Environmentally Benign Synthesis of Enamides via Waste-Free Catalytic Addition of Amides to Terminal Alkynes

Dissertation

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D 386

Vorgelegt von

Kifah S. M. Salih, MSc

geboren in Bagdad (Irak)

Betreuer

Prof. Dr. Lukas J. Gooßen

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Prüfungskommission

Vorsitzender:	Prof. Dr. Helmut Sitzmann
1. Gutachter:	Prof. Dr. Lukas Gooßen
2. Gutachter:	Prof. Dr. Stefan Kubik

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Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit eigenständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet, sowie Literaturzitate kenntlich gemacht habe. Kooperationsprojekte sind ausdrücklich als solche gekennzeichnet.

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Kaiserslautern, den _____ _____

Kifah Salih

Dedication

To mother, father, family

and

all whom I love

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It is quite a challenge to put on paper how much I appreciate all those who have supported me through this experience.

I am sincerely grateful and appreciative to Prof. Dr. Gooßen for giving me the opportunity to carry out my PhD in his group over the last few years, and for his intellectual support, encouragement, and enthusiasm for the work that made this dissertation possible. It has been an invaluable learning experience for me in a number of ways, and I will always be appreciative for the chance to learn and to view chemistry in an entirely new way.

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Before I close, I must mention the precious support form Gooßen's family for the duration of my residence in Kaiserslautern, thank you very much Dr. Käthe, Linus, and Klara.

Publications

Parts of this work were published in the following publications:

- L. J. Goossen, M. Blanchot, K. S. M. Salih, R. Karch, A. Rivas-Nass, *Org. Lett.* **2008**, *10*, 4497-4499: *Ruthenium-Catalyzed Stereoselective anti-Markovnikov Addition of Thioamides to Alkynes.*

- L. J. Gooßen, K. S. M. Salih, M. Blanchot, *Angew. Chem*. **2008**, *120*, 8620-8623; *Angew. Chem. Int. Ed.* **2008**, *47*, 8492-8495: *Synthesis of Secondary Enamides by Ruthenium-Catalyzed Selective Addition of Amides to Terminal Alkynes.*

- L. J. Gooßen, M. Blanchot, K. S. M. Salih, K. Gooßen, *Synthesis* **2009**, 2283-2288: *Ruthenium-Catalyzed Addition of Primary Amides to Alkynes: A Stereoselective Synthesis of Secondary Enamides.*

- L. J. Gooßen, M. Blanchot, M. Arndt, K. S. M. Salih, *Synlett* **2010**, 1685-1687: *Synthesis of Botryllamides and Lansiumamides via Ruthenium-Catalyzed Hydroamidation of Alkynes.*

Abbreviations

2-Fur	*ortho*-furyl
Ac	acetyl
Ar	aryl
Bn	benzyl
calcd	calculated
Cat.	catalyst
cod	1,5-cyclooctadiene
cot	1,3,5,7-cyclooctatriene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
cumene	isopropybenzene
Cy	cyclohexyl
dba	dibenzylideneacetone
dcypb	1,4-bis(dicyclohexylphosphino)butane
dcype	1,2-bis(dicyclohexylphosphino)ethane
dcypm	bis(dicyclohexylphosphino)methane
DMA	*N*,*N*-dimethylacetamide
DMAP	dimethylaminopyridine
DMEDA	N,N'-dimethylethylenediamine
DMF	dimethylformamide
dmfm	dimethyl fumarate
DMSO	dimethylsulfoxide
DPP	4,7-diphenyl-1,10-phenanthroline
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppm	bis(diphenylphosphino)methane
DPPP	1,3-bis(diphenylphosphino)propane
EDTA	ethylenediaminetetraacetic acid

Eq	equivalent
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedianato
glyme	dimethylglycol
HASB	hard and soft acid and base
IC_{50}	half maximal inhibitory concentration
^{i}Pr/*i*-Pr	*iso*-propyl
L	ligand
M	metal
met	methallyl
mim	*N*-methylimidazol-2-yl
MW	microwave heating
NBD	norbornadiene
^{n}Bu/*n*-Bu	*normal*-butyl
nM	nanomolar
nd	not determined
NMP	*N*-methylpyrrolidinone
Ns	4-nitrobenzenesulfonyl, nosyl
Nu	nucleophile
^{n}Pr/*n*-Pr	*normal*-propyl
PNP	2,6-bis-(di-tert-butylphosphinomethyl)pyridine
Pz	pyrazolyl
^{t}Bu/*t*-Bu	*tertiary*-butyl
TEMDP	tetraethyl methylenediphosphonate
Tf	trifluoromethanesulfonyl
Ts	4-toluenesulfonyl, tosyl
X	halide or pseudohalide
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

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1 Introduction

1.1 Fundamental concepts

The concept of green chemistry was being formulated during the 1990s in both the US and Europe, and has since been adopted widely by the chemical industry.[1] Green chemistry consists of chemicals and chemical processes designed to reduce or eliminate negative environmental impacts. Following the principles of green chemistry, companies embrace cleaner and more efficient technologies, with a commitment to a cleaner and healthier environment. The message of green chemistry is not complicated, look for prevention not cure.[2]

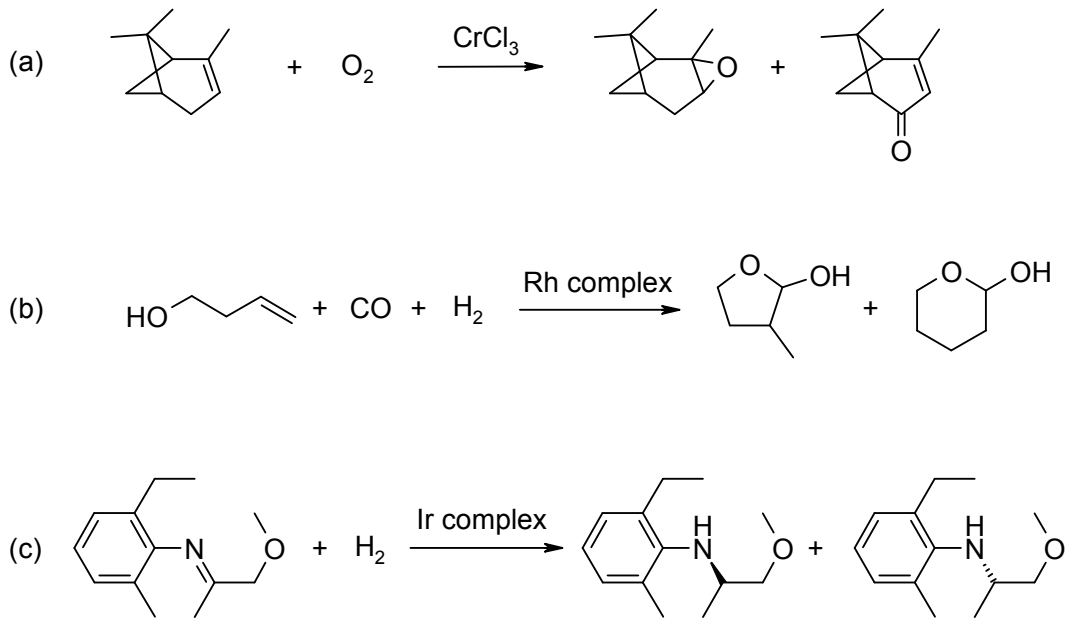
Waste minimization is one of the key objectives of green chemistry. Furthermore, a sustainable process is one that optimizes the use of resource, while still leaving enough resources for future generations. Catalysis is a vital tool in both cases, in fact, as far as chemistry is concerned, catalysis is the mean to sustainability.[3]

A catalyst is a substance that increases the reaction rate or selectivity, or enables the reaction at lower temperatures. Form outside, it seems that the catalyst makes the reaction go faster without being consumed, but this is an excessive simplification. In most cases, the catalyst opens a different and faster reaction path.

As the catalyst is not used up in the reaction, each catalyst molecule can take part in many subsequent cycles, so only a small amount of catalyst relative to the substrate is required. The ratio of substrate/catalyst reflects the catalyst's activity and efficiency, which is measured as turnover number (TON) or turnover frequency (TOF).

The many different types of catalysts are ranged from the proton (H^+), through Lewis acids and bases, organometallic complexes, organic and inorganic polymers, along to enzymes. The type of catalysis is classified into three categories: homogeneous catalysis, heterogeneous catalysis, and biocatalysis. Though the catalysts and the process conditions in each category can be different, the general principles are the same.[2]

The major benefit of catalysis is that the product formation is faster and generating less amount of waste. There are various types of product selectively: **Chemoselectivity**, indicates a situation where two different chemical reactions can take place, giving two different products. In a similar manner, **regioselectivity** arises when the same chemical reaction in different regions of the molecule affords to different products. When a reaction gives two or more diastereomers, the selectivity to each of these is described **diastereoselectivity**. In the particular case when two products are mirror-image diastereomers (enantiomers), then this is designated **enantioselectivity**. Scheme 1 shows examples of the various product selectivity types.[2]

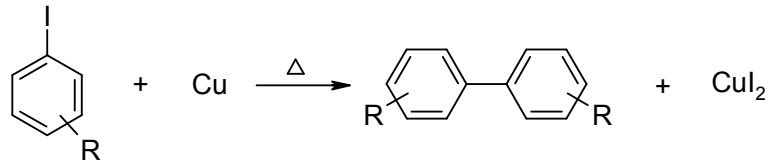


Scheme 1. (**a**) Chemoselectivity in the oxidation reaction of α-pinene. (**b**) Regioselectivity in the hydroformylation of homoallylic alcohol. (**c**) Enantioselectivity in the hydrogenation of the prochiral imine substructure.

Atom economy is an important concept in green chemistry since it was introduced by Trost in 1991.[4] Preferably, every atom that is put into a process should be part of the product. Traditional organic synthesis protocols often use stoichiometric amounts of reagents, that do not become part of the product, but instead must be disposed of,

polluting the environment. This is not only unecological, but also uneconomic – paying twice, the purchase and the waste disposal.

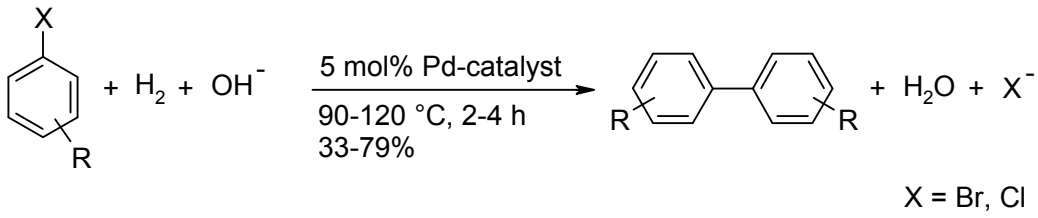
The homocoupling of aryl iodides in the presence of copper, known as the Ullmann reaction, yields symmetric biaryls, which are important intermediates for synthesizing agrochemicals, pharmaceuticals and natural products (Scheme 2).[5]



Scheme 2. Typical Ullmann reaction for coupling of aryl iodides.

Although the Ullmann reaction is over a century old, it is still used in industry. The disadvantage is that it consumes stoichiometric amounts of copper and produces large amount of waste. The reaction works best with aryl iodides, which increases the problem of the waste. This is because chemicals react by their molarity, but prices are based on their mass. One ton of phenyl iodide contains 620 kg of iodide and only 380 kg of phenyl residue.[6] Therefore, nearly two thirds of the reactant and the entire reagent result in chemical waste.

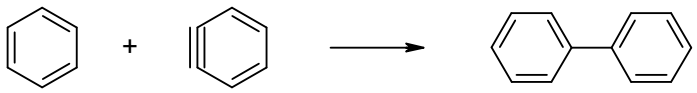
Following the principles of green chemistry, it is possible to replace the stoichiometric amount of copper with a catalytic cycle, using a different reaction. The iodine atoms are not part of the product either they act as leaving groups, finally producing two phenyl-radicals that couple to furnish biphenyl. The copper metal reduces the iodine atoms, affording Cu^{2+} and $2I^-$. The same stoichiometric reaction can be performed using palladium instead of copper. At first sight, this does not seem attractive as palladium is much more expensive than copper. However, the benefit of palladium is that it is easily reduced back from Pd^{2+} to Pd^0. This reduction can bring about, for example, using hydrogen gas, giving Pd^0 and $2H^+$ (Scheme 3).[7]



Scheme 3. (**a**) Reductive coupling of aryl halide with palladium(0) catalyst.

This simple reaction reveals that biphenyl produced catalytically from halobenzene and hydrogen in the presence of base. Advantageously, this catalytic reaction works with aryl bromides and -chlorides, improving the E-factor[8] (the environmental factor, *A reaction's E-factor is the quotient* $kg_{waste}/kg_{product}$, *where waste is everything formed in the reaction except the desired product*) of the reaction and the atom efficiency.

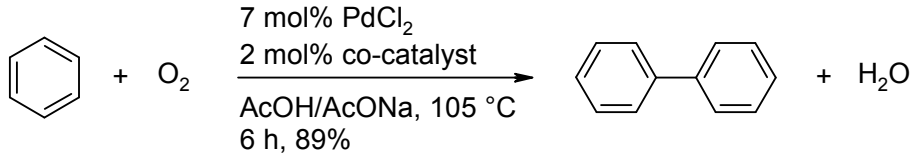
The big question: Is it possible to enhance the atom economy even further without using any halide? The greenest solution is to use no leaving group for synthesizing biphenyl, starting from 12 C atoms and 10 H atoms. This can theorically be performed by coupling benzene with benzyne (Scheme 4), giving 100% atom economy, whereas generating benzyne is very difficult.



Scheme 4. Theoretical approach to biphenyl.

Practically, hydrogen atom is the leaving group that is easily available, obtained by oxidative coupling of two benzene rings to form biphenyl. This reaction can be accomplished by using stoichiometric amounts of palladium(II) chloride in acetic acid, or by using a palladium catalyst and regenerating it with air as the oxidant, yielding water as a by-product (an additional cobalt(II) acetate is used to improve the availability of molecular oxygen in reaction medium).

Although the actual catalytic cycle includes many steps and intermediates, the principle of this reaction is simple, benzene and oxygen go in and biphenyl and water come out (Scheme 5).[6]

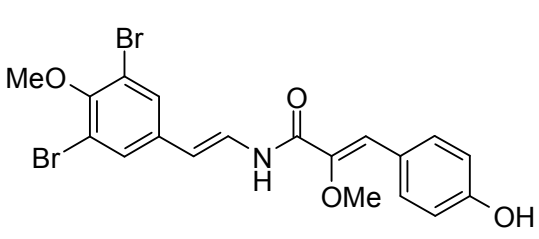


Scheme 5. Catalytic approach of oxidative coupling of two benzene molecules.

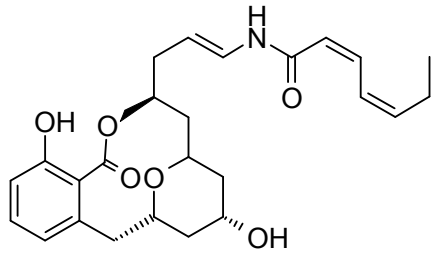
1.2 Enamides

1.2.1 Enamide moieties in natural products

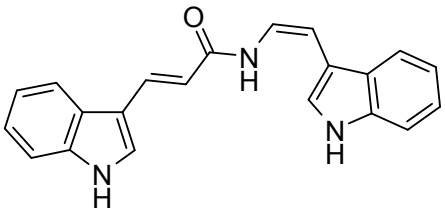
A number of natural products are known that contain an enamide moiety as a key structural feature, such as lansiumamides A-B, lansamide I,[9] TMC-95A-D,[10] crocacins,[11] alatamide,[12] aspergillamides A-B, chondriamide A, C, and a range of marine metabolites.[13] This functionality is an important subunit in various biologically active substrates and pharmaceutical drug lead compounds,[14] including the antibiotic (CJ-15,801),[15] anthelmintic,[16] antifungal, cytotoxic or antineoplastic activity.[17] Recently, a number of natural products with antitumor activity containing a central benzolactone core bearing an unusual enamide side chain have been reported,[18] e.g., salicylihalamides A-B,[19] lobatamides A-F,[20] apicularens A-B,[21] CJ-12,950 and CJ-13,357,[22] and oximidines I-II (Figure 1).[23]



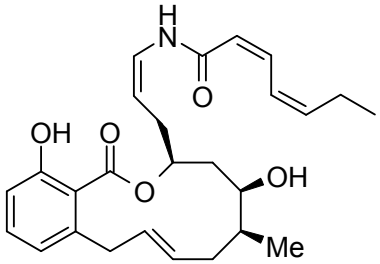
Botryllamide A
cytotoxicity against colon cancer cells



Apicularen A
active against human tumer cells



Chondriamide C
anthelmintic activity

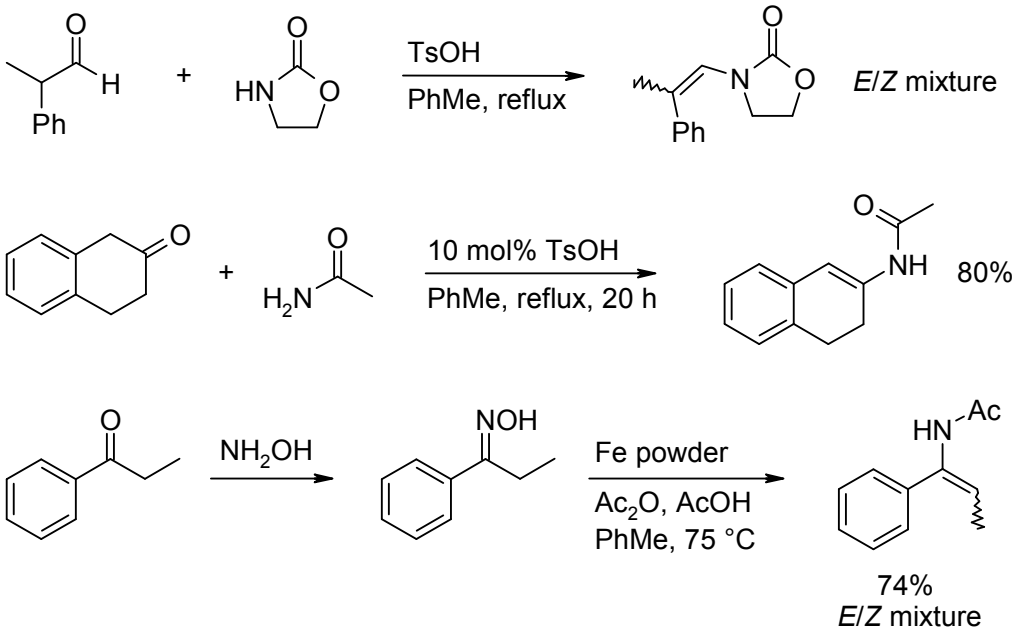


Salicylihalamide A
Potent inhibitor of human cancer cells
(IC_{50} < 1 nM)

Figure 1. Enamides in bioactive molecules.

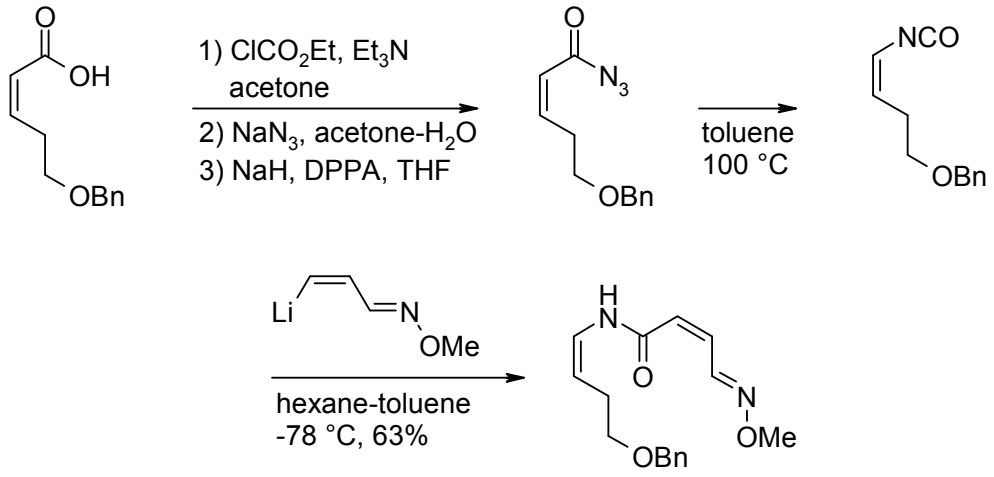
1.2.2 Synthesis of enamides

Several protocols have been disclosed for the preparation of enamides. Conventional approaches include the condensation of amides with aldehydes[24] and ketones[25] in the presence of Lewis acids or bases.[26] Other methods proceed via condensation of hydroxyl amine and ketone, followed by subsequent treatment with acetic anhydride in the presence of iron powder, or the acylation of imines, affording enamide substructures.[27] The main disadvantages of these procedures are the harsh reaction conditions and the lack of stereoselectivity, mixture of *E*/*Z* products (Scheme 6).



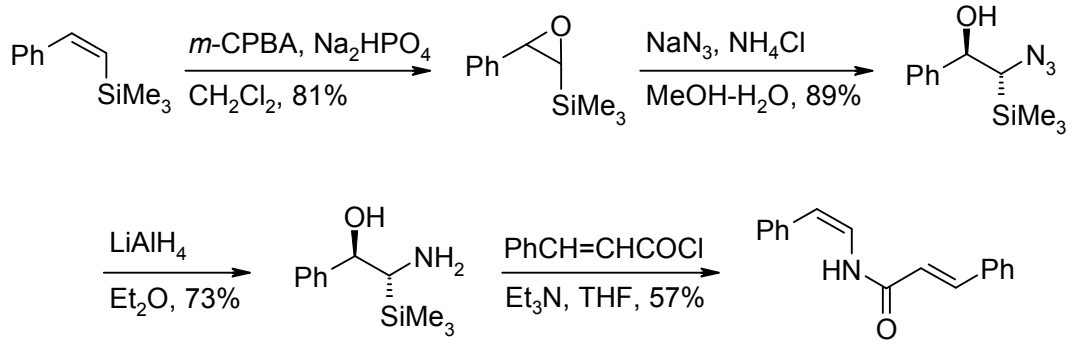
Scheme 6. Condensation of amine and carbonyl compound derivatives.

The Curtius rearrangement of α,β-unsaturated acyl azides is a standard method for synthesis of enamides. The stereoselectivity of the desired product depends on the geometry of the acyl azide, thus both *E*- and *Z*-isomers can be obtained selectively.[28] This method was successfully utilized to synthesize the side-chain moiety of oximidines (Scheme 7)[29] and some natural products isolated from of *Clausena lansium*.[30]



Scheme 7. Synthesis of the side-chain moiety of oximidines via Curtius rearrangement.

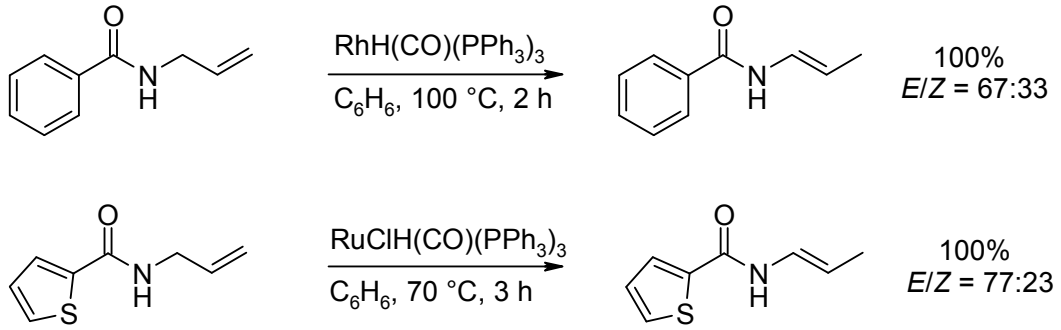
Another selective method for the synthesis of *E*- and *Z*-enamides is Peterson elimination reaction of β-hydroxy-α-silylamides.[31] Enamides are obtainable by multi-steps synthesis and again the *E*/*Z* configuration is highly dependant on the geometry of the starting material. In this case, vinylsilanes are converted into enamides by a sequence comprising epoxidation, nucleophilic ring opening of the resulting epoxysilanes with NaN_3, and reduction of the azide, followed by a one-pot *N*-acylation/elimination process (Scheme 8). Many enamides can be synthesized selectively following this approach, among them the natural occurring crocacin D[32] and lansiumamide A.[33]



Scheme 8. Stereoselective synthesis of lansiumamide A by a Peterson reaction manifold.

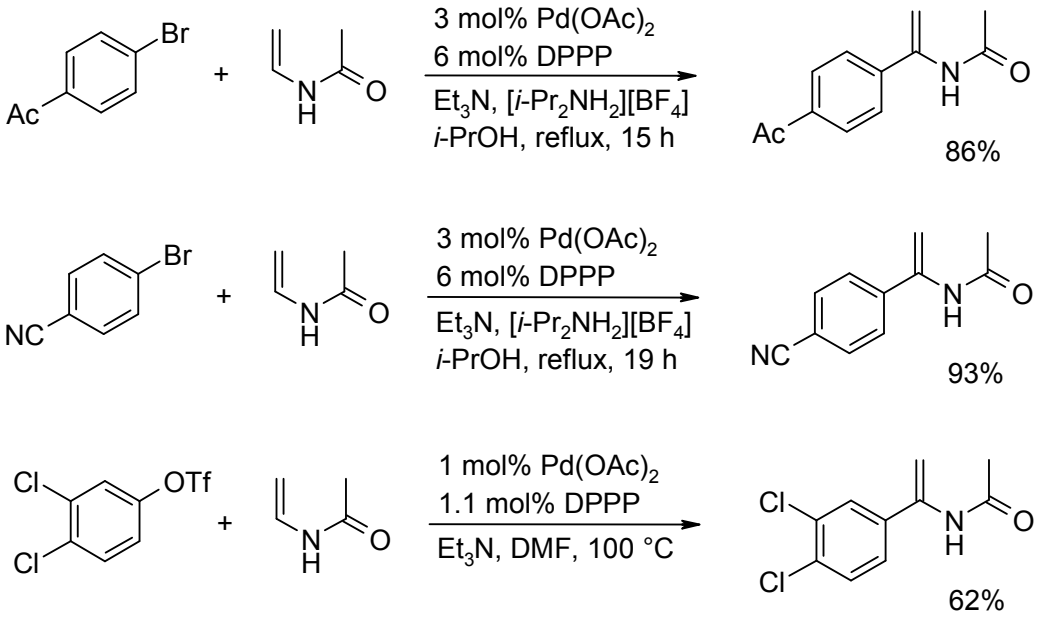
Although these two methodologies afford enamides in excellent stereoselectivity, they require lengthy multi-steps procedure and the yields are often low.

Another synthetic approach to enamides is the isomerization of *N*-allylamides by Fe, Rh, or Ru complexes. The disadvantages of this method are mainly the *E*/*Z* mixture and the poor scope of the reaction is limited to the availability of the appropriate *N*-allyl amides (Scheme 9).[34]



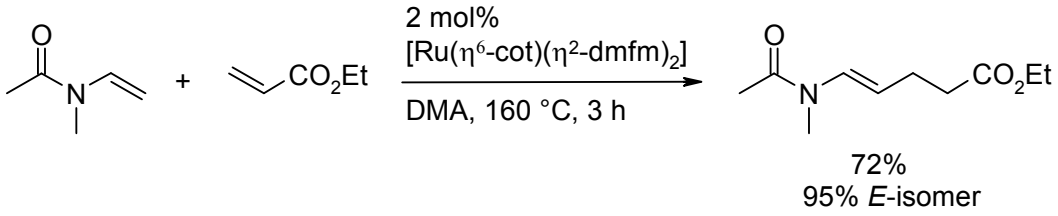
Scheme 9. Isomerization of *N*-allylamides by Rh or Ru complexes.

Carbon-carbon bond formation via Heck reaction allows the regioselective synthesis of enamides.[35] For instance, palladium species catalyze the coupling of vinyl amides with aryl halides[36] or trifluoromethanesulfonates[37] exclusively provides highly branched enamides in moderate to high yields (Scheme 10).



Scheme 10. Heck arylation of *N*-vinylacetamide with aryl halides and trifluoromethanesulfonates.

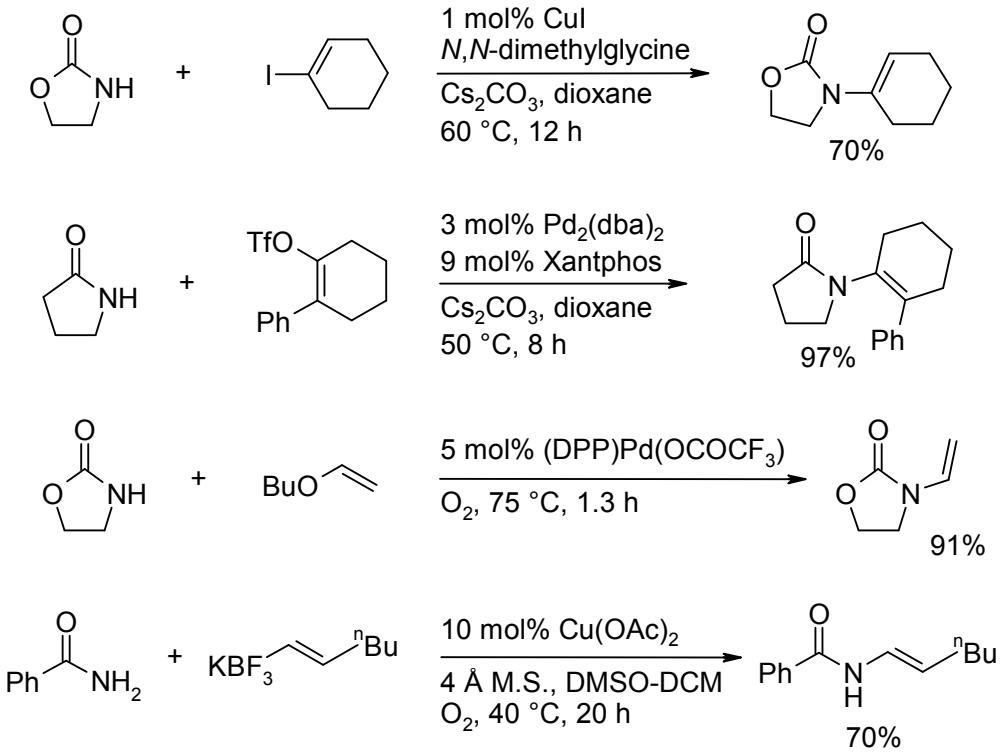
A Ru-catalyzed co-oligomerization allows the synthesis of functionalized *E*-enamides in moderate to good yields starting from *N*-vinylamides. Nevertheless, this recently published transformation moves the problem towards the synthesis of the starting material, which is also not trivial (Scheme 11).[38]



Scheme 11. Co-dimerization of *N*-methyl-*N*-vinylacetamide with ethyl acrylate.

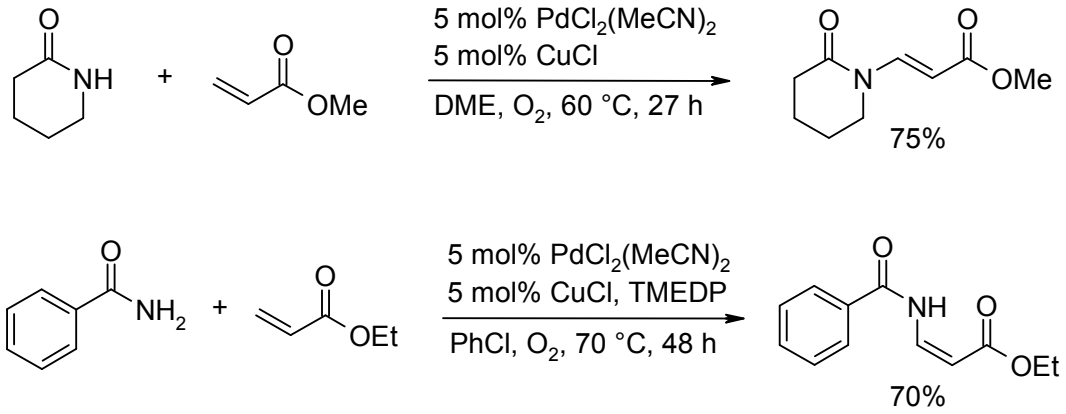
The cross-coupling reaction of amides and vinyl halides[39] or pseudohalides (including triflates,[40] ethers,[41] or trifluoroborate salts[42]) using Pd or Cu catalysts affords *E*- or *Z*-

enamides stereoselectively. Thus, the geometry of the products depends directly on the configuration of employed vinyl substrates (Scheme 12).



Scheme 12. Cross-coupling reaction of amides and vinyl halides or pseudohalides.

The oxidative amidation of electron-deficient alkenes using Pd/Cu co-catalyst system allows the construction of enamide substrates. However, the *E*/*Z* configuration of the products is highly depending on the structure of the employed amides (Scheme 13).[43]



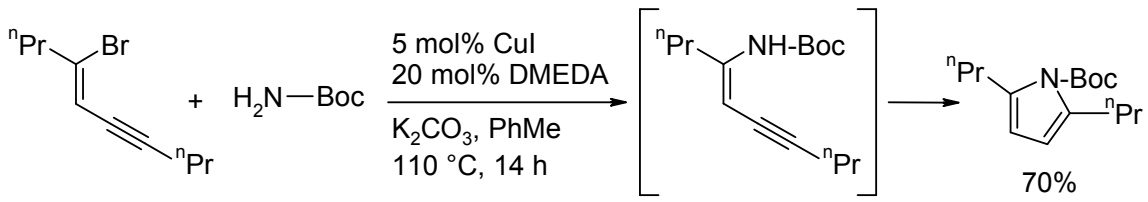
Scheme 13. Pd/Cu System catalyzed oxidative amidation of alkenes.

Despite the numerous examples for the catalytic synthesis of enamides, such reactions often suffer from either low yield, limited substrate scope, harshness of the reaction conditions or difficulty in preparing necessary vinyl halides. More importantly, stereocontrol of the double bond presents an additional challenge, particularly when *Z*-enamides are required,[30,32,44] the less thermodynamically stable products.

1.2.3 Reactions of enamides

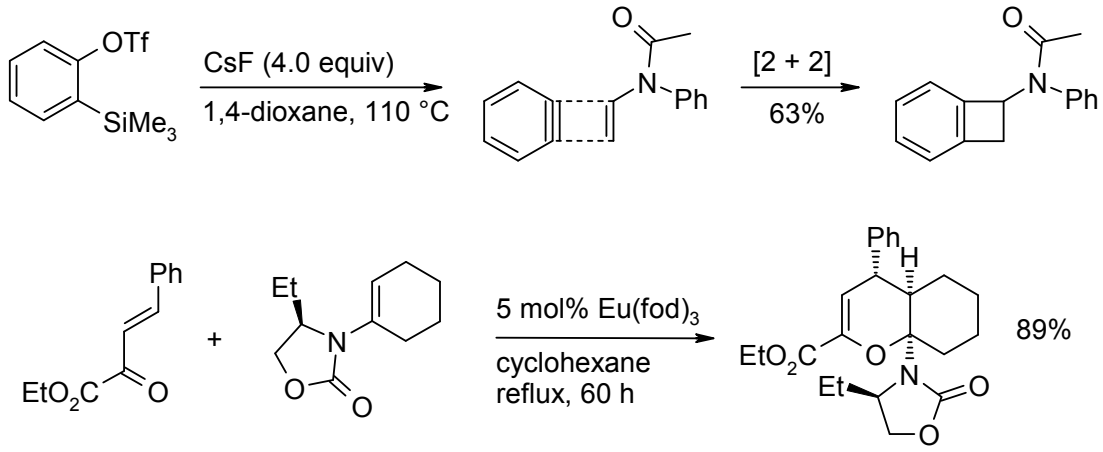
In general, enamides have been shown to have ambident reactivity, both electrophilic at the α-carbon and nucleophilic at the β-carbon. Enamides may be regarded as deactivated enamines and will react with powerful electrophiles such as bromine,[45] peracids,[46] and lead(IV) acetate.[47] They are stable compounds under neutral or basic conditions and with Brønsted acids give rate-determining protonation on carbon, leading to a reactive *N*-acyliminium intermediate that may either undergo hydrolysis of the *N*-vinyl bond to form carbonyl compounds and amides[48] or react with a range of nucleophiles, including oxygen, sulfur, or π-based nucleophiles.[49]

In addition, enamides serve as highly versatile synthetic intermediates, especially in the formation of heterocycles and bioactive natural products.[50] Highly functionalized pyrroles can be synthesized from a domino Cu-catalyzed C−N coupling/hydroamidation sequence. The cyclization of the initially formed enamide from haloenyne gives pyrrole derivatives in good yields (Scheme 14).[51]



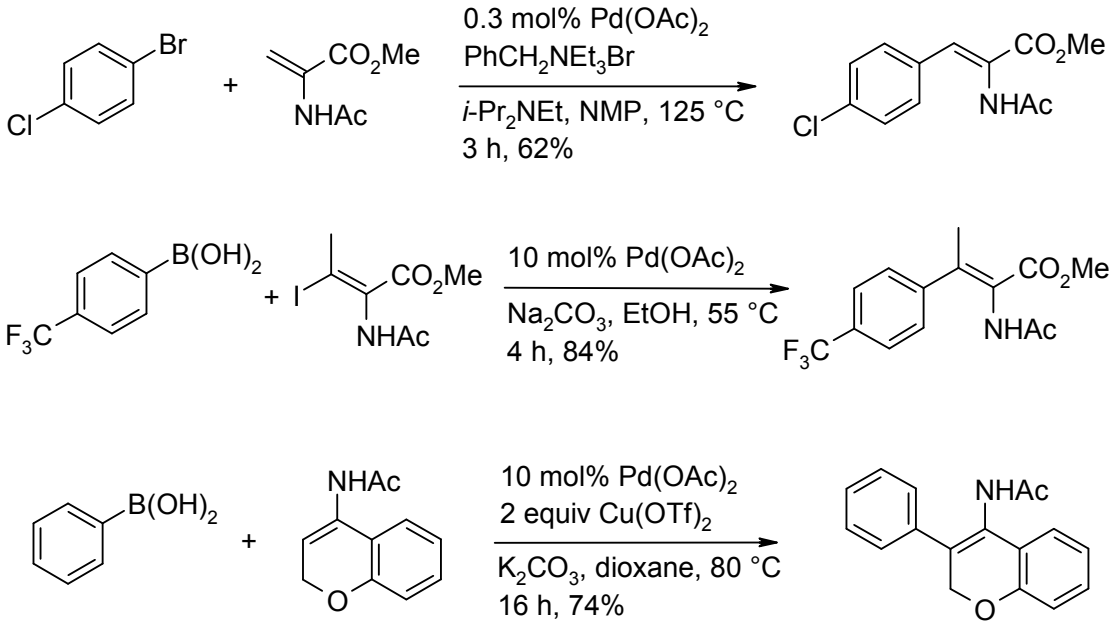
Scheme 14. A domino copper-catalyzed amidation/hydroamidation sequence.

Nitrogen-containing compounds also can be synthesized from [2 + 2][52] or [4 + 2][53] cycloaddition with enamides (Scheme 15).



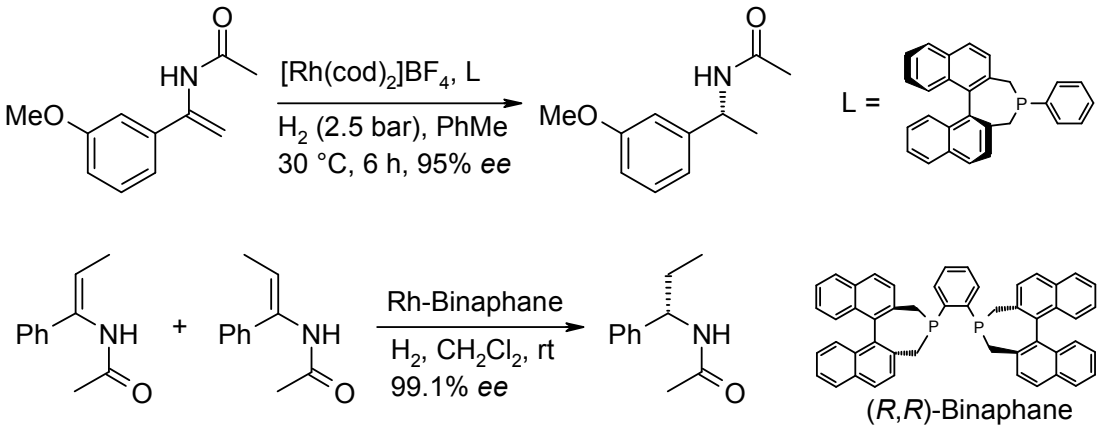
Scheme 15. Regioselective [2 + 2] and [2 + 4] cycloaddition with enamides.

Moreover, enamides serve as substrates for Heck reactions,[54] Suzuki couplings,[55] and C−H functionalizations,[56] forming highly substituted enamides (Scheme 16).



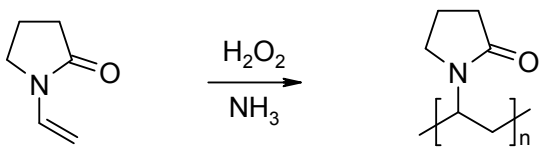
Scheme 16. Enamides as substrates for coupling reactions.

Enamides also display alkene reactivity: For example, they are a substrate for asymmetric hydrogenation, to generate chiral amines. Recently, rhodium catalysts have been reported for enantioselective hydrogenation of enamides,[57] even with isomeric mixture of *E*- and *Z*-configurations,[58] in the presence of chiral phosphanes (Scheme 17).[59]



Scheme 17. Rhodium-catalyzed enantioselective hydrogenation of enamides.

Simple enamides such as *N*-vinyllactams can be used as monomers in polymerization reaction forming *N*-vinylamide-based polymers. Polyvinylpyrrolidinone (PVP) is of persistently high importance to formulators of personal-care, pharmaceutical, agricultural, and industrial products because of desirable performance attributes and very low toxicity profiles. This polymer is synthesized from *N*-vinylpyrolidinone, initiated by hydrogen peroxide or organic peroxides in ammonia or water as a solvent via radical polymerization (Scheme 18).[60]



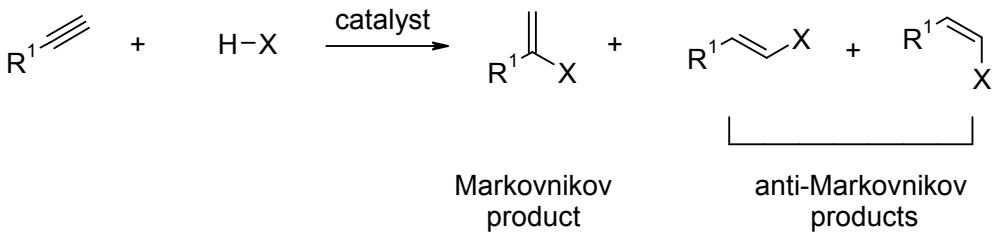
Scheme 18. Polymerization of *N*-vinylpyrrolidinone.

1.3 Addition of heteroatom-hydrogen bonds to alkynes

The catalytic addition of heteroatom-hydrogen (X−H) bonds such as N−H, O−H, S−H, Se−H, and P−H across the carbon-carbon triple bonds is of considerable interest for organic chemists. These reactions are very important from the synthetic point of view because, in principle, the addition reactions can be performed with 100% atom efficiency, without any waste formation, and for this reason they fulfill the requirements of green chemistry better than substitution reactions leading to the same products.

Transition-metal complexes are capable to carry out transformations far more efficiently than nonmetallic compounds. The reactivity of the X−H can be completely different depending on the electronegativity of the heteroatom, its oxidation state, and the nature of the organic residue. It is possible to expect the impact of the electronic effects in the alkyne, i.e., the presence of strong electron-withdrawing or strong electron-donating groups. Certainly, the nature of the transition-metal complex also plays a key role in the reaction.

