without further purification.

A solution of the obtained cholestane derivate (890 mg, 2.15 mmol) in pyridine (6 mL) was treated with phosphorus oxychloride (0.8 mL, 8.58 mmol) and heated at reflux overnight. The reaction was then cooled to rt and quenched with 6 M HCl (1 mL). The solution was then treated with EtOAc (20 mL) and water (20 mL), and the biphasic mixture was stirred vigorously for 5 min. The aqueous layer was separated and extracted with EtOAc (2 x 20 mL). The organic phases were combined, washed with brine and evaporated. The desired compound **198** (747 mg, 88%) was obtained as a colorless oil which solidifies at rt.

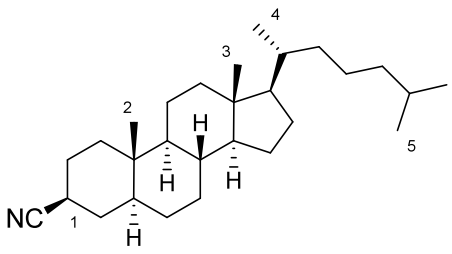
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 6.54 (m, 1H, H-1), 2.19-0.94 (steroid skeleton), 0.89 (d, *J* = 6.5 Hz, 3H, H-4), 0.86 (dd, *J* = 6.6 Hz, *J* = 1.8 Hz, 6H, H-5), 0.74 (s, 3H, H-2), 0.65 (s, 3H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 144.3 (CH), 119.5 (C_q), 111.1 (C_q), 56.3 (CH), 56.3 (CH), 53.5 (CH), 42.4 (C_q), 40.8 (CH), 40.3 (CH_2), 39.8 (CH_2), 39.5 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.5 (CH), 34.1 (C_q), 31.4 (CH_2), 31.1 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 28.0 (CH), 24.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.0 (CH_2), 18.7 (CH_3), 12.0 (CH_2), 11.9 (CH_3).

IR (ATR): ν (cm^{-1}) = 2930 (s), 2867 (m), 2849 (m), 2216 (w), 1739 (w), 1635 (w), 1468 (w), 1457 (w), 1386 (w), 1043 (w).

HRMS-ESI (MH^+, $C_{28}H_{46}N$) = calcd: 396.3630, found: 396.3637.

(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-hexadeca hydro-1H-cyclopenta[α]phenanthrene-3-carbonitrile 199



$C_{28}H_{47}N$
397.68 g/mol

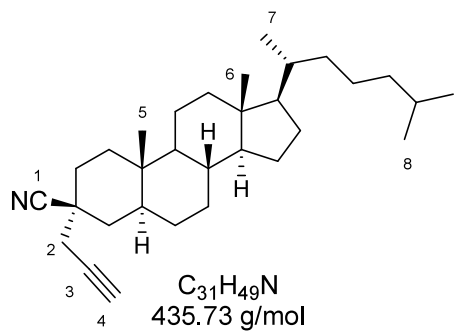
Following the standard hydrogenation procedure described earlier in Section 5.2.1, a solution of cholestane derivate **198** (450 mg, 1.25 mmol) in a 1:1 CH_2Cl_2/MeOH mixture (20 mL) with 1% AcOH and 60 mg 10% Pd/C was hydrogenated at rt and 20 bar H_2 pressure over 24 h. After usual work up the product **199** (440 mg, 97%) was isolated as a colorless oil which solidifies at rt.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 2.41 (m, 1H, H-1), 1.99-0.94 (steroid skeleton), 0.89 (d, *J* = 6.7 Hz, 3H, H-4), 0.85 (dd, *J* = 6.6 Hz, *J* = 1.8 Hz, 6H, H-5), 0.81 (s, 3H, H-2), 0.64 (s, 3H, H-3).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 122.9 (C_q), 56.4 (CH), 56.2 (CH), 54.1 (CH), 45.8 (CH), 42.5 (C_q), 39.9 (CH_2), 39.5 (CH_2), 37.3 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.5 (C_q), 35.3 (CH), 31.9 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 28.5 (CH), 28.3 (CH_2), 28.2 (CH_2), 28.0 (CH), 25.7 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.6 (CH_3), 20.8 (CH_2), 18.7 (CH_3), 12.1 (CH_3), 12.1 (CH_3).

IR (ATR): ν (cm^{-1}) = 2936 (s), 2866 (m), 2850 (m), 2237 (w), 1736 (w), 1464 (m), 1444 (m), 1383 (m), 1374 (m), 1366 (m).

(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-3-(prop-2-ynyl)-hexadecahydro-1H-cyclopenta[α]phenanthrene-3-carbonitrile 200



$C_{31}H_{49}N$
435.73 g/mol

DIPA (0.42 mL, 2.99 mmol) was dissolved in THF (6 mL) and BuLi (1.18 mL of a 2.5 M solution in hexane) was slowly added at -78 °C. The solution was warmed up to rt for 30 min and then cooled again to -78°C. A solution of carbonitrile **199** (360 mg, 0.91 mmol) in THF (35 mL) was then added maintaining the temperature below -70 °C, and after 30 min propargyl bromide (445 mg, 3.74 mmol) was likewise added. The reaction mixture was stirred overnight and warmed up to rt during this time. Aqueous sat. solution of $NaHCO_3$ was then added and the layers were

separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried (Mg_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/EtOAc 1:1) to yield 310 mg (0.71 mmol, 78%) of alkyne derivate **200** as a white solid.

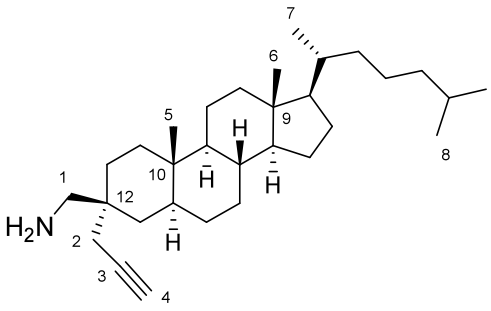
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 2.48 (d, *J* = 2.4 Hz, 2H, H-2), 2.17 (t, *J* = 2.4 Hz, 1H, H-4), 2.00-0.77 (steroid skeleton), 0.89 (d, *J* = 6.4 Hz, 3H, H-7), 0.86 (dd, *J* = 6.5 Hz, *J* = 1.8 Hz, 6H, H-8), 0.76 (s, 3H, H-5), 0.64 (s, 3H, H-6).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 123.2 (C-1), 78.2 (C-3), 72.4 (C-4), 56.3 (CH), 56.2 (CH), 53.7 (CH), 43.1 (CH), 42.6 (C_q), 39.9 (CH_2), 39.5 (CH_2), 39.2 (C_q), 36.6 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.7 (C_q), 35.4 (CH), 35.3 (CH_2), 31.6 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 28.1 (CH), 24.2 (CH_3), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 21.0 (CH_2), 18.7 (CH_3), 12.1 (CH_3), 12.0 (CH_3).

IR (ATR): ν (cm^{-1}) = 3284 (m), 3267 (m), 2926 (s), 2866 (s), 2851 (s), 2235 (w), 1467 (m), 1446 (m), 1385 (m), 689 (m).

HRMS-ESI (MH^+, $C_{31}H_{50}N$): calcd: 436.3943, found: 436.3953.

((3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-3-(prop-2-ynyl)-hexadecahydro-1H-cyclopenta[α]phenanthren-3-yl)methanamine 201



$C_{31}H_{53}N$
439.76 g/mol

Carbonitrile **200** (250 mg, 0.573 mmol) was dissolved in anhydrous Et_2O (8 mL) and added to a suspension of $LiAlH_4$ (87 mg, 2.29 mmol) in Et_2O (3 mL). The reaction mixture was stirred overnight at rt, quenched with wet MeOH, filtrated over Celite several times, and concentrated. The crude material was dissolved in CH_2Cl_2, filtrated again over Celite and concentrated under reduced pressure. Amine **201** was obtanied as white solid and used without further purification.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 2.73 (m, 2H, H-1), 2.08 (d, *J* = 2.5 Hz, 2H, H-2), 1.97 (t, *J* = 2.5 Hz, 1H, H-4), 1.96-0.96 (steroid skeleton), 0.89 (d, *J* = 6.5 Hz, 3H, H-7), 0.86 (dd, *J* = 6.5 Hz, *J* = 1.6 Hz, 6H, H-8), 0.77 (s, 3H, H-5), 0.64 (s, 3H, H-6).