The main challenge that everyone has to face in these reactions is to control the regio- and stereoselectivity of the product, since the addition of X−H across carbon-carbon triple bond of the terminal alkyne is more likely to produce three product isomers, one resulting from Markovnikov addition and two from anti-Markovnikov addition with *E*- and *Z*-stereochemistry (Scheme 19).



Scheme 19. Regio- and stereoselectivity in addition of heteroatom-hydrogen (X−H) bonds to terminal alkynes.

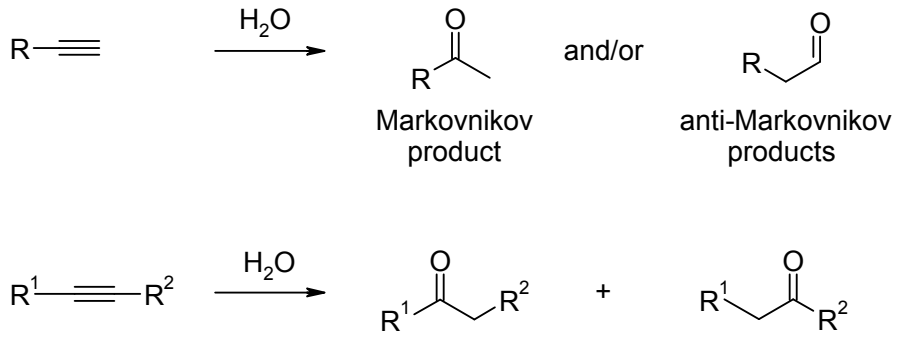
As a result, many synthetically useful alkenyl organic compounds can be obtained. Moreover, the intramolecular version of this reaction (the heteroannulation reaction) is one of the best and straightforward methods to obtain nitrogen- and oxygen-containing heterocycles.

In comparison with other addition reactions, such as radical reactions or those catalyzed by acids and bases, the catalytic X−H addition reactions proceed, as a rule, under much milder conditions, giving higher yields of the products. Without any doubt, this approach to the synthesis of many useful biologically active compounds, building blocks, new materials, monomers, and fine chemicals, among others, has great potential, particularly because the starting materials are relatively readily available and cheap.[61]

In this section, the addition of *O*- and *N*-nucleophiles to alkynes will be covered because of the close relation with the field of this dissertation, particularly from a mechanistic point of view.

1.3.1 Addition of water to alkynes

The addition of water to alkynes is a synthetic method for generating carbonyl compounds. The transformation proceed via the hydration of a triple bond, followed by the tautomerization of the intermediary alkenol. The hydration of terminal alkynes gives either a methyl ketone (Markovnikov addition) or an aldehyde (anti-Markovnikov addition), whereas non-symmetrical internal alkynes can give two regioisomeric ketones (Scheme 20).

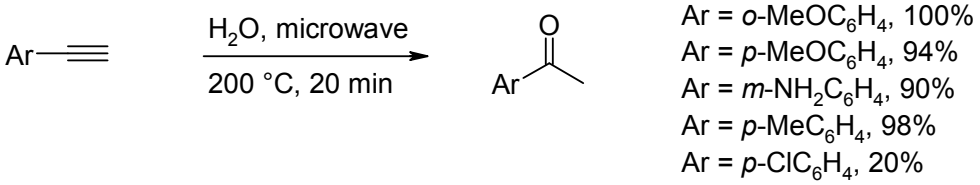


Scheme 20. General scheme of alkyne hydration.

Unlike many other syntheses of carbonyl compounds, the hydration of alkynes is an atom-economical addition without energy-intensive redox chemistry.[62] Since Kucherov's observation (*M. G. Kucherov*; *M. Kutscheroff* in German transliteration) in 1881 that mercury(II) salts catalyze the hydration of alkynes under mild conditions,[63] the reaction has seen many applications in synthesis. The toxicity of mercury compounds and the problems associated with their handling and disposal make the Kucherov reaction unsuitable for modern, sustainable organic synthesis or any large-scale application.[62]

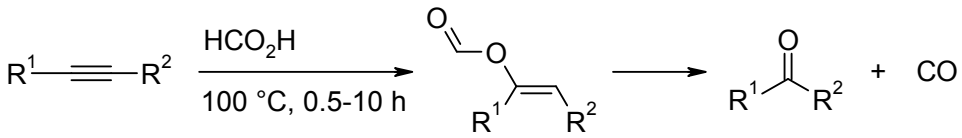
On the other hand, a number of reports have described the utilization of Brønsted acids as an accelerator for the hydration of alkynes. For instance, acetylene and terminal alkynes have been hydrated to Markovnikov products in pure water at elevated temperatures (200–350 °C). More recently, microwave irradiation has become the procedure of choice.[64] Electron-rich aryl-alkynes react readily with high yields, while aliphatic

substrates react with more difficulty (Scheme 21). These reactions are probably catalyzed by H_3O^+, and the addition of protic acids certainly increases the reaction velocity.[65]



Scheme 21. Hydration of alkynes mediated by water.

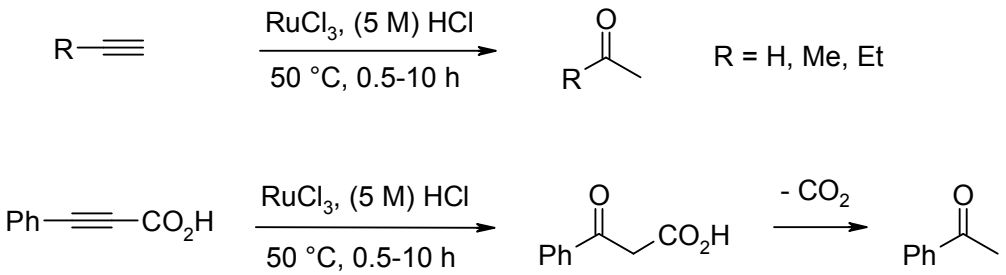
Alkynes are hydrated to ketones in the presence of various acids, such as sulfuric acid at 280 °C,[66] *p*-toluenesulfonic acid (*p*-TsOH) in alcohols at reflux[67] or with microwave heating,[68] catalytic amounts of trifluoromethanesulfonic acid (TfOH) or trifluoromethanesulfonimide (Tf_2NH) in hot dioxane,[69] or a mixture of phosphoric acid and boron trifluoride in benzene-acetonitrile.[70] Moreover, many alkynes are hydrated in refluxing formic acid. Notably, formic acid catalyzes its own addition to the alkyne, and the intermediary enol formate undergoes decarbonylation (Scheme 22).[71]



Scheme 22. Formic acid mediated alkyne hydrations.

A steady development of alternative alkyne hydration catalysts has taken place over the past 30 years, nurtured by the desire to replace mercury(II) by less toxic and more active metal catalysts.[62] Mainly, noble metals such as ruthenium, palladium, and platinum have

been used as catalysts for hydration of alkynes. In 1961, Halpern et al. demonstrated that ruthenium(III) chloride was an effective catalyst for the hydration of acetylene and mono- and disubstituted alkynes under relatively mild reaction conditions. Thus, simple acetylenes and phenylpropiolic acid were converted into methyl ketones and acetophenone, respectively, the latter derived from decarboxylation of the corresponding β-keto acid (Scheme 23).[72]

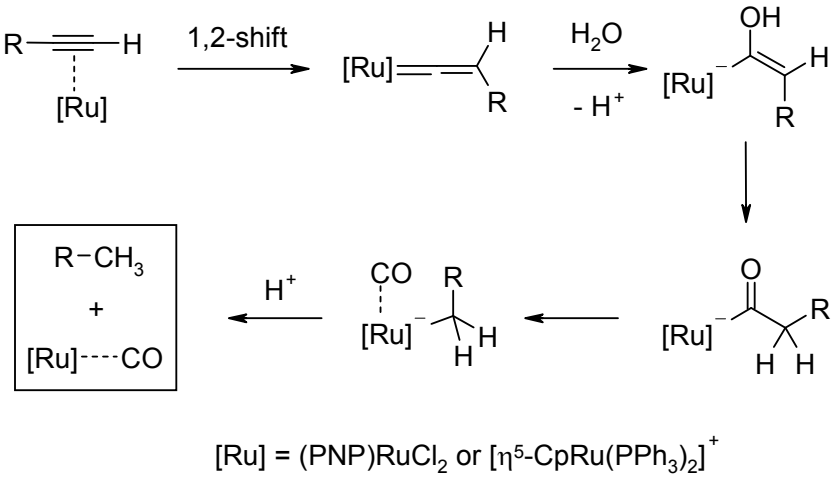


Scheme 23. Ruthenium-catalyzed hydration of alkynes.

Since the catalytically less efficient complex $[Ru^{II}Cl_4(CO)(H_2O)]^{2-}$ and eventually inactive $[Ru^{II}Cl_4(CO)_2]^{2-}$ were formed, catalysis stopped after some time, and the deactivation was faster for higher alkynes.[73]

Khan et al. reported in 1990 the hydration of acetylene catalyzed by the water-soluble complex $K[Ru^{III}Cl(EDTA\text{-}H)]\cdot 2H_2O$ to give cleanly acetaldehyde in neutral aqueous solution at 80 °C.[74]

In spite of precedent reports on the hydration of alkynes using Ru-catalysts,[62] a broadly applicable hydration catalyst has not been found over the years. A mechanistic study by Bianchini and coworkers shed light on possible reasons for catalyst deactivation, whereas ruthenium(II) readily forms vinylidene complexes that add water to give ruthenium-acyl species, the latter decompose to inactive carbonyl complexes with release of alkane rather than aldehyde (Scheme 24).[75]



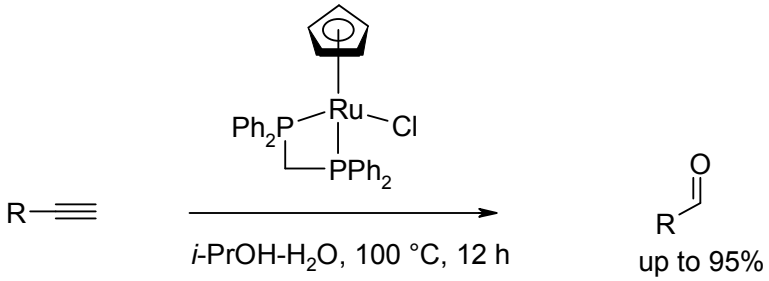
Scheme 24. Bianchini mechanism for the alkyne splitting by water.

The anti-Markovnikov hydration of terminal alkynes could not have been considered a straightforward extension of the reaction principle. As illustrated in Scheme 53, the hydration of alkynes by the vinylidene pathway would stop at the stage of ruthenium(II)–carbonyl complexes with poisoning of the catalyst.

Before 1998, the only reliable method for generating aldehydes from terminal alkynes involved hydroboration using stoichiometric amounts of hindered boranes. Tokunaga and Wakatsuki described the first anti-Markovnikov hydration catalyzed by ruthenium(II) complexes yielding aldehydes from terminal alkynes. The reactions were carried out in the presence of 10 mol% of $[RuCl_2(C_6H_6)(PPh_2(C_6F_5))]$ and 30 mol% of additional ligand $PPh_2(C_6F_5)$ in aqueous isopropanol at temperature between 65-100 °C. The selectivities (aldehyde/ketone) range from 9:1 to 67:1 to alkyl alkynes, but phenylacetylene hardly reacts (< 2% conversion, selectivity 1:1).[76]

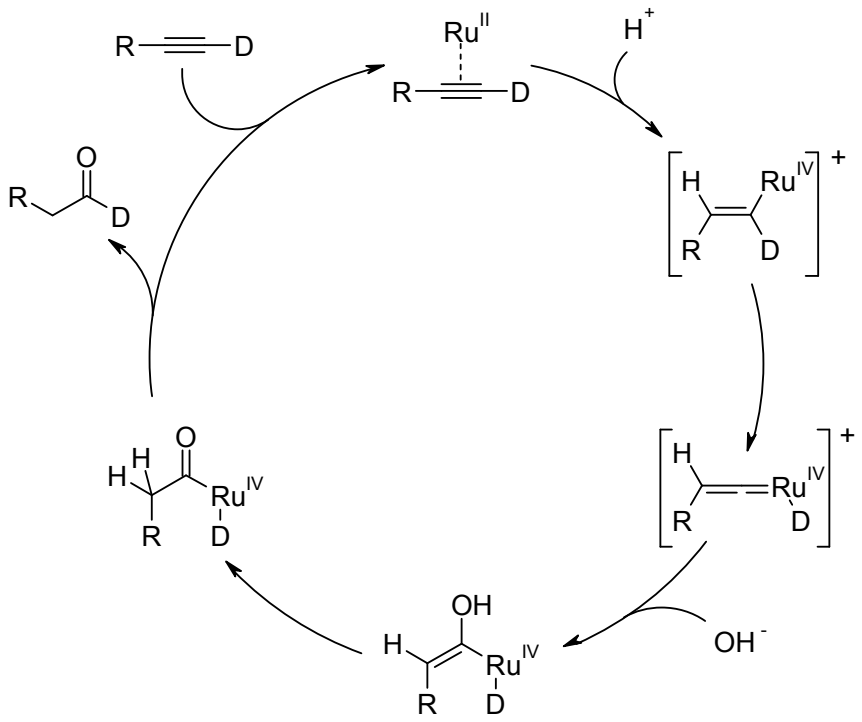
In a further advance, Wakatsuki and co-workers observed a remarkable increase in reaction rate and selectivity with complexes $[CpRu(PR_3)_2]X$ as catalysts (R = aryl, alkyl, bridging alkyl; X = Cl, nonnucleophilic counterion). These hydrations are best carried out with 2-10 mol% of [CpRuCl(dppm)] in isopropanol-water (3:1) at 100 °C and give the aldehydes in good to excellent yields after 12 hours. Various alkynes were converted to the corresponding aldehydes smoothly, including phenylacetylene and the bulky *tert*-

butylacetylene. Moreover, ketones were no longer detected as side-products (Scheme 25).[77]



Scheme 25. Anti-Markovnikov hydration of terminal alkynes.

A plausible reaction mechanism was proposed based on isolating organic and organometallic byproducts, deuterium-labeling experiments, and DFT calculations. An external attack of an η^2-alkyne complex by H^+ leads to a vinyl-ruthenium(IV) species, which is tautomerized to a vinylidene complex by a 1,2-shift of deuterium. Nucleophilic attack by OH^- (or water) at the vinylidene α-carbon atom forms α-hydroxyvinyl complex and then an acyl intermediate. Finally, reductive elimination releases aldehyde in which the original acetylenic hydrogen is bound to the carbonyl carbon (Scheme 26).[78]

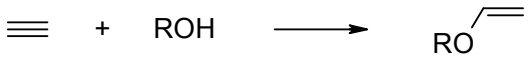


Scheme 26. Mechanistic proposal for the anti-Markovnikov hydration.

Nowadays, Alkynes can be hydrated catalytically to give synthetically useful carbonyl compounds. The reaction has an enormous potential for synthesis, and its importance will probably grow further in the context of sustainable chemistry, since catalytic hydrations can generate products in a fully atom-economic way from unsaturated hydrocarbon feedstocks and water.

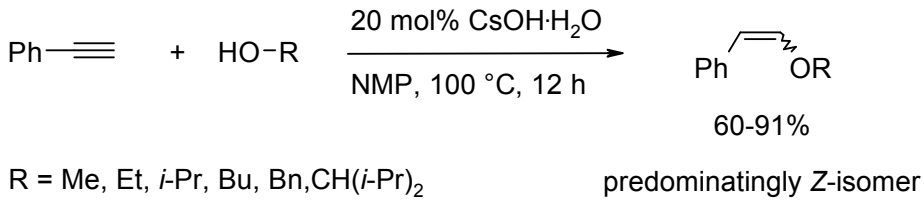
1.3.2 Addition of alcohols to alkynes

The addition of alcohols to alkynes, hydroalkoxylation or alcoholation, represent a direct synthesis of enol ethers and a wide variety of oxygen-containing heterocycles, according to the inter- or intramolecular mode of reaction, respectively. Enol ethers with substituted vinyl groups are of laboratory interest only, whereas vinyl ethers achieved industrial importance as a feedstock for production of poly(vinyl ether)s.[79] Vinyl ethers can be manufactured via the addition of alcohols to acetylene in the presence of strong alkalis in the liquid phase, either at normal pressure or 3 to 20 bar at 120 to 180 °C (Reppe vinylation) (Scheme 27).[80]



Scheme 27. Reppe vinylation.

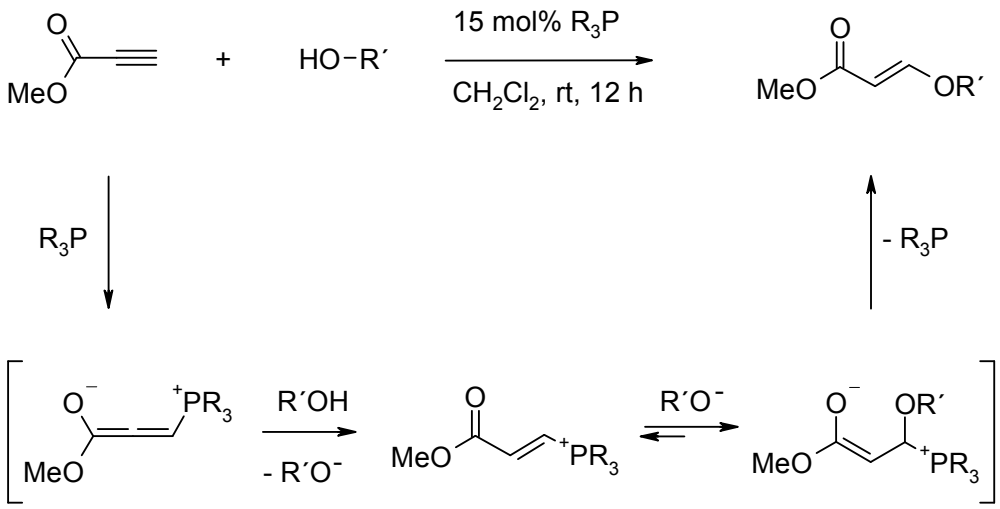
Knochel et al. reported a straightforward synthesis of functionalized enol ethers, based on cesium hydroxide catalyzed alkynylation of aldehydes and ketones, where alcohols undergo intermolecular addition to phenylacetylene in NMP at temperatures of 100 °C (Scheme 28).[81]



Scheme 28. Cesium hydroxide mediated addition of alcohols to phenylacetylene.

In 1993, Inanaga et al. reported that the conjugate addition of alcohols to propargylic acid esters gives rise to the corresponding β-alkoxy-α,β-unsaturated alkenic acid esters in the presence of catalytic amounts of trialkylphosphine. Good to excellent yields were

obtained for the addition of various alcohols under neutral conditions within 10 min at room temperature (Scheme 29).[82]



R = *n*-Bu_3P. R´-OH= primary, secondary allylic, benzylic, and homoallylic alcohols

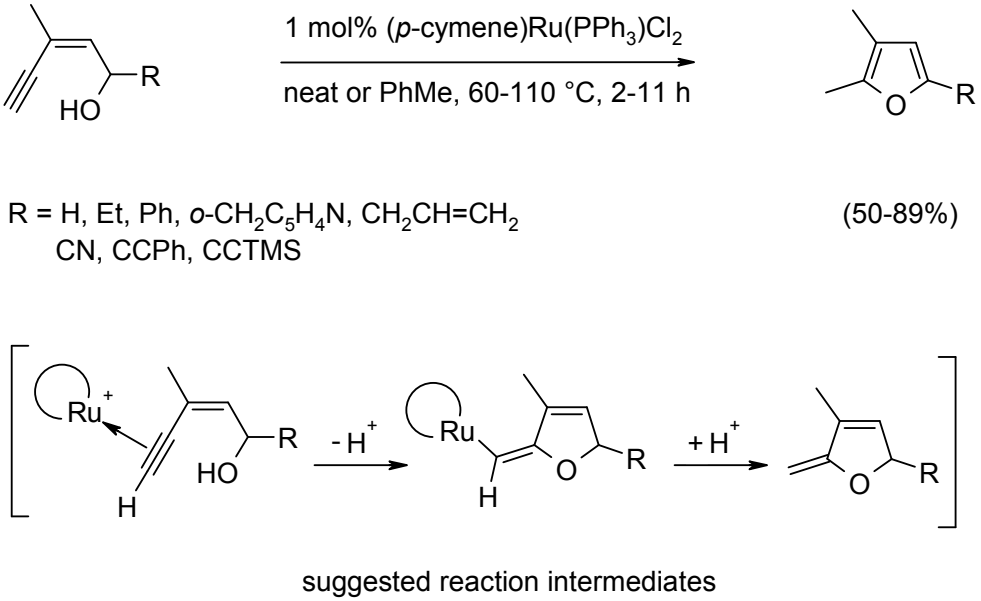
Scheme 29. Phosphine mediated addition of alcohol to methyl propiolate.

The proposed reaction mechanism is that trialkylphosphine attacks the β-position of methyl propiolate to give a phosphonium enolate intermediate. It then abstracts proton from alcohol to form a phosphonium alkoxide. Conjugated addition of the alkoxy anion, followed by elimination of the phosphine leads to 3-alkoxyacrylate as the final product.

Further reports showed that some transition metal complexes such as Mo, W, Ru, Pd, Pt, Cu, Ag, and Au are useful for the activation of alkynes either for inter- or intramolecular hydroalkoxylation processes.[61]

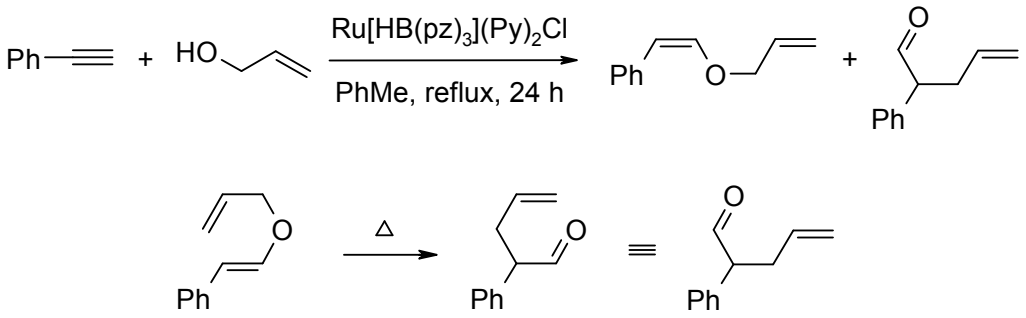
Dixneuf et al. described an effective synthesis of furans by selective cyclization of (*Z*)-pent-2-en-4-yn-1-ols in the presence of $Ru(PPh_3)(p\text{-cymene})Cl_2$ as catalyst precursor. Although the reaction is specific for terminal alkynes, participation of a vinylidene-ruthenium intermediate was ruled out since that pathway would lead to a six membered cyclic product not detected by the authors. Instead, a mechanism based on the

electrophilic activation of the carbon-carbon triple bond followed by intramolecular addition of the hydroxy group to the internal alkyne carbon atom was suggested (Scheme 30).[83]



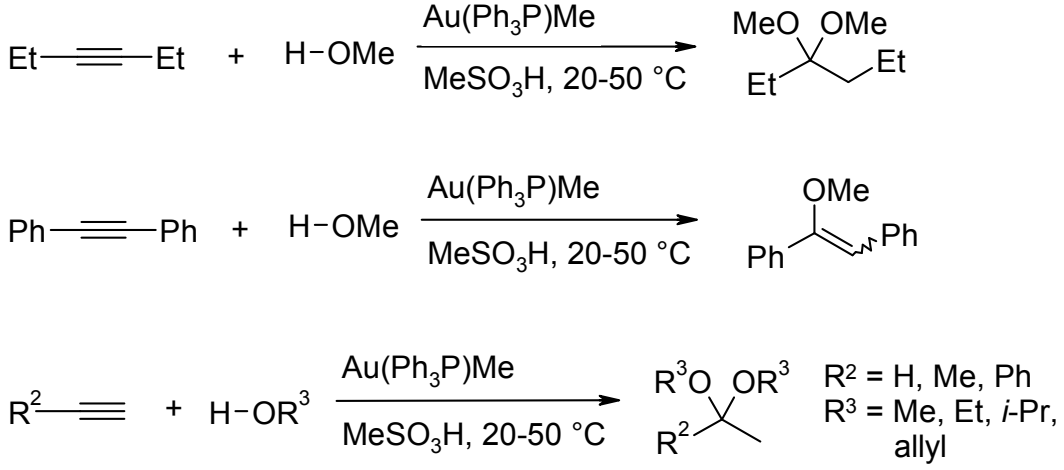
Scheme 30. Markovnikov hydroalkoxylation catalyzed by a ruthenium complex.

In 1996, Kirchner et al. reported the first intermolecular addition of allyl alcohols to acetylenes via ruthenium catalysis. Thus, by heating phenylacetylene and an excess amount of allyl alcohol with 2 mol% of ruthenium complexes bearing the tris(pyrazolyl)borate ligand [$HB(pz)_3$], a 1:1 mixture of the *Z*-allyl vinyl ether and the aldehyde derived from the Claisen rearrangement of the *E*-allyl vinyl ether was obtained in 72% overall yield (Scheme 31).[84]



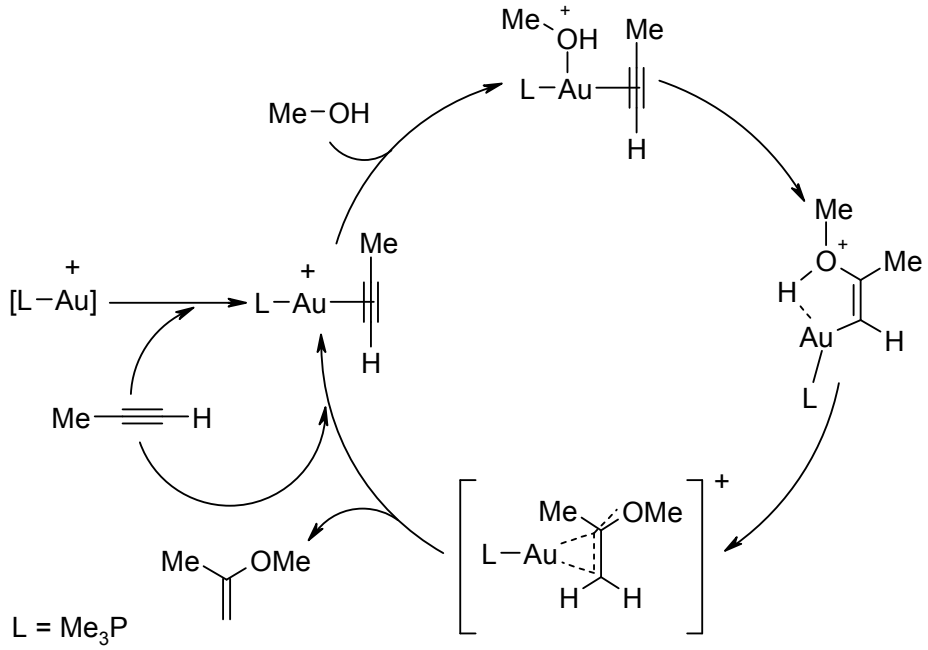
Scheme 31. Ruthenium-catalyzed addition of allyl alcohol to phenylacetylene.

In 1998, Teles et al. used methyl(triphenylphosphine)gold(I) and methanesulfonic acid (cocatalyst) as precursors for the in situ generation of the catalyst in the addition of alcohols to differently substituted alkynes under mild reaction conditions. With internal symmetrical alkynes, the corresponding acetals were formed, unsymmetrical and terminal alkynes leading to addition products exclusively at the more substituted carbon atom. The reactivity of the substrates was found to increase with increasing electron density of the carbon-carbon triple bond and decreasing steric hindrance. However, the reactivity of the alcohols decreased by a factor of 10 when going from primary to secondary alcohols, tertiary alcohols and phenols being unreactive (Scheme 32).



Scheme 32. Highly active gold(I) catalyzed addition of alcohols to alkynes.

The proposed reaction mechanism based on experimental evidence and ab initio calculations, starting with the formation of a cationic gold(I) complex by protonolysis of the methylgold complex, nucleophilic attack of the alcohol onto the activated gold(I) propyne complex through an associative mechanism involving coordination of methanol to gold. A rearrangement of the resulting complex by a 1,3-hydrogen migration, and final ligand exchange leads back to the initial cationic gold-alkyne complex, closing the catalytic cycle (Scheme 33).[85]

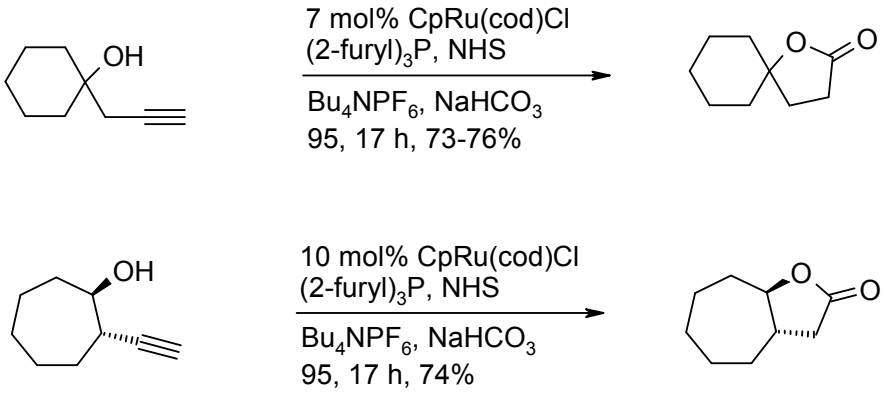


Scheme 33. Proposed mechanism for the addition of MeOH to propyne by $Au(Me_3P)^+$.

A few years later, an extension of this catalyst system for alkyne hydration was achieved simply by the choice of aqueous methanol as a solvent and a range of simple alkynes as substrates.[86]

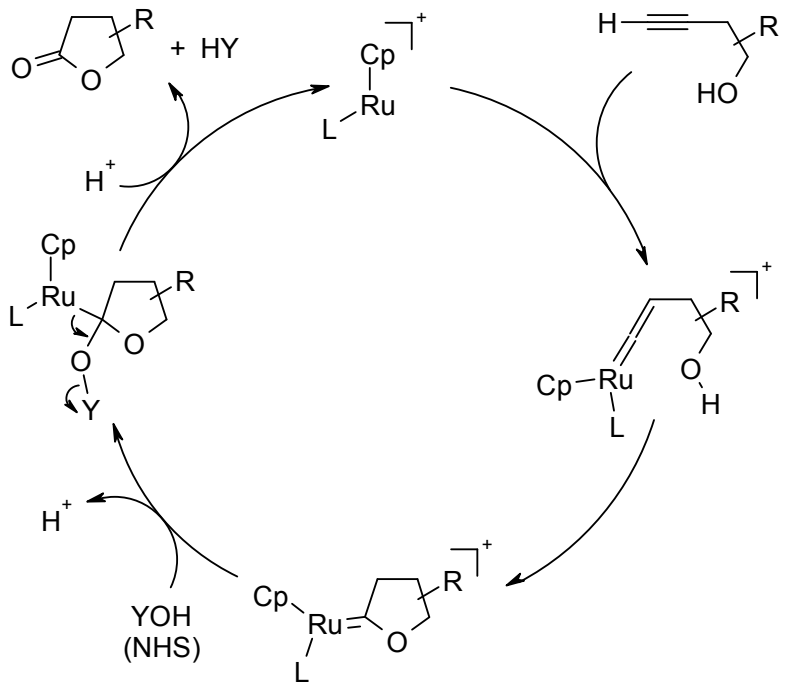
Moreover, Trost and Rhee developed a mild oxidative cyclization of homopropargylic alcohols to the corresponding γ-butyrolactones, catalyzed by a ruthenium complex. The reactions were performed with 5-10 mol% of CpRu(cod)Cl and tri(furyl)phosphine as

precatalyst, in the presence of tetra-*n*-butylammonium bromide or hexafluorophosphate, sodium bicarbonate, and *N*-hydroxysuccinimide (NHS) as the oxidant, in DMF-H_2O at 95 °C. A wide variety of γ-butyrolactones were synthesized by this method, most of them being natural products with important biological activities (Scheme 34).



Scheme 34. Selected examples of oxidative cyclization of homopropargylic alcohols.

In the proposed catalytic cycle, the homopropargylic alcohol reacts with a ruthenium complex to form an oxacarbene species, presumably via nucleophilic addition to a vinylidene carbene intermediate. Oxidation of the oxacarbene species with the nucleophilic *N*-hydroxysuccinimide and subsequent release of the tetrahydrofuran moiety closes the catalytic cycle of the cycloisomerization (Scheme 35).[87]



Scheme 35. Plausible catalytic cycle of oxidative cyclization of homopropargylic alcohols.

Despite the different studies carried out on the nucleophilic addition of alcohols to alkynes in super basic catalytic systems, namely, alkali-metal hydroxides, transition-metal compounds are still the catalysts of choice to carry out the hydroalkoxylation of alkynes due to their effectiveness and wide scope of application.[88]

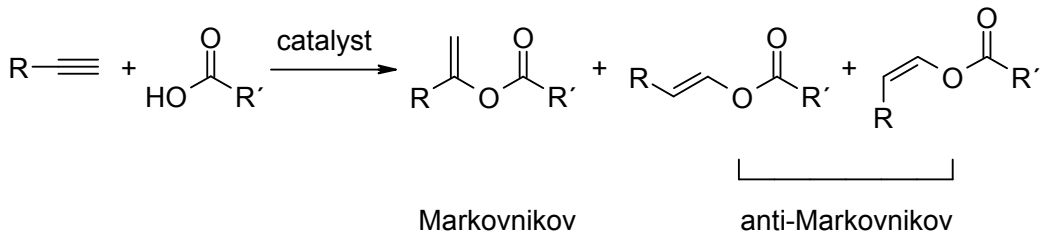
1.3.3 Addition of carboxylic acids to alkynes

The catalytic addition of carboxylic acids to alkynes is of paramount importance primarily for the large scale production of industrially useful simple compounds such as vinyl acetate, monomer precursor of poly(vinyl acetate) and poly(vinyl alcohol).[88]

Klatte in 1912 prepared the first vinyl esters, vinyl trichloroacetate and vinyl acetate, by treatment of acetylene with the corresponding carboxylic acids using mercury salt as catalyst. Initially, the reaction was used for the industrial production of vinyl chloroacetate. The polymer obtained from this vinyl ester was used during World War I as a varnish for airplanes.[89]

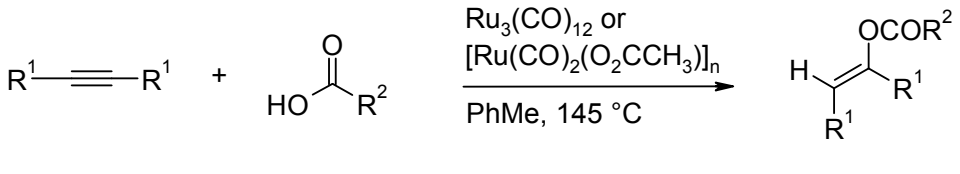
Vinyl acetate was also prepared by addition of sodium acetate to acetylene catalyzed by zinc acetate on charcoal at about 200 °C. At present the most common method is a modification of the Wacker reaction with a $PdCl_2$-$CuCl_2$ catalyst. However, there is still no general method for the effective catalytic addition of carboxylic acids to alkynes. It is worth noting that the most significant achievements in this field have been attained using ruthenium complexes as precatalysts, mainly for intermolecular processes, whereas palladium catalysts have found wide application for intramolecular reactions.[61]

The addition of carboxylic acids, hydro-oxycarbonylation, to alkynes often affords a mixture of three possible 1-alkenyl esters, one Markovnikov-type adduct and two anti-Markovnikov-type, *E* and *Z* adducts (Scheme 36).



Scheme 36. Possible isomers formed from addition of carboxylic acid to terminal alkynes.

Rotem and Shvo reported the first ruthenium-catalyzed intermolecular addition of carboxylic acids to alkynes using $Ru_3(CO)_{12}$ as catalyst precursor, which allows the *syn*-selective addition of aliphatic or aromatic carboxylic acids to electron-poor and -rich internal alkynes to the corresponding *E*-enol esters (Scheme 37).[90]

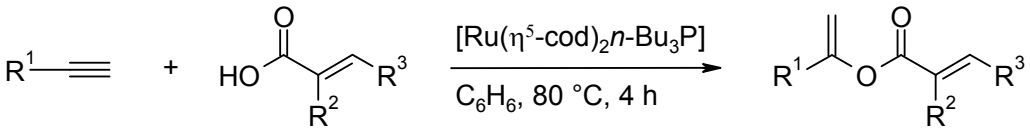


R^1 = *n*-Pr, Ph, CO_2Me
R^2 = Me, *t*-Bu, Ph, *p*-MeC_6H_4, *p*-FC_6H_4

(50-95%)

Scheme 37. First ruthenium-catalyzed addition of carboxylic acids to alkynes.

Mitsudo, Watanabe et al. reported the reaction of α,β-unsaturated carboxylic acids with terminal alkynes in the presence of a catalytic amount of Ru(η^5-cod)$_2$*n*-Bu_3P in benzene at 80 °C, furnishing the corresponding Markovnikov enol esters with high regioselectivity (Scheme 38).



R^1 = *n*-Pr, *t*-Bu
R^2 = H, Me
R^3 = H, Me, *E*-MeCH=CH

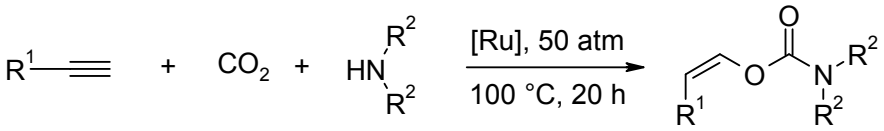
(40-79%)

Scheme 38. Markovnikov addition of unsaturated carboxylic acids to alkynes.

A postulated reaction pathway suggests the formation of a hydrido(carboxylate)-ruthenium(IV) complex by oxidative addition of the O–H bond of the carboxylic acid to the Ru(II) complex, followed by insertion of the alkyne into the Ru–H bond. Reductive elimination releases the product and regenerates the active catalyst.[91]

The ruthenium-catalyzed addition of carboxylic acids and related substrates like carbamates to alkynes has been better understood by the group of Dixneuf due to the deep studies and outstanding contributions. The early work focused on the ruthenium-catalyzed synthesis of vinyl carbamates from terminal alkynes, carbon dioxide, and diethylamine. The reaction was performed under 50 atm CO_2 at 140 °C for 20 h using $Ru_3(CO)_{12}$ as catalyst. However, the reaction exhibited low selectivity, giving mixtures of regio- and stereoisomers (similar product as in Scheme 36).[92]

Better results were observed for mononuclear ruthenium catalysts such as $RuCl_3 \cdot XH_2O$, $[(p\text{-cymene})RuCl_2]_2$, $[(p\text{-cymene})Ru(PMe_3)Cl_2]$, $[(C_6Me_6)Ru(PMe_3)Cl_2]$, or $[(NBD)Ru(Py)_2Cl_2]$. Both the yield and selectivity were notably improved, the carbamate adding exclusively to the terminal carbon of the alkyne with major *Z*-stereochemistry (Scheme 39).[93]

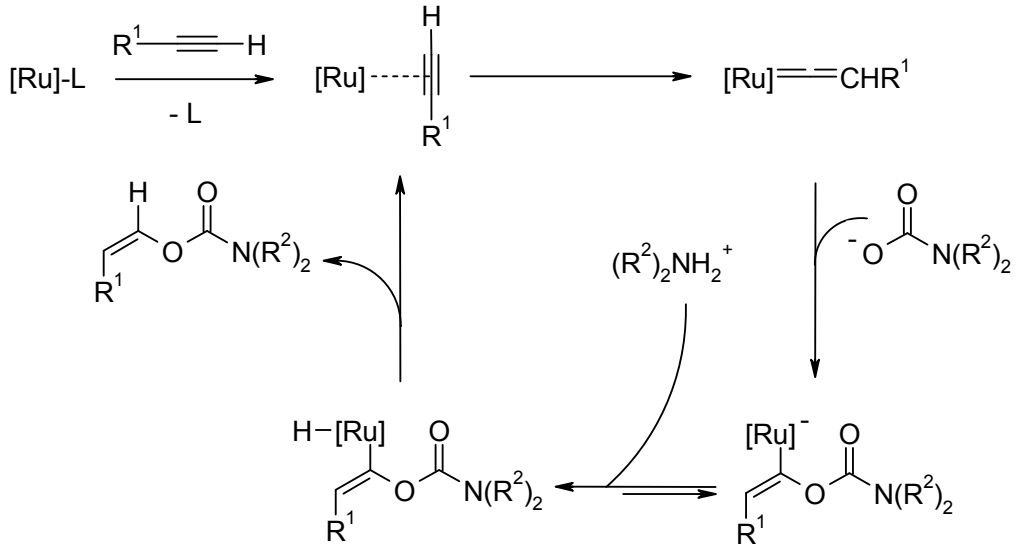


R¹ = *n*-Bu, Ph
R² = Me, Et, $(CH_2)_5$, $(CH_2CH_2)_2O$

(16-67%)

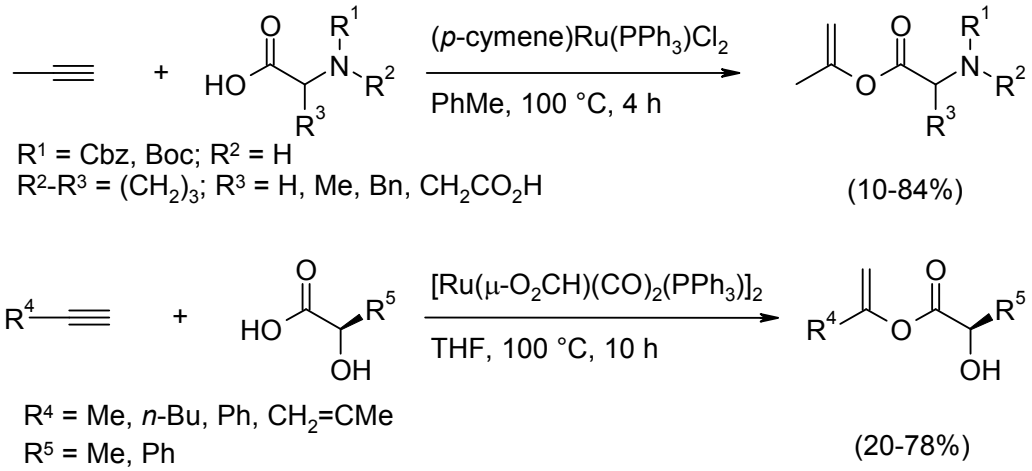
Scheme 39. Ruthenium-catalyzed addition of carbamates to alkynes.

It is noteworthy that this catalytic formation of vinyl carbamates is restricted to secondary alkylamines, no addition being observed for primary amines. The fact that only terminal but not internal alkynes react, led the authors to propose a mechanism involving vinylidene-ruthenium species.[94] Thus, rearrangement of the η^2-alkyne-metal complex to a η^1-vinylidene-metal intermediate followed by addition of the carbamate to the more electrophilic carbon atom. Protonation takes place at the metal center and final reductive elimination would account for the formation of the vinylcarbamate. Though no comment is made regarding the stereoselectivity of the reaction, the *Z*-stereochemistry may be preferred in order to minimize the steric repulsion between the R^1 group and the bulkier ruthenium atom (Scheme 40).[93]



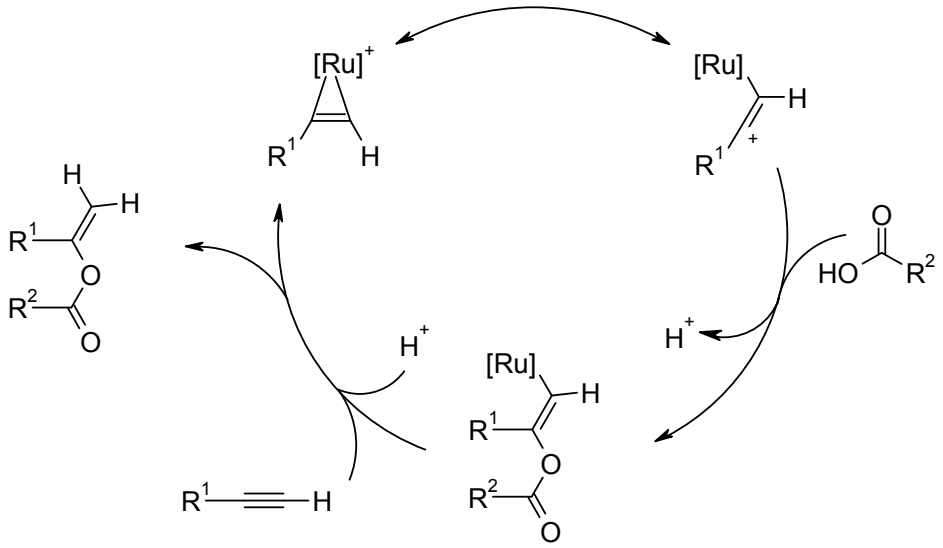
Scheme 40. Proposed mechanism for ruthenium-catalyzed addition of carbamates to alkynes.