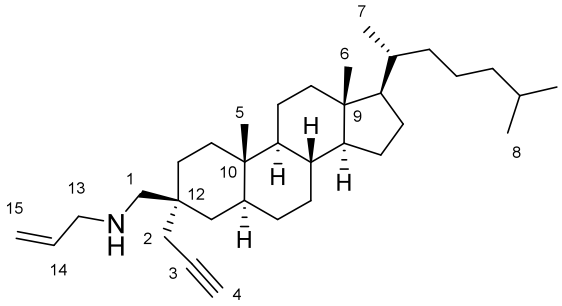
^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 82.1 (C-3), 70.1 (C-4), 56.6 (CH), 56.3 (CH), 54.6

(CH), 45.03 (C-1), 42.6 (C-9), 41.4 (C-11), 40.1 (CH_2), 39.5 (CH_2), 37.83 (C-10), 36.2 (CH_2), 36.1 (C-12), 35.8 (CH), 35.6 (CH), 35.3 (CH_2), 34.2 (CH_2), 32.1 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.2 (CH_2), 23.9 (CH_2), 22.8 (C-8), 22.5 (C-8), 21.0 (CH_2), 18.7 (C-7), 12.1 (C-6), 11.7 (C-5).

IR (ATR): ν (cm^{-1}) = 3309 (w), 2929 (s), 2867 (s), 2114 (w), 1718 (m), 1667 (m), 1466 (m), 1324 (s), 1260 (m), 1128 (m), 1064 (m), 749 (m).

HRMS-ESI (MH^+, $C_{31}H_{54}N$) = calcd: 440.4256, found: 440.4218.

_N_-(((3_S_,5_S_,8_R_,9_S_,10_S_,13_R_,14_S_,17_R_)-10,13-dimethyl-17-((_R_)-6-methylheptan-2-yl)-3-(prop-2-ynyl)-hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)methyl)prop-2-en-1-amine 202



$C_{34}H_{57}N$
479.82 g/mol

Amine **201** (50 mg, 0.11 mmol) was dissolved in DMF (1 mL) and allyl bromide (10 µL, 0.11 mmol) and K_2CO_3 (47 mg, 0.33 mmol) were added under N_2 atmosphere. The mixture was heatd at 50 °C during 48 h. After concentration, purification by column chromatography (SiO_2, pentane → pentane/ Et_2O 10:3) gave the desired compound **202** (8 mg, 15%) as a yellowish clear oil.

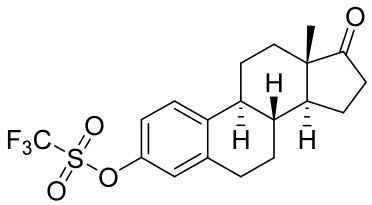
^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 5.84 (m, 1H, H-14), 5.15-5.09 (m, 2H, H-15), 3.15 (m, 2H, H-1), 2.50 (m, 2H, H-13), 2.15 (d, *J* = 2.7 Hz, 2H, H-2), 1.96 (m, 1H, H-4), 1.85-0.95 (steroid skeleton), 0.90 (d, *J* = 6.2 Hz, 3H, H-7), 0.86 (dd, *J* = 6.6 Hz, *J* = 1.6 Hz, 6H, H-8), 0.76 (s, 3H, H-5), 0.64 (s, 3H, H-6).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 136.1 (C-14), 116.8 (C-15), 83.2 (C-3), 70.0 (C-4), 58.6 (CH_2), 56.7 (CH_2), 56.7 (CH), 56.4 (CH), 54.7 (CH), 42.6 (C_q), 41.6 (CH), 40.1 (CH_2), 39.5 (CH_2), 38.5 (CH_2), 36.2 (C_q), 36.1 (CH), 35.8 (CH), 35.6 (CH_2), 35.3 (CH_2), 34.7 (CH_2), 32.2 (CH_2), 30.6 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.2 (CH_2), 23.9 (CH_2), 22.8 (C-8), 22.5 (C-8), 21.0 (CH_2), 18.7 (C-7), 12.1 (C-6), 11.7 (C-5).

IR (ATR): ν (cm^{-1})=3310 (m), 3074 (w), 2926 (s), 2866 (s), 2853 (s), 2115 (w), 1740 (w), 1666 (w), 1642 (w), 1466 (m), 1445 (m), 1383 (w), 994 (w), 917 (m).

HRMS (MH^+, $C_{34}H_{58}N$) = calcd: 480.4569, found: 480.4541.