The Markovnikov-selective addition of carboxylic acids to terminal alkynes producing geminal enol esters has been carried out with a variety of efficient ruthenium precursors by Dixneuf and coworkers. Under relatively mild reaction conditions (100 °C, 2-3 bar, 4 h), the regioselective addition of *N*-protected amino acids to propyne is catalyzed by arene-ruthenium-phosphine complexes, providing the corresponding isopropenyl amino esters. The reaction occurs with neither deprotection of the amino group and nor racemization, while no addition can be taken place for unprotected amino acids.[95] Moreover, α-hydroxy acids also could be added to terminal alkynes, catalyzed by [Ru(μ-O_2CH)$(CO)_2(PPh_3)]_2$. The reaction is performed in THF and the corresponding enol esters can be obtained in moderate to good yields, without any racemization (Scheme 41).[96]



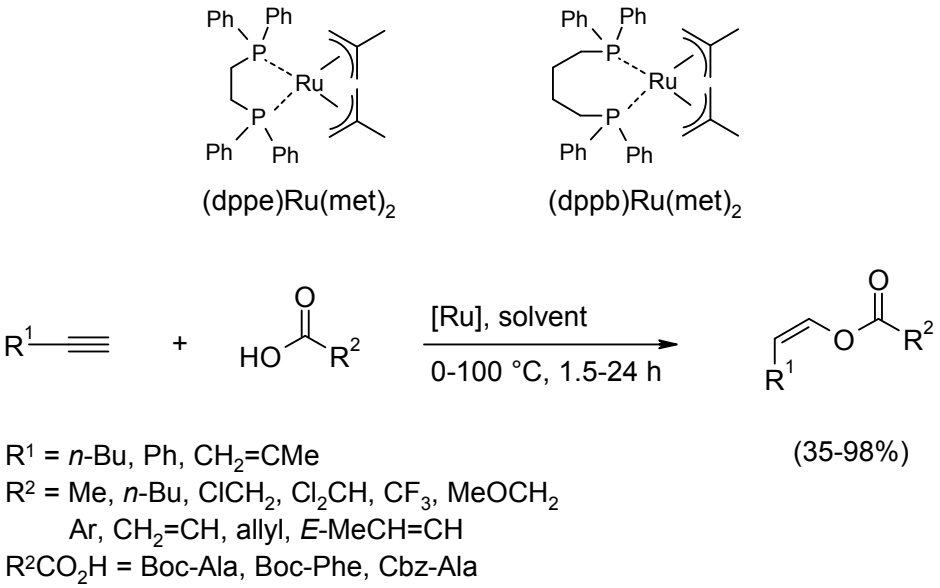
Scheme 41. Ruthenium-catalyzed Markovnikov addition of carboxylic acid derivatives to alkynes.

The following catalytic cycle was proposed including an electrophilic activation of the carbon-carbon triple bond by ruthenium, followed by a nucleophilic *trans*-attack of the carboxylate to the substituted carbon, and finally protonation of the resulting intermediate gives rise to the product with regeneration of the active catalyst (Scheme 42).[97]



Scheme 42. Proposed catalytic cycle for Markovnikov addition of carboxylic acids to alkynes.

In the early 1990s, Dixneuf et al. introduced a bis-(2-methylallyl)ruthenium complex containing chelating ligands like dppe or dppb. The use of $[Ph_2P(CH_2)_nPPh_2]Ru[\eta^3\text{-}CH_2{=}C(Me)CH_2]_2$ (n = 2, 4) as a catalyst, completely reversed the previously observed regiochemistry for the addition of carboxylic acids to alkynes.[98] The corresponding anti-Markovnikov *Z*-enol esters can be obtained in a stereoselective manner as a result of direct addition of the carboxylic acid to the terminal alkyne. The best selectivity can be observed for the catalyst precursor with the dppb ligand, except for the addition to the bulky $HC{\equiv}CSiMe_3$, where the dppe ligand is superior (Scheme 43).[99]

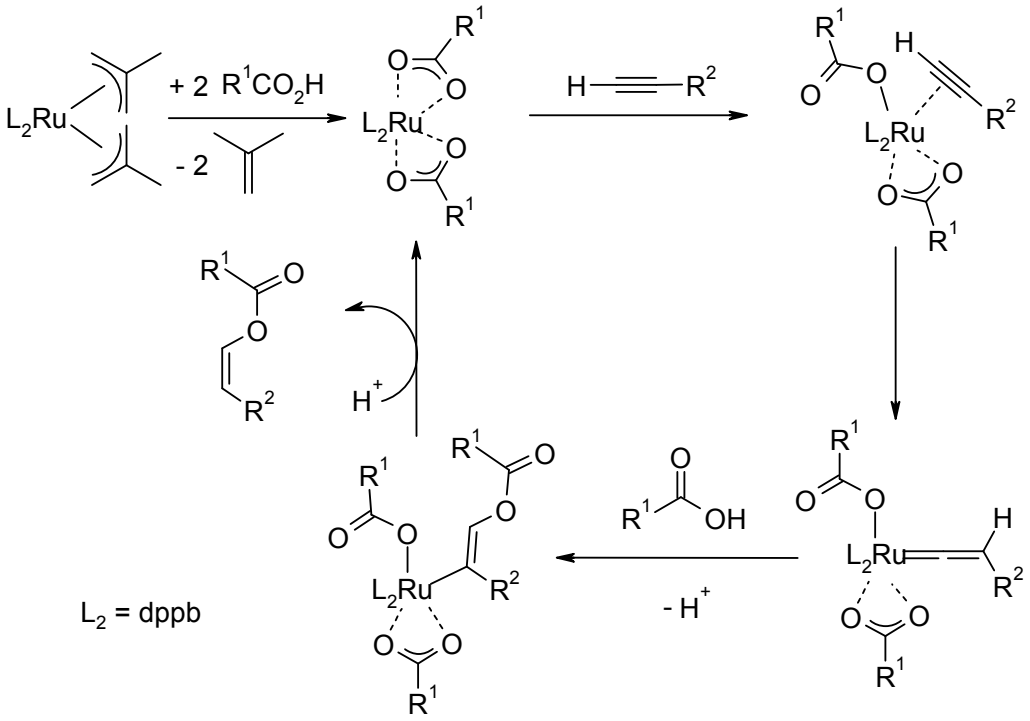


Scheme 43. Ruthenium-catalyzed anti-Markovnikov addition of carboxylic acids to alkynes.

Thus, steric effects (also in the substrates) rather than electronic factors are used to control the regio- and stereoselectivity.

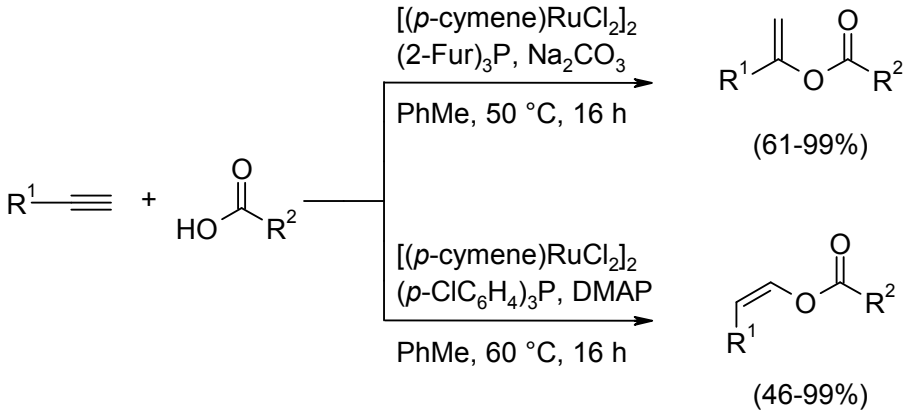
It was also established that these complexes lead to the in situ formation of the corresponding $[Ph_2P(CH_2)_nPPh_2]Ru(\eta^2\text{-}O_2CR)_2$ (R = Ph, CF_3) intermediates acting as efficient catalyst precursors. A mechanism of this catalytic reaction was proposed in a way that terminal alkyne coordinates to Ru-carboxylate complex, after displacement of the 2-methylpropene ligands by carboxylic acids. A subsequent rearrangement of the η^2-

alkyne-metal complex to a η^1-vinylidene-metal intermediate (including 1,2-H shift) followed by addition of the carboxylic acid to the more electrophilic carbon atom. Protonation at the metal center, and final reductive elimination would account for the formation of vinyl carboxylate and generation of the active catalyst (Scheme 44).[99]



Scheme 44. Proposed mechanism for anti-Markovnikov addition of carboxylic acids to alkynes.

A contribution to this field was made by Gooßen and Paetzold, who found that catalytic addition of carboxylic acids to terminal alkynes was drastically enhanced by the addition of small quantities of base. In presence of 0.4-1.0 mol% of [(*p*-cymene)$RuCl_2$]$_2$ as ruthenium precursor, both Markovnikov and anti-Markovnikov products are easily accessible in excellent selectivities, controlled only by the choice of the base and the ligand (Scheme 45).[100]

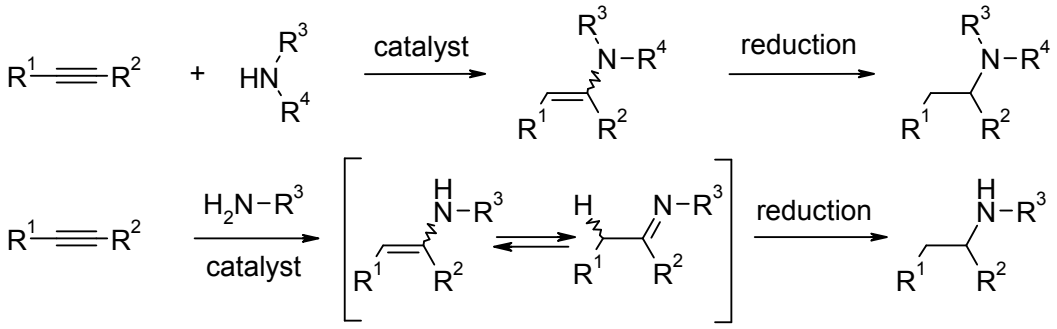


Scheme 45. Ruthenium-catalyzed regioselective addition of carboxylic acids to alkynes

In summary, the wide scope and application of the addition of carboxylic acids to alkynes using ruthenium catalysts is reflected in the numerous protocols which appeared in the literature covering or including the addition of carboxylic acids to alkynes.[101] A better understanding of the reaction mechanism could be the key for optimizing the catalyst system and increasing the selectivity and the scope of the reaction.

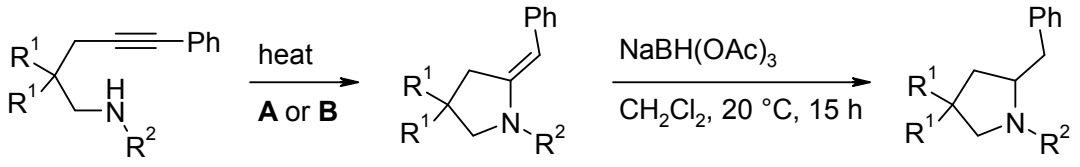
1.3.4 Addition of amines to alkynes

Primary and secondary amines can undergo addition reactions with C−C multiple bonds to furnish valuable amines and imines, which are important bulk and fine chemicals, biologically interesting compounds, or versatile synthetic intermediates. These reactions of fundamental simplicity are known as hydroaminations of alkynes and they take place without any formation of side products, as can be seen in Scheme 46. Though, for electrostatic reasons, amines generally do not react spontaneously with alkynes, as long as they are not activated by electron withdrawing substituents, because both reactants are electron rich. As a consequence, the addition of amines to alkynes can efficiently be achieved only in the presence of certain catalysts.[102]



Scheme 46. General reaction of addition of amines to alkynes.

A variety of both catalytic and non-catalytic methods have been disclosed in the literature to overcome the high activation energy required for this process. For example, Cossy et al. reported the simple thermal- and acid promoted cyclization of aminoalkynes, the main weakness of this methodology being the elevated temperatures required (150-210 °C) and the need of having a phenyl acetylene moiety in the starting structure (Scheme 47).[103]



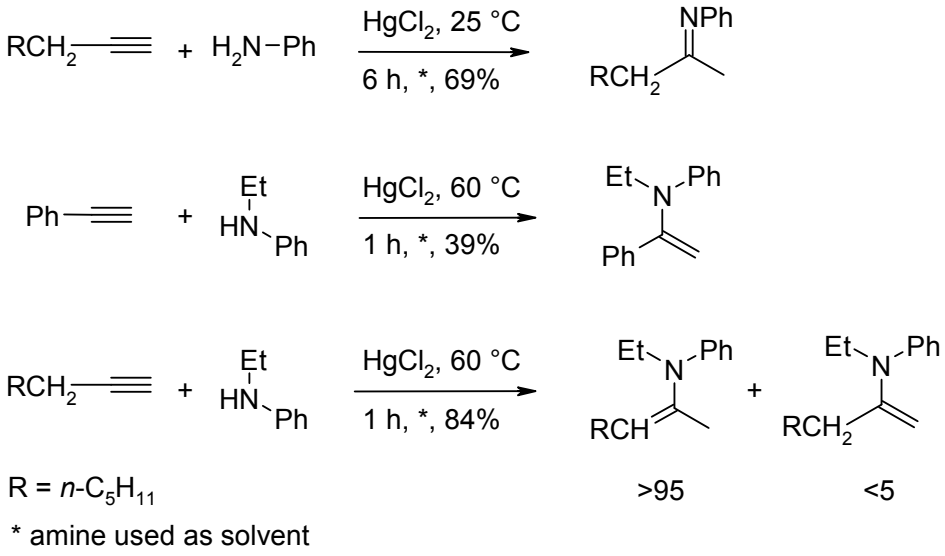
A: AcOH (1 eq), 150 °C
R^1 = Me; R^2 = *n*-Bu; 50 min; 95%
R^1 = Me; R^2 = $CH(CH_3)Ph$; 17 h; 66%
R^1, R^1 = $(CH_2)_5$; R^2 = Bn; 1.5 h; 97%

B: 180-210 °C
R^1 = Me; R^2 = *n*-Bu; 2 h; 58%
R^1 = Me; R^2 = $CH(CH_3)Ph$; 27 h; 35%
R^1, R^1 = $(CH_2)_5$; R^2 = Bn; 2.5 h; 60%

Scheme 47. Thermal and acid promoted cyclization of aminoalkynes.

Metallic salts and oxides were employed since 1877 and until the mid of the 20th century to promote mainly the addition of ammonia or simple amines to acetylene, with the aim of manufacturing valuable nitrogen-containing products.[88]

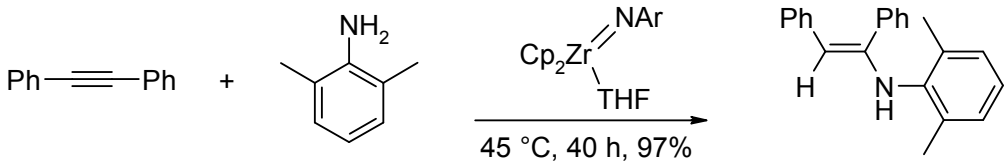
Other metallic salts such as $HgCl_2$, $Hg(OAc)_2$, or $Tl(OAc)_3$ were extensively studied by Barluenga et al. in the catalytic and noncatalytic addition of various amines to alkynes.[104] Terminal alkynes and aniline react in the presence of mercury(II) chloride (5%) at room temperature to produce *N*-phenylalkylideneamines arising from the isomerization of the initially formed vinylamines. On the other hand, phenylacetylene and secondary aromatic amines afford a *N*-vinylamine as a stable Markovnikov hydroamination product, but aliphatic terminal alkynes and secondary aromatic amines give rise to a mixture of enamines (Scheme 48).[105]



Scheme 48. Hydroamination of terminal alkynes catalyzed by $HgCl_2$.

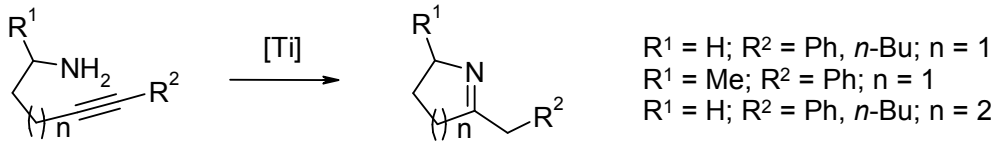
Catalysis based on titanium and zirconium complexes has significant advantges compared to that based on some toxic (Hg, Tl) or more expensive metals (Ru, Rh, Pd, U, Th). There are many titanium complexes that can be used as precursors, some of them are readily available and relatively cheap however others can be generated in situ. The main difference among them is the presence or absence of a cyclopentadienyl group (Cp). Nevertheless, it seems to be quite clear that the real catalyst must contain an imido-titanium fragment.[106]

The monomeric titanium complexes of the type $CpTi(NHR)Cl_2$ undergo self-condensation to provide the corresponding imido dimers at room temperature. While several thermally stable monomeric imidozirconocene complexes of the type $Cp_2Zr{=}NR$ were first described by Bergman et al., in addition to their reaction with alkynes.[107] Moreover, this group utilized bisamides of the type $Cp_2Zr(NHR)_2$, as catalyst precursors, in the addition of 2,6-dimethylaniline to diphenylacetylene (Scheme 49).[108]



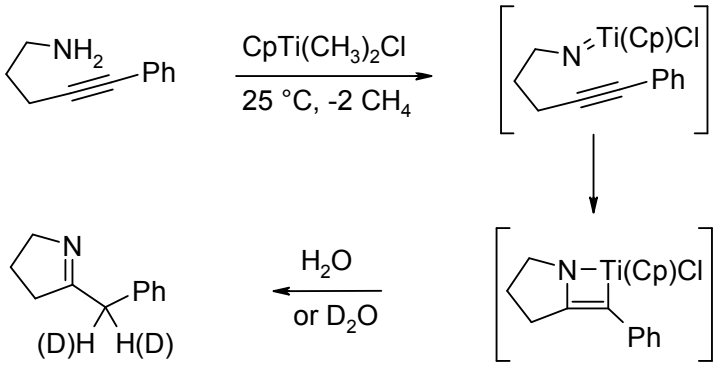
Scheme 49. Zirconium-catalyzed addition of 2,6-dimethylaniline to diphenylacetylene.

Livinghouse et al. used $CpTiMe_2Cl$ and $CpTiCl_3$ as catalyst precursors for a variety of intramolecular hydroaminations leading to the construction of functionalized dihydropyrrole and tetrahydropyridine derivatives (Scheme 50).[109]



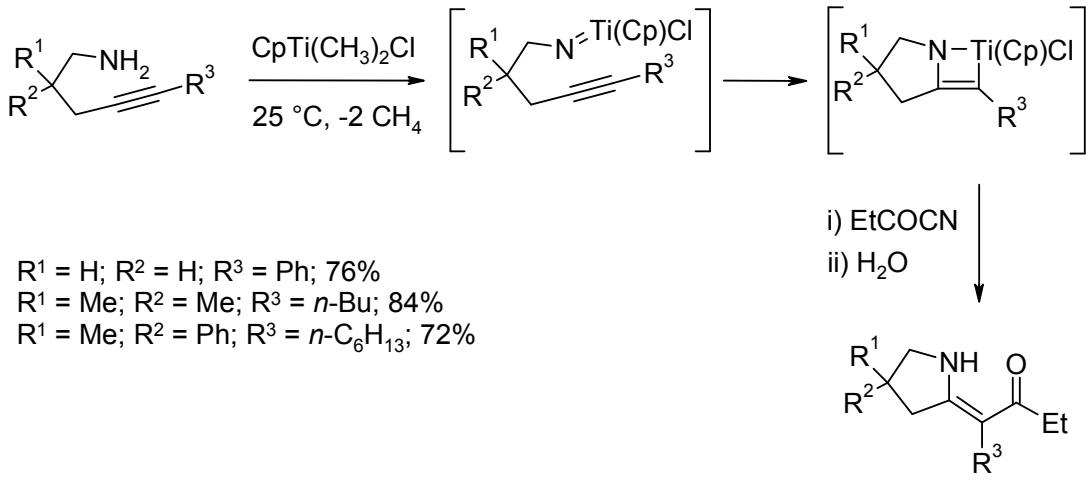
Scheme 50. Titanium-catalyzed intramolecular hydroamination of aminoalkynes.

All reactions proceed under mild reaction conditions and in high yields. The proposed mechanism involves the formation of an imido complex, followed by a [2 + 2] cycloaddition, and protonolysis or deuteriolysis (Scheme 51).



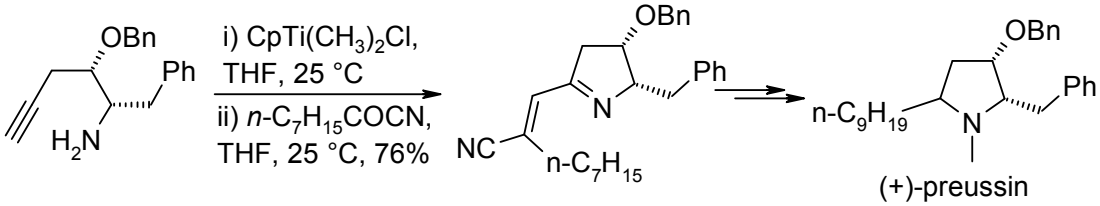
Scheme 51. Proposed mechanism for intramolecular hydroamination of aminoalkyne.

On the other hand, the predisposition of acyl cyanides to take part in chemoselective *C*-acylation of azatitanetines generated via [2 + 2] cycloaddition of transient Ti-imido complexes with alkynes, provided a range of functionalized tetrahydropyrroles in good to excellent yields (Scheme 52).[110]



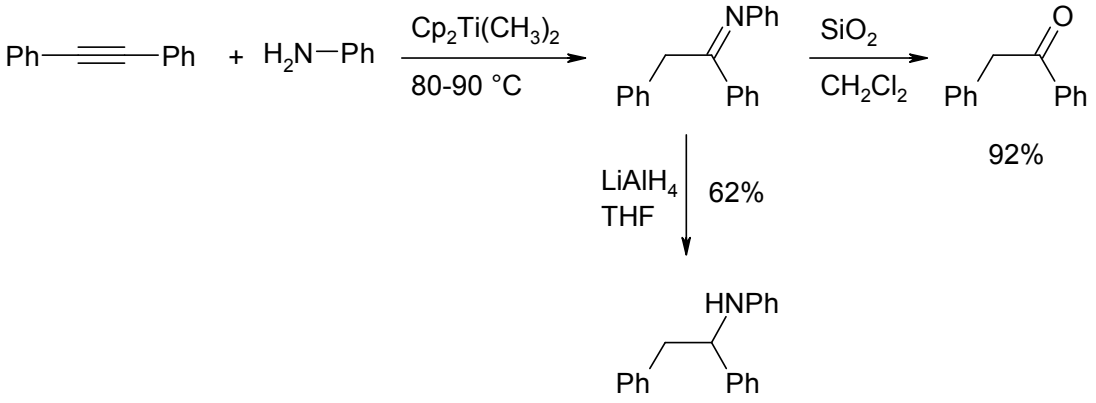
Scheme 52. Synthesis of a range of functionalized tetrahydropyrroles via hydroamination reaction.

This catalytic reaction was successfully applied to the total synthesis of physiologically active indolizidine alkaloids (±)-monomorine[111] and the antifungal agents (+)-preussin (Scheme 53).[112]



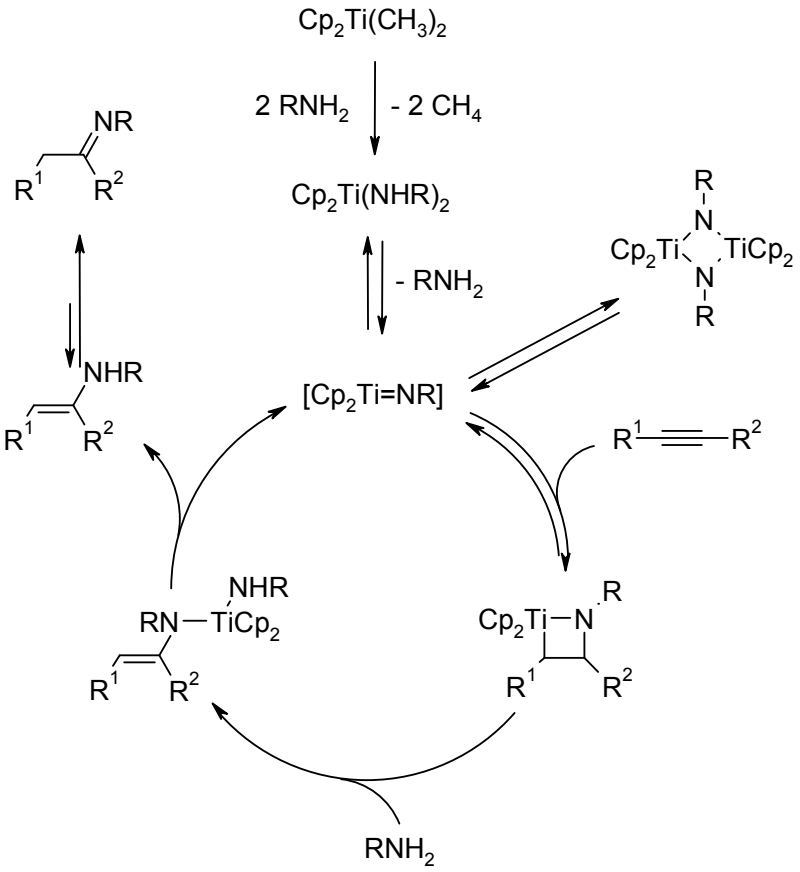
Scheme 53. Consecutive synthesis of (+)-preussin via hydroamination reaction.

The catalytic intermolecular hydroamination of alkynes is more difficult to achieve than the intramolecular version. In 1999, Doye et al. reported on this transformation, relatively inexpensive and readily available catalyst, dimethyltitanocene [Cp_2TiMe_2]. As an example, the reaction of diphenylacetylene with aniline in the presence of 1 mol% Cp_2TiMe_2 in C_6D_6 at 80-90 °C gives *N*-(1,2-diphenylethylidene)aniline, which can be detected by ^{1}H-NMR spectroscopy. The enamine structures tautomerize to imines, which due to their potential low stability are subjected to in situ hydrolysis or reduction, affording the corresponding carbonyl compounds and amines, respectively (Scheme 54).[113]



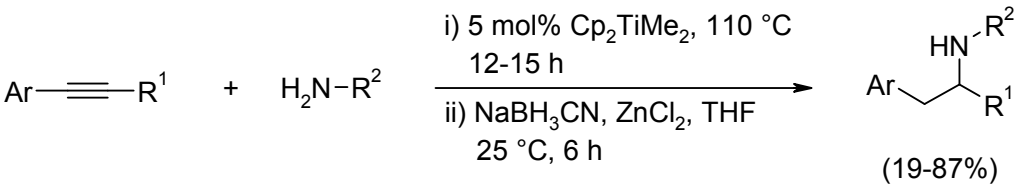
Scheme 54. First intermolecular hydroamination of alkynes.

The proposed catalytic cycle starts with the reaction of the Cp_2TiMe_2 precursor with an amine. By loss of methane, would give the catalytically active titanium-bisamide or titanium-imido species, which undergoes a reversible [2 + 2] cycloaddition to the alkyne. Protonolysis of the Ti-C(sp^2) bond by RNH_2 in the azatitanacyclobutene leads then to a bisamide Ti complex, which thermally eliminates the product and generating the catalytic species (Scheme 55).



Scheme 55. Proposed catalytic cycle for intermolecular hydroamination of alkynes.

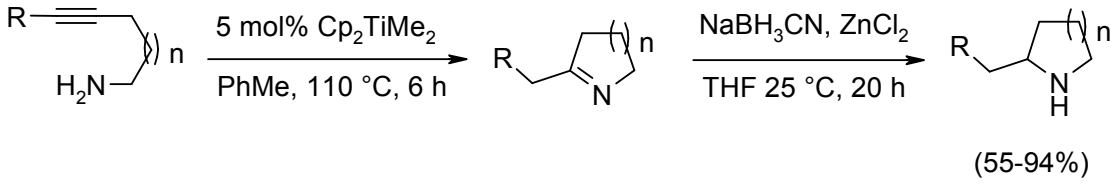
Siebeneicher and Doye reported a one-pot synthetic method for the generation of 2-arylethylamines. These compounds represent interesting building blocks for the synthesis of complex nitrogen-containing molecules and also attractive molecules for medicinal chemistry. Regioselective hydroamination at the 2-position of alkyl(aryl)alkyne, gives access to an α-arylketimine. A final in situ reduction with $NaBH_3CN/ZnCl_2 \cdot Et_2O$ results in the formation of the secondary derivative. (Scheme 56).[114]



Ar = *m*-$MeOC_6H_4$, *o*-$CF_3C_6H_4$, *p*-$CF_3C_6H_4$, 2-pyridyl
R^1 = *n*-Pr, *c*-C_3H_5, cyclohex-1-enyl
R^2 = *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *t*-Bu, Bn, Ph_2CH

Scheme 56. One-pot synthetic method for generation of 2-arylethylamines.

This methodology seems to be applicable only for aromatic, benzylic, and bulky aliphatic amines, however, it was extended to the intramolecular version of this reaction to afford cyclic amines after reduction (Scheme 57).[115]

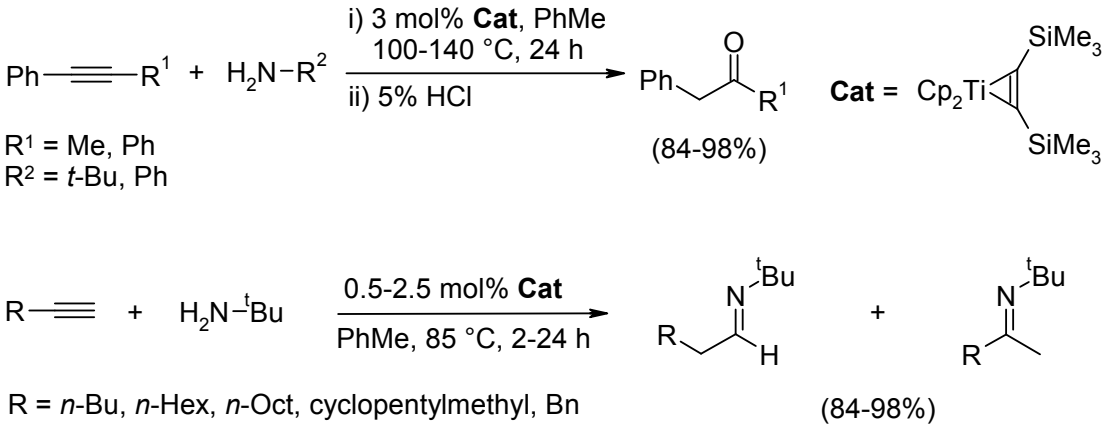


R = H, *n*-Hex, Ph, *p*-$MeOC_6H_4$, *o*-BrC_6H_4, *o*-$CF_3C_6H_4$,
3,5-$(CF_3)_2C_6H_3$, 2-chloro-5-(trifluoromethyl)phenyl

n = 1, 2

Scheme 57. Synthesis of cyclic amines via intramolecular hydroamination of alkynes.

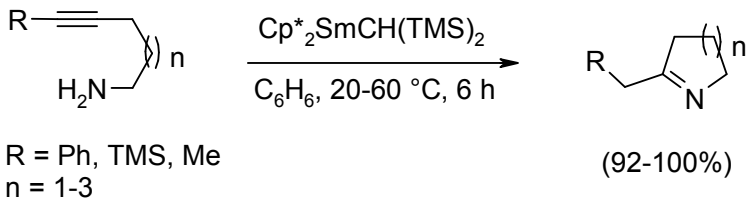
The use of two titanocene alkyne complexes of the type $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CR)$ (R = $SiMe_3$, Ph) has recently been described by Beller et al. for the hydroamination of internal and terminal alkynes. Both catalysts gave high yield of the products with aromatic and aliphatic amines. However, the catalyst with R = $SiMe_3$ was slightly more active than the one with R = Ph (Scheme 58).



Scheme 58. Beller intermolecular hydroamination of internal and terminal alkynes.

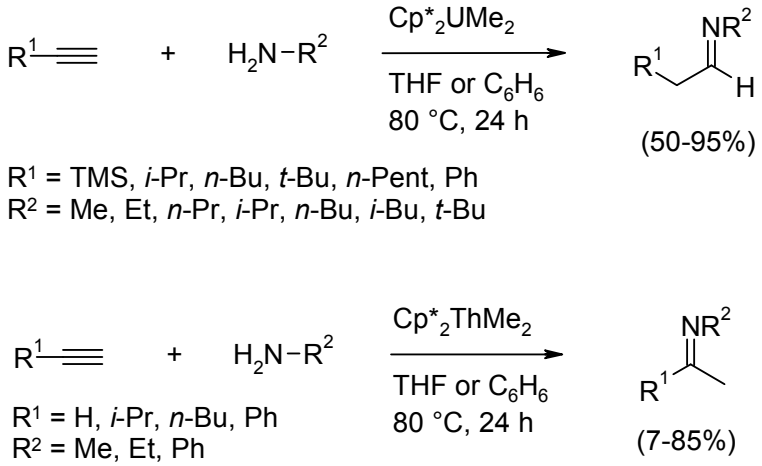
The most important feature of these catalysts is the fact that they lead, very selectively, to the anti-Markovnikov product (63:1 to 100:1) with a plethora of aliphatic terminal alkynes and a bulky amine, *t*-Bu-NH_2. The yield was very high with less bulky aliphatic amines, the anti-Markovnikov products being obtained preferentially also, though with a decrease in the selectivity (2:1 to 4:1).[116]

Due to the electrophilicity of the *f* element centers, relatively large ionic radii, the absence of conventional oxidative-addition/reductive-elemination step, and high kinetic ability,[117] organolanthanide and organoactinide complexes exhibit unique reactivity for the activation of unsaturated organic compounds.[118] Thus $Cp^*_2SmCH(TMS)_2$, under rigorously anaerobic reaction conditions, was shown to catalyze the hydroamination-cyclization of a series of aminoalkynes in a regiospecifical manner with full conversion, giving rise to cyclopenta-, cyclohexa-, and cycloheptaimines (Scheme 59).[119]



Scheme 59. Samarium-catalyzed cyclization of a series of aminoalkynes to cycloimines.

Eisen et al. reported the reactivity and selectivity of actinide catalysts of the type Cp^*AnMe_2 (An = U, Th) in the intermolecular hydroamination of terminal alkynes by aliphatic primary amines. The chemoselectivity and regioselectivity of the reactions were shown to depend strongly on the nature of the catalyst and the bulkiness of the amine, with less dependence on the nature of the alkyne. Therefore, regioselective anti-Markovnikov formation of the corresponding imines was achieved in high yields with $Cp^*_2UMe_2$. However, $Cp^*_2ThMe_2$ showed less chemoselectivity, lower yields being obtained as a result of partial alkyne oligomerization, and surprisingly leads to the opposite regioselectivity (Markovnikov product) (Scheme 60).[120]



Scheme 60. Actinide complexes catalyzed intermolecular hydroamination of terminal alkynes.

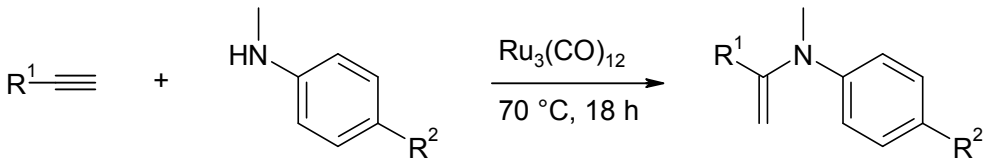
One main benefit of employing late transition metals as catalysts, compared to the previously described (early transition metals, lanthanide, and actinides metals), is the fact that the low oxophilicity (affinity to oxygen) of the formers allows high functional group tolerance with substrates that would be excluded in the catalyst with highly oxophilic metals.[61]

In 1995, Heider et al. patented the first example of intermolecular hydroamination of acetylene catalyzed by a ruthenium complex. $RuCl_3$ was used as catalyst in the reaction

of acetylene with imidazole, performed in a reactor heated at 150 °C and at 15-22 bar, giving the corresponding *N*-vinylimidazole.[121]

Four years later, Uchimaru[122] and Wakatsuki et al.[123] reported independently the examples of ruthenium-catalyzed addition of amines to terminal alkynes.

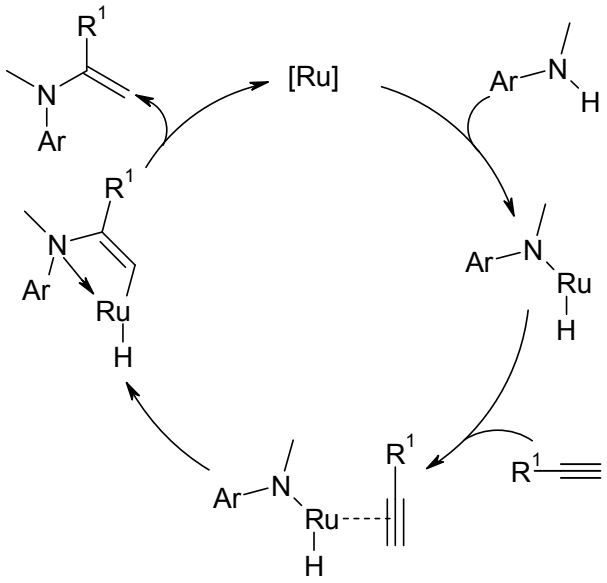
Uchimaru described the hydroamination of phenylacetylene and its derivatives with *N*-methylanilines catalyzed by $Ru_3(CO)_{12}$, affording *N*-methyl-*N*-(α-styryl)anilines in high yields, as a result of the regioselective Markovnikov addition (Scheme 61).



R^1 = Ph, *p*-MeC_6H_4, *p*-FC_6H_4, cyclohex-1-enyl (76-85%)
R^2 = H, Me

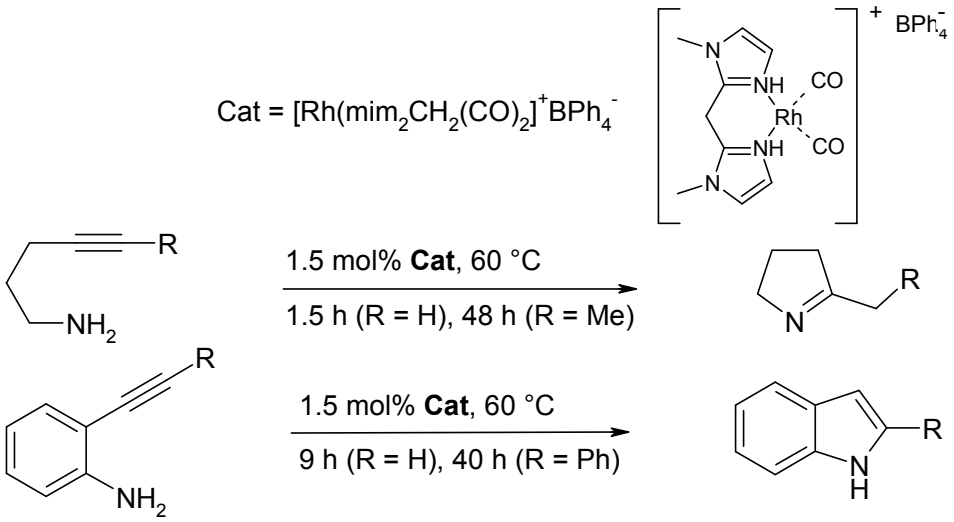
Scheme 61. Ruthenium-catalyzed hydroamination of terminal alkynes.

A reaction mechanism was proposed involving the oxidative addition of the N−H bond of the amine to the Ru(0) species, followed by coordination of the alkyne to the ruthenium center, intramolecular nucleophilic attack of nitrogen on the coordinated carbon-carbon triple bond, release of the product through reductive elimination, and regenerating the catalytically active species (Scheme 62).[122]



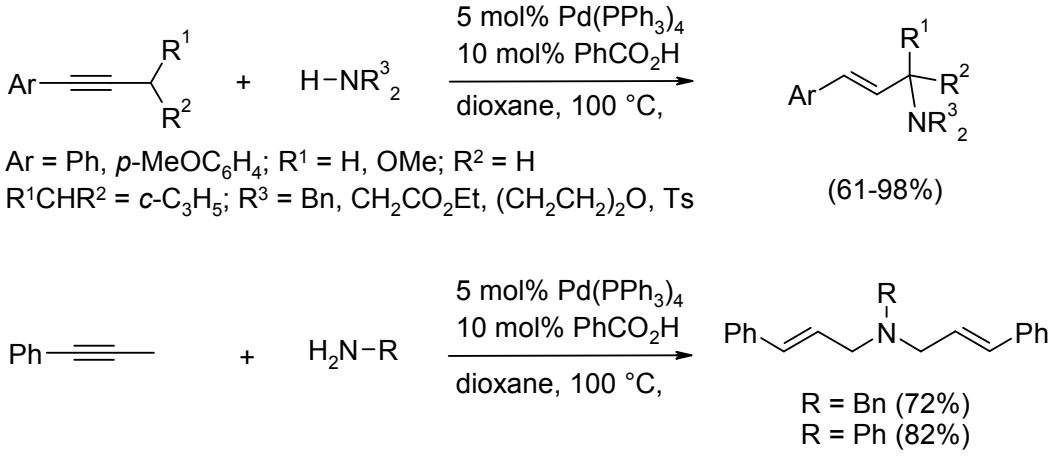
Scheme 62. Proposed catalytic cycle for ruthenium-catalyzed hydroamination of terminal alkynes.

There are few reports on rhodium catalysts that promote the addition of amines to alkynes. Messerle et al. synthesized the cationic Rh(I) dicarbonyl complex $[Rh(mim_2\text{-}CH_2)(CO)_2]^+BPh_4^-$, containing a bidentate bisimidazolylmethane ligand, which proved to be an effective catalyst for the intramolecular hydroamination of aliphatic and aromatic alkynes. Aliphatic internal alkynes reacted slower than terminal ones but regioselectively, whereas 2-alkynylanilines gave the expected indoles with complete conversion. The mechanism is not yet fully understood; the authors have not detected the formation of metal hydrides, metal-coordinated enamines, or free CO (Scheme 63).[124]



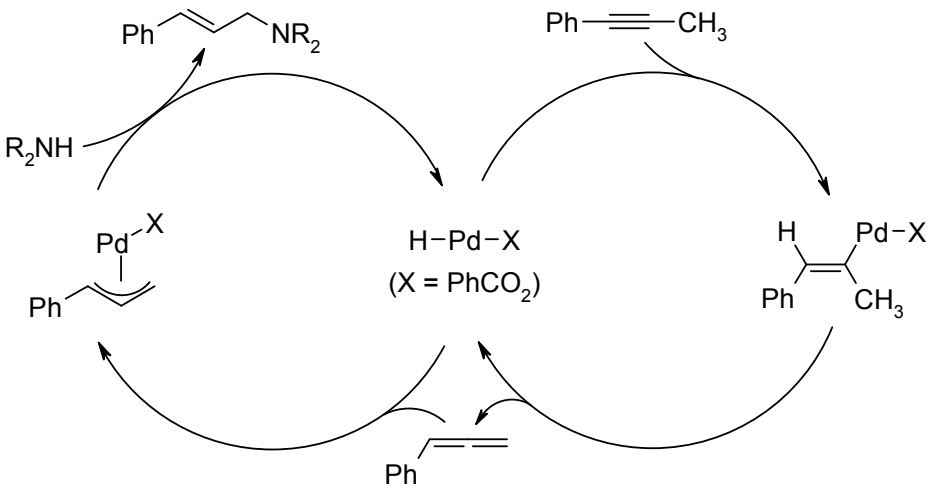
Scheme 63. Rhodium-catalyzed intramolecular hydroamination of alkynes.

Palladium is by far the most utilized metal in the catalytic hydroamination of alkynes.[61] Yamamoto et al. disclosed the intermolecular hydroamination of various aromatic internal alkynes with secondary amines in the presence of 5 mol% $Pd(PPh_3)_4$ and 10 mol% benzoic acid in dioxane at 100 °C, furnishing the corresponding allylic amines with good to excellent yields. Though, the presence of benzoic acid is essential for the reaction to occur (Scheme 64).



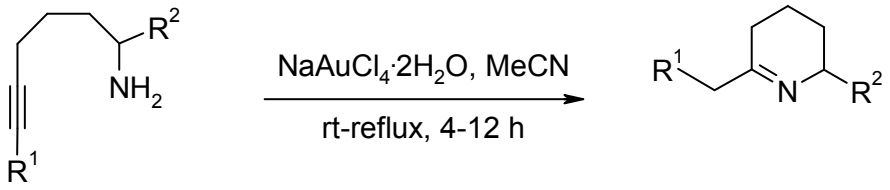
Scheme 64. Palladium-catalyzed intermolecular hydroamination of alkynes.

Substrates bearing electron-donating groups on the aromatic ring tend to result in higher yields. The reaction with primary amines leads to the corresponding double-hydroaminated products, whereas no reaction was observed for aliphatic acetylenes, independent of the type of amine. A plausible catalytic cycle includes the hydropalladation of the alkyne (with hydridopalladium species formed from Pd(0) and benzoic acid), intermediate formation of an arylallene and the active catalyst H-Pd-X (via β-elimination), hydropalladation of the arylallene to give a π-allylpalladium species, and reaction of the latter with the amine to furnish the product and the active catalyst (Scheme 65).[125]



Scheme 65. Proposed catalytic cycle for palladium-catalyzed hydroamination of alkynes.

Gold-based catalysts have been utilized for efficient catalytic hydroaminations of alkynes. For instance, the formation of 2,6-dialkyl- and 6-alkyl-2,3,4,5-tetrahydro-pyridines from the corresponding 5-alkynylamines can be catalyzed by Au(III). The reactions were performed under mild and neutral conditions, providing quantitative yields of the tetrahydropyridines. The results obtained under the action of $NaAuCl_4 \cdot 2H_2O$ as catalyst were better in comparison with those obtained with $Pd(MeCN)_2Cl_2$ (Scheme 66).[126]



R^1 = *n*-Pent, *n*-Hex; R^2 = H, Me

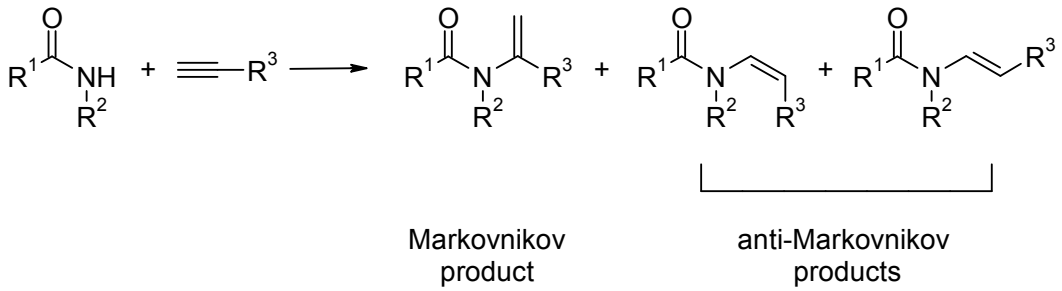
Scheme 66. Gold-catalyzed intramolecular hydroaminations of alkynes.

Finally, the presented examples indicate that great progress has been made in developing hydroamination procedures for alkynes. Titanium complexes bearing two labile ligands seem to be the most effective catalysts, as the employed reaction conditions are comparably mild. The functional group tolerance of titanium-based hydroamination procedures is low because of the high oxophilicity of this metal. Better functional group tolerance is provided by late transition metal catalysts which have also been successfully used for this reaction type. Unfortunately, the scope of corresponding intermolecular processes is often limited to special substrate structures.

1.3.5 Addition of amides to alkynes

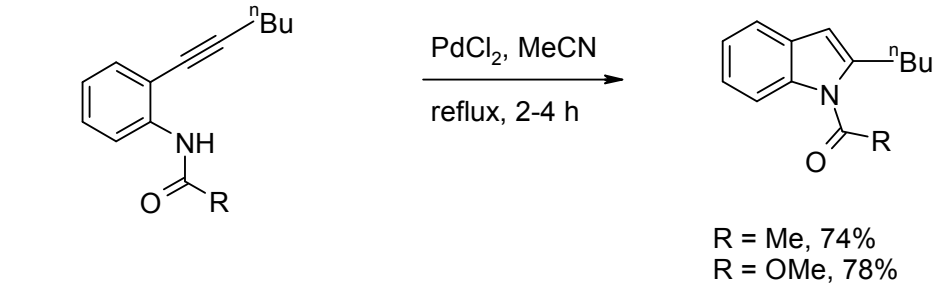
The hydroamidation reaction, i.e. the catalytic addition of the N−H bond of an amide to carbon-carbon multiple bonds, is a particularly desirable transformation as it represents an atom-economic access to valuable enamide substructures. Unlike the well-developed hydroamination reaction,[102] it is not yet fully investigated, although the higher stability of the resulting enamides (compared to the respective enamines) at ambient temperatures facilitates this endeavor.

As illustrated in Scheme 67, the hydroamidation of terminal alkynes gives rise for two regioisomers, Markovnikov and anti-Markovnikov products.



Scheme 67. Possible compounds for hydroamidation of terminal alkynes.

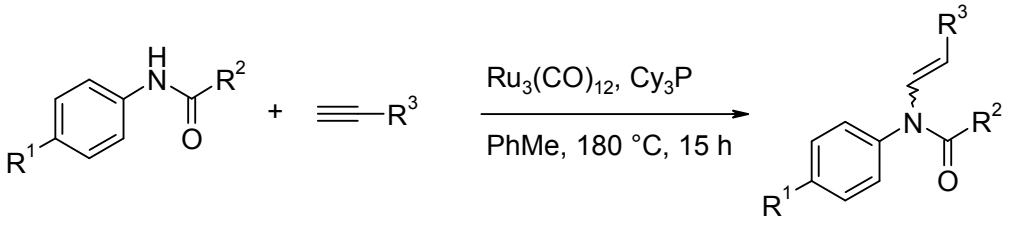
The intramolecular hydroamidation of internal alkynes was described in a number of publications, in particular towards the synthesis of indoles.[61] For instance, Utimoto et al. described the aminopalladation of *N*-substituted-2-alkynylaniline derivatives with a catalytic amount of $PdCl_2$ leading to the corresponding indoles in high yields (Scheme 68).[127]



Scheme 68. Palladium-catalyzed intramolecular cyclization of 2-alkynylanilines.

1.3.5.1 Anti-Markovnikov additions

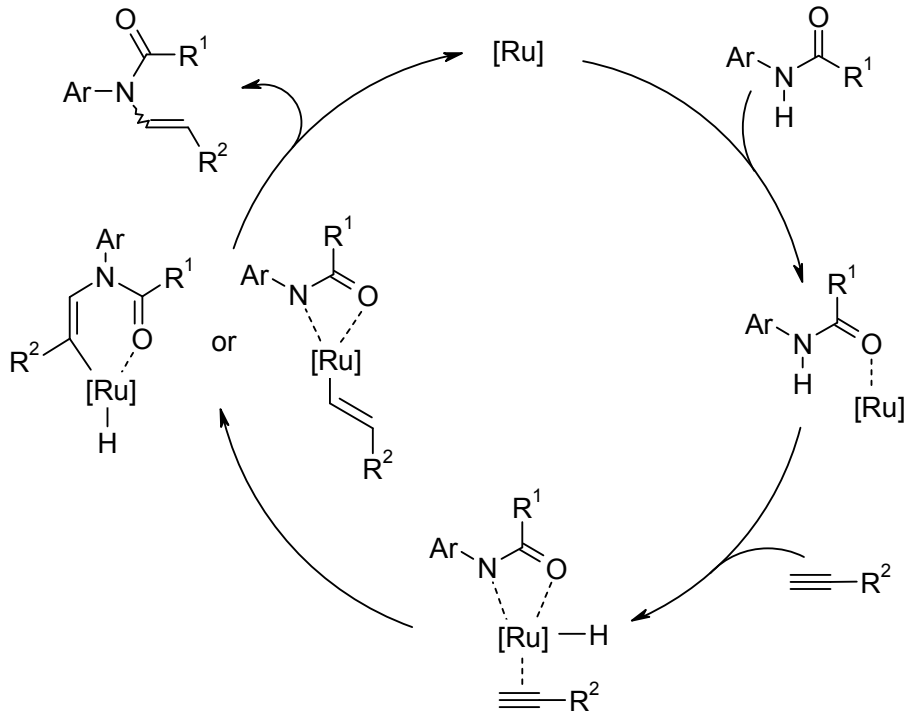
In the mid 1990s Watanabe et al. reported the first examples of intermolecular addition of amides to terminal alkynes catalyzed by a zerovalent ruthenium catalyst. This group described that a $Ru_3(CO)_{12}$-PCy_3-based system is an effective catalyst for the addition of *N*-aryl-substituted amides to 1-octyne, affording the corresponding *E*-enamides in high regio- and stereoselectivity. The reaction is restricted to *N*-aryl amides, since *N*-alkyl amides lead to intractable mixtures and the corresponding enamides can not be obtained selectively. Among the ruthenium catalysts examined, Ru(cod)(cot)-PCy_3 also shows good catalytic activity, whereas di- and tri-valent ruthenium complexes show low or almost no catalytic activity. These observations led the authors to the assumption that Ru(0)-complexes are catalytically active species for this type of reaction (Scheme 69).



R_1 = H, R_2 = H, 67%; R_1 = Cl, R_2 = H, 49%
R_1 = MeO, R_2 = H, 58%; R_1 = H, R_2 = Me, 65%

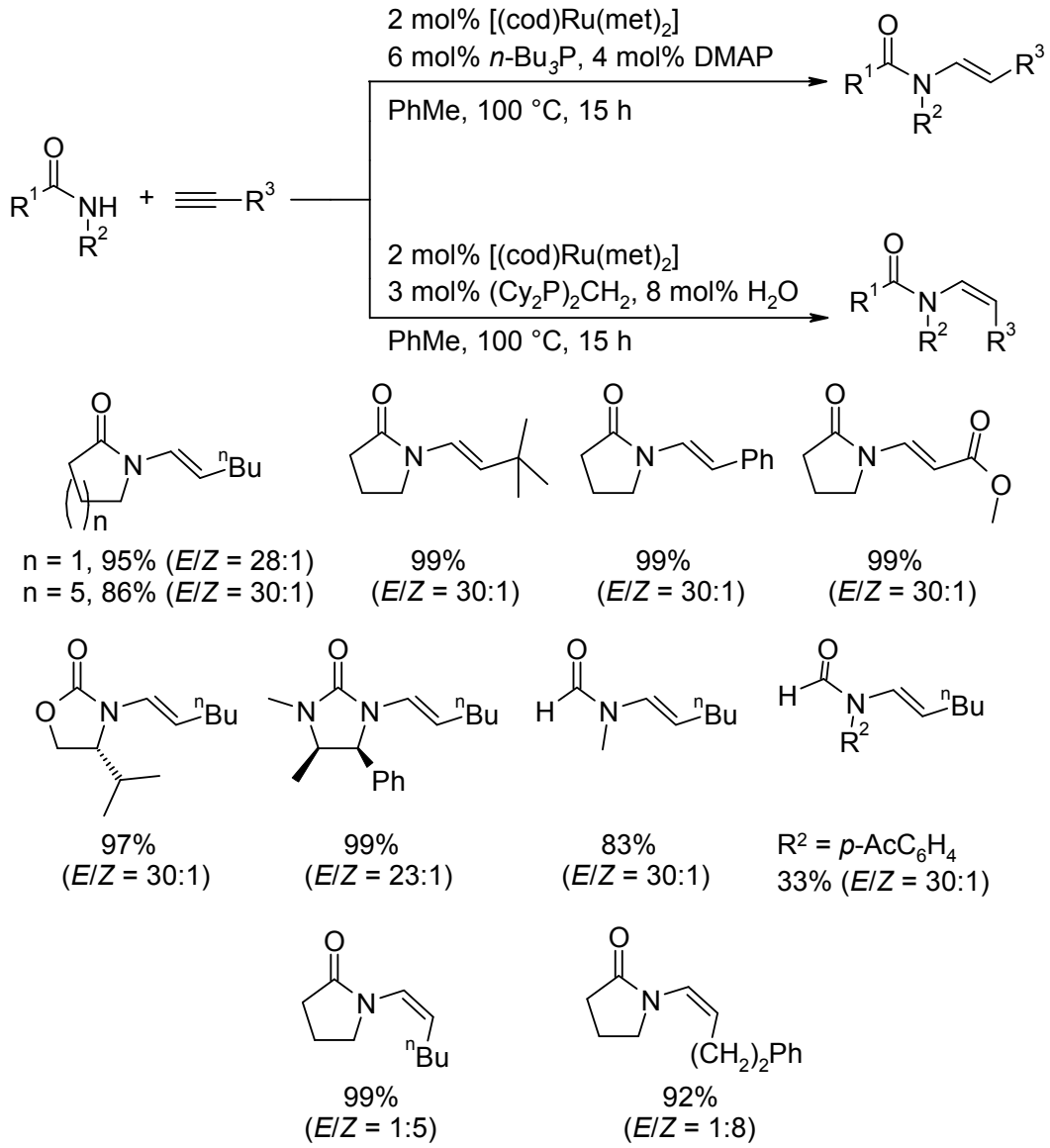
Scheme 69. Ruthenium-catalyzed addition of *N*-aryl amides to terminal alkynes.

A plausible reaction mechanism was proposed with initial coordination of the *N*-aryl-substituted amide to the active zerovalent ruthenium complex through its carbonyl oxygen atom, followed by alkyne coordination, oxidative addition to the N−H bond, and alkyne insertion. Finally, a subsequent reductive elimination furnished the enamide and regenerating the active zerovalent ruthenium species (Scheme 70).[128]



Scheme 70. Proposed catalytic cycle for the addition of *N*-aryl amides to terminal alkynes.

Baseed on this pioneering work by Watanabe and coworker, Rauhaus and Gooßen developed the first practical and general catalysts for the addition of secondary amides to terminal alkynes. *E*-Enamides are formed in high regio- and stereoselectivity in presence of a catalyst system based on bis(2-methylallyl)-cycloocta-1,5-dieneruthenium(II) [(cod)Ru(met)$_2$], tri-*n*-butylphosphine, and DMAP in toluene at 100 °C (Scheme 71).



Scheme 71. Ruthenium-catalyzed addition of *N*-nucleophiles to terminal alkynes.

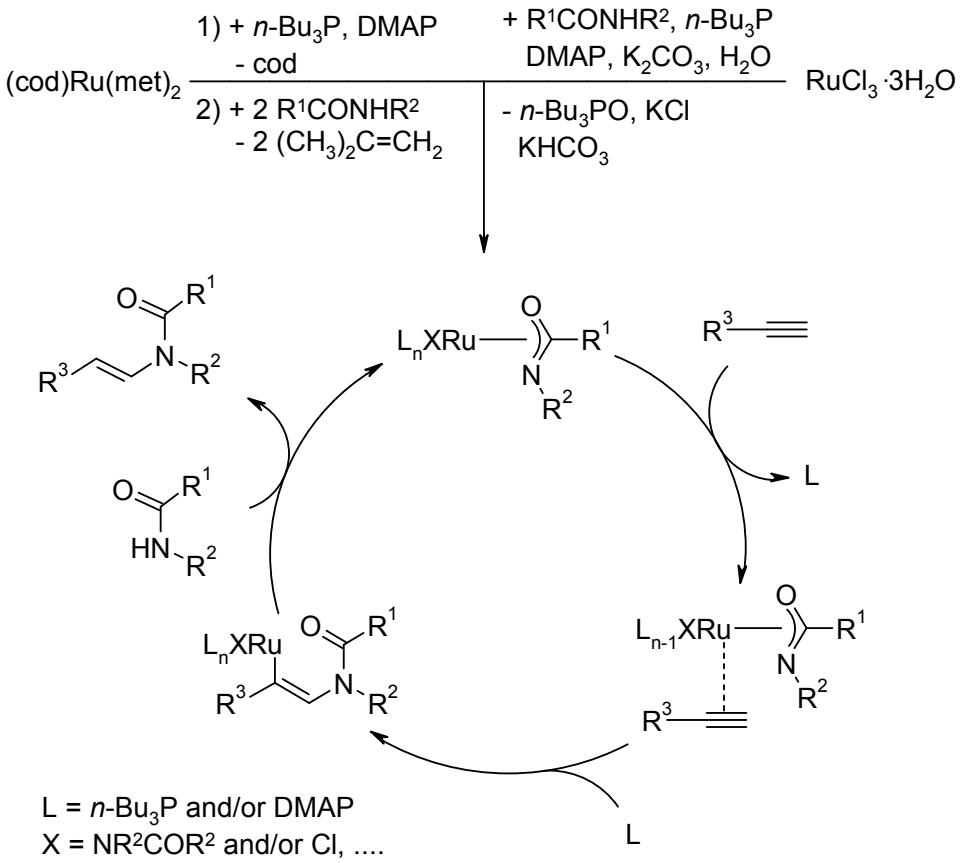
Under similar conditions, but in the presence of $Cy_2PCH_2PCy_2$ and water as additive, instead of *n*-Bu_3P and DMAP, the catalytic anti-Markovnikov addition selectively provides the *Z*-isomers in moderate selectivities and high yields.

The reaction has been applied to a broad variety of nitrogen nucleophiles (secondary amides, anilides, lactams, ureas, bislactams, and carbamates) and several terminal

alkynes (phenylacetylene, acetylenecarboxylic ester, trimethylsilylacetylene, and even conjugated enyne) leading to the corresponding enamides.[129]

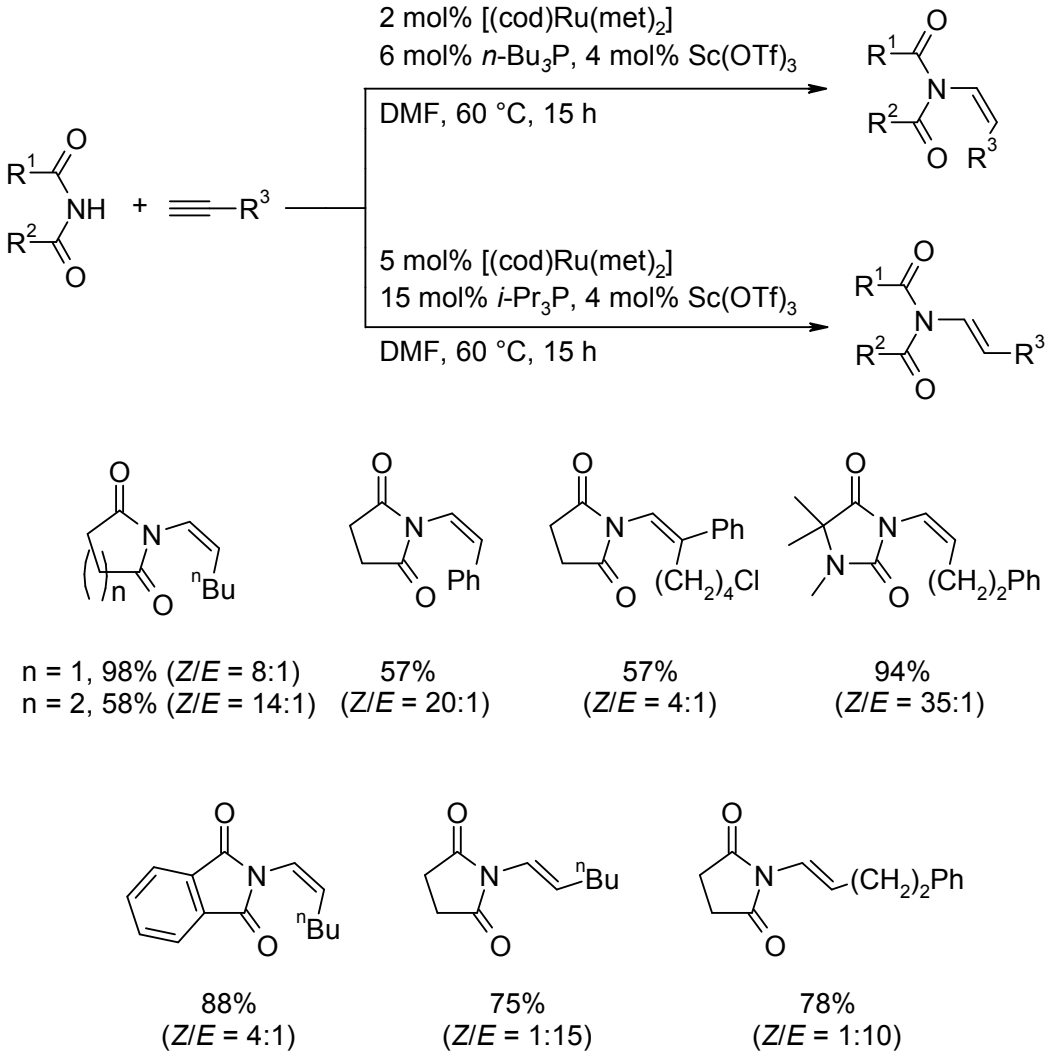
Recently, a second generation catalyst for the aforementioned hydroamidation reaction was developed in the Gooßen group. Rather than on expensive [(cod)Ru(met)$_2$], it is based on cost-efficient Ru(III) salt. The active catalyst is generated in situ from ($RuCl_3 \cdot 3H_2O$), *n*-Bu_3P, DMAP, K_2CO_3 and water, leading to *E*-enamides in high yields and selectivities from addition of amides to alkynes, matching or exceeding the results obtained by the original protocol.

A first partitive catalytic cycle for this transformation was proposed based on ^{1}H-NMR, ^{31}P-NMR, and ESI-MS. A phosphine-stabilized ruthenium(II) amide species was proposed to be the active catalyst, generated from the catalyst precursor (cod)Ru(met)$_2$ or $RuCl_3 \cdot 3H_2O$. The coordination of an alkyne replaces one of the ligands and gives rise to a π-complex, followed by a subsequent rearrangement of this complex to a ruthenium-alkenyl species. The enamide product is finally released by protonolysis, thus regenerating the active catalytic species (Scheme 72).[130]



Scheme 72. Proposed catalytic cycle for the addition of *N*-nucleophiles to terminal alkynes.

In 2006, Gooßen and Brinkmann disclosed a protocol that for the first time allows the catalytic addition of imides to alkynes. A catalyst system formed in situ from [(cod)Ru(met)$_2$], a phosphine, and scandium(III) trifluoromethanesulfonate [Sc(OTf)$_3$] in DMF at 60 °C was found to efficiently catalyze the anti-Markovnikov addition of imides to terminal alkynes, allowing mild and atom-economic syntheses of enimides. Depending on the phosphine employed, both the *E*- and the *Z*-isomer can be accessed stereoselectively (Scheme 73).

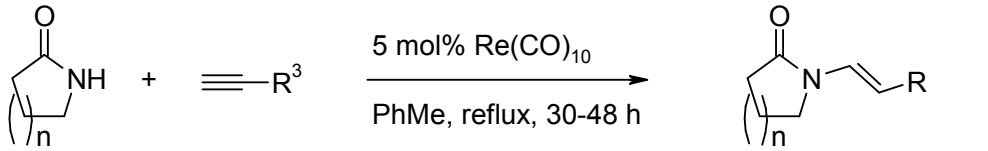


Scheme 73. Ruthenium-catalyzed addition of imides to terminal alkynes.

With regard to the coupling partners, the scope of these two protocols was tested with aliphatic and aromatic substrates. However, the focus was set on cyclic derivatives giving that the products are not easily accessible by the traditional methods.[131]

A year after these reports, Takai et al., based on their experience in the field of rhenium-catalysed C−C bond-forming reactions, discovered that $Re_2(CO)_{10}$ can also serve as a catalyst for the hydroamidation of terminal alkynes. High regio- and stereoselectivities of *E*-enamides were afforded in moderate to good yields through a catalytic addition of amides to alkynes in the presence of 5 mol% $Re_2(CO)_{10}$ and heated to reflux in toluene.

Nevertheless, the reaction is limited to specific substrates such as cyclic amides and aliphatic alkynes, moreover, the long reaction times are disadvantageous (Scheme 74).[132]

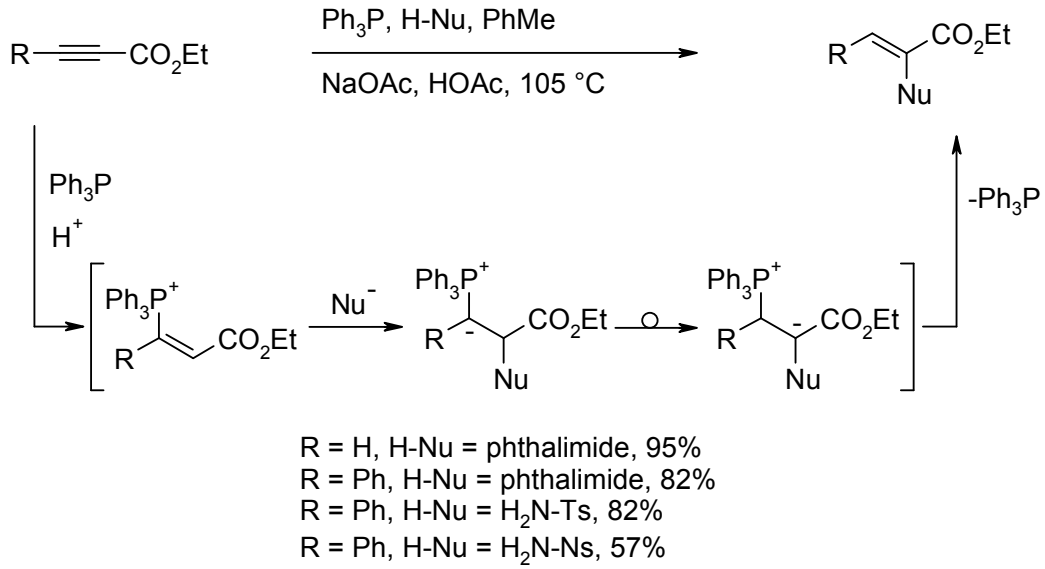


n = 1, R = *n*-C_5H_{11}, 80%
n = 1, R = *t*-Bu, 71%
n = 1, R = $(CH_2)_2$Ac, 62%
n = 2, R = *n*-C_5H_{11}, 35%
n = 2, R = Bn, 20%

Scheme 74. Rhenium-catalyzed addition of cyclic amides to terminal alkynes.

1.3.5.2 Markovnikov additions

Similar to phosphine-catalyzed addition of alcohols to activated alkynes, Trost and Dake described the intermolecular addition of nitrogen nucleophiles to conjugated alkynoates. Moderate to high yields were afforded by heating a 1:1 mixture of ethyl propiolate and *N*-nucleophile at 105 °C in toluene with 10 mol% triphenylphosphine, 50 mol% acetic acid, and 50 mol% sodium acetate (Scheme 75).



Scheme 75. Phosphine-catalyzed addition of imides and sulfonamides to alkynes.

This methodology allows the α-addition to Michael acceptor type alkynes, but it is restricted to specific starting materials such as aromatic imides and sulfonamides.[133]

2 Aims of the present work

Traditional methods for the synthesis of enamides lack of limitations such as limited substrate scope, low or missing stereoselectivity and harsh reaction conditions. However, the frequent occurrence of the enamide moiety in natural products creates a strong demand for a broadly applicable, high-yielding and stereoselective synthetic method for this entity. It is moreover desirable to use readily available starting materials in an atom economical transformation. We identified the Ruthenium-catalyzed addition of amides to alkynes to be a promising approach in this direction, but it was far from being generally applicable, in particular not for primary amides or thioamides.

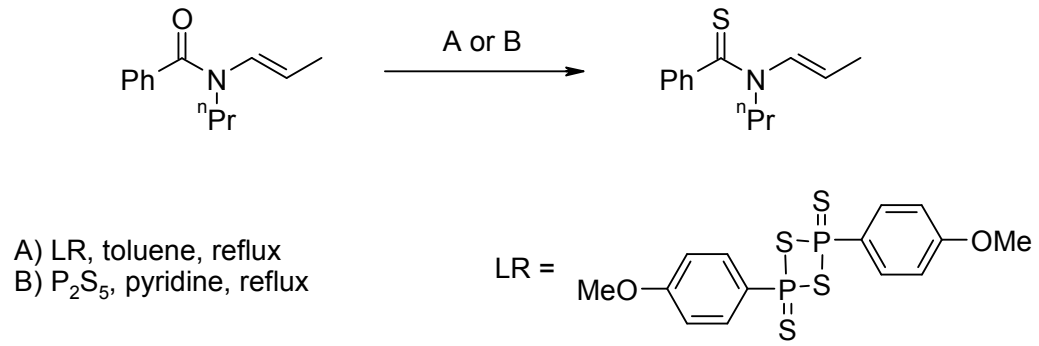
Therefore, the following goals should be pursued in the presented work:

- Development of new catalyst systems capable to perform anti-Markovnikov addition of *thioamides* to terminal alkynes.
- Development of new catalyst systems capable to perform anti-Markovnikov addition of *primary amides* to terminal alkynes, giving rise to secondary enamides.
- Reversing the regioselectivity of hydroamidation of terminal alkynes in favor of the *Markovnikov addition*.
- Applying the developed hydroamidation protocols in the synthesis of a number of *natural products*.
- Investigation of the *reaction mechanism* of the Ru-catalyzed addition of X−H to terminal alkynes with the help of deuterium labeled starting materials and in situ NMR and GC-MS studies.

3 Results and discussion

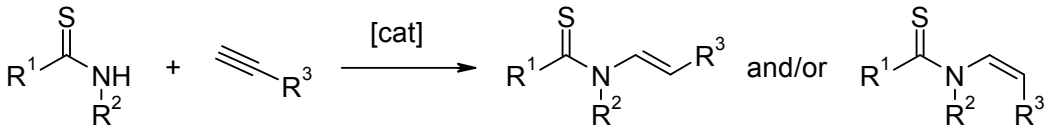
3.1 Anti-Markovnikov addition of thioamides to alkynes

A number of sulfur-containing compounds have been found to possess biological activity and were used e.g. in multitargeted cancer prevention and treatment. They have been shown to inhibit or retard the growth of various cancer cells in culture and in implanted tumors in vivo.[134] In comparison, thioenamide substructures are neglected in organic synthesis and drug discovery. In contrast with their oxo-analogues, thioenamides, which should be of considerable interest as structural variants of such subunits, with distinct electronic and steric properties, are only scarcely found in the chemical literature. This is easily explained by the lack of a concise and an applicable synthetic entry to this substrate class. Thioenamides are only accessible by treating the analogous enamides, which themselves are not easily synthesized, with Lawesson's reagent (LR)[135] or other similarly aggressive sulfurizing agents (Scheme 76).[136]



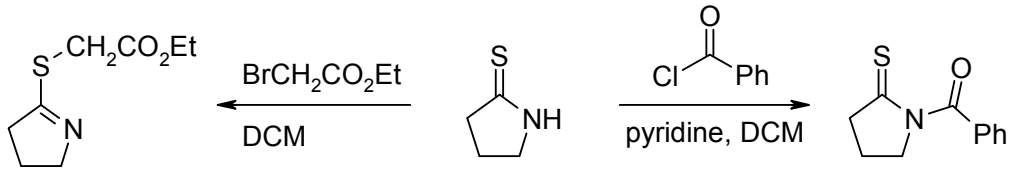
Scheme 76. Conventional synthesis of thioenamides.

These synthetic approaches do not tolerate many sensitive functionalities, and the required purification steps are rather difficult. Thus, the development of an expedient synthetic entry to the thioenamide substrate class is highly desirable. An efficient method for the preparation of thioenamides would be the catalytic addition of thioamides to alkynes (Scheme 77).



Scheme 77. Expedient synthetic entry to thioenamides.

The thioamide structures give rise to an additionl selectivity isssue: They are ambident nucleophiles and can react at the nitrogen or the sulfur terminus depending on the electrophile used, following the HSAB concept.[137] For example, the reaction of pyrrolidine-2-thione with ethyl bromoacetate affords the corresponding thioimino ester,[138] while with benzoyl chloride, the *N*-benzoyl-thionolactam is formed (Scheme 78).[139]



Scheme 78. Thioenamides as ambident nucleophiles.

This chemoselectivity issue, in addition to regio- and stereocontrol, also had to be controlled in our planned transition metal-catalyzed hydrothioamidation of alkynes.

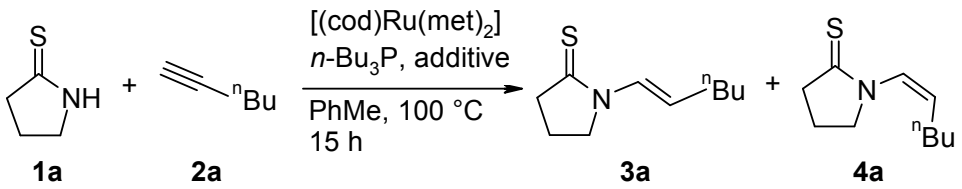
This development was performed together with Mathieu Blanchot, and is a part of both our dissertations.

3.1.1 Development of efficient catalyst systems

As a starting point for a catalyst development for the desired hydrothioamidation, we chose the reaction of pyrrolidine-2-thione (**1a**) with 1-hexyne (**2a**) as a model system. However, we did not achieve a satisfactory conversion of thioamides to the respective thioenamide with any of the catalyst systems employed for the addition of secondary amides or imides.[128,130] This may be ascribed to the significantly higher acidity of thioamides compared to amides (pK_a of 2-pyrrolidone, 24.2; pyrrolidine-2-thione, 18.1),[140] along with the fact that sulfur-containing compounds are known catalyst poisons due to their strong interaction with late transition metals.[141]

We started with the most effective system for the analogous addition of amides to alkynes, by employing a combination of bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [(cod)Ru(met)$_2$] with tri(*n*-butyl)phosphine (*n*-Bu$_3$P) and DMAP in toluene (Table 1). Under these conditions, *N*-((*E*)-hex-1-enyl)pyrrolidine-2-thione (**3a**) was obtained in rather low yield and unsatisfactory stereoselectivity along with alkyne oligomerization products (entry 1).

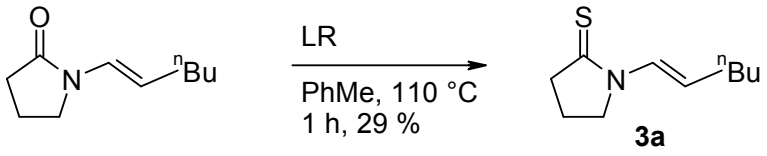
Table 1. Screening of different additives.



Entry	Additive	Yield (%)[a]	Ratio (**3a**:**4a**)[b]
1	DMAP	40	6:1
2	Na_2CO_3	87	5:1
3	K_2CO_3	84	5:1
4	KO*t*-Bu	90	7:1
5	LiCl	87	7:1
6	CsCl	90	6:1
7	$Yb(OTf)_3$	8	-
8	3 Å MS	93	12:1

Reaction conditions: 0.50 mmol pyrrolidine-2-thione, 1.00 mmol 1-hexyne, 1 mol% [(cod)Ru(met)$_2$], 3 mol% *n*-Bu_3P, 2 mol% additive or 250 mg 3 Å molecular sieves, 1.5 mL toluene, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by GC.

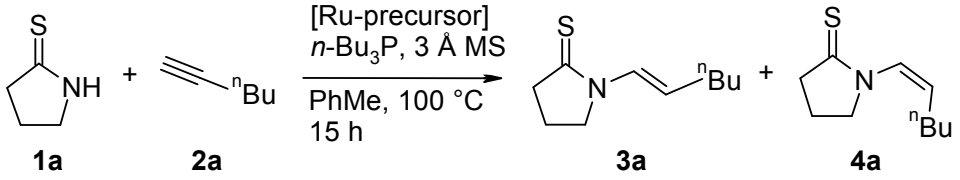
Substituting DMAP with inorganic bases led to higher yields but no improvements in selectivity (entries 2-4). However, mild Lewis acids such as lithium chloride, cesium chloride or 3 Å molecular sieves improved both yield and selectivity. The beneficial effect of the addition of molecular sieves is that water is removed from the reaction mixture, thus protecting the products from hydrolysis. As a result, **3a** was obtained in 93% yield and 12:1 stereoselectivity (entries 5-7). Its identity was confirmed by comparison to an authentic sample that was prepared via treating the analogous enamide with Lawesson's reagent (Scheme 79).[139]



Scheme 79. Synthesis of an authentic sample for **3a**.

Other ruthenium precursors were found to be less effective than the [(cod)Ru(met)$_2$], in terms of yield and selectivity (Table 2).

Table 2. Screening of other ruthenium precursors.

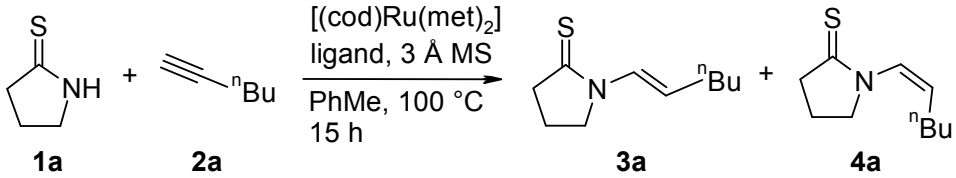


Entry	Ru-precursor	Yield (%)[a]	Ratio (**3a**:**4a**)[b]
8	[(cod)Ru(met)$_2$]	93	12:1
9	[(*p*-cymene)RuCl$_2$]$_2$	72	10:1
10	[(cod)RuCl$_2$]	80	9:1
11	[Ru(CO)$_{12}$]	0	-
12	[RuCl$_3$]	33	8:1

Reaction conditions: 0.50 mmol pyrrolidine-2-thione, 1.00 mmol 1-hexyne, 1 mol% [Ru-precursor], 3 mol% *n*-Bu$_3$P, 250 mg 3 Å molecular sieves, 1.5 mL toluene, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by GC.

On our trail towards a higher yield and selectivity, we tested various phosphine ligands instead of *n*-Bu_3P (entry 8). In this study, it became clear that the use of tri-*n*-alkyl-phosphines is crucial for achieving high selectivities in favor of the *E*-products (Table 3). Best results were obtained with tri-*n*-octylphosphine (entry 14). It is likely a combination of steric and electronic effects is responsible for the high selectivity. Less electron-rich triarylphosphines (entries 15-17) and sterically more demanding trialkylphosphines or triarylphosphine resulted in low yields and decreased stereoselectivities (entries 18-20).

Table 3. Screening of different ligands.



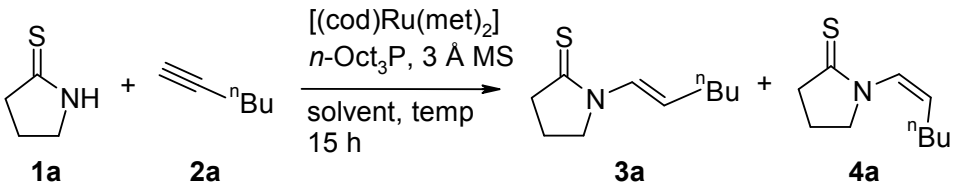
1a **2a** **3a** **4a**

Entry	Ligand	Yield (%)[a]	Ratio (**3a**:**4a**)[b]
8	*n*-Bu_3P	93	12:1
13	*t*-Bu_3P	10	2:1
14	*n*-Oct_3P	96	16:1
15	$(2\text{-Fur})_3P$	66	10:1
16	Ph_3P	43	8:1
17	*i*-$Pr(Ph)_2P$	40	4:1
18	dppm	48	4:1
19	dcypm	15	1:1
20	dcype	0	-

Reaction conditions: 0.50 mmol pyrrolidine-2-thione, 1.00 mmol 1-hexyne, 1 mol% $[(cod)Ru(met)_2]$, 3 mol% ligand (1.5 mol% for chelating phosphines), 250 mg 3 Å molecular sieves, 1.5 mL toluene, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by GC.

Finally, we set up a range of experiments to investigate the influence of solvent and temperature on the reaction (Table 4). Nonpolar aromatic solvents such as toluene or mesitylene were most effective (14, 21), other solvents decrease either the yield (glyme, ethanol) or the selectivity (DMF) (entries 22-24). A temperature of 100 °C represents the best compromise between turnover rate and stereoselectivity, while at lower temperature the reaction slowed down. At higher temperatures, decomposition of the product was observed (entries 25, 26).

Table 4. Screening of the reaction conditions.



1a **2a** **3a** **4a**

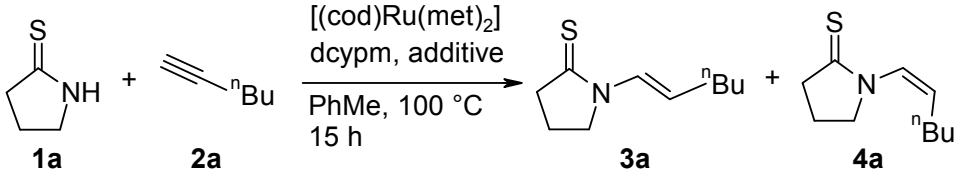
Entry	Solvent	Temp. °C	Yield (%)[a]	Ratio (**3a**:**4a**)[b]
14	toluene	100	96	16:1
21	mesitylene	"	91	13:1
22	glyme	"	85	12:1
23	EtOH	"	55	10:1
24	DMF	"	98	6:1
25	mesitylene	80	82	12:1
26	"	120	87	16:1
27[c]	toluene	100	84	14:1

Reaction conditions: 0.50 mmol pyrrolidine-2-thione, 1.00 mmol 1-hexyne, 1 mol% [(cod)Ru(met)$_2$], 3 mol% *n*-Oct$_3$P, 250 mg 3 Å molecular sieves, 1.5 mL solvent, temperature, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by GC. c) 0.50 mmol pyrrolidine-2-thione, 0.50 mmol 1-hexyne.

Under all conditions, the alkyne need to be used in excess to ensure complete conversion of the thioamide, as some alkyne is consumed by competing oligomerizations (entry 27).

As the choice of phosphine appeared to influence the stereochemical outcome of the reaction, we set out to identify one that would invert the stereochemistry of the transformation. In an attempt (Table 5), we combined the ligand with the lowest *E*-selectivity (entry 19), dcypm, with various additives (entries 28-31), and found that the *Z*-isomer can indeed be obtained as the major product with 76% yield and 1:2 selectivity in the presence of potassium *tert*-butoxide (entry 32)

Table 5. Screening of different additives.

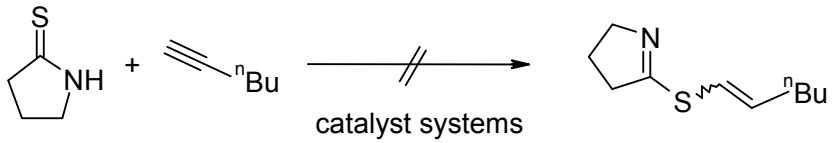


1a **2a** **3a** **4a**

Entry	Additive	Yield (%)[a]	Ratio (**3a**:**4a**)[b]
19	3 Å MS	15	1:1
28	-	45	1:1
29	$Yb(OTf)_3$	9	-
30	DMAP	20	2:1
31	K_3PO_4	51	1:1.5
32	K_2CO_3	64	1:1.5
33	KO*t*-Bu	76	1:2

Reaction conditions: 0.50 mmol pyrrolidine-2-thione, 1.00 mmol 1-hexyne, 2.5 mol% [(cod)Ru(met)$_2$], 3 mol% dcypm, 2 mol% additive or 250 mg 3 Å molecular sieves, 1.5 mL toluene, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by GC.