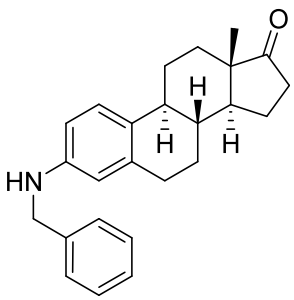
(13*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[α]-phenanthren-3-yl trifluoromethanesulfonate 204



$C_{19}H_{21}F_3O_4S$
402.43 g/mol

The published procedurewas modified as follows:[241] A slurry of estron (100 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was cooled to -13 °C under nitrogen and triethylamine (0.15 mL) was added. Trifluorosulfonic acid anhydride (65 µL, 0.39 mmol) was slowly added to the mixture over 15 min and stirred at 0 °C for 3 h. After, the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (3 mL) and the organic phase was dried over $MgSO_4$ and evaporated. After purification by column chromatography (cyclohexane → cyclohexane/EtOAc 10:1) was obtained as white solid. The analytical data of triflate **204** are identical to those reported in the literature.[241]

(13*S*)-3-(benzylamino)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta-[α] phenanthren-17(14*H*)-one 205

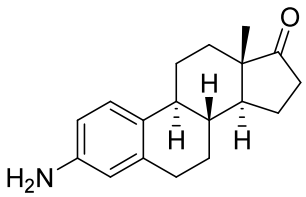


$C_{25}H_{29}NO$
359.49 g/mol

The published protocol was modified as follows:[231] To a solution of triflate **204** (310 mg, 0.77 mmol) in a 10 mL oven dried Schlenk flask in anhydrous toluene (5 mL), palladium acetate (17.29 mg, 69 µmol), cesium carbonate (248 mg, 0.76 mmol) and X-Phos (37.2 mg, 78 µmol) were subsequently added under nitrogen atmosphere. After degassing the solution *via* three freeze-pump-thaw cycles freshly distilled benzylamine (124 µL, 1.13 mmol), was added. The reaction mixture was heated at 120 °C for 12 h, filtered through a pad of Celite and evaporated. After purification on column chromatography (SiO_2, CH_2Cl_2/cyclohexane 3:2) the desired product **205** (250 mg, 91%) was obtained as a colorless oil. The analytical data of 3-benzyl aminoestrone are in full agreement to those reported in the literature.[231]

(13*S*)-3-amino-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[α]-phenanthren -17(14H)-one 206

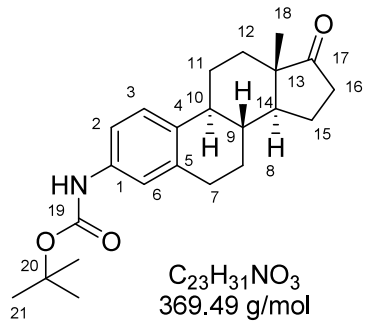
The published protocol was modified as follows:[231] Benzylamino derivative **205** (968 mg, 2.69 mmol) was hydrogenated over 10% palladium on carbon (150 mg) in a methanol/CH_2Cl_2



$C_{18}H_{23}NO$
269.38 g/mol

mixture (10 mL each) containing 5% acetic acid for 24 h at 20 bar hydrogen pressure at ambient temperature in an autoclave. The catalyst was filtered off over Celite and the solvent mixture was removed under reduced pressure. The product was then dissolved in CH_2Cl_2 and washed once with aqueous sat. $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Further purification was not needed and the desired amine **206** was obtained as a white solid (920 mg, 95%). The analytical data of 3-aminoestrone are identical to those reported in the literature.[231]

Tert-butyl (13*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta [α]phenanthren-3-ylcarbamate



$C_{23}H_{31}NO_3$
369.49 g/mol

Amine **206** (120 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (2 mL, 0.22 M) and pyridine (0.5 mL) and Boc_2O (117 mg, 0.53 mmol) were subsequently added at 0 °C. The mixture was stirred overnight at rt, washed with aqueous solutions of 1 M HCl and 2 M NaOH, dried and concentrated. After purification by column chromatography (cyclohexane → cyclohexane/EtOAc 3:1) the desired product was obtained as colorless oil (158 mg, 96%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.22-7.16 (m, 2H, H-2, H-6), 7.03 (dd, *J* = 8.4 Hz, *J* = 2.7 Hz, 1H, H-3), 6.36 (br s, NH), 2.89 (dd, *J* = 9.1 Hz, *J* = 4.4 Hz, 2H, H-7), 2.54-1.34 (steroid skeleton), 1.51 (s, 9H, H-21), 0.91 (s, 3H, H-18).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 220.8 (C-17), 152.9 (C-19), 137.3 (C-4), 136.0 (C-5), 134.6 (C-1), 125.8 (C-3), 118.9 (C-6), 116.4 (C-2), 80.4 (C-20), 50.5 (CH), 48.0 (C-13), 44.1 (CH), 38.3 (CH), 35.9 (CH_2), 31.6 (CH_2), 29.5 (C-7), 28.4 (C-21), 26.5 (CH_2), 25.8 (CH_2), 21.6 (CH_2), 13.9 (C-18).