Under the optimized conditions (entries 14, 33), anti-Markovnikov-products are observed exclusively, and products arising from reaction at the *S*- rather than the *N*-terminus of the thioamide could never be detected (Scheme 80).

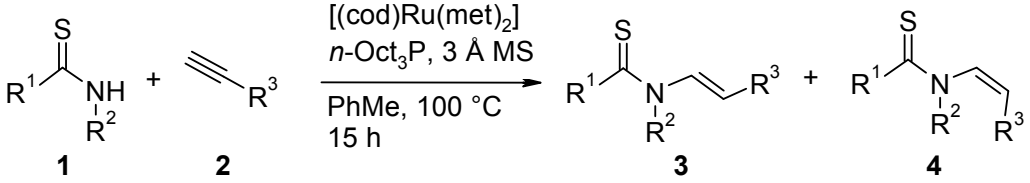


Scheme 80. Hypothetic addition of *S*-terminus of thioamides to alkyne.

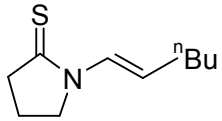
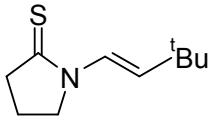
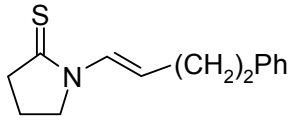
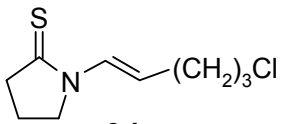
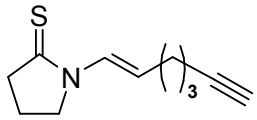
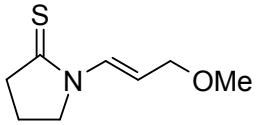
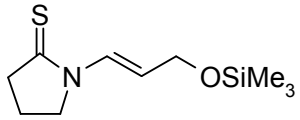
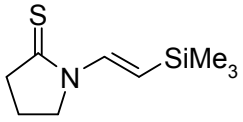
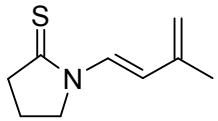
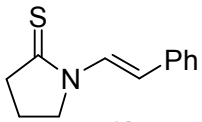
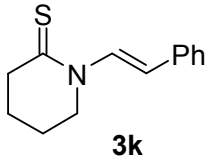
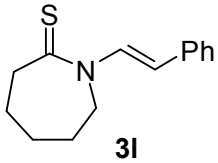
3.1.2 Scope of the optimized catalyst systems

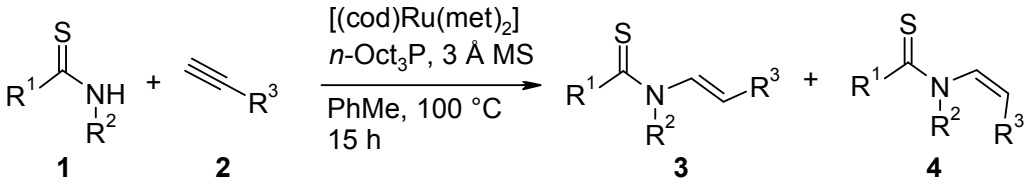
The generality of the new *E*-selective hydrothioamidation protocol was examined by applying it to the addition of a plethora of thioamides to several terminal alkynes (Table 6). We found that on one hand, pyrrolidine-2-thione added smoothly to various alkynes, among them alkyl and aryl-substituted alkynes, trimethylsilylacetylene, and conjugated enynes. On the other hand, phenylacetylene reacted with a range of secondary thioamides bearing aromatic or aliphatic substituents, as well as with an example for a thiocarbamate. In most cases, the products were obtained in good yields and high selectivities for the *E*-configured anti-Markovnikov-thioenamides. These representative examples illustrate that this protocol is likely to be generally applicable to the synthesis of functionalized tertiary *E*-thioenamides. Primary thioamides and internal alkynes were not converted.

Table 6. Substrate scope of *E*-thioenamide synthesis.

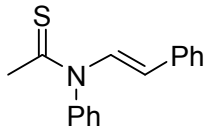
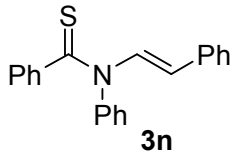
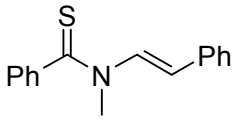
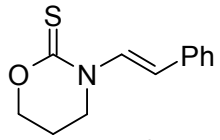


1 **2** **3** **4**

Product	Yield (%)[a] (ratio **3**:**4**)	Product	Yield (%)[a] (ratio **3**:**4**)
 **3a**	98 (16:1)	 **3b**	97 (13:1)
 **3c**	95 (7:1)	 **3d**	79 (15:1)[b]
 **3e**	76 (11:1)	 **3f**	76 (11:1)[b]
 **3g**	57 (19:1)	 **3h**	88 (11:1)[b]
 **3i**	71 (3:1)[b]	 **3j**	97 (6:1)
 **3k**	89 (5:1)[b]	 **3l**	84 (30:1)[b]



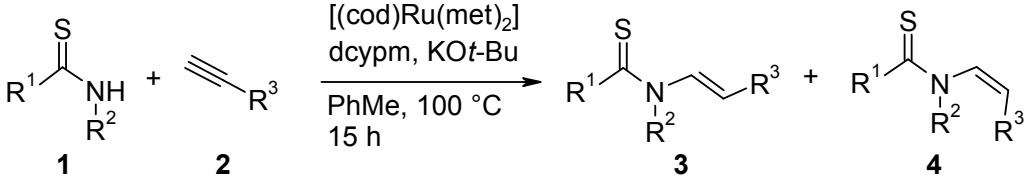
1 **2** **3** **4**

Product	Yield (%)[a] (ratio **3**:**4**)	Product	Yield (%)[a] (ratio **3**:**4**)
 **3m**	98 (30:1)[b,c]	 **3n**	97 (30:1)
 **3o**	91 (15:1)[b]	 **3p**	42 (2:1)[b]

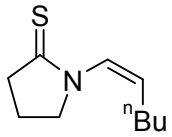
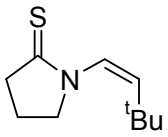
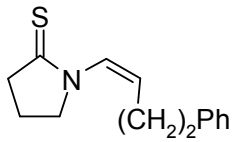
Reaction conditions: 1.00 mmol thioamide, 2.00 mmol alkyne, 2 mol% [(cod)Ru(met)$_2$], 6 mol% *n*-Oct$_3$P, 500 mg 3 Å molecular sieves, 3 mL toluene, 100 °C, 15 h. a) Isolated yields, in brackets the stereoisomeric ratio as determined by GC. b) 5 mol% [(cod)Ru(met)$_2$], 15 mol% *n*-Oct$_3$P. c) Stereoisomeric ratio as determined by ^{1}H-NMR.

The scope of the complementary *Z*-selective hydrothioamidation was tested on a number of examples. The protocol appears to be as high-yielding, but so far, the level of stereoselectivity never exceeded a moderate 1:8 ratio (Table 7). Further work is aimed at extending the synthetic utility of this complementary protocol by improving the *Z*-selectivity with the help of customized ligands.

Table 7. Substrate scope of *Z*-thioenamide synthesis.



1 **2** **3** **4**

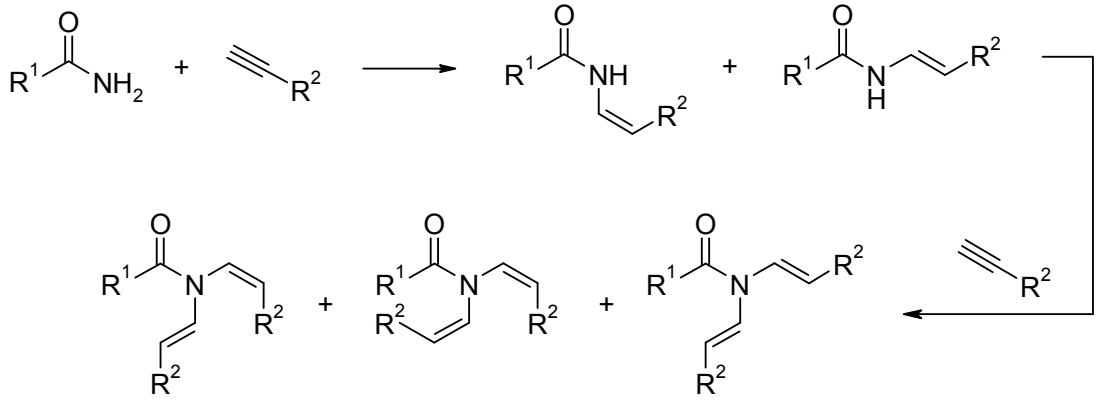
Product	Yield (%)[a] (ratio **3**:**4**)	Product	Yield (%)[a] (ratio **3**:**4**)
 **4a**	74 (1:2)	 **4b**	70 (1:8)
 **4c**	64 (1:2)		

Reaction conditions: 1.00 mmol thioamide, 2.00 mmol alkyne, 5 mol% [(cod)Ru(met)$_2$], 6 mol% dcypm, 4 mol% KO*t*-Bu, 3 mL toluene, 100 °C, 15 h. a) Isolated yields, in brackets the stereoisomeric ratio as determined by GC.

In summary, a Ru-based catalyst system has been developed that efficiently mediates the addition of thioamides to terminal alkynes, giving rise to *E*-configured anti-Markovnikov products. Various thioenamides can thus be obtained in high regio- and stereoselectivities, among them substrates attractive for further derivatization, for example, trimethylsilyl-thioenamides for cross-couplings, and thiodienamides for hetero-Diels-Alder reactions. A reversal of the stereoselectivity in favor of the *Z*-products was also achieved by modifying the phosphine ligand and the base.[142]

3.2 Anti-Markovnikov addition of primary amides to alkynes

The addition of primary amides to terminal alkynes would give access to the more valuable secondary enamides. Unfortunately, the catalyst systems previously developed in our group for the hydroamidation of terminal alkynes are not extendable to the addition of primary amides. Either no conversion at all, or mostly double vinylation products in traces and as mixtures of *E*/*Z* isomers and rotamers are observed. Many reasons could explain this lack of the reactivity; among them the lower reactivity of primary compared to secondary amides is easily explained by their lower nucleophilicity. Also, the product obtained from the initial addition of a primary amide to an alkyne can react as secondary amide with another equivalent of the alkyne to give the double addition product. Depending on the stereo- and chemoselectivity of the catalyst, a mixture of up to five different products could result from a single transformation (Scheme 81).



Scheme 81. Stereo- and chemoselectivity in hydroamidation reactions.

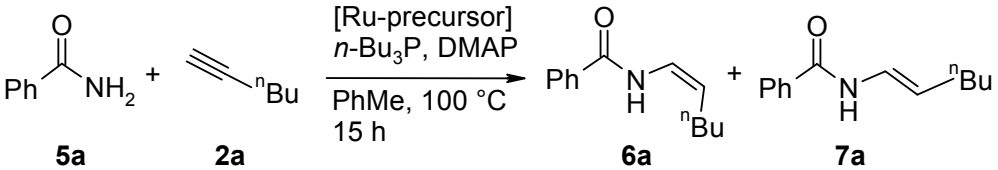
Therefore, an efficient and selective synthesis is a great challenge presented by this class of substrates. A highly developed catalyst system is required that reaches new levels of activity and selectivity for the anti-Markovnikov addition of primary amides to alkynes. However, this catalyst must be designed such that it does not allow further conversion of the more nucleophilic and sterically only slightly more demanding monovinylated products.

This development was performed in collaboration with Mathieu Blanchot during his PhD project.

3.2.1 Development of efficient catalyst systems

To identify an efficient catalyst system for monoaddition of amide to alkyne with such unique attributes, we selected the reaction of benzamide with 1-hexyne as the model system to examine the catalytic activity of various ruthenium sources in combination with a range of ligands, solvents, and additives. As anticipated, a combination of bis(2-methallyl)(cycloocta-1,5-diene)ruthenium(II) with tri-*n*-butylphosphine and 4-(dimethylamino)pyridine, the most effective system for the analogous reaction of secondary amides (Table 8, entry 1), led to only marginal conversion and displayed no selectivity for the monoaddition products (entry 1). However, other ruthenium precursors were found to be even less effective (entries 2-6).

Table 8. Screening of other ruthenium sources.



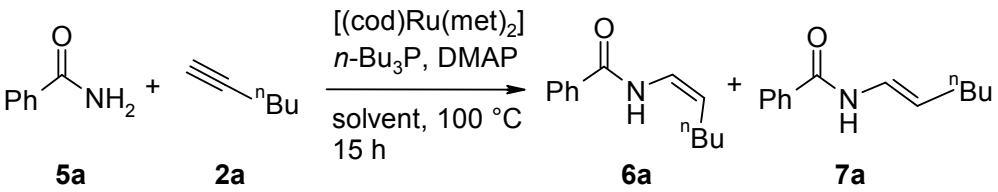
5a **2a** **6a** **7a**

Entry	Ru-precursor	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
1	$[(cod)Ru(met)_2]$	2	-
2	$[(p\text{-cymene})RuCl_2]$	2	-
3	$[Ru(acac)_3]$	0	-
4	$[Ru(CO)_{12}]$	0	-
5	$[RuCl_2(CO)_3]_2$	0	-
6	$[RuCl_2(C_6H_6)]_2$	0	-

Reaction conditions: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% [Ru-source], 15 mol% *n*-Bu_3P, 4 mol% DMAP, 3 mL toluene, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by HPLC.

Since the choice of solvent caused a dramatic increase of the catalytic activity of the previuos hydroamidation reaction, we performed a solvent screening, which revealed that the use of DMF is effective, resulting in an increase in yield (Table 9, entry 12). Other aprotic solvents appear to be inefficient for such reaction (entries 7-11).

Table 9. Screening of different solvents.



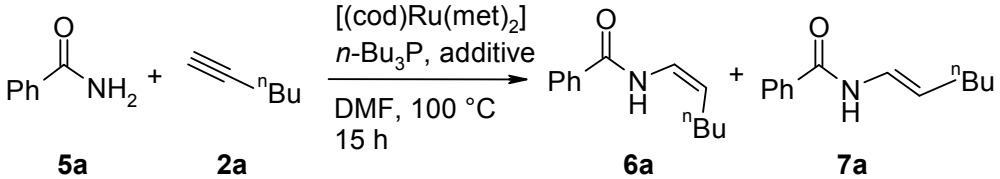
Entry	Solvent	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
1	toluene	2	-
7	THF	2	-
8	acetonitrile	3	-
9	quinoline	12	2:1
10	ethanol	0	-
11	DMSO	0	-
12	DMF	17	1:2

Reaction conditions: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% [(cod)Ru(met)$_2$], 15 mol% *n*-Bu$_3$P, 4 mol% DMAP, 3 mL solvent, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by HPLC.

We next studied the effect of different additives (e.g. Lewis bases and acids and salts), as we experienced during the previous work that the presence of appropriate additive is crucial to improve the yields and selectivities. Replacing DMAP by basic or neutral salts did not appear to have any beneficial effect (Table 10, entries 13-17). However, the use of Lewis acids led to a dramatic increase in catalyst activity, we assume that the

coordination of a Lewis acid to the carbonyl oxygen would acidify the amide protons, and therefore serve the same purpose as an added base. A 59% yield was achieved with ytterbium triflate, while other triflate sources did not reach this activity (entries 18-24). It can be excluded that the increase of the yield is due to the traces of triflic acid, as no product formation can be detected when TfOH is used (entry 25).

Table 10. Screening of different additives.



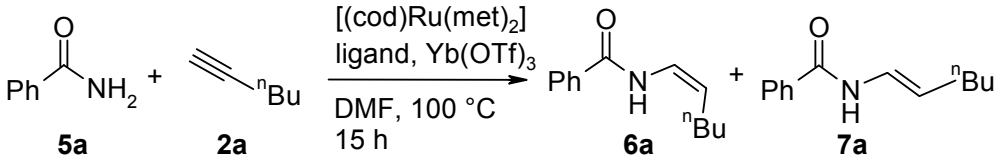
5a **2a** **6a** **7a**

Entry	Additive	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
12	DMAP	17	1:2
13	Na_2CO_3	16	1:3
14	K_2CO_3	19	1:2
15	KO*t*-Bu	12	1:1
16	K_3PO_4	8	1:1
17	KI	17	1:1
18	LiOTf	5	-
19	$Al(OTf)_3$	40	1:2
20	$Mg(OTf)_2$	45	1:2
21	$Bi(OTf)_3$	7	-
22	$Sc(OTf)_3$	35	1:1
23	$Cu(OTf)_2$	2	-
24	$Yb(OTf)_3$	59	3:2
25	TfOH	0	-

Reaction conditions: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% $[(cod)Ru(met)_2]$, 15 mol% *n*-Bu_3P, 4 mol% additive, 3 mL DMF, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by HPLC.

To investigate the influence of different ligands, we set up a range of experiments to enhance the selectivity and achieve completion of the reaction. Sterically demanding trialkylphosphines, nitrogen-containing ligands and electron poor phosphines slow down or inhibit the reaction (Table 11, 26-34). Moreover, sterically demanding, electron-rich chelating phosphines resulted mainly in no yield, only 1,4-bis-(dicyclohexylphosphino)-butane led to an increased selectivity for the *Z* product **6a** to a 4:1 ratio (entry 38).

Table 11. Screening of different ligands.

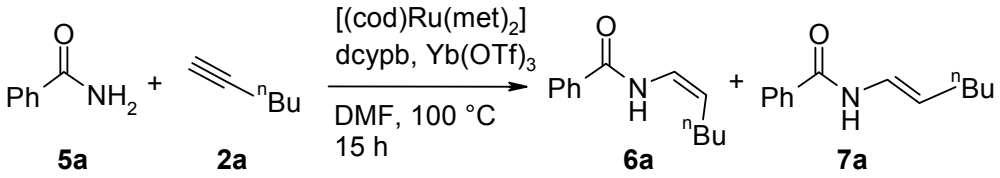


Entry	Ligand	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
24	*n*-Bu_3P	59	3:2
26	*n*-Bu_3N	0	-
27	Phenanthroline	0	-
28	Ph_3P	10	1:1
29	$(2\text{-Fur})_3P$	0	-
30	(*i*-Pr)Ph_2P	14	2:1
31	johnphos	0	-
32	*i*-Pr_3P	4	-
33	*t*-Bu_3P	2	-
34	Cy_3P	0	-
35	dppb	5	-
36	dcypm	2	-
37	dcype	0	-
38	dcypb	55	4:1

Reaction conditions: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% $[(cod)Ru(met)_2]$, 15 mol% ligand (6 mol% for bidentate), 4 mol% $Yb(OTf)_3$, 3 mL DMF, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by HPLC.

An optimization of the reaction temperature led us to conclude that a temperature of 60 °C leads to substantially increased yields of the monoaddition products, largely because their hydrolysis by traces of water was slowed down (Table 12, entries 38-41). Under these conditions, the presence of water was even found to enhance the selectivity (entries 42-45), so that nearly complete conversion and an impressive 18:1 selectivity for the thermodynamically unfavorable and thus more interesting *Z*-enamide **6a** was reached within 6 h reaction time (entry 46).

Table 12. Screening of the reaction conditions.



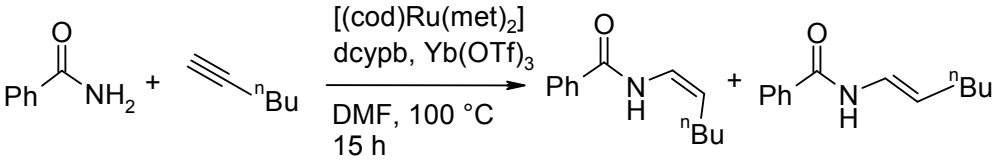
Entry	Temperature (°C)	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
38	100	55	4:1
39	80	82	5:1
40	60	95	7:1
41	30	4	-

Entry	H_2O (mmol)[c]	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
40	0	95	7:1
42	2	97	10:1
43	4	97	14:1
44	6	98	18:1
45	8	96	17:1
46[d]	6	97	18:1

Reaction conditions: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% $[(cod)Ru(met)_2]$, 6 mol% dcypb, 4 mol% $Yb(OTf)_3$, 3 mL DMF, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by HPLC. c) 60 °C. d) 6 h.

The reaction can also be carried out at lower temperatures, like 50 °C for 15 h, as an alternative condition for temperature sensitive substrates (Table 13, entry 47). High yields and selectivities can also be afforded, when magnesium or aluminum triflate is used as additive (entries 48-50). Moreover, a less costly alternative ligand, tri-*n*-butylphosphine, gives also good conversion but somewhat lower stereoselectivity than the model reaction (entry 51).

Table 13. Further options for the optimized hydroamidation reaction.



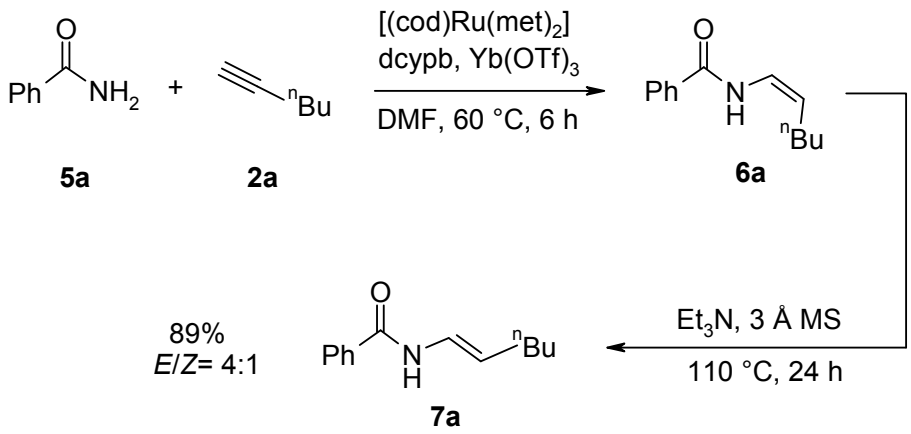
5a **2a** **6a** **7a**

Entry	Ligand	Additive	Yield (%)[a]	Ratio (**6a**:**7a**)[b]
46	dcypb	$Yb(OTf)_3$	97	18:1
47[c]	"	"	96	18:1
48	"	$Mg(OTf)_2$	95	14:1
49	"	$Al(OTf)_3$	93	13:1
50	"	$Sc(OTf)_3$	85	10:1
51	*n*-Bu_3P	$Yb(OTf)_3$	95	13:1
52[d]	*n*-Oct_3P	"	94	1:2
53[d]	*n*-Bu_3P	"	95	1:2.5
54[e]	dcypb	"	89	1:4

Reaction conditions: 1.00 mmol benzamide, 2.00 mmol 1-hexyne, 5 mol% [(cod)Ru(met)$_2$], 6 mol% dcypb (15 mol% *n*-Bu_3P), 4 mol% additive, 3 mL DMF, 6 mmol H_2O, 60 °C, 6 h. a) Corrected GC yields with *n*-tetradecane as internal standard. b) Ratio determined by HPLC. c) 50 °C, 15 h. d) Without H_2O, 500 mg 3 Å molecular sieves, 100 °C, 15 h. e) After complete reaction (entry 46), triethylamine (200 µL) and 3 Å molecular sieves (500 mg) were added, and the resulting mixture was stirred at 110 °C for 24 h.

We next tried to invert the selectivity of the reaction in favor of the *E*-enamide **4a** by modifying the catalyst system to further improve the synthetic utility of the hydroamidation process. The best result, obtained with *n*-Bu_3P as the ligand and 3 Å molecular sieves as additives, was a 1:2.5 ratio of *Z*/*E* isomer (entry, 52, 53).

Comparative studies revealed that the in situ isomerization of the double-bond isomers is a superior strategy for accessing the *E*-isomers.[143] After the reaction to form **6a** is complete, triethylamine is added and heating the reaction mixture to 110 °C, using molecular sieves to reduce the hydrolytic cleavage to a minimum (entry 54). In this way, an *E*/*Z* ratio of 4:1 and 89% yield was achieved for the model system (Scheme 82).

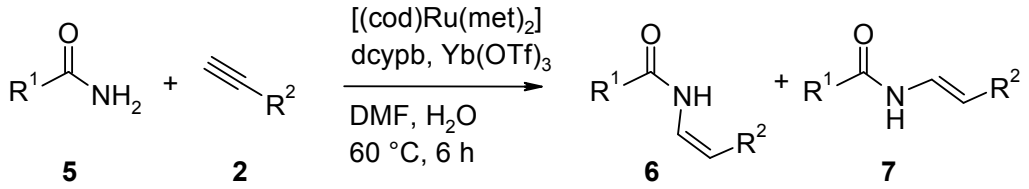


Scheme 82. One-pot addition/isomerization sequence.

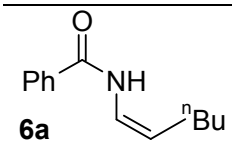
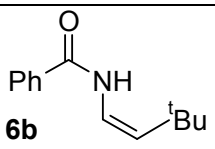
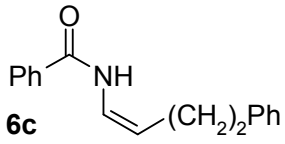
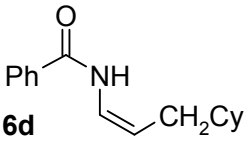
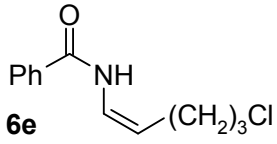
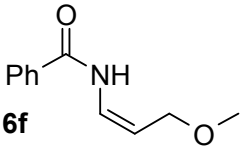
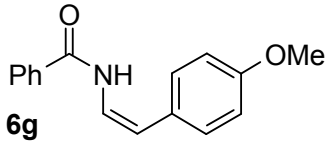
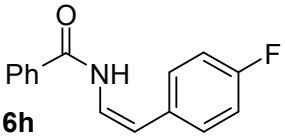
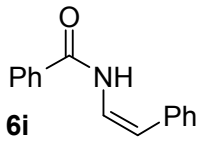
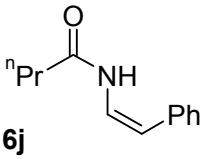
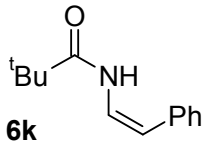
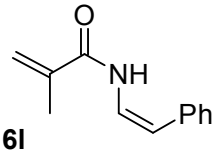
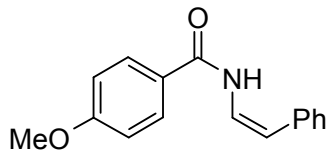
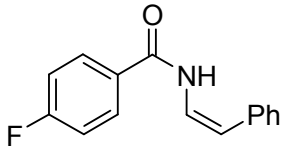
3.2.2 Scope of the optimized catalyst systems

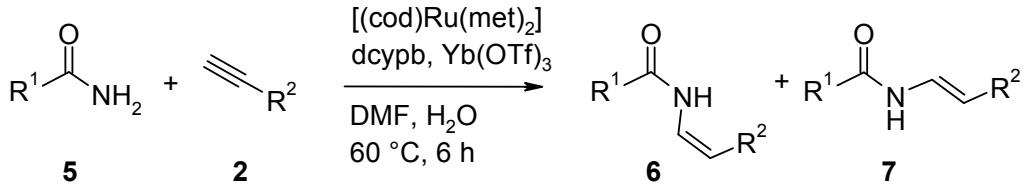
To investigate the scope and synthetic utility of the *Z*-selective anti-Markovnikov protocol, we applied it to the addition of plethora of primary amides to several terminal alkynes (Table 14). Benzamide was reacted with various alkynes, such as aliphatic, alicyclic, haloalkyl, and aromatic derivatives, yielding enamides **6a-i** in high yields and good to excellent *Z*/*E* selectivities. A range of primary amides, among them sensitive, highly functionalized derivatives, were added to phenylacetylene (**6i-u**). Common functional groups, such as ester, ether, alkene, nitrile, nitro, and halide groups are tolerated, and even fragile acrylic, oxalic, malonic or α-cyanoacetic amides were efficiently converted. The most remarkable example was the synthesis of the enamide **6t**, in which a primary amide functionality was selectively vinylated in the presence of a secondary amide group.

Table 14. Substrate scope of *Z*-enamide synthesis.

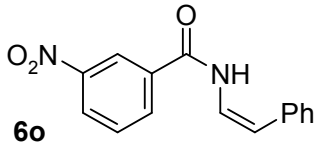
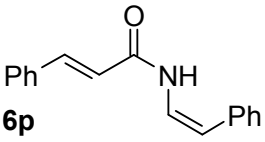
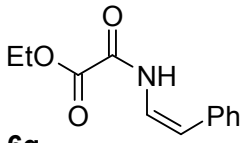
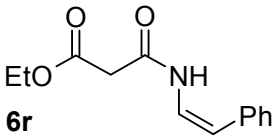
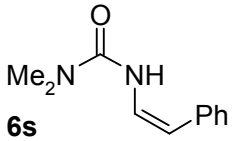
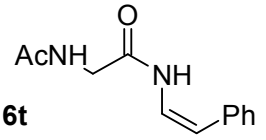
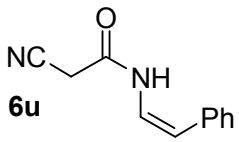
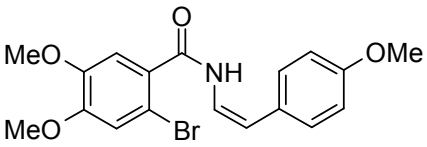


5 **2** **6** **7**

Product	Yield (%)[a] (ratio **6**:**7**)	Product	Yield (%)[a] (ratio **6**:**7**)
 **6a**	94 (18:1)	 **6b**	91 (>40:1)
 **6c**	92 (17:1)	 **6d**	86 (23:1)
 **6e**	91 (31:1)	 **6f**	41 (15:1)
 **6g**	83 (19:1)	 **6h**	99 (20:1)
 **6i**	97 (18:1)	 **6j**	84 (14:1)
 **6k**	88 (10:1)	 **6l**	90 (19:1)
 **6m**	96 (18:1)	 **6n**	93 (19:1)



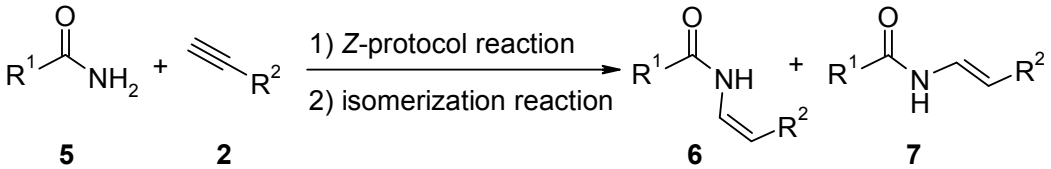
5 **2** **6** **7**

Product	Yield (%)[a] (ratio **6**:**7**)	Product	Yield (%)[a] (ratio **6**:**7**)
 **6o**	80 (20:1)	 **6p**	98 (20:1)
 **6q**	78 (35:1)[b]	 **6r**	71 (19:1)[b]
 **6s**	46 (30:1)	 **6t**	96 (22:1)
 **6u**	31 (>40:1)	 **6v**	60 (>40:1)

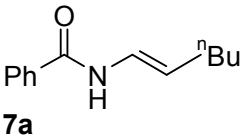
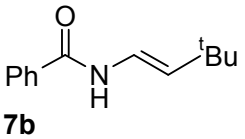
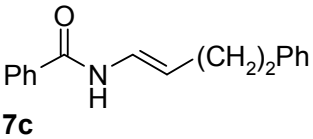
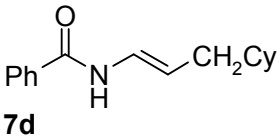
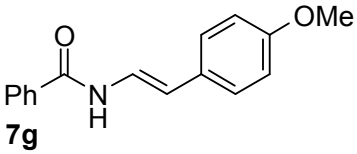
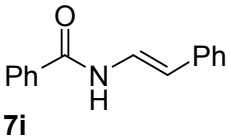
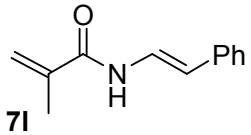
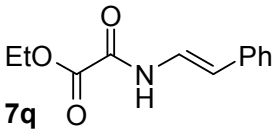
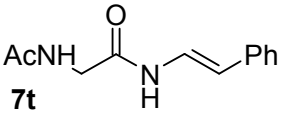
Reaction conditions: 1.00 mmol amide, 2.00 mmol alkyne, 5 mol% [(cod)Ru(met)$_2$], 6 mol% dcypb, 4 mol% Yb(OTf)$_3$, 3 mL DMF, 108 µL H_2O, 60 °C, 6 h. a) Yields reported are of isolated products; selectivities were determined by HPLC. b) The reaction was performed without H_2O to avoid hydrolysis of the sensitive products.

The one-pot addition/isomerization sequence was successfully applied to the synthesis of a representative selection of *E*-enamides (Table 15). This sequence proved to be highly efficient and general in its application. The *E*-selectivities were usually high and functional groups were well-tolerated. As a result, terminal alkynes and amides can now utilized as starting materials for the synthesis of *E*-enamides.

Table 15. Substrate scope of *E*-enamide synthesis.

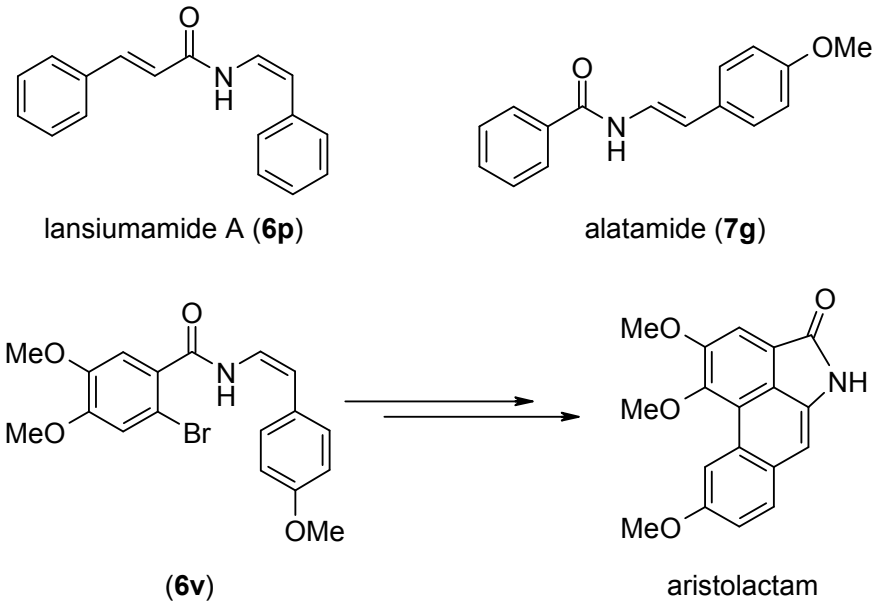


5 **2** **6** **7**

Product	Yield (%)[a] (ratio **6**:**7**)	Product	Yield (%)[a] (ratio **6**:**7**)
 **7a**	89 (1:4)	 **7b**	79 (1:20)
 **7c**	85 (1:4)	 **7d**	85 (1:4)
 **7g**	79 (1:18)	 **7i**	92 (1:18)
 **7l**	83 (1:17)	 **7q**	68 (1:14)[b]
 **7t**	77 (1:20)		

Reaction conditions: 1.00 mmol amide, 2.00 mmol alkyne, 5 mol% [(cod)Ru(met)$_2$], 6 mol% dcypb, 4 mol% Yb(OTf)$_3$, 3 mL DMF, 108 µL H_2O, 60 °C, 6 h. After complete reaction, 3 Å molecular sieves (500 mg) and triethylamine (200 µL) were added, and the mixture was heated to 110 °C for 24 h. a) Yields reported are of isolated products; selectivities were determined by HPLC. b) The reaction was performed without H_2O to avoid hydrolysis of the sensitive products.

The enamides are accessible in only one step from easily available materials, including the natural products lansiumamide A (**6p**)[33] and alatamide (**7g**).[12] Their previously published syntheses involved three to four steps and rather low product yields. This also applies to compound **6v**, which is a key intermediate in Castedo's total synthesis of aristolactam (Scheme 83).[50a]



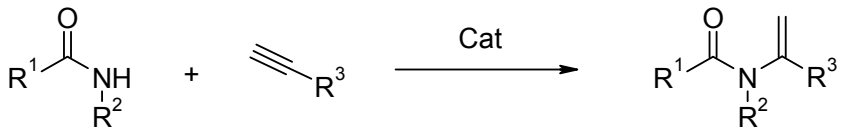
Scheme 83. Synthesized natural products via hydroamidation reactions.

In summary, a new catalyst system has been developed that allows the chemo-, regio-, and stereoselective synthesis of secondary *Z*-enamides from easily available primary amides and terminal alkynes. In combination with an optional in situ isomerization to the *E*-enamides, this catalyst system gives access to a fast synthetic route to the structural motif that is present in many natural products.[144]

3.3 Markovnikov addition of amides to alkynes

Products resulting from the Markovnikov addition of amides to terminal alkynes would give rise to a valuable class of enamides, which can subsequently used for the synthesis of cycloadducts[52] and enantiomerically pure compounds.[57] Syntheses leading to this substrate class are scarcely found in the chemical literature, and mainly involve Heck reactions.[35-37] Thus, an effective, practical, and atom-economic synthetic entry remains a highly desirable target for such products, starting from readily available substrates.

Based on our Ru-catalyzed anti-Markovnikov addition of many N−H acidic amides across C≡C bonds, we concentrated our efforts on finding a method to reverse the regioselectivity of the addition in favor of the Markovnikov products (Scheme 84).



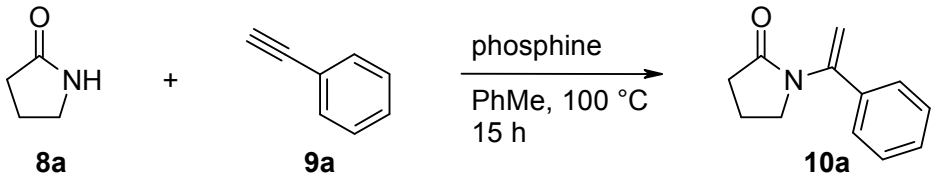
Scheme 84. Markovnikov addition of amides to terminal alkynes.

In spite of numerous experiments carried out, such products have not been observed under any set of conditions, even in the case of using some gold complexes (in the oxidation states I and III), which are known to activate alkynes as Lewis acids for the nucleophilic addition.[145]

Inanaga et al.[82] and Trost and Dake[133] reported that phosphines mediate the addition of nucleophiles to activated alkynes. Taking the reaction of 2-pyrrolidone with phenylacetylene as a model system, the desired hydroamidation reaction was investigated following their protocols. We observed that trialkylphosphines catalyzed the formation of Markovnikov product in toluene at 100 °C. *n*-Bu_3P and Me_3P were found to be the catalyst of choice rather than sterically more demanding trialkylphosphines and less electron-rich triarylphosphines, which give much lower yields (Table 16). Toluene is the almost uniquely effective solvent, while other protic and aprotic solvents suppress

product formation. Moreover, a reaction temperature of 100 °C turned out to be sufficient, a further decrease to 80 °C slows down the reaction, and higher promotes the decomposition of the product.

Table 16. Test of different phosphines as a catalyst.



8a **9a** **10a**

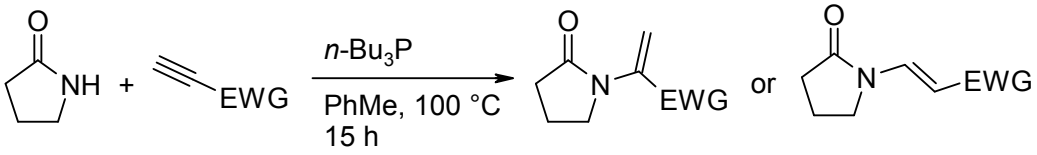
Entry	phosphine	Yield (%)[a]
1	Ph_3P	2
2	$(2\text{-Fur})_3P$	3
3	Cy_3P	0
4	$i\text{-Pr}_3P$	25
5	$t\text{-Bu}_3P$	0
6	$n\text{-Bu}_3P$	89
7	$n\text{-Oct}_3P$	40
8	Me_3P	90
9	dcypm	0
10	dcype	0

Reaction conditions: 1.00 mmol 2-pyrrolidone, 2.00 mmol phenylacetylene, 9 mol% phosphine, 3 mL toluene, 100 °C, 15 h. a) Corrected GC yields with *n*-tetradecane as internal standard.

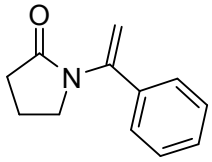
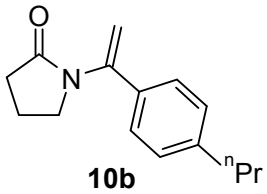
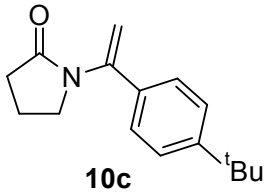
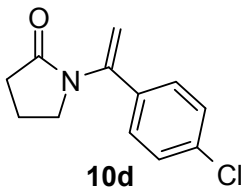
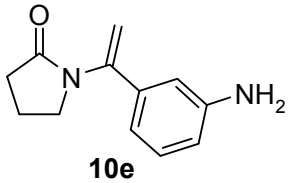
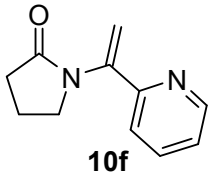
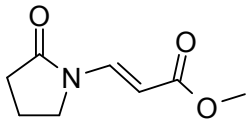
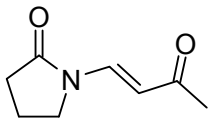
After optimizing the reaction conditions, we tested the generality of this methodology and found that the protocol allows the Markovnikov-selective addition of 2-pyrrolidone to phenylacetylene derivatives in moderate to high yields (Table 17, **10a-f**). In the case of

acetylenic carbonyl compounds, the regioselectivity of the reaction was inverted and anti-Markovnikov products were obtained in high yields and stereoselectivities (**11a**-**b**).

Table 17. Substrate scope of phosphine-catalyzed addition of 2-pyrrolidone to activated alkynes.

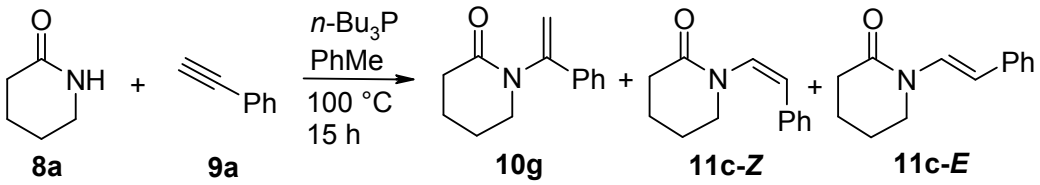


8 **9** **10** **11**

Product	Yield (%)[a]	Product	Yield (%)[a]
 **10a**	85	 **10b**	42
 **10c**	40	 **10d**	81
 **10e**	77	 **10f**	56
 **11a**	87	 **11b**	74

Reaction conditions: 1.00 mmol 2-pyrrolidone, 2.00 mmol alkyne, 9 mol% *n*-Bu_3P, 3 mL toluene, 100 °C, 15 h. a) Isolated yields.

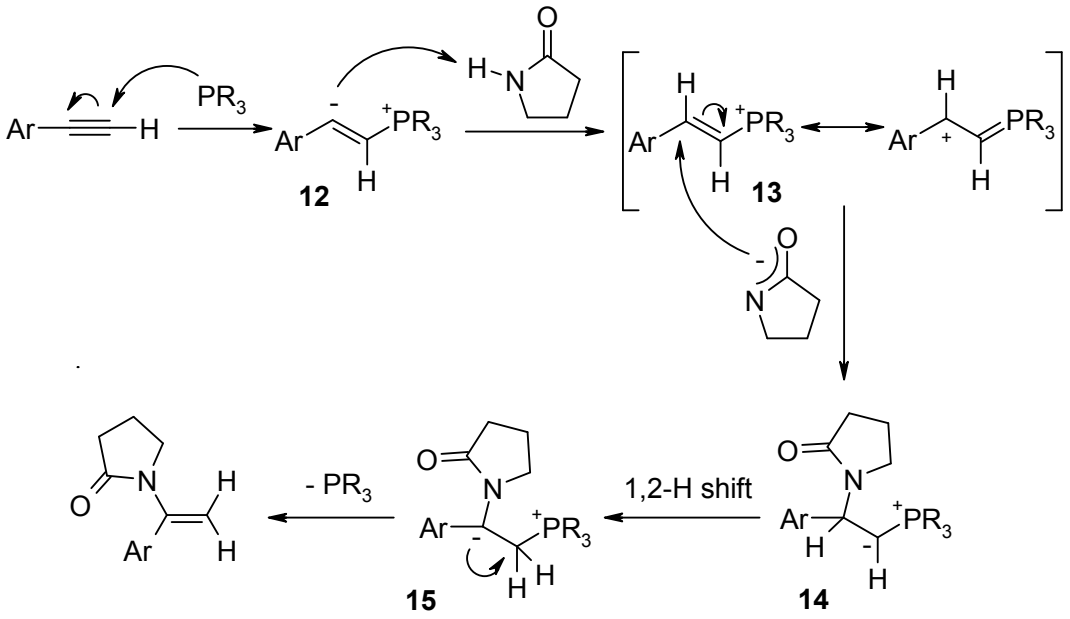
For the addition of the six-membered cyclic amide, 2-piperidone, to phenylacetylene, yields and selectivities were drastically decreased, following the optimized reaction conditions. Further modifications did not lead to satisfactory results only when the amount of amide was increased, a higher yield was obtained and the regioselectivity shifted in favor of the anti-Markovnikov products (Scheme 85).



(a)	15%	12%	7%
(b)	10%	51%	19%

Scheme 85. Addition of 2-piperidone to phenylacetylene. *Reaction conditions:* (a) 1.00 mmol 2-piperidone, 2.00 mmol phenylacetylene, 9 mol% *n*-Bu_3P, 3 mL toluene, 100 °C, 15 h. (b) 3.00 mmol 2-piperidone, 1.00 mmol phenylacetylene, 9 mol% *n*-Bu_3P, 3 mL toluene, 100 °C, 15 h.

A similar mechanism to that postulated by Trost et al. (Scheme 75) can be proposed for the phosphine-catalyzed Markovnikov-selective addition to phenylacetylenes. A nucleophilic attack of the trialkylphosphine to the β-position of the phenylacetylene derivative gives a 1,3-dipolar phosphonium intermediate **12**, which abstracts a proton from 2-pyrrolidone, forming a phosphonium enyl intermediate (**13**). Subsequent addition of the 2-pyrrolidone anion, followed by 1,2-H shift and elimination of the phosphine leads to the corresponding product as the final step of the catalytic reaction (Scheme 86).

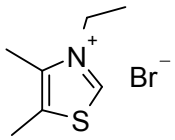


Scheme 86. Plausible mechanism for phosphine-catalyzed addition of amides to alkynes.

For the formation of anti-Markovnikov products via addition of 2-pyrrolidone to acetylenic carbonyl compounds, a similar mechanism to that proposed for the addition of alcohols to methyl propiolate can be postulated (Scheme 29). The formation of anti-Markovnikov products from the reaction of 2-piperidone and phenylacetylene may also proceed via deprotonation of the amide, followed by its conjugated addition to the alkyne.

Our next attempt was to use *N*-heterocyclic carbines (NHCs) as a catalyst for our reaction, since it is known to be an even stronger σ-donor than phosphines. For instance, thiazolium salts as a precursor to NHCs[146] have been reported as a catalyst for benzoin-type reactions,[147] and in asymmetric synthesis.[148]

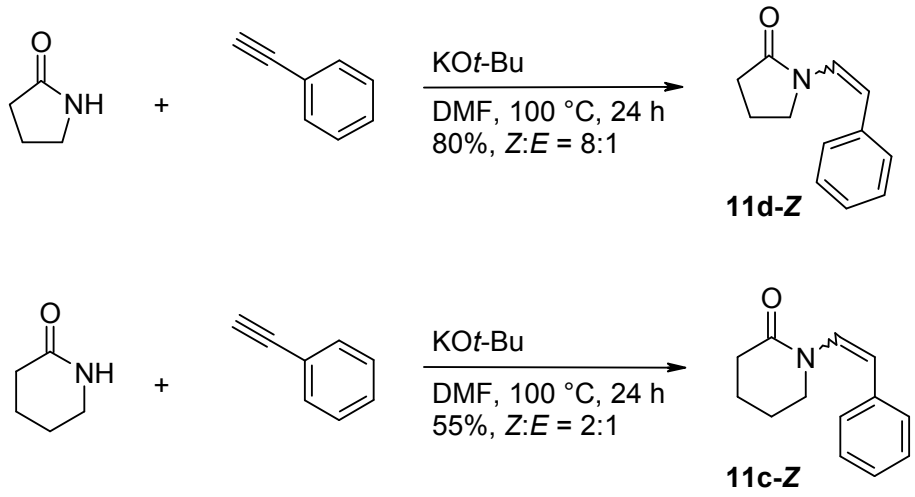
The NHC can be generated from thiazolium salt by the addition of base. We used a catalyst of the type **16** instead of *n*-Bu_3P in our model reaction, as it has less sterical hindrance. However, under various sets of conditions (by using different organic and inorganic bases, solvents, additives, and various temperatures), no product was observed.



16

Figure 2. Thiazolium salt as a source for NHC.

However, some bases showed influence on the reaction by forming anti-Markovnikov product, particularly when KO*t*-Bu was employed in DMF. After optimizing the conditions of this reaction, the scope was tested and found that just cyclic amides such as 2-pyrrolidone and 2-piperidone can be transformed with phenylacetylene to the corresponding products (Scheme 87).



Scheme 87. Base-catalyzed addition of 2-pyrrolidone and 2-piperidone to phenylacetylene. *Reaction conditions:* 1.00 mmol amide, 1.50 mmol phenylacetylene, 15 mol% KO*t*-Bu, 2 mL DMF, 100 °C, 24 h.

In summary, trialkylphosphines mediate the addition of 2-pyrrolidone to phenylacetylene derivatives and acetylenic carbonyl compounds giving rise to Markovnikov and *E*-anti-Markovnikov products, respectively. Although the reaction is limited to the aforementioned substrates, to the best of our knowledge, this is the first time that the Markovnikov addition was achieved for aryl acetylenes. Moreover, cyclic amides can be added to phenylacetylene forming anti-Markovnikov product in the presence of inorganic base.[149]

3.4 Synthesis of natural products

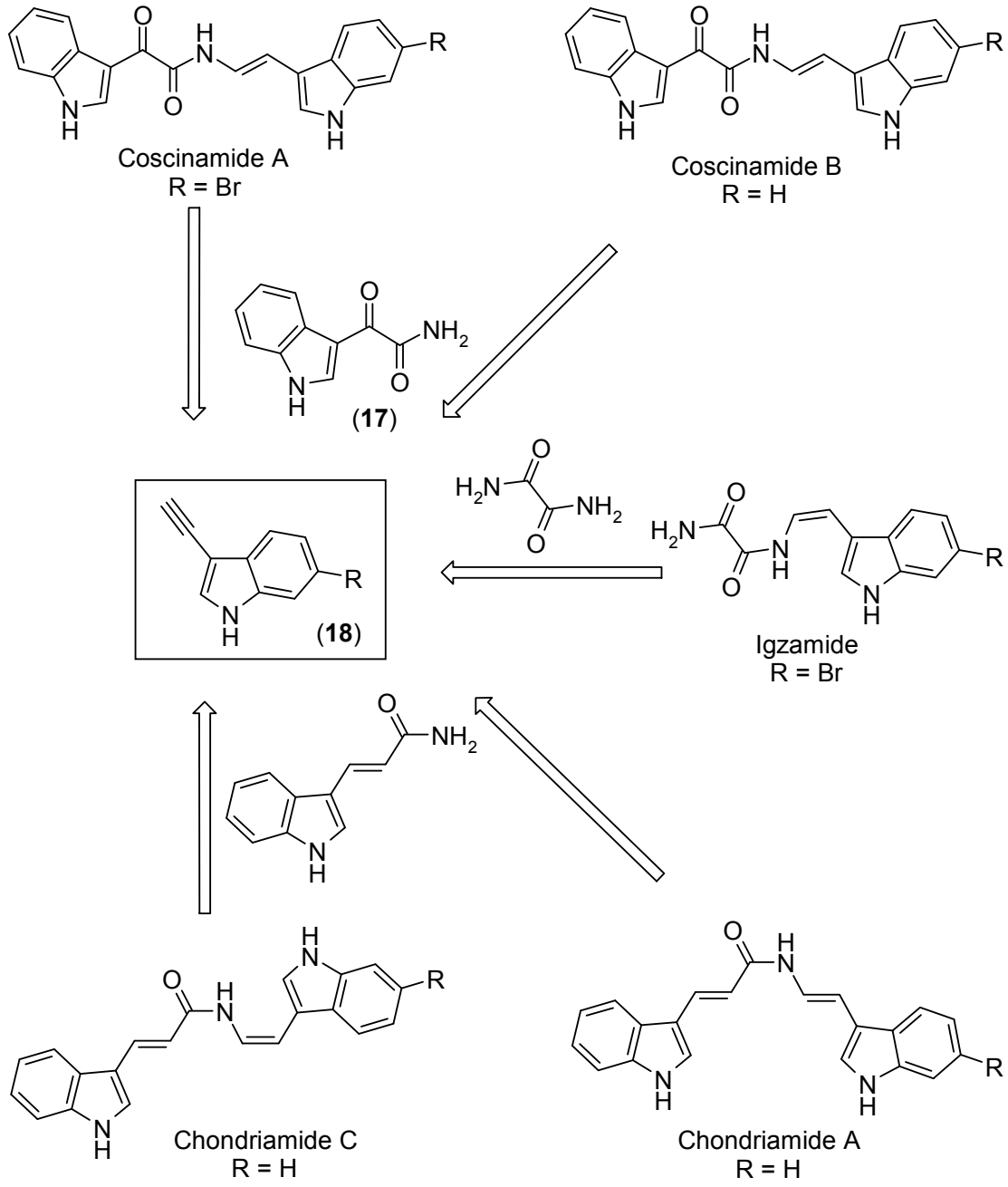
Once a synthetic protocol has newly been developed, it is an attractive goal to employ it in the synthesis of natural products. Our new methodology for the synthesis of secondary enamides shows a wide functional group tolerance and has been successfully applied in the synthesis of lansiumamide A, alatamide, and a key intermediate in Castedo's total synthesis of aristolactam (Scheme 83).

This project was performed in collaboration with Mathieu Blanchot and Matthias Arndt.

3.4.1 Attempted synthesis of naturally occurring indolic compounds

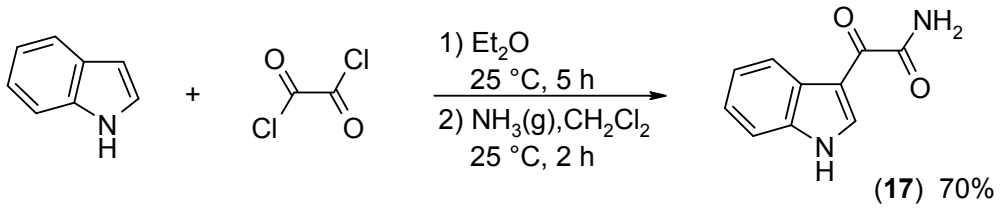
To extend the applicability of our methodology, we selected some naturally occurring indolic compounds as target, such as coscinamide A, B (HIV-inhibitory activity), chondriamide A, C (cytotoxity, antiviral, and anthelmintic activity), and igzamide (citotoxicity against murine leukemia). Previously reported total syntheses involved lengthy multi-steps procedure, resulting in overall poor yields.[150]

The convergent retrosyntheses of these products are illustrated in Scheme 88, which are based on 3-ethynylindoles (**18**) as main building blocks, along with amides as coupling partners.



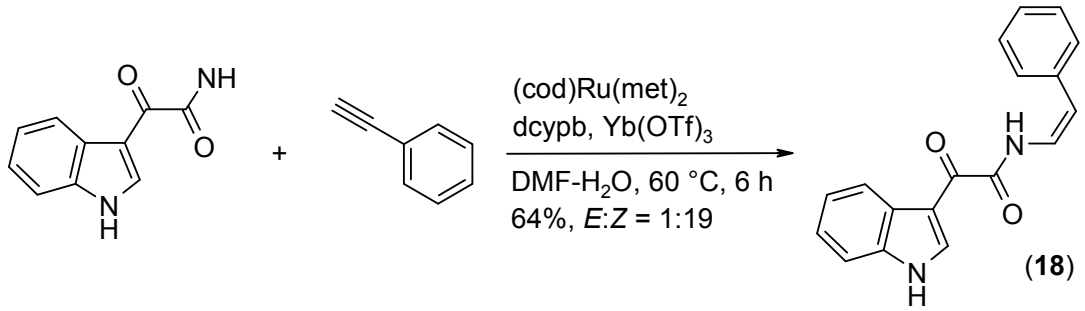
Scheme 88. Retrosynthesis of coscinamides, chondriamides, and igzamide.

We chose the synthesis of coscinamide B as a starting point because indole-3-glyoxylamide (**17**) is easily accessible from indole, oxalyl chloride, and ammonia gas following a procedure reported by Stoltz and coworker (Scheme 89).[151]



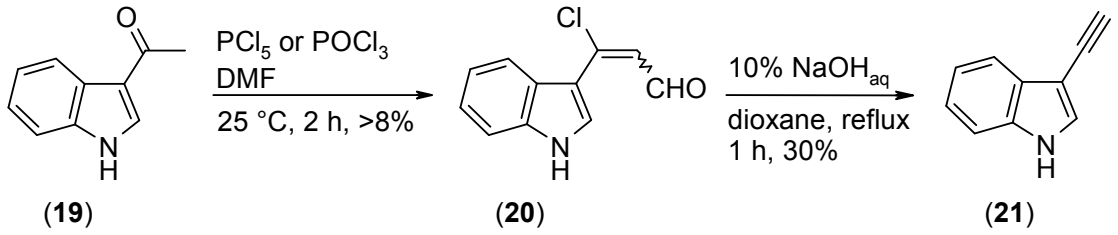
Scheme 89. Synthesis of indole-3-glyoxylamide.

The presence of additional functional groups, such as N−H, in the building blocks makes control experiments essential. Therefore, we carried out the reaction of amide **17** with phenylacetylene to give **18** following the hydroamidation protocol for primary amides. This experiment indicated that the transformation can be successfully completed in a good yield without the need for protecting groups (Scheme 90).



Scheme 90. Catalytic addition of indole-3-glyoxylamide to phenylacetylene.

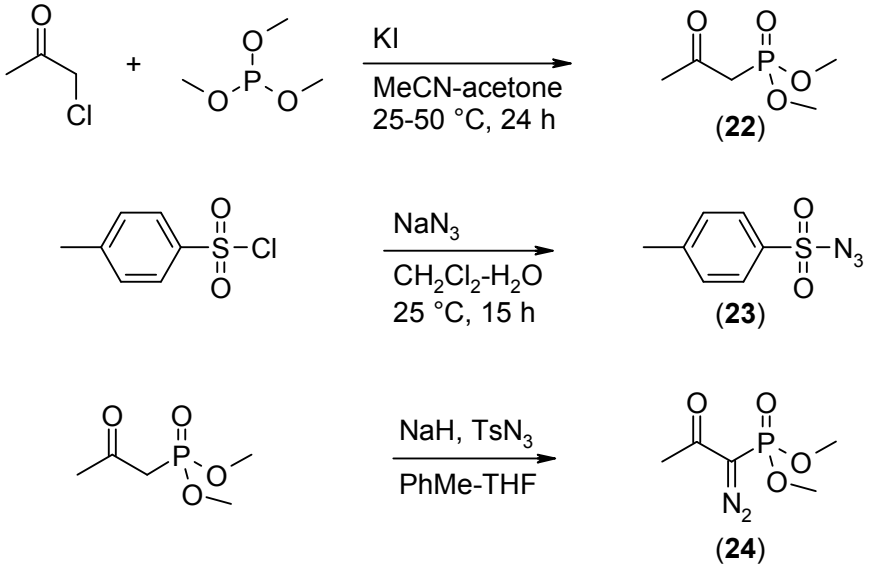
The 3-ethynylindole could be conventionally synthesized by a conversion of 3-acetoxy-indole or 3-formylindole with appropriate reagents. The reaction of **19** with Vilsmeier reagent, generated from phosphorous pentachloride or phosphoryl chloride with DMF, did not lead to a satisfactory result; the literature yield of 60% for aldehyde **20** was not reached at all (Scheme 91).[152] Other literature approaches also led to decomposition of the starting material or resulted in very low yields.[153]



Scheme 91. Conventional synthetic approach for 3-ethynylindole.

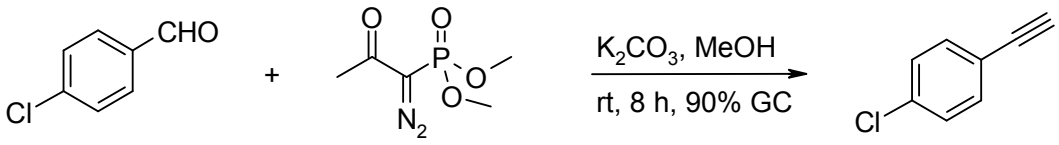
We therefore evaluated the alternative procedures for synthesizing **21**, normally the transformation of 3-formylindole with Bestmann-Ohira reagent[154] (BOR, **24**) and the Sonogashira coupling of 3-halo-indole with trimethylsilylacetylene.[155] The latter is however not applicable for the synthesis of coscinamide A and igzamide, as the bromo substituent in 6-position of the indole moiety would also be coupled with trimethylsilylacetylene under Sonogashira coupling conditions.

The BOR was synthesized via three steps from commercially available starting materials (Scheme 92).[156]



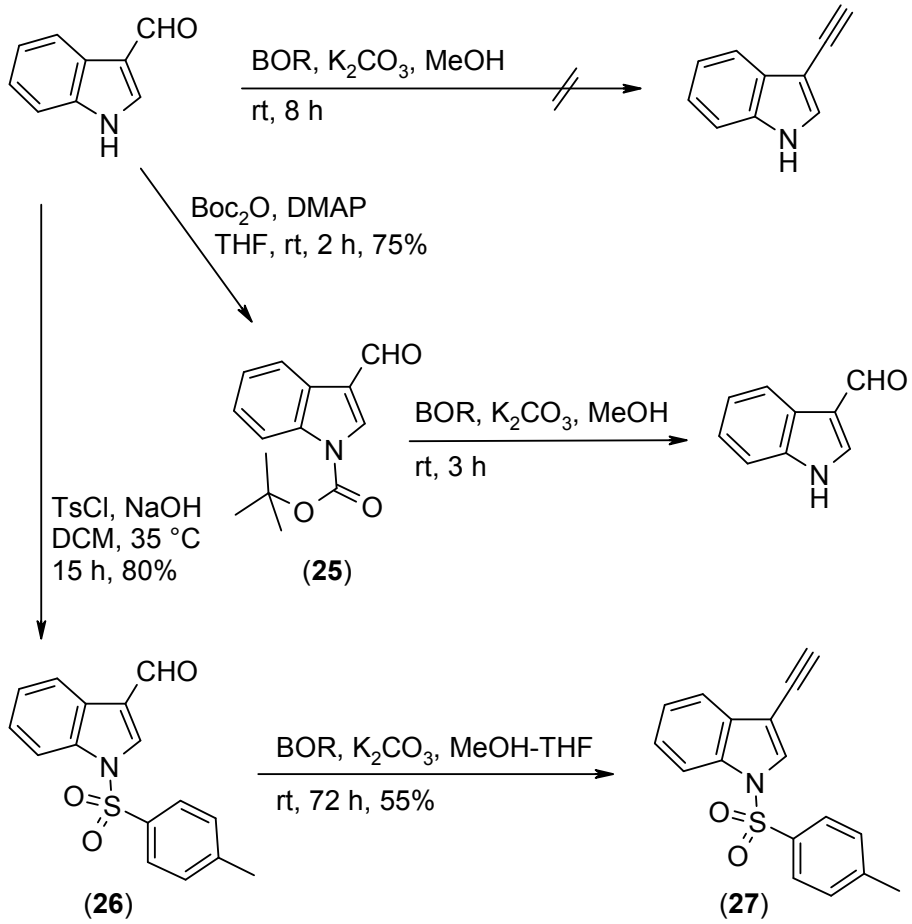
Scheme 92. Synthesis of Bestmann-Ohira reagent.

A control experiment was applied on a selected literature example, *p*-chloro-benzaldehyde,[154] proving the efficiency of the BOR in turning a formyl group into an ethynyl substituent. A high yield was obtained with full conversion of the starting material (Scheme 93).



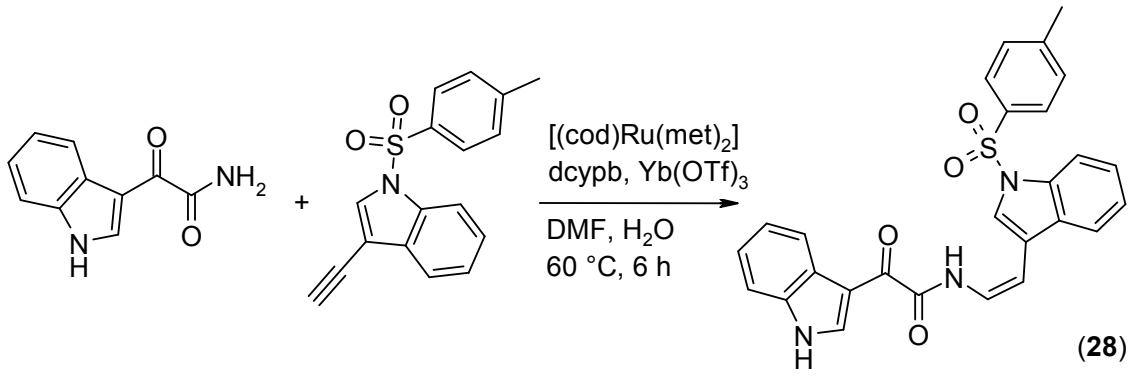
Scheme 93. Control experiment for Bestmann-Ohira reagent.

Unfortunately, a direct reaction of BOR with 3-formylindole under different sets of conditions led to the recovery of the starting material in all the cases. Protecting indole moiety[157] prior to this transformation allowed the successful conversion of *N*-Ts-3-formylindole (**26**) under the optimized reaction conditions, while *N*-Boc-3-formylindole (**25**) underwent hydrolysis (Scheme 94).



Scheme 94. Transformation of 3-formylindoles to 3-ethynylindoles.

However, in the catalytic addition of indole-3-glyoxylamide to *N*-Ts-3-ethynylindole we observed a very poor conversion to the product **28** by MALDI (Scheme 95). Attempts to optimize the reaction conditions did not lead to improved yields. Undoubtedly, *N*-Ts-3-ethynylindole exhibits extremely low reactivity in the hydroamidation reaction, even with simple amides like benzamide and at catalyst loading as high as 20 mol%.

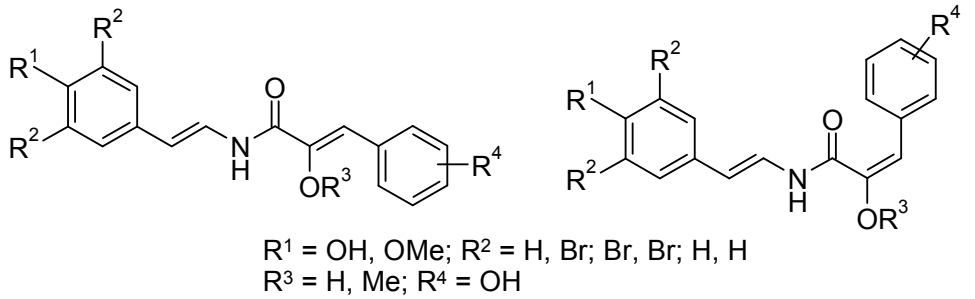


Scheme 95. Hydroamidation reaction of *N*-tosyl-3-ethynylindoles.

The last step of our attempted synthesis was the deprotection of the tosylated nitrogen atom by suitable reagents. The use of sodium methoxide[44] led to *N*-methylation of the indole moiety, while decomposition or no reaction took place when using other alkali bases.[158]

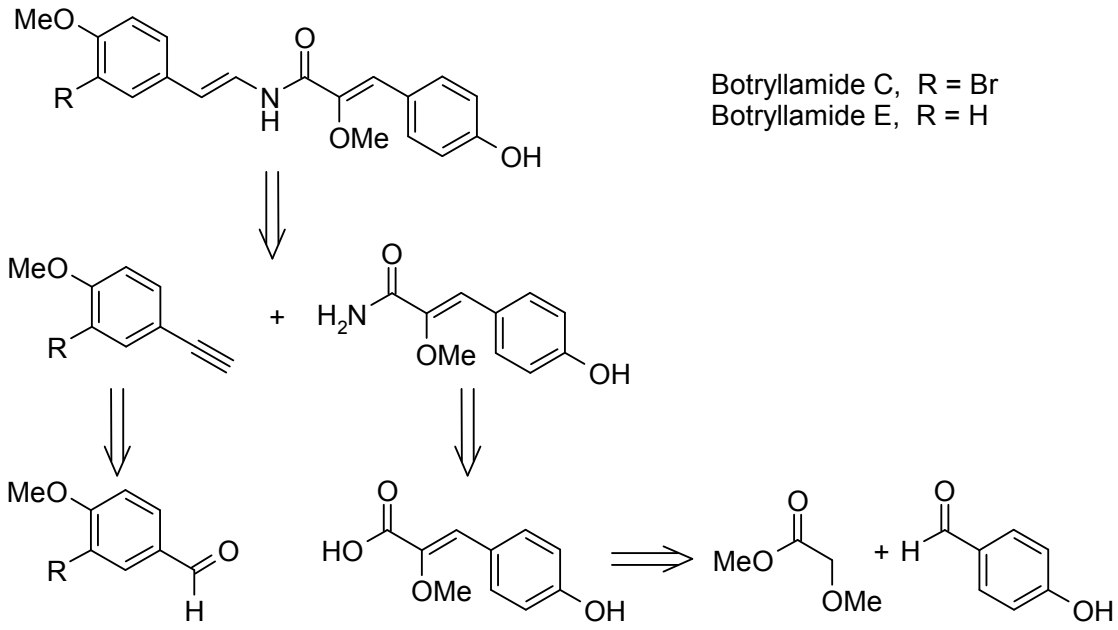
3.4.2 Synthesis of botryllamides

As all our efforts failed to employ our hydroamidation methodology to the synthesis of indole-containing molecules, we abandoned the synthesis of such compounds at this stage. We next evaluated hydroamidation reactions for the synthesis of another class of natural products, the botryllamides, which also bear an enamide moiety that can be prepared via catalytic hydroamidation (Scheme 96). Several members of the class of botryllamides (A-J, revised botryllamide H) have been isolated from the marine ascidian *Botryllus* species.[159-161] The substance class represents an interesting target for pharmaceutical research, as some members exhibit cytotoxicity against human colon tumors[160] and inhibit ABCG2.[161,162]



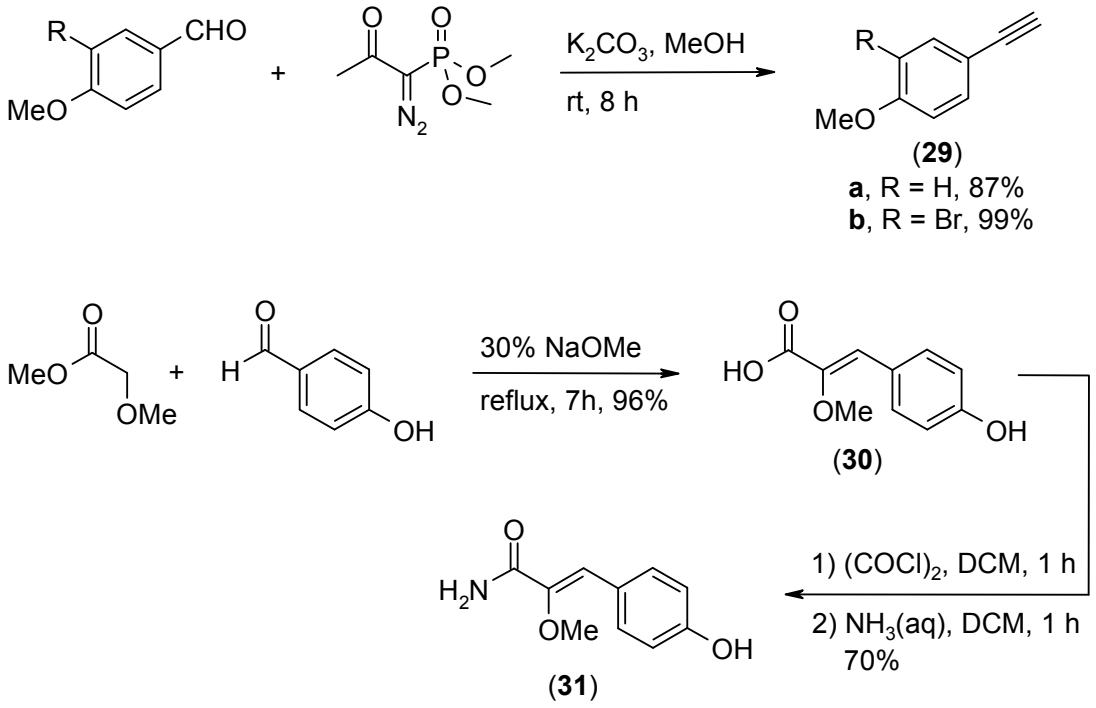
Scheme 96. Structures of botryllamides.

As representative examples, we chose botryllamides C and E for our total syntheses. Scheme 97 shows the convergent retrosynthesis of these two substances, taking commercially available benzaldehyde derivatives as a starting point.



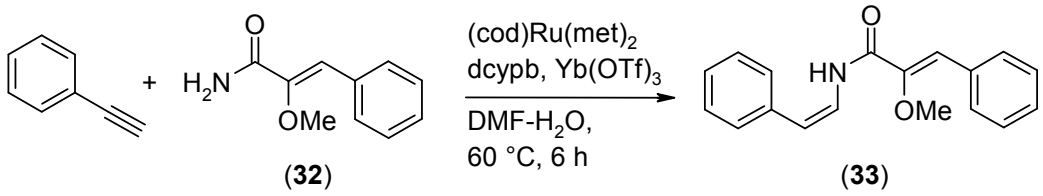
Scheme 97. Retrosynthesis of botryllamides C, E.

The required alkynes were successfully synthesized using Bestmann-Ohira reagent, whereas the amide **31** was prepared from the corresponding carboxylic acid, which was obtained following a literature procedure by Woltering et al. (Scheme 98).[163]



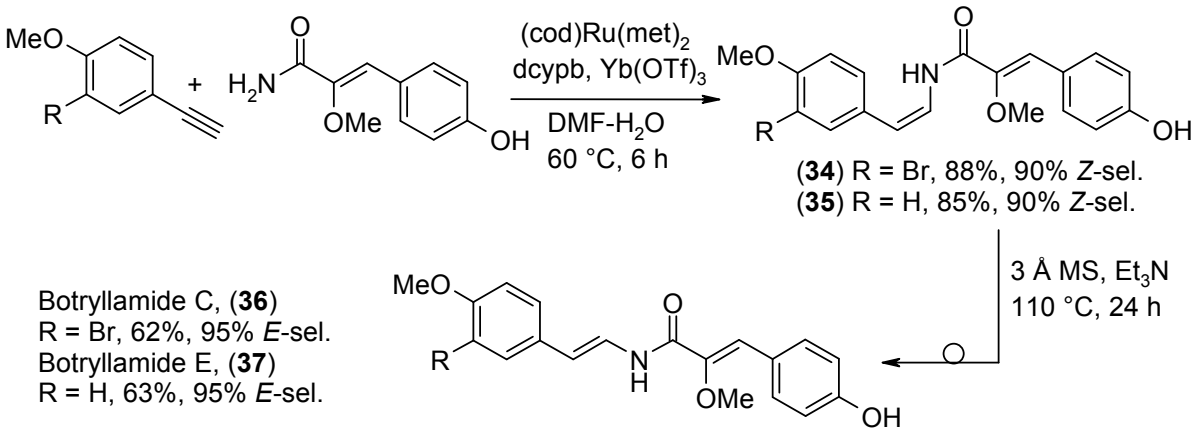
Scheme 98. Synthesis of the building blocks.

Believing that the hydroxyl group will not inhibit the catalytic reaction, a control experiment to investigate the tolerance of methyl vinyl ether group was performed to amide **32** with phenylacetylene, showed a smooth transformation to enamide substructure **33** (Scheme 99).



Scheme 99 Synthesis of the analogous botryllamide, reaction was monitored by GC-MS.

Finally, the *Z*-products (**34**, **35**) were formed upon the catalytic addition of amide **31** to the alkynes **29** in high yields and selectivities, followed by one-pot in situ isomerization of the latter ended with unprecedented synthesis of botryllamides C and E in quantitative yields (Scheme 100).[162]

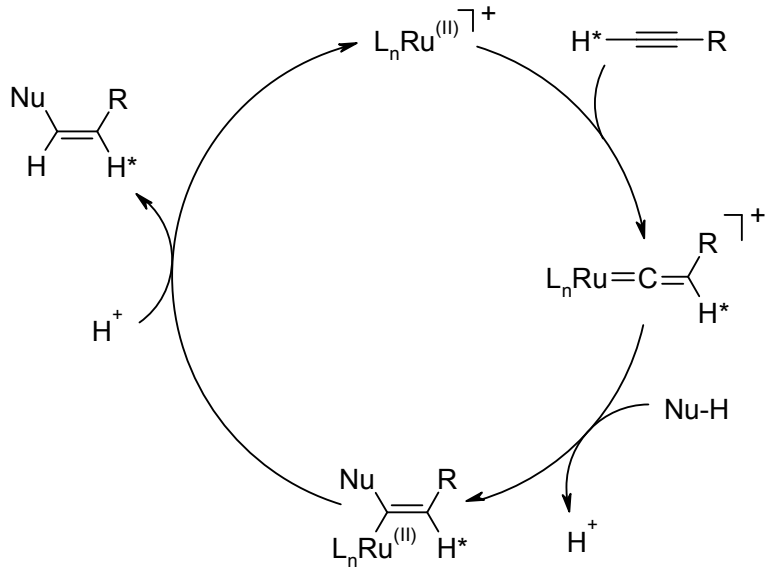


Scheme 100 Synthesis of botryllamides C and E.

In conclusion, we have demonstrated the applicability of our newly developed hydroamidation protocol by achieving the first synthesis of botryllamides C and E, providing a method which could also be applied for the synthesis of other botryllamide classes.

3.5 Mechanistic studies of catalytic addition of nucleophiles to alkynes

A good understanding of the catalytic steps for our hydroamidation reactions is the key factor in the development in these reactions. Prior to our endeavor in addition reactions, Dixneuf and coworkers have proposed a catalytic cycle involves a Ru-vinylidene species with 1,2-H shift of the acetylenic hydrogen to the neighbor carbon atom (see Scheme 40 and 44). The Ru-alkenyl complex is formed by an attack of the nucleophile to the most electrophilic carbon atom. A reductive elimination would release the product, regenerating the active catalyst species (Scheme 101).[93,99]



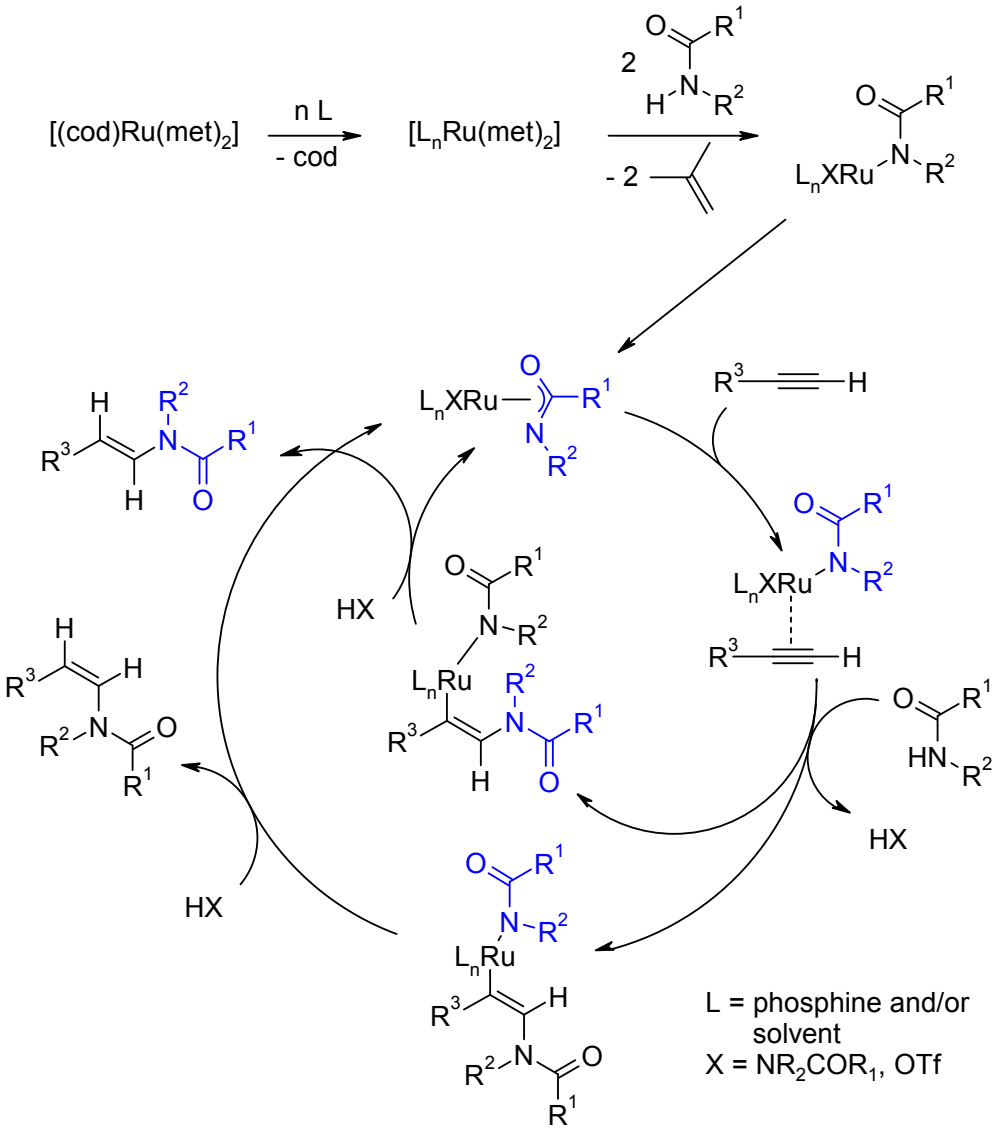
Scheme 101. Dixneuf type mechanism for addition of nucleophiles to terminal alkynes.

The authors based their proposal on some isolated and synthesized complexes for elucidation of the mechanism. This proposal was adopted by many researchers[164] and recently has been suggested for interamolecular addition of alcohols to terminal alkynes, which is supported by deuterium-labeling experiments.[165]

Another interesting catalytic cycle was reported by Wakatsuki and coworkers for the hydration of terminal alkynes (see Scheme 26). It is somehow similar to the one

mentioned above, but includes 1,2-H shift of the acetylenic proton to the Ru-center (instead to the adjacent carbon atom). Finally, the proton retains its original position on the product. This mechanism is well-supported by isolated organic and organometallic byproducts, deuterium-labeling experiments, and DFT calculations.[78]

Our preliminary proposed mechanism in this area was based on the preformation of the active catalyst species, ESI-MS, and in situ NMR studies.[130,131,144a] The catalytic cycle includes a coordination of alkyne to the catalytically active species, L_nXRu-amide, followed by addition of an amide nucleophile to the η^2-coordinated alkyne, yielding η^1-ruthenium vinyl complexes. The *E*- or the *Z*-configured amidoalkenyl ruthenium species will be formed depending on whether the amide comes from inside or outside the coordination sphere of ruthenium, respectively. Protonolysis of these intermediates would probably proceed with preservation of the stereochemistry, regenerating the catalytically active species (Scheme 102).



Scheme 102. Our preliminary proposed mechanism for addition of amides to terminal alkynes.

After that, we performed further in situ NMR experiments and intensive studies including deuterium-labeled starting material for all protocols that were invented in our group for the addition of nucleophiles to alkynes, believing that the outcomes from these reactions would be critical to investigate the 1,2-H shift of the terminal alkynes and the formation of ruthenium-vinylidene species.

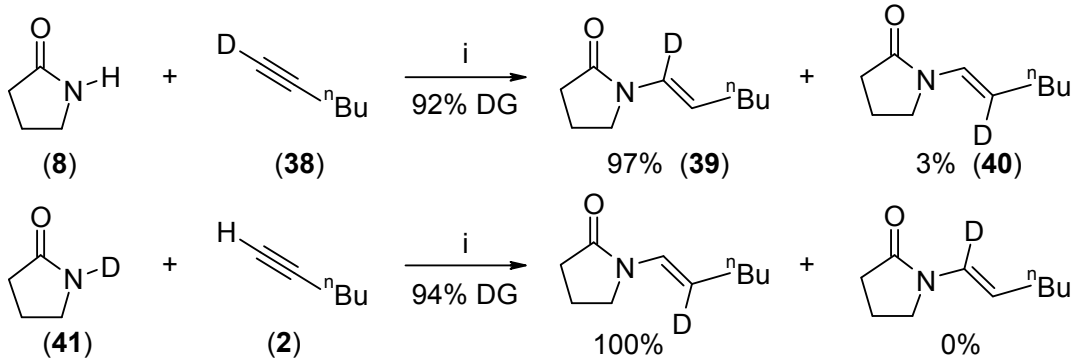
3.5.1 Deuterium-labeling experiments

3.5.1.1 Addition of secondary amides to alkynes

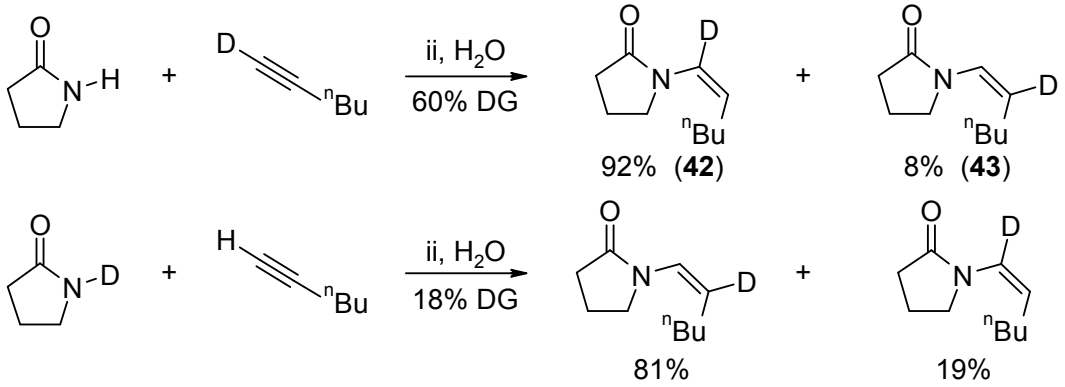
The catalytic addition of 2-pyrrolidone (**8**) to 1-D-hexyne (**38**) showed a high abundance of the deuterium in 1'-position (**39**,**42**) in the corresponding enamides for *E*- and *Z*-protocols (97% and 92%, respectively), while traces of deuterium found in 2'-position (**40**,**43**) could be attributed to the exchange with adjacent protons during the coordination on the metal center or through the exchange with the solvent.