IR (ATR): ν (cm^{-1}) = 3333 (m), 2974 (m), 2929 (m), 2866 (m), 1724 (s), 1590 (m), 1527 (s), 1366 (m), 1240 (m), 1158 (s), 1050 (m).

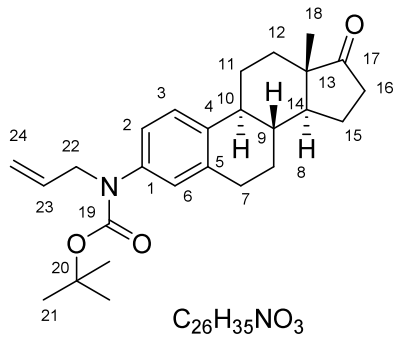
LRMS-ESI: *m/z* (%) = 370 (50) [MH^+], 314 (100) [M^+-$C(CH_3)_3$], 288 (20).

HRMS-ESI (MH^+, $C_{23}H_{32}NO_3$) = calcd: 370.2382, found: 370.2384.

R_f (SiO_2, cyclohexane/EtOAc 5:1) = 0.26.

Tert-butyl *N*-allyl((13*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta [α]phenanthren-3-yl)carbamate

The previous estron derivative (94 mg, 0.254 mmol) was dissolved in DMF (4 mL) and KH (13 mg, 0.33 mmol) was added in one portion. After H_2 evolution ceased allybromide (66 mg, 0.38 mmol) was added and the reaction mixture was stirred for 3 h at rt. Concentration under reduced pressure afforded 120 mg of a mixture of **206** and the desired product.



^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.20 (d, *J* = 8.3 Hz, 1H, H-2), 7.00 (d, *J* = 8.3 Hz, 1H, H-3), 6.97 (s, 1H, H-6), 5.91 (ddt, *J* = 17.2 Hz, *J* = 10.2 Hz, *J* = 5.3 Hz, 1H, H-23), 5.19-5.11 (m, 2H, H-24), 4.19 (dt, *J* = 5.4 Hz, *J* = 1.5 Hz, 2H, H-22), 2.89 (m, 2H, H-7), 2.54-1.39 (steroid skeleton), 1.45 (s, 9H, H-21), 0.91 (s, 3H, H-18).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 220.7 (C-17), 154.6 (C-19), 140.6 (C-4), 137.2 (C-1), 136.8 (C-5), 134.5 (C-23), 126.4 (C-3), 125.5 (C-6), 123.5 (C-2), 116.1 (C-24), 80.3 (C-20), 53.0 (C-22), 50.5 (CH), 48.0 (C-13), 44.2 (CH), 38.1 (CH), 35.8 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 28.3 (C-21), 26.5 (CH_2), 25.7 (CH_2), 21.6 (CH_2), 13.9 (C-18).

IR (ATR): ν (cm^{-1}) = 2975 (m), 2930 (m), 2888 (w), 2867 (w), 1740 (s), 1700 (s), 1609 (m), 1501 (m), 1389 (m), 1367 (s), 1242 (m), 1169 (m), 1151 (s), 1115 (w).

LRMS-ESI: *m/z* (%) = 410 (20) [MH^+], 366 (70), 354 (100) [M^+-$C(CH_3)_3$], 348 (25).

HRMS-ESI (MH^+, $C_{26}H_{36}NO_3$) = calcd: 410.2695, found: 410.2694.

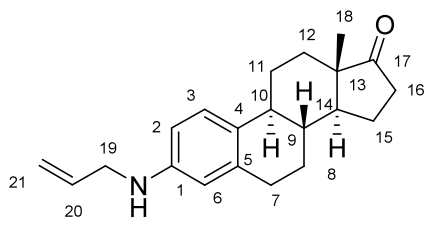
R_f (SiO_2, cyclohexane/EtOAc 5:1) = 0.26.