Furthermore, 1-D-pyrrolid-2-one (**41**) was employed in a parallel reaction with 1-hexyne (**2**) to follow the source of the proton on C-2'. For the *E*-protocol, the deuterium was found only in the 2'-position of the enamide products, while in case of the *Z*-protocol, only 81% of the deuterium was detected in 2'-position and 19% in 1'-position. As the presence of water plays a role for increasing the selectivity towards *Z*-enamide, we believe it may help exchanging the deuterium during the reaction. Two alternative reactions for *Z*-protocol were carried out in the presence of D_2O instead of water, unsurprisingly, high deuteration values of enamide products (**44**) were obtained that demonstrate the exchange state (Scheme 103). Unfortunately, the scrambling of deuterium was also taken place even in the absence of water or using deuterated solvent, toluene-d_8. These results clearly rule out a mechanism which includes a 1,2-H shift of the acetylenic proton to the neighbor carbon atom.

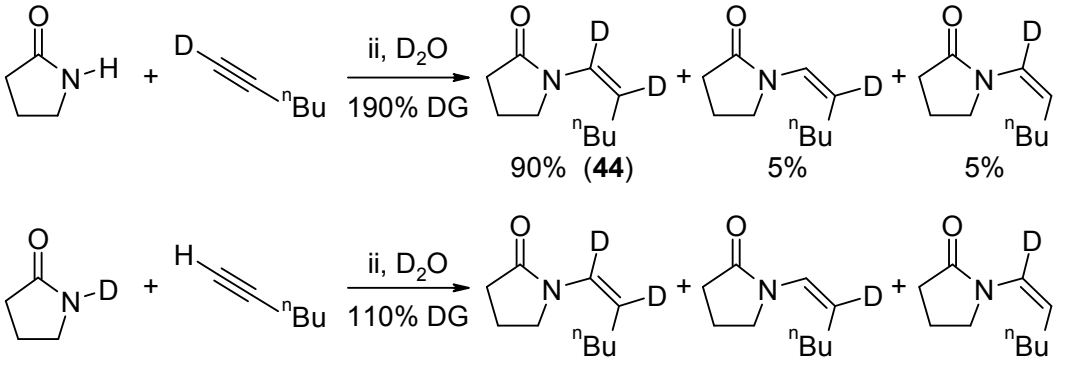
E-selective protocol



Z-selective protocol



Z-selective protocol with D_2O



Scheme 103. Deuteration experiment of addition of secondary amides, *conditions*: (i) 1.0 mmol amide, 2.0 mmol alkyne, 0.02 mmol [(cod)Ru(met)$_2$], 0.06 mmol *n*-Bu_3P, 0.04 mmol DMAP, 3 mL toluene, 100 °C, 15 h. (ii) 1.0 mmol amide, 2.0 mmol alkyne, 0.02 mmol [(cod)Ru(met)$_2$], 0.03 mmol $Cy_2PCH_2PCy_2$, 2.0 mmol H_2O, 3.0 mL toluene, 100 °C, 15 h. (iii) Same condition of ii, but with 4.0 mmol D_2O. Isomeric ratio was determined by ^{1}H-NMR.

Furthermore, we have followed the reaction by an in situ ^{2}H-NMR experiment using 1-D-hexyne as a labeled starting material. As anticipated, an intermediate η^2-alkyne-metal complex was detected as a new triplet peak (Figure 3), which illustrates the coordination of the deuterated alkyne to the Ru-center and coupling with two coordinated phosphine ligands.[166] Unfortunately, no further significant peak was detected in the region of +40 to –40 ppm for Ru-hydride species, which is expected in the area around –25 ppm.[167]

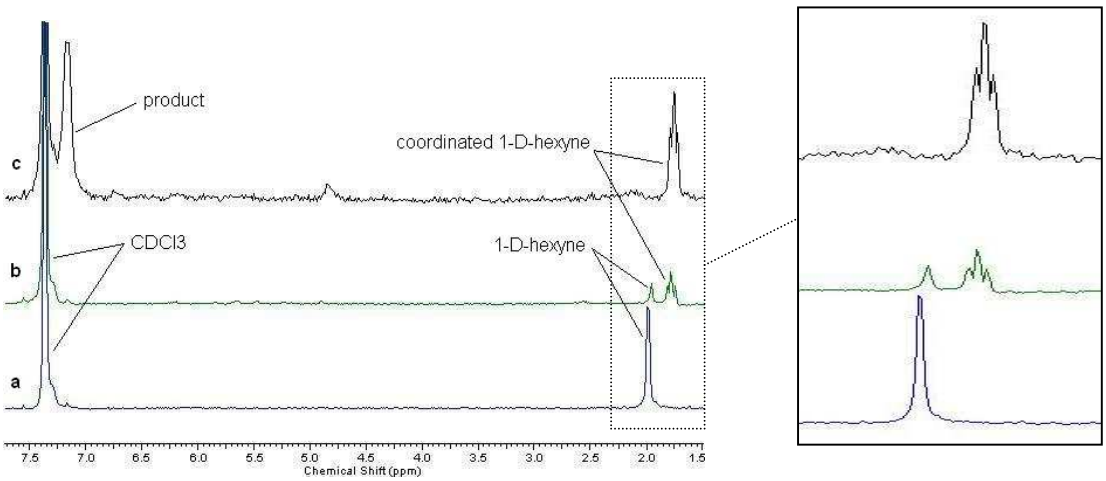
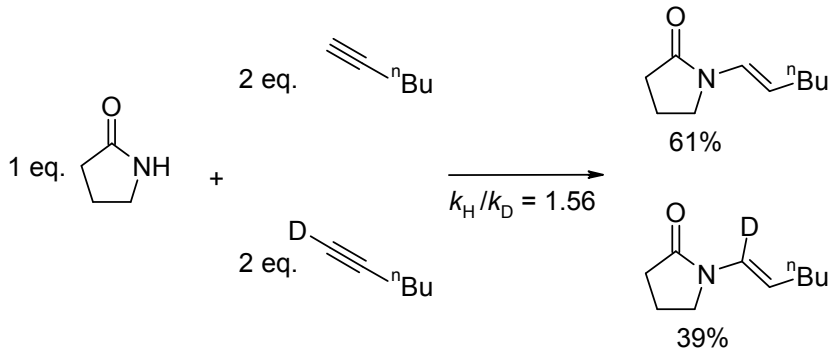


Figure 3. In situ ^{2}H-NMR experiments for hydroamidation of 1-D-hexyne. (a) Reaction mixture without 2-pyrrolidone at ambient temperature. (b) Reaction mixture without 2-pyrrolidone at ≥70 °C. (c) Reaction mixture with 2-pyrrolidone after 10 minutes of heating (95-100 °C).

Afterwards, we followed the reaction by measuring the kinetic isotope effect (KIE), believing it could give a statement for the step subsequent to the π-coordination of the alkyne to the ruthenium center. In a competition reaction between deuterated and non-deuterated 1-hexynes, a KIE of 1.56 was observed for addition of 2-pyrrolidone, which has been verified by various control experiments (Scheme 104). However, we were unable to determine the KIE of the *Z*-protocol because of the scrambling of deuterium in 1'- and 2'-positions in the enamide products.



Scheme 104. KIE for the addition of 2-pyrrolidone to deuterated and non-deuterated 1-hexynes.

Since there is not a sharp numerical division between primary and secondary kinetic isotope effects, especially in the range between 1 and 2, the observed KIE, although rather small, might be a primary kinetic effect which consists of a C−H(D) bond cleavage. The result of a hybridization change of the above hydroamidation is not in the direction: $sp^3 \rightarrow sp^2$ or $sp^2 \rightarrow sp$ that is observable in normal secondary kinetic effects or the value of KIE is not < 1 to be in the range of inverse secondary kinetic effects, $sp \rightarrow sp^2$ or $sp^2 \rightarrow sp^3$.[168] Moreover, a relatively low primary isotope effect implies that the bond to hydrogen is either only slightly or nearly completely broken at the transition state (TS). That is, the TS must occur quite close to the reactant (early TS) or to the product (later TS) (Figure 4).[169]

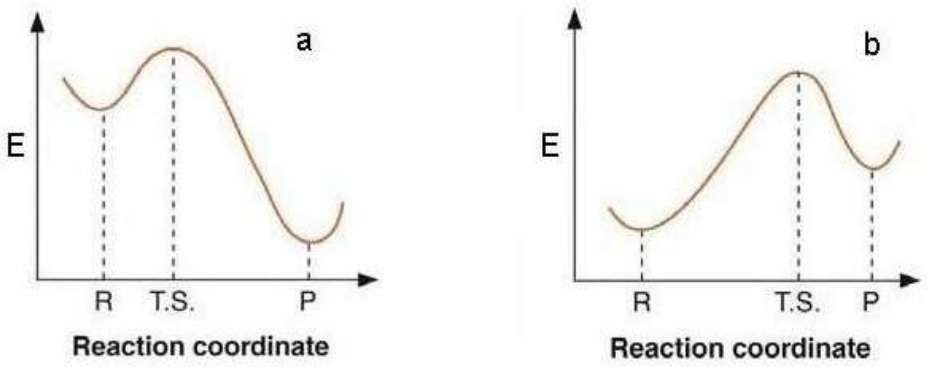


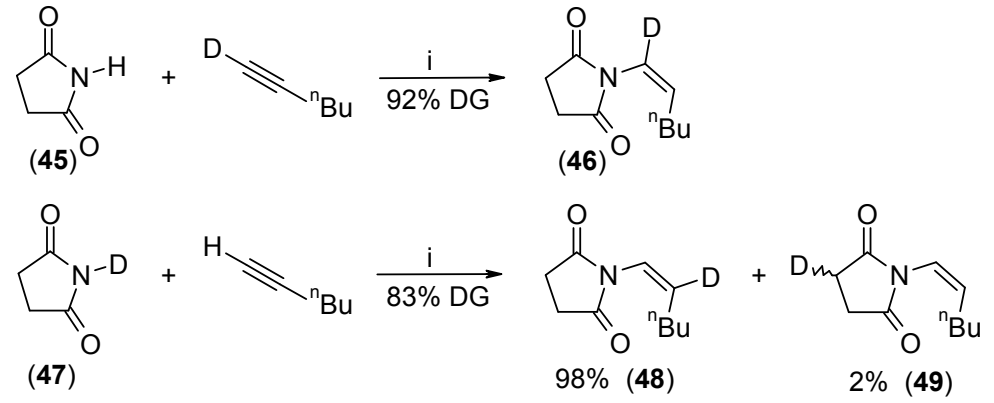
Figure 4. Hypothetical transition states diagram; (a) Early TS, the TS is very reactant-like; (b) Later TS, the TS is very product-like.

As a result, a Ru-vinylidene species is possible to occur as an intermediate including a 1,2-H shift to the Ru-center.

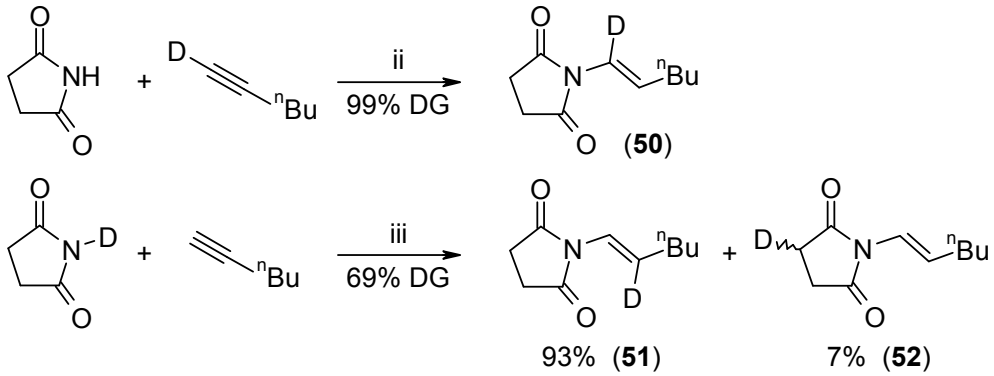
3.5.1.2 Addition of imides to alkynes

To investigate the mechanistic pathway of this protocol, we pursued the model reaction with deuterated starting materials. The catalytic addition of succinimide (**45**) to 1-D-hexyne completely showed the deuterium in 1'-position (**46**, **50**) in the corresponding enimide products for both the *Z*- and *E*-protocols. When *N*-D-succinimide (**47**) and 1-hexyne were used in parallel reactions, the deuterium was found in 2'-position (**48**, **51**) in addition to low exchanged value in 3-position (**49**, **52**). This exchange could be ascribed to the activated hydrogen on that position which is as well assisted by the ruthenium precursor.[170] A 1,2-H shift of the acetylenic proton to 2'-position can clearly be ruled out from the reaction mechanism (Scheme 105).

Z-selective protocol

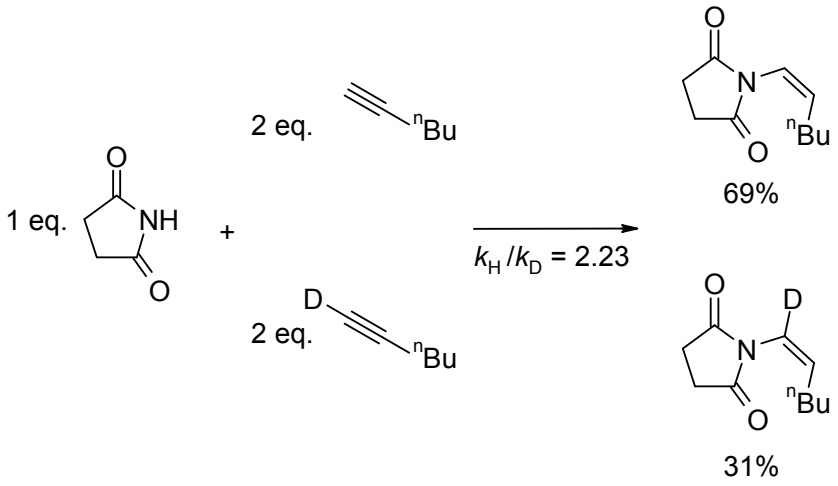


E-selective protocol



Scheme 105. Deuteration experiment of addition of imides to alkynes; *conditions*: (i) 1.0 mmol imide, 2.0 mmol alkyne, 0.02 mmol [(cod)Ru(met)$_2$], 0.06 mmol *n*-Bu$_3$P, 0.04 mmol Sc(OTf)$_3$, 3 mL DMF, 60 °C, 15 h. (ii) 1.0 mmol imide, 2.0 mmol alkyne, 0.05 mmol [(cod)Ru(met)$_2$], 0.15 mmol *i*-(Pr)$_3$P, 0.04 mmol Sc(OTf)$_3$, 3 mL DMF-d_7 (just in this experiment the deuterated solvent is required to reduce the scrambling of deuterium to minimum), 60 °C, 15 h. (iii) Same like ii but with DMF instead of DMF-d_7.

The KIE of addition of succinimide to 1-alkynes showed a value of 2.23 (Scheme 106), which obviously is strong evidence to primary isotope effect that consists of C−H(D) cleavage of the terminal alkynes in the rate-determining step.[169]



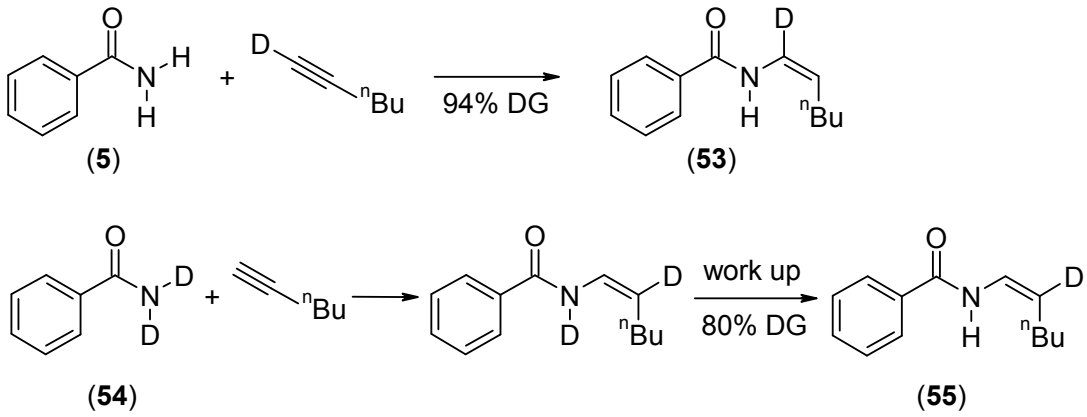
Scheme 106. KIE for the addition of succinimide to deuterated and non-deuterated 1-hexynes.

In addition to the NMR studies, two GC control reactions were separately performed to compare the reaction rates of deuterated and non-deuterated 1-hexynes. The reaction with non-deuterated hexyne was finished within 50 min, while the deuterated starting material required 70 min to complete.

Based on the abovementioned results, it's possible that an intermediacy of Ru-vinylidene complex is formed in the catalytic cycle of the hydroamidation, although such intermediate was not detected so far by instrumental methods.[78]

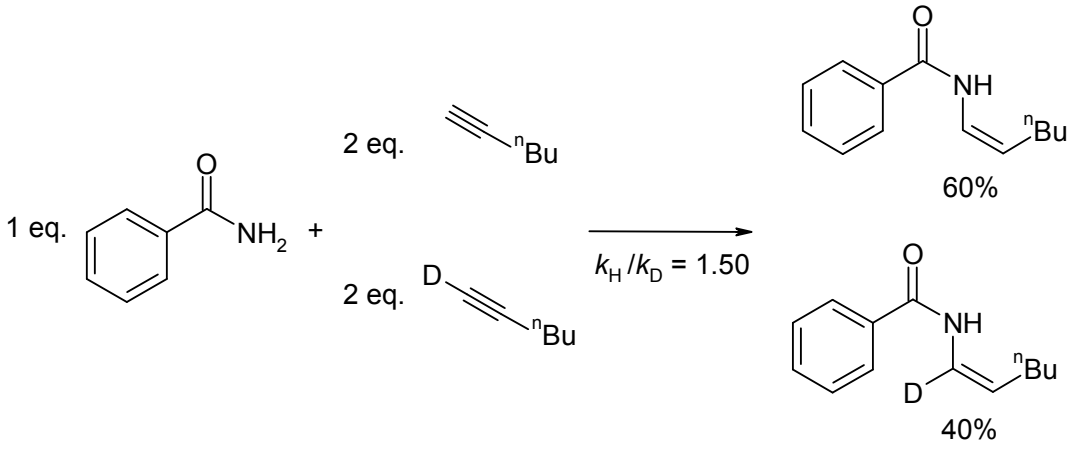
3.5.1.3 Addition of primary amides to alkynes

The addition of benzamide (**5**) to 1-D-hexyne showed a clear result, the deuterium was exclusively found in 1-position (**53**) of the enamide products. However, the deuterium in 2-position (**55**) was solely observed when *N,N*-D_2-benzamide (**54**) and 1-hexyne were utilized in the catalytic reaction (Scheme 107).



Scheme 107. Deuteration experiment of addition of benzamides to alkynes. *condition*: 1.0 mmol amide, 2.0 mmol alkyne, 0.05 mmol $[(cod)Ru(met)_2]$, 0.06 mmol $Cy_2P(CH_2)_4PCy_2$, 0.04 mmol $Yb(OTf)_3$, 3 mL DMF, 60 °C, 15 h.

Furthermore, a KIE of 1.50 was observed in a competition reaction between deuterated and non-deuterated 1-hexynes with benzamide. Despite the fact that this value is rather small, similar to the case of the addition of 2-pyrrolidone, might be a primary kinetic effect (Scheme 108).

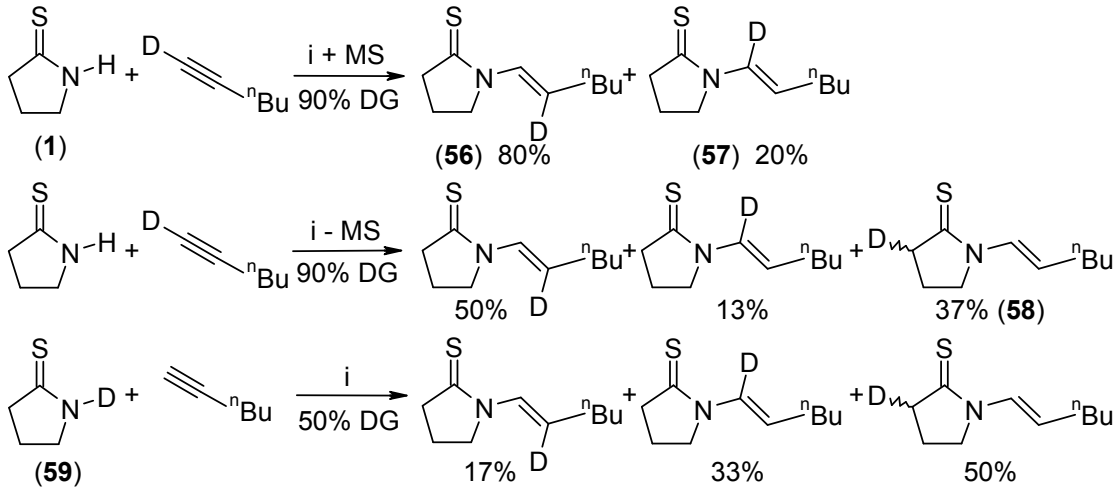


Scheme 108. KIE of the model reaction for the addition of primary amide.

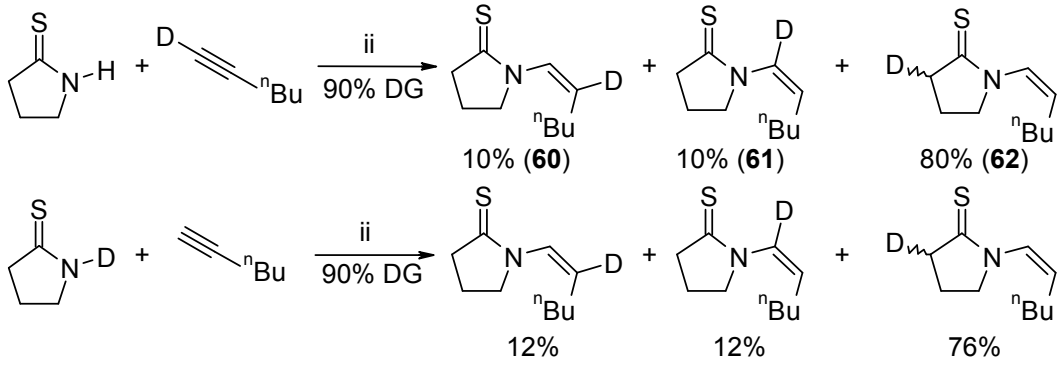
3.5.1.4 Addition of thioamides to alkynes

The addition of thioamides to alkynes deviated from the aforementioned amides. The addition of pyrrolidine-2-thione (**1**) to 1-D-hexyne showed high abundance of the deuterium in 2'-position (**56**) of the corresponding enamides, 80% for *E*-protocol, while a scrambling of the deuterium in 1'- and 2'-position (**60**, **61**) was observed for the *Z*-protocols. Like the case of the addition of 1-D-succinimide to 1-hexyne, the deuterium was found in 3-position (**62**) of the products (Scheme 109).

E-selective protocol



Z-selective protocol



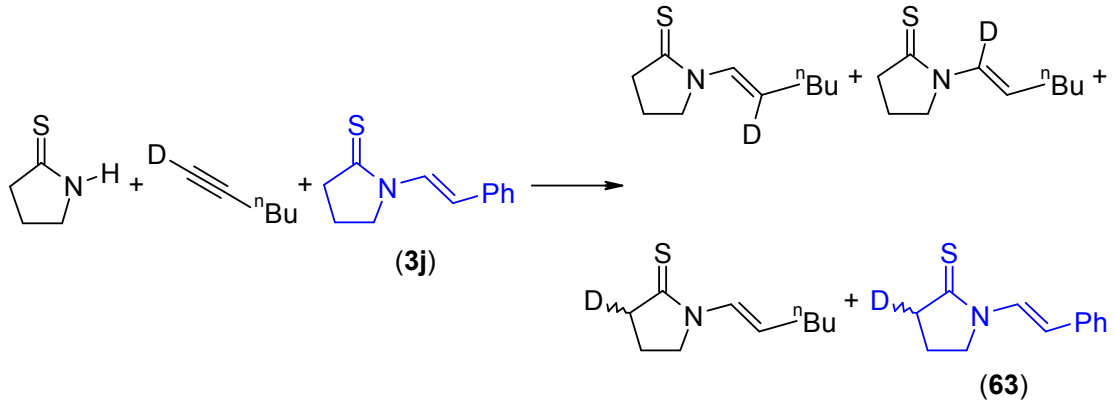
Scheme 109. Deuteration experiment of addition of thioamides. *condition*: (i) 1.0 mmol thioamide, 2.0 mmol alkyne, 0.02 mmol [(cod)Ru(met)$_2$], 0.06 mmol *n*-Oc$_3$P, 500 mg 3 Å MS, 3 mL toluene, 100 °C, 15 h. (ii) 1.00 mmol thioamide, 2.00 mmol alkyne, 5 mol% [(cod)Ru(met)$_2$], 3 mol% dcypm, 4 mol% KO*t*-Bu, 3 mL toluene, 100 °C, 15 h.

Surprisingly, the presence of molecular sieves inhibited the deuterium exchange in 3-position of the enamide products.

Furthermore, when 1-D-pyrrolidine-2-thione (**59**) was used in an analogous reaction with 1-hexyne, a double amount of the deuterium was found on 1'-position than in 2'-position, along with a product with deuterium in 3-position (**58**) for *E*-protocol. For the *Z*-protocol, we observed a scrambling of the deuterium in 1'- and 2'-positions occurred in addition to a great amount of deuterium in 3-position.

Based on these findings, we conclude that a 1,2-H shift of the acetylenic proton to the 2'-position is likely to happen, leading to a Ru-vinylidene species as an intermediate in the catalytic cycle, which would be similar to Dixneuf's proposal.

An interesting observation is that, when the hydroamidation reaction was carried out in the presence of other pyrrolidone-2-thione derivatives (**3j**), deuterium was also observed in 3-position of that derivative (**63**), which clarifies that the exchange in 3-position is independent of the product formation, due to the high mobility of the deuterium under the reaction conditions (Scheme 110).

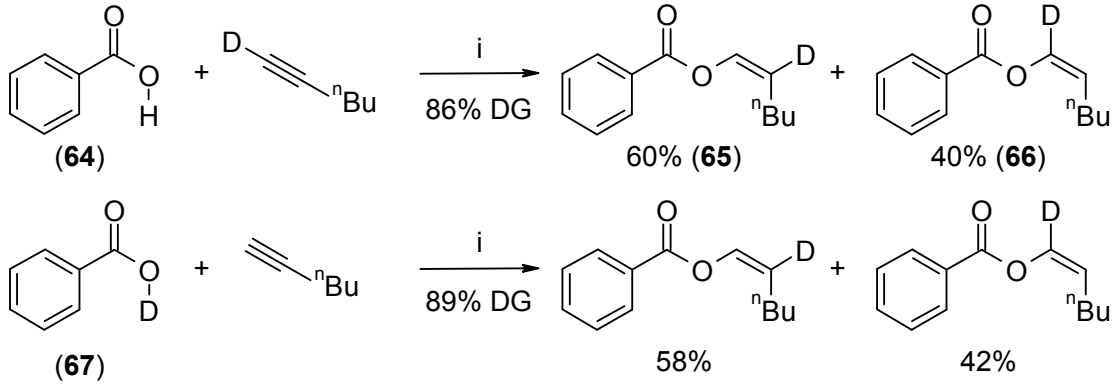


Scheme 110. Exchange of deuteration in hydrothioamidation reaction. *condition*: 1.0 mmol pyrrolidone-2-thione, 2.0 mmol 1-D-hexyne, 0.02 mmol [(cod)Ru(met)$_2$], 0.06 mmol *n*-Oc$_3$P, 200 mg thioenamide **3j**, 500 mg 3 Å MS, 3 mL toluene, 100 °C, 15 h.

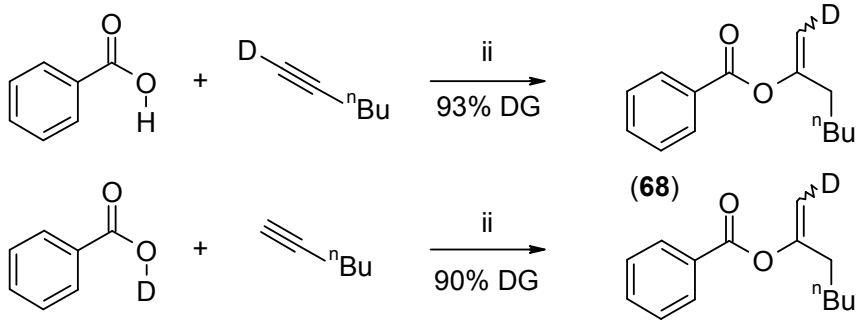
3.5.1.5 Addition of carboxylic acids to alkynes

To compare the aforementioned results with those for the addition of carboxylic acids to alkynes, which was improved in our group, we performed the model reaction with labeled starting materials. Starting with the anti-Markovnikov addition of benzoic acid (**64**) to 1-D-hexyne, the 1-hexenyl benzoate showed 60% of the deuterium in 2-position (**65**) and 40% in 1-position (**66**). In the corresponding product resulting from the addition of *O*-D-benzoic acid (**67**) to 1-hexyne, the deuterium was distributed between 2- and 1-position in a ratio of 58% and 42%, respectively.

Anti-Markovnikov selective protocol



Markovnikov selective protocol

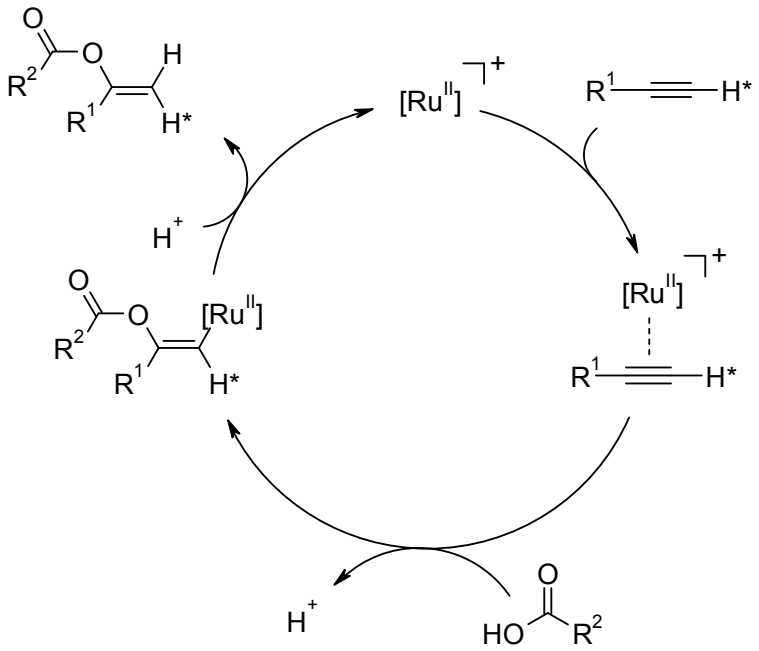


Scheme 111. Deuteration experiment for addition of benzoic acids to alkynes. *conditions*: (i) 1.0 mmol carboxylic acid, 1.3 mmol alkyne, 0.01 mmol $[(p\text{-cumene})RuCl_2]_2$, 0.03 mmol $(p\text{-Cl-}C_6H_4)_3P$, 0.04 mmol DMAP, 3 mL toluene, 60 °C, 15 h. (ii) 1.0 mmol carboxylic acid, 1.3 mmol alkyne, 0.01 mmol $[(p\text{-cumene})RuCl_2]_2$, 0.02 mmol $(2\text{-Fur})_3P$, 0.02 mmol Na_2CO_3, 3 mL toluene, 60 °C, 15 h.

Possibly, the deuterium was scrambled by the metal or the solvent, like in the case of the thioenamides.

Moreover, Markovnikov-selective addition of benzoic acid to 1-D-hexyne or *O*-D-benzoic acid to 1-hexyne, the deuterium was exclusively found in 1-position (**68**) (Scheme 111).

The formation of the product possibly includes an electrophilic activation of the carbon-carbon triple bond by ruthenium complex, followed by a nucleophilic attack of the carboxylate to the substituted carbon. Finally, protonation of the ruthenium-vinyl intermediate affords the product with regeneration of the active catalyst species (Scheme 112).



Scheme 112. Markovnikov-selective addition of carboxylic acids to 1-alkynes.

3.5.2 Mechanistic studies on the catalyst preformation step

The preformation of the catalytically active species for the model reaction of addition of primary amides was studied using GC-MS and NMR techniques, in a similar way for catalyst preformation of addition of 2-pyrrolidone to 1-hexyne.[130] For technical reasons, toluene was used as the solvent and *n*-Bu_3P as the ligand. In a 5 mm NMR tube, bis(2-methallyl)cycloocta-1,5-diene-ruthenium(II) (16.0 mg, 0.05 mmol) was dissolved in degassed toluene-d_8 and an ^{1}H-NMR was recorded of the resulting solution (Figure 5, Spectrum H_0). The signals labeled "A" correspond to coordinated 1,5-cyclooctadiene (cod), those labeled with "B" correspond to the coordinated methallyl ligand.

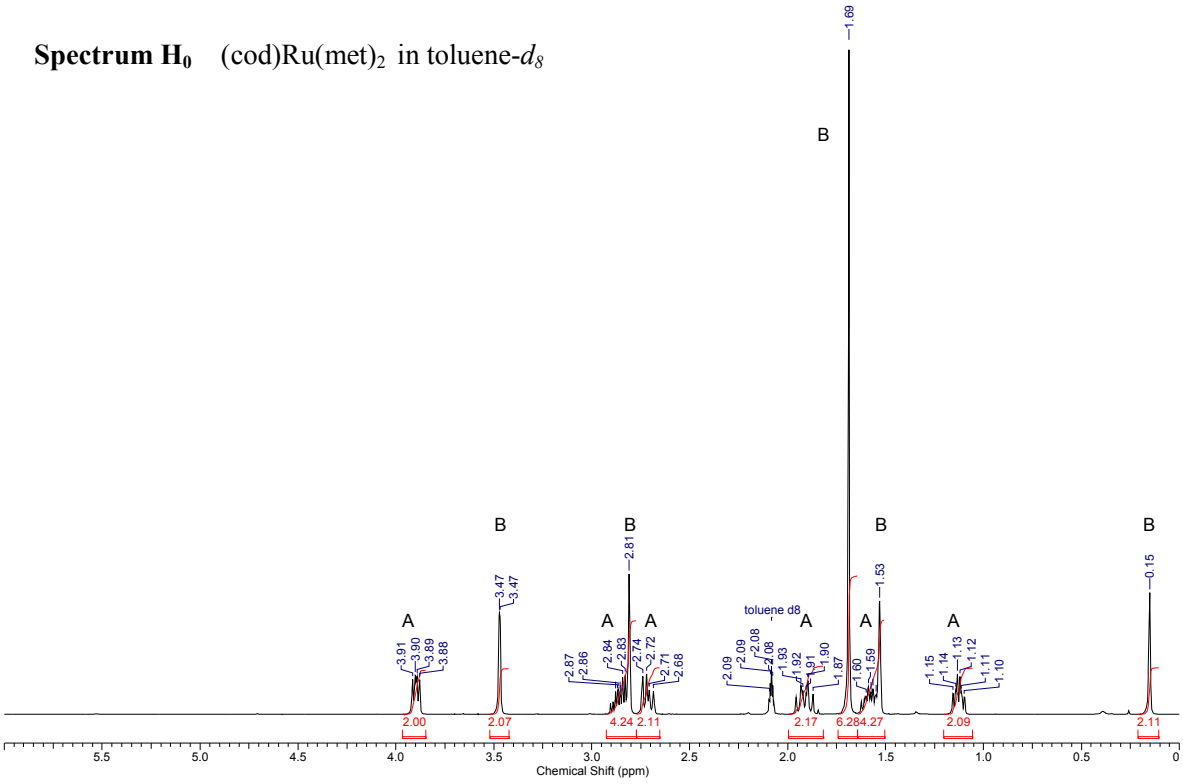
In the next experiment, an oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (12.8 mg, 0.04 mmol) and flushed with nitrogen. Subsequently, dry toluene-d_8 (0.5 mL) and tri-*n*-butylphosphine (20 mL, 0.08 mmol) were added via syringe. The resulting solution was stirred for 1 h at 60 °C. The resulting mixture was transferred to a NMR tube under nitrogen and another ^{1}H-NMR was recorded (Figure 5, Spectrum H_1). Only small residual signals were detected for coordinated cod ("A"), whereas two strong signals at 2.20 and 5.53 ppm, indicative of free cod ("C"), are present in this spectrum, confirming that the cod ligand is displaced by the phosphines. This ligand exchange was confirmed by ^{31}P-NMR: Besides the signal at –31.3 ppm for the free phosphine, a new signal at 20.8 ppm is now visible (Figure 7, Spectrum P_1).

The next experiment was carried out analogously, except that benzamide (4.9 mg, 0.04 mmol) was weighed in along with the catalyst system. As the signals for the methallyl ligands in the ^{1}H spectrum and the phosphine signals in ^{31}P spectrum are almost identical (Figure 6, Spectra H_2 and Figure 7, P_2), it can be concluded that no exchange of the methallyl at the Ru-center takes place in the absence of a Lewis acid.

In the final experiment, both benzamide (4.9 mg, 0.04 mmol) and ytterbium triflate (24.8 mg, 0.04 mmol) were weighed in with the catalyst system. The ^{1}H-NMR spectrum no longer contains the signals around 1.53 ppm and 1.69 ppm corresponding to the

coordinated methallyl ligand, but two singlets are now present at 1.62 ppm and 4.68 ppm ("D"), indicating the formation of isobutene (Figure 6, Spectrum H_3). The ^{31}P spectrum shows a single signal at 14.5 ppm, confirming that a reaction at the Ru-center has taken place (Figure 7, Spectrum P_3). The GC-MS chromatogram of this reaction mixture (Figure 8) contains a peak at 1.18 minutes with a mass pattern very similar to the literature spectrum of isobutene, along with a group of peaks that can be assigned to double-bond isomers of cyclooctadiene. No further peak was detected with the mass pattern of a dimethylhexadiene isomer, which could refer to reductive dimerization of methallyl ligands.

Spectrum H_0 (cod)Ru(met)$_2$ in toluene-d_8



Spectrum H_1 (cod)Ru(met)$_2$ and n-Bu$_3$P in toluene-d_8

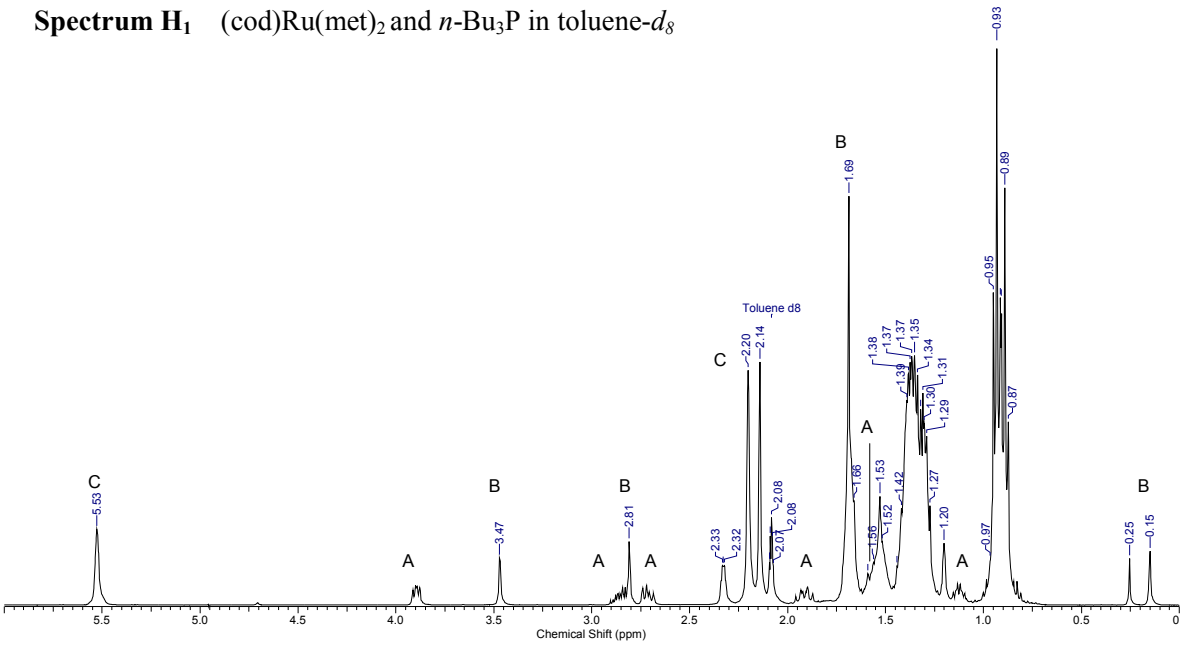
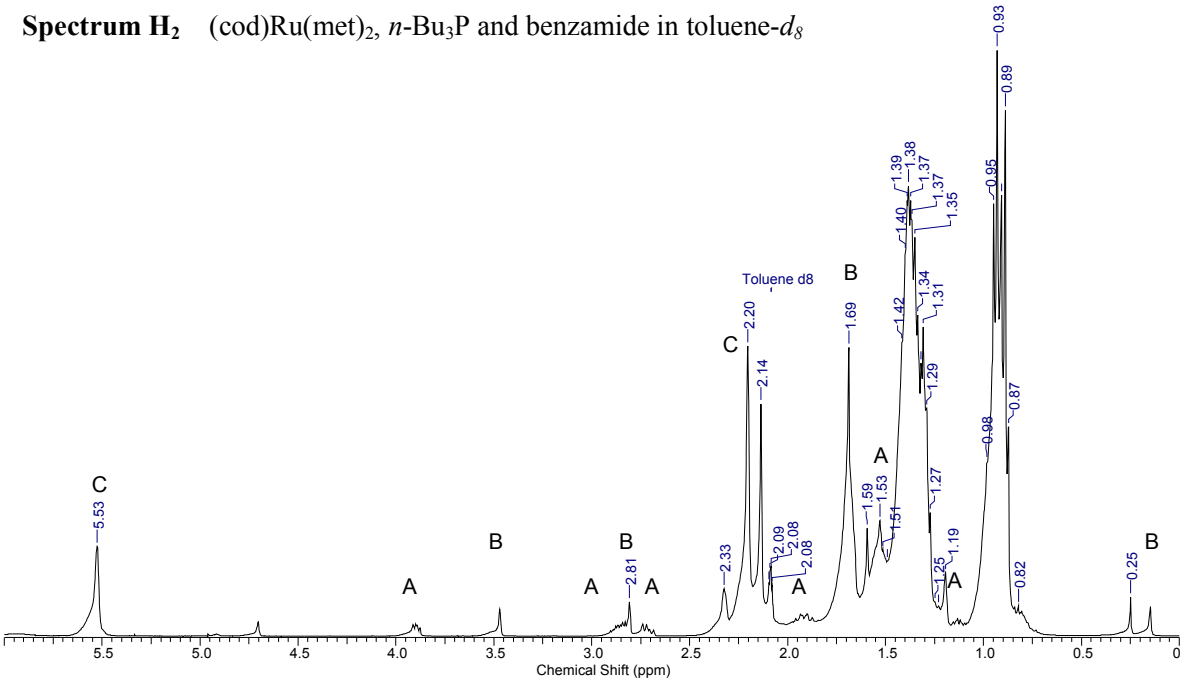


Figure 5. ^{1}H-NMR of the catalyst preformation.