(13*S*)-3-(allylamino)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[α]-phenanthren-17(14H)-one 207

*From derivative **206**:* The crude mixture containing **206** and the previous compound (120 mg) was dissolved in CH_2Cl_2 (10 mL) and 10 eq TFA was added (0.25 mL) at 0 °C. The stirring

continued at rt for 10 h and the organic phase was then neutralized with sat. $NaHCO_3$ solution. The organic layer was then dried over $MgSO_4$ and concentrated. Purification by column chromatography (cyclohexane → EtOAc) afforded the desired product **207** (38 mg, 48% from **206**) as a light yellow solid, along with 30 mg amino estron **206**.

*From triflate **204**:* To a solution of triflate **204** (50 mg, 0.12 mmol) in a 10 mL oven dried Schlenk flask in anhydrous toluene (1mL), palladium acetate (2.5 mg, 10 mol%), cesium carbonate (40 mg, 0.12 mmol) and X-Phos (6 mg, 10 mol%) were subsequently added under nitrogen atmosphere. After degassing the solution *via* three freeze-pump-thaw cycles freshly distilled allylamine (10 mg, 0.18 mmol) was added. The reaction mixture was heated at 120 °C for 12 h, filtered through a pad of Celite and evaporated. After purification on column chromatography (SiO_2, CH_2Cl_2/cyclohexane 3:2) the desired product **207** (4 mg, 10%) was obtained as a white solid.



$C_{21}H_{27}NO$
309.45 g/mol

^{1}H-NMR (C_6D_6, 400 MHz): δ (ppm) = 7.08 (d, *J* = 8.3 Hz, 1H, H-3), 7.00 (dd, *J* = 8.3 Hz, *J* = 2.6 Hz, 1H, H-6), 6.28 (d, *J* = 2.6 Hz, 1H, H-2), 5.73 (ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 5.3 Hz, 1H, H-20), 5.14 (dq, *J* = 17.2 Hz, *J* = 1.7 Hz, 1H, H-21), 5.00 (dq, *J* = 10.3 Hz, *J* = 1.5 Hz, 1H, H-21), 3.47 (dt, *J* = 5.3 Hz, *J* = 1.7 Hz, 2H, H-19), 2.75 (m, 2H, H-7), 2.18-0.90 (steroid skeleton), 0.62 (s, 3H, H-18).

^{13}C-NMR (C_6D_6, 100 MHz): δ (ppm) = 217.9 (C-17), 146.6 (C-1), 137.1 (C-5), 136.3 (C-20), 129.4 (C-4), 126.5 (C-3), 115.7 (C-21), 113.5 (C-6), 111.8 (C-2), 50.5 (CH), 47.0 (C-13), 47.0 (C-19), 44.8 (CH), 38.0 (CH), 35.8 (CH_2), 32.3 (C-7), 30.3 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 21.7 (CH_2), 13.9 (C-18).

IR (ATR): ν (cm^{-1}) = 338 (w), 2925 (s), 2854 (m), 1737 (s), 1614 (m), 1511 (m), 1260 (m).

LRMS-ESI: *m/z* (%) = 310 (15) [MH^+], 269 (100) [M^+ -allyl].

HRMS-ESI (MH^+, $C_{21}H_{28}NO$) = calcd: 310.2171, found: 310.2173.

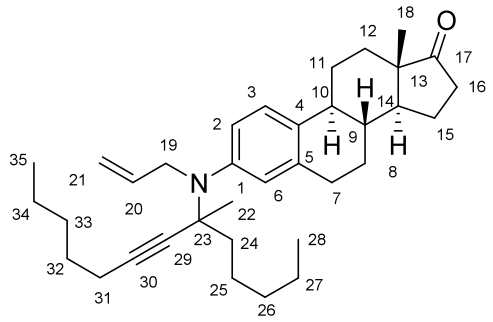
R_f (SiO_2, cyclohexane/EtOAc 5:1) = 0.33.

(8*R*,9*S*,13*S*,14*S*)-3-(allyl(6-methyltridec-7-yn-6-yl)amino)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one 208

The tandem reaction was performed in a flame-sealed NMR tube and was prepared as

follows: Steroid derivative **207** (6 mg, 12.5 µmol), which was previously filtered through a pad of cotton to separate the silica residue from the column chromatography, was dissolved in CH_2Cl_2 (0.5 mL) and introduced in the NMR tube, which was then placed with a septum. Vacuum was applied through a needle and once the solvent was evaporated, the tube was filled with nitrogen. In a glovebox catalyst **182** (12 mg, 12.5 µmol) and co-catalyst **183** (6 mg, 12.5 µmol) were dissolved with C_6D_6 (2 mL) (methane evolution should be observed) and heptyne (30 mg, 0.31 mmol) was added. 0.2 mL of the mixture was carefully introduced in the previous NMR tube and the Pasteur pipette was rinsed once with 0.1 mL C_6D_6. The NMR tube was then closed again with a septum and taken out of the Glovebox. After freezing the NMR tube with liquid nitrogen under N_2 atmosphere, high vacuum was applied and the tube was flame-sealed. The reaction mixture was heated at 80 °C for 48 h. complete conversion was observed to a mixture of products (approx. 10 to 1), with the major one probably being the hydroamination product intermediate. Further heating up to 100 °C provided no change according to analysis via ^{1}H-NMR. After subsequent heating at 120 °C for 12 h one new product was formed, and the intermediate formed at 80 °C had been consumed. Attempts to purify the hydroamination product resulted in decomposition (SiO_2, Al_2O_3, aqueous extraction). Unfortunately, by reverse phase chromatography it was also not possible to separate all the impurities.

Note: When the sample is not previously filtered, the residual silica gel present in the sample decomposes the catalyst partially and conversion decreases. Concentration is also important in order to obtain reproducible results.



$C_{35}H_{51}NO$
501.79 g/mol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) = characteristic signals: 5.87 (m, 1H, H-20), 5.24 (dt, *J* = 17.4 Hz, *J* = 1.7 Hz, 1H, H-21), 5.13 (dq, *J* = 10.4 Hz, *J* = 1.5 Hz, 1H, H-21), 3.82 (m, 2H, H-19), 2.78 (m, 2H, H-7), 2.55-0.75 (steroid skeleton and alkyl chains).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ (ppm) = characteristic signals: 221.1 (C-17), 136.5 (C-20), 124.2 (C-3), 120.0 (C-2), 115.4 (C-21), 108.1 (C-1), 45.9 (C-13), 47.02 (C-19), 18.0 (C-22), 14.1, 13.9 (C-28, C-35).[33]

HRMS-ESI (MH^+, $C_{35}H_{52}NO$) = calcd: 502.4049, found: 502.4051.

[33] ^{13}C resonances identified *via* HMBC correlation.

Annex

Abbreviations

°C	celcius degree
Å	Ångström
Ac	acetyl
AIBN	azo-bis-butyronitrile
approx.	approximately
app	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bn	benzyl
br	broad
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
calcd	calculated
cat	catalytic
Cbz	benzyloxycarbonyl
CM	cross metathesis
d	diastereoselective
d	day
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DEPT	distortionless Enhancement by Polarization Transfer
DIAD	diisopropylazodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylamino pyridine
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
ebthi	ethylene-bis(η5-tetrahydroindenyl)
EI	electronic ionization

eq	equivalent
Et	ethyl
GC	gas chromatography
h	hour
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectroscopy
IR	infra red
*i*Pr	isopropyl
LDA	lithium diisopropylamine
M	molar
m	multiplett
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
Mes	mesityl
mp	melting point
min	minutes
MIDA	methyliminodiacetic acid
mL	milliliter
MS	massspectroscopy
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NaHMDS	sodium hexamethyldisilazide
NBSH	*o*-nitrobenzenesulfonylhydrazide
NHC Ligand	*N*-heterocyclic ligand
NMO	*N*-methyl-morpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nosyl: nitrotoluene sulfone
o	ortho
p	para
PG	protecting group
Ph	phenyl
PMP	*p*-methoxyphenyl
ppm	part per million
Pr	propyl
*p*TSA	*p*-toluenesulfonic acid
q	quartet
RCM	ring-closing metathesis

ROM	ring-opening metathesis
RRM	ring-rearrangement metathesis
rt	room temperature
s	singlet
sat.	saturated
t	triplet
TBAF	tetrabutyl ammonium floride
TBDMS, TBS	*tert*-butyl-dimethylsilyl chloride
THF	tetrahydrofurane
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetra methyl ethylene diamine
TMS	trimethylsilane
TMP	2,2,5,5-tetramethyl pyrrolidin
TPAP	tetrapropylammonium perruthenate
Ts	toluene-4-sulfonyl
Vol	volumen
UV	ultra violet

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