Spectrum H_2 (cod)Ru(met)$_2$, *n*-Bu$_3$P and benzamide in toluene-d_8



Spectrum H_3 (cod)Ru(met)$_2$, *n*-Bu$_3$P, benzamide and Yb(OTf)$_3$ in toluene-d_8

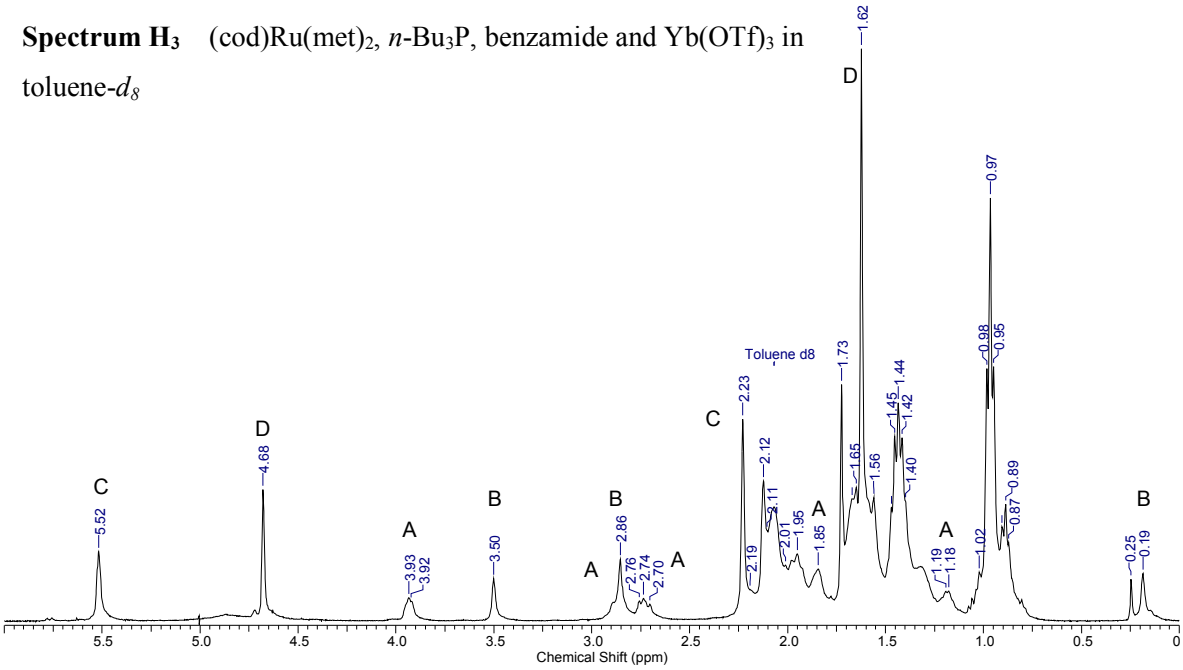
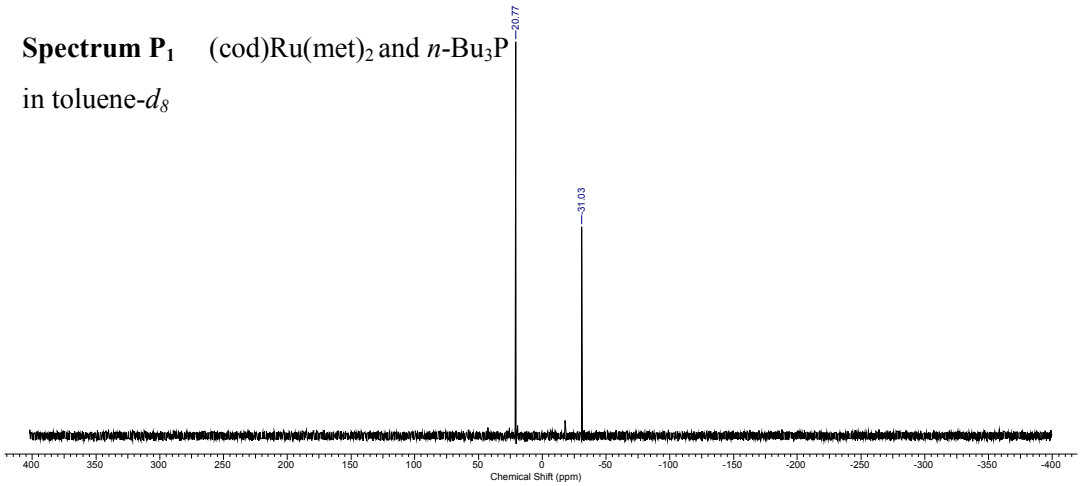
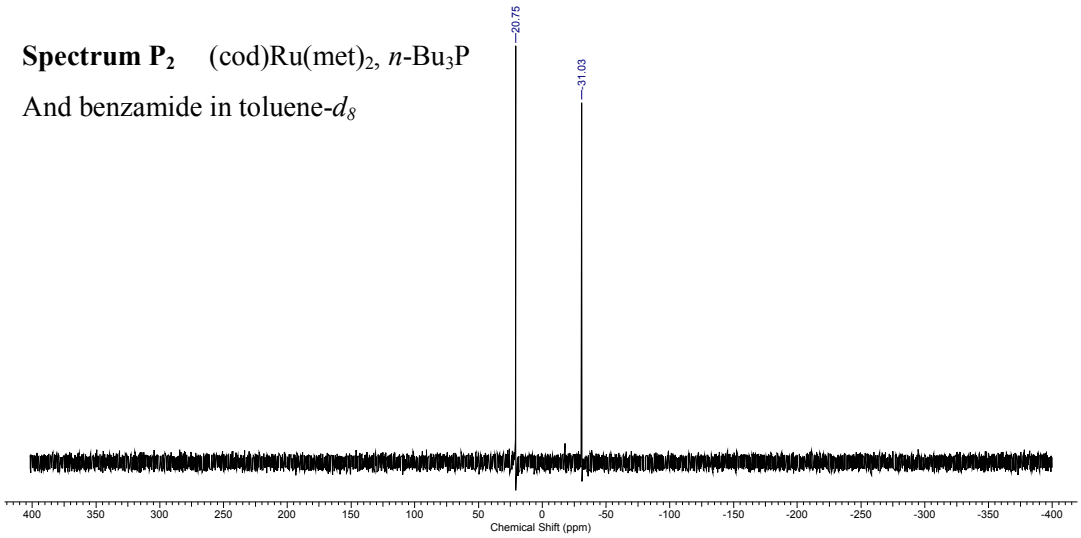


Figure 6. ^{1}H-NMR of the catalyst preformation.

Spectrum P_1 (cod)Ru(met)$_2$ and *n*-Bu_3P in toluene-d_8



Spectrum P_2 (cod)Ru(met)$_2$, *n*-Bu_3P And benzamide in toluene-d_8



Spectrum P_3 (cod)Ru(met)$_2$, *n*-Bu_3P, benzamide and Yb(OTf)$_3$ in toluene-d_8

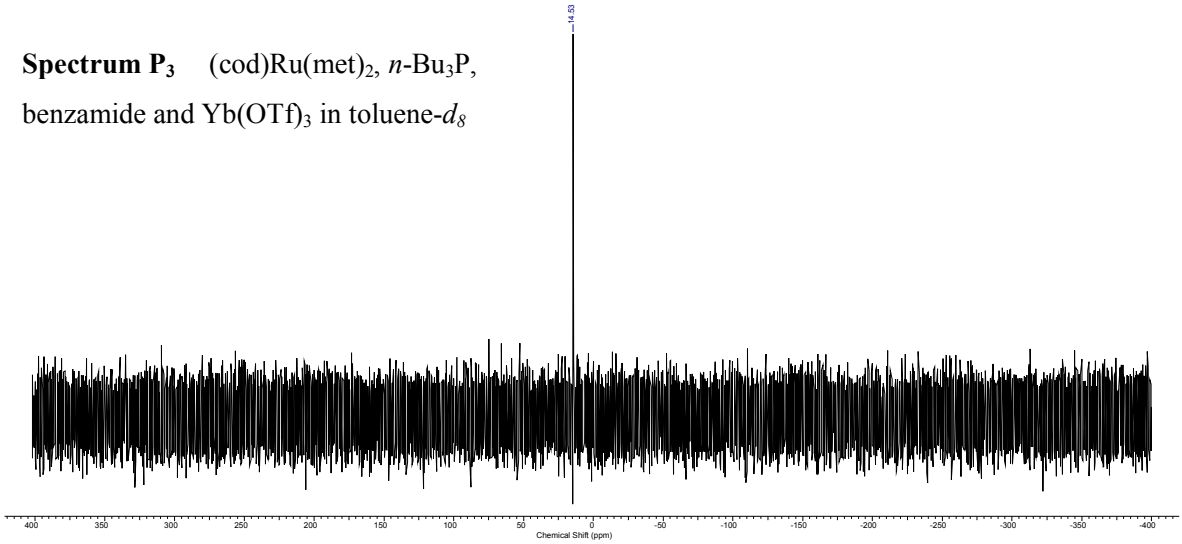
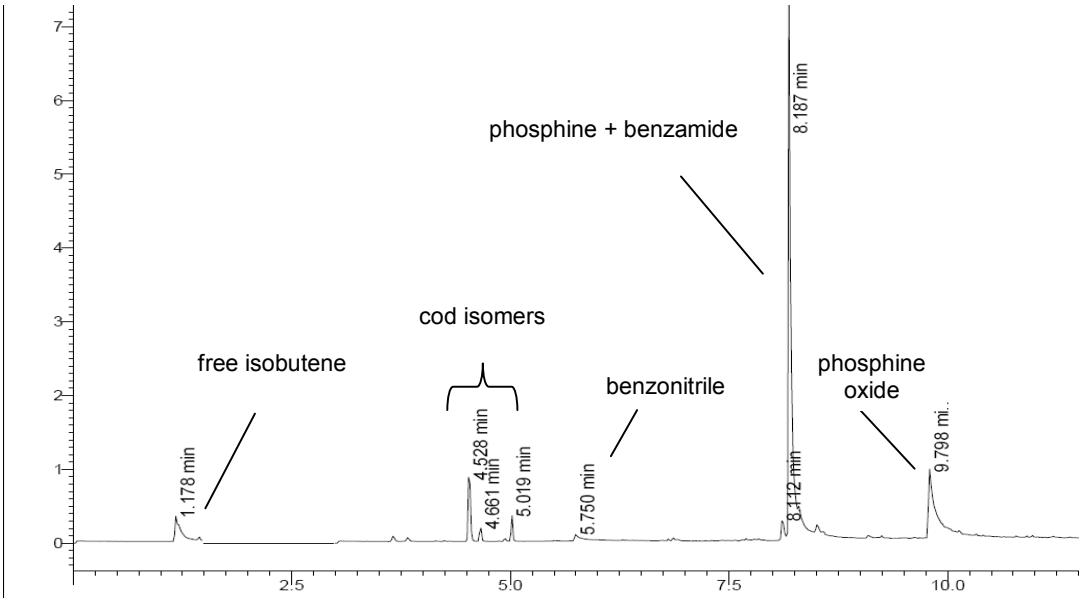
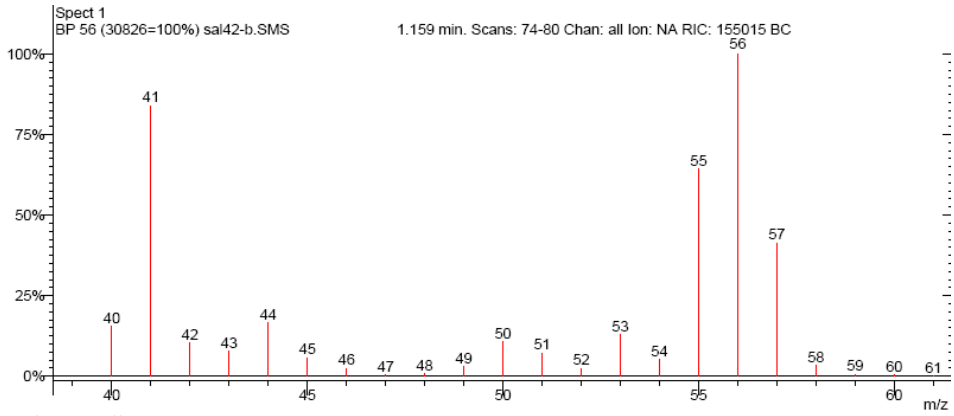


Figure 7. ^{31}P-NMR of the catalyst preformation.

GC of the reaction mixture.



MS of isobutene.



MS of cyclooctadienes.

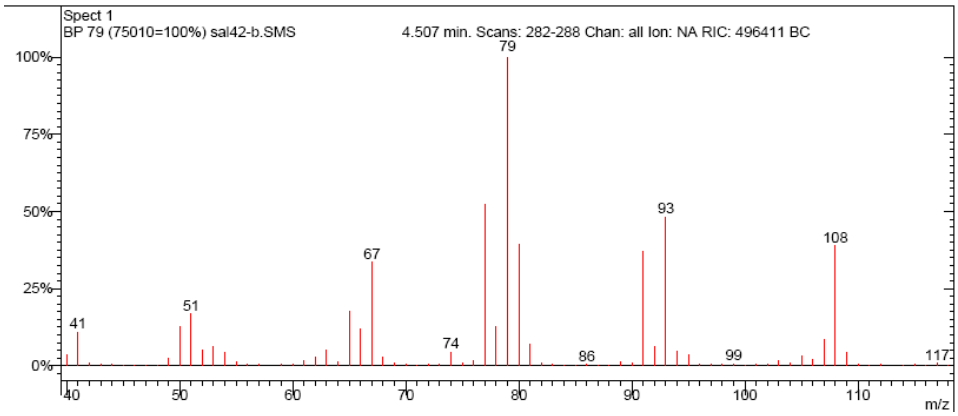
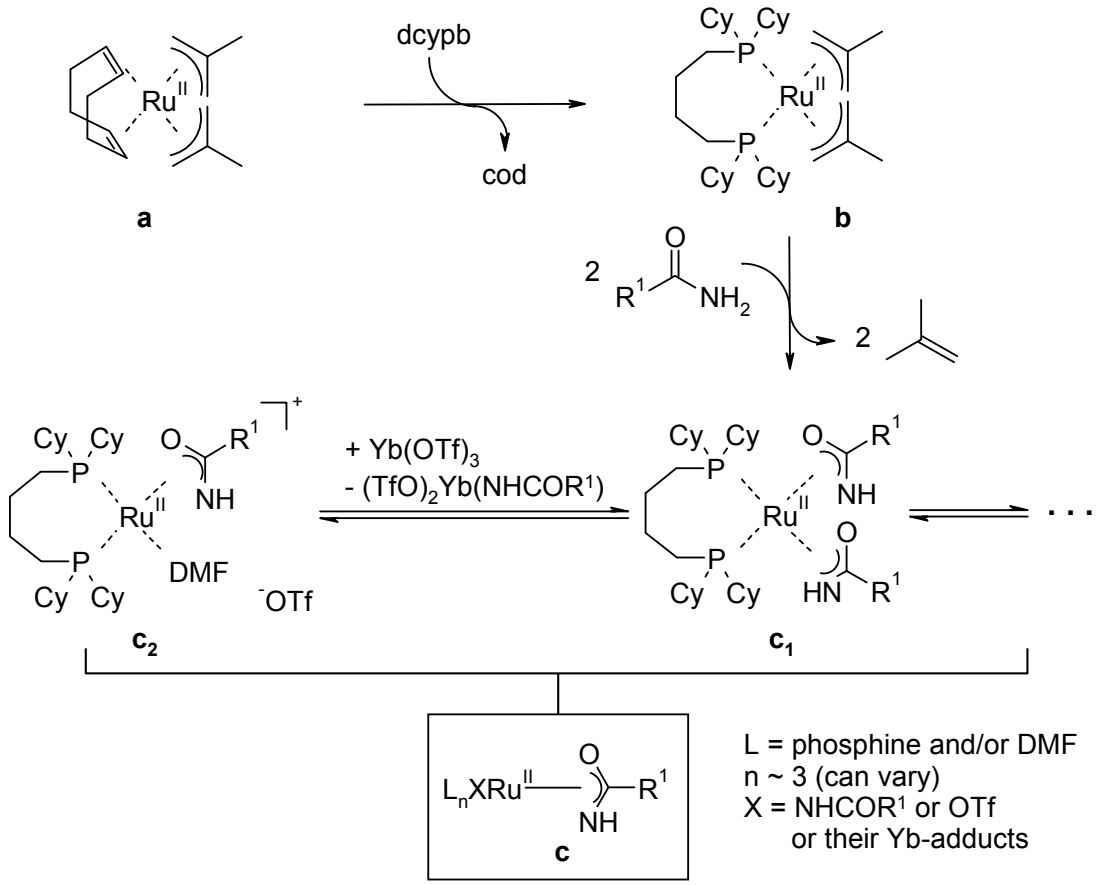


Figure 8. GC-MS Chromatogram of the reaction mixture.

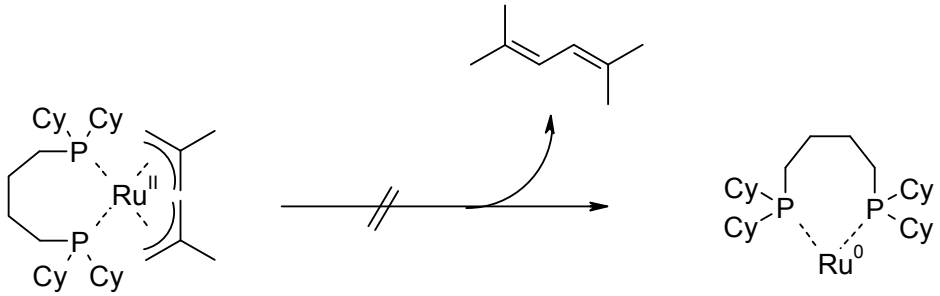
Based on the aforementioned results, we believe that the catalytically active species in such hydroamidations are phosphine-stabilized ruthenium(II) amides, such as **c** (Scheme 113), generated from the catalyst precursor [(cod)Ru(met)$_2$] by substitution of the labile 1,5-cyclooctadiene ligand (cod) with phosphine ligands (dcypb), and replacement of the basic methallyl by amide groups acidified with Yb(OTf)$_3$.



Scheme 113. Catalyst preformation of hydroamidation reaction.

^{1}H-NMR spectroscopic studies, after catalyst preformation show that the coordinated cod is liberated and 2-methylbutene is formed. In addition, 2,5-dimethylhexenes could not be detected by NMR spectroscopy or by GC-MS. These observations rule out the possibility of the ruthenium(0) species as the active catalyst, because their formation using

[(cod)Ru(met)$_2$] (**a**) would most likely involve a reductive dimerization of the two methallyl ligands (Scheme 114).



Scheme 114. Hypothetic reductive dimerization of methallyl ligands.

In the presence of an ytterbium salt with non-coordinating triflate ligands, both ruthenium and ytterbium are likely to compete for the coordinating amide ligands, so that neutral ruthenium bisamide complexes (**c$_1$**) will be in equilibrium with cationic solvent- and ligand-stabilized monoamide species (**c$_2$**).

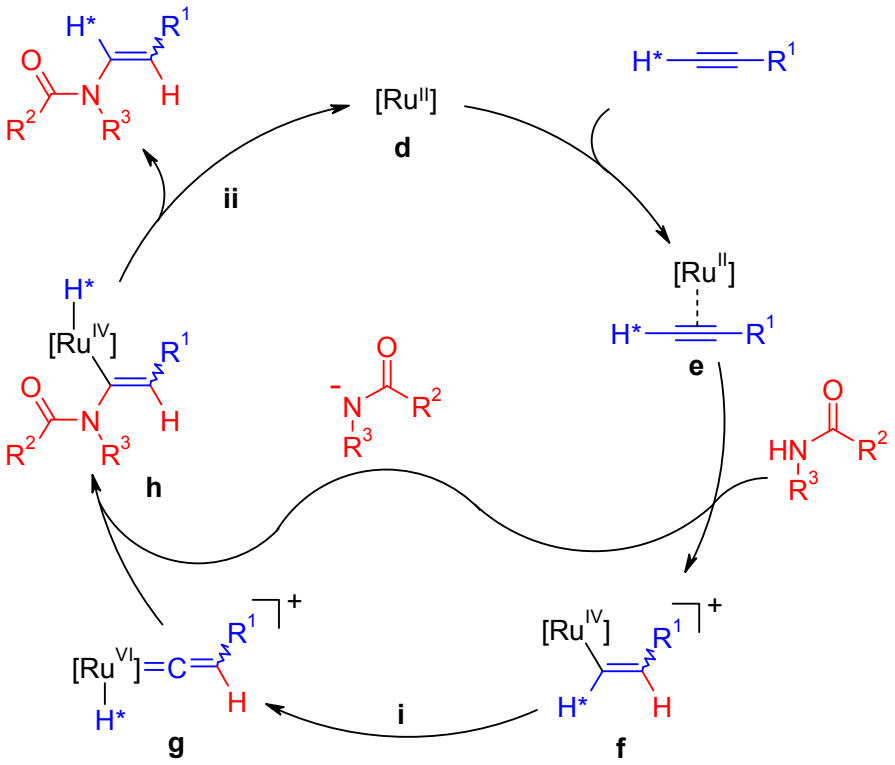
3.5.3 Proposed catalytic cycle for hydroamidations

The results from the KIE invalidate our previous catalytic cycle (Scheme 102), which would be in agreement in case of inverse secondary isotope effect. A sound proposal for catalytic cycle of hydroamidations of terminal alkynes must be in accordance with the experimental results of the deuteration experiments, kinetic studies, catalyst preformation, and the fact that only terminal but not internal alkynes react.

We postulate a catalytic cycle that starts with the coordination of an alkyne to a ruthenium(II) amide complex **d** to afford η^2-alkyne complex (**e**). Protonation of the latter gives a cationic vinyl complex (**f**), which is well-known in the literature to be formed from the protonation of η^2-coordinated alkynes.[171] Complex **f** will then undergo an α-hydride transfer to form Ru(VI)-hydride-vinylidene intermediate (**g**). The α-carbon atom of this intermediate easily accepts nucleophilic attack by a deprotonated amide affording species **h**. This would explain that we were never able to detect this intermediate by ^{2}H-NMR due to its short lifetime. Eventually, a reductive elimination releases the enamide in which the original acetylenic hydrogen is now bound to the α-carbon atom in the corresponding enamide, thus regenerating the original catalytic species **d** (Scheme 115).

It can be suggested that either the formation of Ru-vinylidene (step i, Scheme 115) or the C−H* bond-forming reductive elimination (step ii) is the rate limiting. We proposed that the formation of Ru-vinylidene is the rate limiting in these systems on the base of KIE, where the C−H(D) bond breaking is involved in the rate limiting step of the reaction.[169]

Moreover, intermediate **e** or **f** would be expected to be the resting state of the catalyst, since the in situ ^{2}H-NMR showed a triplet, resulting from coupling of the deuterium with two phosphine ligands (Figure 3).



Scheme 115. Plausible catalyst cycle for hydroamidations of terminal alkynes.

The stereoselectivity of the products may depend on the geometry of intermediate **g**, on which the employed phosphine ligands and the additives have a strong influence.

We believe that this cycle is consistent with all observations concerning the addition of amides (1° and 2°) and imides, the outcome from deuteration experiments in particular. However, a Dixneuf-type mechanism would be more suitable for the addition of thioamides and also carboxylic acids.

A continuous investigation of the reaction mechanism is making progress in our group to elucidate the structure of the catalytically active species and the resting state of the catalyst by ESI-MS measurements and DFT calculations. Furthermore, the isolation of reaction intermediates would be a decisive point, which has not turned out successful so far.

4 Conclusions and future prospects

We have shown that enamides and thioenamids can be efficiently prepared in high yields and with excellent stereoselectivity by ruthenium-catalyzed addition of primary amides and thioamides, respectively, to terminal alkynes. A wide range of amides and thioamides are readily reacted with a plethora of alkynes, giving impressive and elegant enamide substructures. Common functional group tolerance shows the generality of the newly developed methodologies, which shown in Table 18.

Table 18. Functional group tolerance for hydroamidation protocols.

Entry	Functional group	Result with primary amide protocol	Result with thioamide protocol
1	Carboxylic acid	–	–
2	Ester	+	nd
3	Ether	+	+
4	Oxalic	+	nd
5	Carbamate	–	+
6	Urea	+	nd
7	Nitrile	+	nd
8	Nitro	+	nd
9	Het. amine	+	nd
10	2° amide	+	nd
11	1° thioamide	–	–
12	Sulfonamide	–	–
13	Acrylic	+	nd
14	Phenolic	+	nd
15	Enyne	–	+
16	Silyl	–	+
17	Halo	+	+
18	Bulky group	+	+

The protocol of addition of primary amides to terminal alkynes was successfully employed as a strategic step in the synthesis of natural products, including lansiumamide A, alatamide, botryllamides C, E and the key intermediate for aristolactam.

On the other hand, the regioselectivity of the addition of cyclic amides to phenylacetylene derivatives was reversed in favor of the Markovnikov products, when trialkylphosphines used as a catalyst. Although the reaction is limited to such substrates, it represents the first intermolecular hydroamidation fashion of terminal alkynes.

The reaction mechanism was intensively investigated by in situ NMR studies and GC-MS techniques. Phosphine-stabilized ruthenium(II) amide complexes are expected to be the catalytically active species, generated from the catalyst precursor [(cod)Ru(met)$_2$] by substitution of the labile cod with phosphine ligands, and replacement of the basic methallyl by amide groups assisted by the additives. The model reactions for all developed protocols in our group were pursued by deuterium labeled starting materials to investigate the terminal 1,2-H shift, either to the adjacent carbon atom or to the Ru-center during the formation ruthenium-vinylidene intermediate. A similar mechanism for hydration of terminal alkynes is proposed for addition of amides and imides; however thioamides and carboxylic acids are expected to obey the Dixneuf mechanism in their addition to terminal alkynes.

Some substrates, however, failed to react due to inconvenient reaction condition are still open to trial and optimization. The choice of proper conditions, improvements in the scope, mildness of the procedures, stereo- and regioselectivity, and catalyst loading are still necessary to investigate. These improvements require a better understanding of the catalytic cycle. Its elucidating will be an exciting task for the development of more efficient hydroamidation reactions.

Finally, an extension to synthesize the other botryllamide classes will be ideal to support further biological tests of these compounds, since the isolation leads to a barely separable mixture in very low yield for each class.

5 Experimental

5.1 Chemicals, methods, and instruments

All used solvents were purified by general described procedures.[172] All commercially available reagents were distilled either from P_2O_5 or CaH_2 under an inert atmosphere before use. All commercially available thioamides were used a received, while all others were obtained by converting the corresponding amides into thioamides using the method of Lawesson et al.[173] All commercial amides were used as obtained without further purification, while the other were synthesized by treating the commercially corresponding carboxylic acid with oxalyl chloride and ammonia gas or solution.[151] The deuterated starting materials were synthesized by H/D exchange of the commercially corresponding nucleophiles with D_2O or EtOD consecutively.[173] The $[Ru(cod)(met)_2]$ was supplied by Umicore AG and used as obtained without further purification.

In order to perform a vast number of experiments, a specially manufactured setup was used. All reactions were carried out in 20 mL headspace vials that were closed and clamped shut with aluminum caps fitted with a Teflon-coated butyl rubber septum (both commercially available at Macherey & Nagel). In 8 cm high round aluminum cases, which fit the hot plate of a regular laboratory heater in diameter, 10 of the thus equipped 20 mL headspace vials can be tempered between 25 °C and 180 °C. An 11^{th} smaller hole drilled in the middle of the case creates room to hold the thermometer of the heater (Figure 9, left). To correctly evacuate and refill 10 reaction vessels with inert gas at the same time, special vacuum distributors were manufactured to be connected to the Schlenck-line (Figure 9, right). A steel tubing is linked to ten 3 mm Teflon tubes, which are equipped on the opposite end with adaptors for Luer-Lock syringe needles. The steel tubing can be connected to the Schlenck-line just like any other laboratory equipment by a steel olive and vacuum tubing.

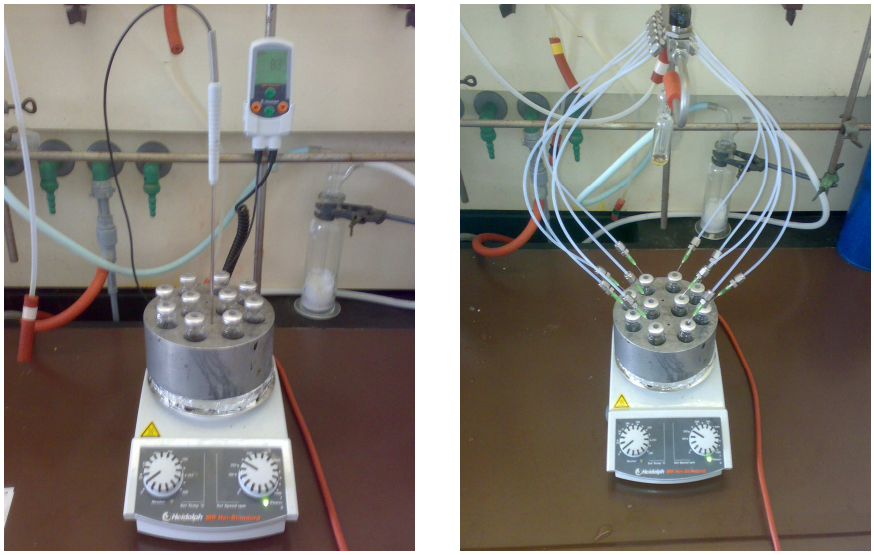


Figure 9. Ten-vessel aluminum reaction block with heater and vacuum distributor (right).

To perform 10 or more reactions parallel the following protocol was used. All solid substances were weighed in the reaction vessels, an oven-dried, hot 20 mm stir bar added and each vessel closed with a separate cap using flanging pliers. All 10 vessels were transferred to one of the aforementioned aluminum cases and evacuated using syringe needles connected to the vacuum steel tubing.

The reaction vessels were evacuated and refilled with nitrogen. An oil bubbling valve at the top of the steel tubing was used to guarantee a pressure release. Using standard sterile and Hamilton syringes all liquid reagents, stock solutions of reagents, solvents and the standard (*n*-tetradecane) were added and the vessels were evacuated and refilled with nitrogen 3 times. After removal of the needles, the aluminum case was tempered to the desired temperature. Every temperature description is the case temperature, which only differs by maximum 2 °C from the actual reaction media temperature.

At the end of the reaction time and after cooling to room temperature, the reaction vials were opened carefully. Two milliliters of ethyl acetate were added to dilute the reaction mixture and with a disposable pipette mixed thoroughly to ensure a homogenous mixture. A 0.25 mL sample was withdrawn and extracted with 2 mL of ethyl acetate and 2 mL of

brine-solution or 2 mL of saturated potassium carbonate solution. The organic layer was filtered through a pipette filled with a cotton plug and magnesium sulfate into a GC-vial.

After evaluating the contents on the GC and if necessary GC-MS, the contents of all work-up and analysis vials were recombined and the product isolated using standard procedures, deposed on silica-gel and purified by flash chromatography using CombiFlash® Companion personal flash chromatography apparatus from Isco Inc. (Figure 10).

Figure 10. CombiFlash® Companion personal flash chromatography.

The developed experimental setups and an electronic laboratory journal allowed a substantial amount of reactions to be performed during the course of this work. Approximately 2500 reactions would have consumed a much longer time using standard laboratory techniques. Preparative reactions were performed mostly in standard laboratory oven-dried glass ware. Yields are isolated yields if nothing else is mentioned. All isolated compounds were analyzed using the following techniques and instruments:

1. For GC-analysis, a Hewlett Packard 6980 chromatograph was used. The gas carrier was nitrogen with a flow rate of 149mL/min (0.5 bar pressure). The temperature of the injector was 220 °C. The split-ratio was 1:100. For separation an Agilent HP-5-column with 5% phenyl-methyl-siloxane (30 x 320 µm x 1.0 µm, 100/ 2.3-30-300/ 3) was used. The following temperature program was implemented: starting temperature 60 °C (2 min), linear temperature increase (30 °C/min) to 300 °C, end temperature 300 °C (13 min).

2. Mass spectrometry was performed with a GC-MS Varian Saturn 2100 T. The ionization was done by EI AGC. The intensities of the signals are relative to the highest peak. For fragments with isotopomers only the more intensive peak of the isotopomer is given.

3. A Shimadzu High Performance Liquid Chromatograph with a Merck Reversed Phase LiChroCat© PAH C 18 column with a particle diameter of 5 µm was used at a constant oven temperature of 60 °C and a column pressure of 125 bar. The eluents used were acetonitrile and water with a flow rate of 1 mL/min. Gradient: 15% acetonitrile for 2 min, linear increase to 85% acetonitrile during the course of 8 min, constant gradient for 3.5 min, decrease to 15% within 0.1 min and constant for 3 min. The standard configuration injected 10 µL of the sample. This amount could be manually changed with the control and interpretation program Shimadzu Class-VP.

4. Proton-, deuterium-, and decoupled carbon-NMR spectra were recorded with a Bruker FT-NMR DPX 200, DPX 400 and a Bruker Avance 600. The frequency and solvent used is described separately for each substance. Chemical shifts are given in units of the δ-scale in ppm. Shifts for ^{1}H-spectra are given respectively to the proton signal of the solvent used (chloroform: 7.25 ppm, dimethyl sulfoxide: 2.50 ppm, methanol: 3.35 ppm, water: 4.75 ppm), for ^{13}C-spectra respectively to the deuterated solvent (chloroform: 77.0 ppm, dimethyl sulfoxide: 37.7 ppm, methanol: 49.3 ppm). *The atom numbering within products is not according to the IUPAC rules*. Coupling constants are given in Hertz (Hz). Processing and interpretation was performed with ACD-Labs 7.0 (Advanced Chemistry Development Inc.)

5. CHN-Elemental analysis was performed with a Perkin-Elmer Elemental Analyzer EA 2400 CHN.

6. Infrared spectra were recorded with a Perkin-Elmer Fourier Transform Infrared Spectrometer FT/IR. Solids were thoroughly ground and mixed with potassium bromide and pressed into a pellet. Liquids were measured as a thin film in between sodium chloride plates. Absorbancebands are shown in wave numbers (cm^{-1}). Intensities are abbreviated: s (strong), m (medium) and b (broad).

5.2 Anti-Markovnikov addition of thioamides to alkynes

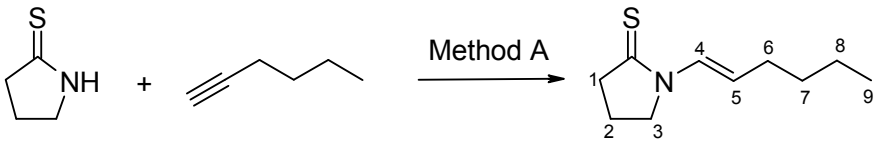
5.2.1 General methods

Method A: An oven-dried flask was charged with the bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [Ru(cod)(met)$_2$] (6.4 mg, 0.02 mmol), thioamide (1.00 mmol), and molecular sieves (500 mg) and flushed with nitrogen. Subsequently, dry toluene (3.0 ml), tri-*n*-octylphosphine (27 μL, 0.06 mmol), and alkyne (2.00 mmol) were added via syringe. The resulting solution was stirred for 15 h at 100 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the *E*-thioenamide. The identity and purity of the products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, mass spectroscopy, elemental analysis, and IR spectroscopy.

Method B: An oven-dried flask was charged with the bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), thioamide (1.00 mmol), potassium *t*-butoxide (5.6 mg, 0.04 mmol), and bis(dicyclohexylphosphino)methane (12.3 mg, 0.06 mmol) and flushed with nitrogen. Subsequently, dry toluene (3.0 ml) and alkyne (2.00 mmol) were added via syringe. The resulting solution was stirred for 15 h at 100 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the *Z*-thioenamide. The identity and purity of the products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, elemental analysis, mass spectroscopy, and IR spectroscopy.

5.2.2 Synthesis of thioenamides

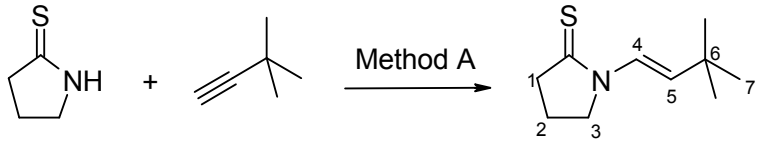
Synthesis of *N*-[(*E*)-hex-1-enyl]pyrrolidine-2-thione (3a).



The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (6.4 mg, 0.02 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol), and 1-hexyne (229 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the title product as a yellowish oil (16:1 mixture with the *Z*-isomer 179.7 mg, 98%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, *J* = 14.5 Hz, 1H, *H-4*), 5.28 (dt, *J* = 14.5, 7.1 Hz, 1H, *H-5*), 3.72 (t, *J* = 7.4 Hz, 2H, *H-3*), 2.96 (t, *J* = 7.9 Hz, 2H, *H-1*), 2.03 (m, 4H, H-2, *H-6*), 1.24-1.30 (m, 4H, *H-7*, *H-8*), 0.79 (t, *J* = 7.1 Hz, 3H, *H-9*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 199.0 (*C=S*), 126.6 (*C-4*), 119.4 (*C-5*), 52.5 (*C-3*), 45.3 (*C-1*), 31.8 (*C-6*), 29.8 (*C-2*), 22.2 (*C-7*), 19.4 (*C-8*), 13.9 (*C-9*) ppm. **EA** Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35; N, 7.64. Found: C, 65.09; H, 9.45; N, 7.41. **MS** (Ion trap, EI): *m/z* (%) = 183 (27, $[M^+]$), 126 (100), 98 (45), 85 (7), 45 (7). **IR** (KBr): υ (cm^{-1}) 2958, 2924, 2856, 1654, 1482, 1464, 1418, 1133, 954, 742.

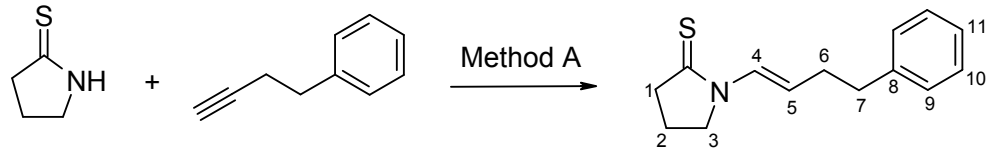
Alternative synthesis of ***N*-[(*E*)-hex-1-enyl]pyrrolidine-2-thione** (**3a**). An oven-dried flask was charged with Lawesson's reagent (404.5 mg, 3.00 mmol) and flushed with nitrogen. Dry toluene (7.0 ml) and a solution of *N*-[(*E*)-hex-1-enyl]pyrrolidine (836.3 mg, 5.0 mmol) in toluene (3.0 mL) were added via syringe. The resulting solution was stirred for 1 h at 110 °C, then the solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford product **3a** as a yellowish oil (265.5 mg, 29%). The ^{1}H-, ^{13}C-NMR, and MS were correspondent to those above.

Synthesis of *N*-[(*E*)-3,3-Dimethyl-but-1-enyl]pyrrolidine-2-thione (3b)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (6.4 mg, 0.02 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol) and 3,3-dimethyl-1-butyne (246 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (13:1 mixture with the *Z*-isomer, 177.8 mg, 97%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, *J* = 14.7 Hz, 1H, *H-4*), 5.33 (d, *J* = 14.7 Hz, 1H, *H-5*), 3.72 (t, *J* = 7.4 Hz, 2H, *H-3*), 2.98 (t, *J* = 7.8 Hz, 2H, *H-1*), 2.03 (tt, *J* = 7.8, 7.6 Hz, 2H, *H-2*), 1.01 (s, 9H, *H-7*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 199.4 (*C=S*), 130.7 (*C-4*), 123.5 (*C-5*), 52.5 (*C-3*), 45.4 (*C-1*), 32.6 (*C-6*), 29.9 (*C-7*), 19.5 (*C-2*) ppm. **EA** Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35; N, 7.64. Found: C, 65.23; H, 9.36; N, 7.70. **MS** (Ion trap, EI): *m/z* (%) = 184 (51, [M^+]), 134 (4), 128 (7), 127 (14), 126 (100). **IR** (KBr): υ (cm^{-1}) 2954, 2898, 1597, 1414, 1282, 836.

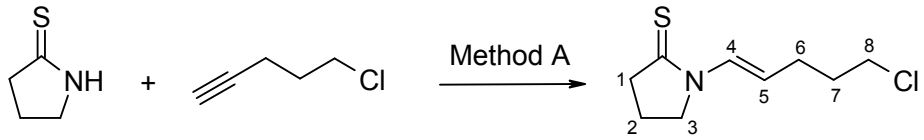
Synthesis of *N*-[(*E*)-4-Phenylbut-1-en-1-yl]pyrrolidine-2-thione (3c)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (6.4 mg, 0.02 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol) and 4-phenyl-1-butyne (281 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 2:3) to afford the product as a yellowish oil (7:1 mixture with the *Z*-isomer, 219.8 mg, 95%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.63 (d, *J* = 14.3 Hz, 1H, *H-4*), 7.33 (m, 2H, *H-9*), 7.23-7.24 (m, 3H, *H-10*, *H-11*), 5.42 (dt, *J* = 16.3, 7.1 Hz,

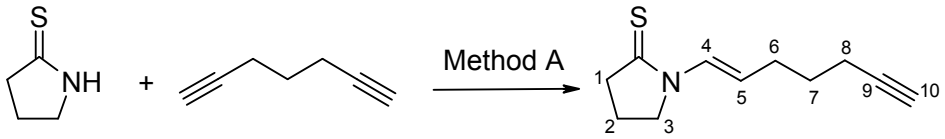
1H, *H-5*), 3.79 (t, *J* = 7.4 Hz, 2H, *H-3*), 3.10 (t, *J* = 7.8 Hz, 2H, *H-1*), 2.79 (t, *J* = 7.6 Hz, 2H, *H-7*), 2.50-2.55 (m, 2H, *H-6*), 2.07-2.13 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 199.0 (*C=S*), 140.7 (*C-8*), 128.0 (*C-9, C-10*), 126.6 (*C-4*), 125.6 (*C-11*), 117.8 (*C-5*), 52.0 (*C-3*), 44.9 (*C-1*), 35.8 (*C-7*), 31.6 (*C-6*), 18.9 (*C-2*) ppm. **EA** Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05. Found: C, 72.37; H, 7.60; N, 5.90. **MS** (Ion trap, EI): *m/z* (%) = 231 (2, [M^+]), 126 (100), 98 (10), 58 (4), 45 (4). **IR** (KBr): υ (cm^{-1}) 2924, 2856, 1654, 1480, 1456, 1414, 1274, 1133, 955, 750, 696.

Synthesis of *N*-[(*E*)-5-chloro-pent-1-enyl]pyrrolidine-2-thione (3d)



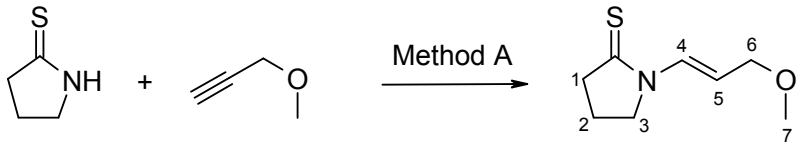
The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), molecular sieves (500 mg) and pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and 5-chloro-1-pentyne (210 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (15:1 mixture with the *Z*-isomer, 161,1 mg, 78%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.51 (d, *J* = 14.5 Hz, 1H, *H-4*), 5.28 (dt, *J* = 14.5, 7.2 Hz, 1H, *H-5*), 3.74-3.79 (m, 2H, *H-3*), 3.47-3.53 (m, 2H, *H- 8*), 3.02 (t, *J* = 7.9 Hz, 2H, *H-1*), 2.24-2.30 (m, 2H, *H-6*), 2.05-2.11 (m, 2H, *H-2*), 1.82-1.88 (m, 2H, *H-7*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 199.5 (*C=S*), 127.4 (*C-4*), 116.8 (*C-5*), 52.2 (*C-3*), 45.1 (*C-1*), 44.0 (*C-8*), 32.2 (*C-6*), 27.2 (*C-7*), 19.3 (*C-2*) ppm. **EA** Calcd for $C_9H_{14}NSCl$: C, 53.06; H, 6.93; N, 6.87. Found: C, 53.42; H, 6.60; N, 7.09. **MS** (Ion trap, EI): *m/z* (%) = 203 (6, [M+]), 168 (9), 126 (100), 98 (8), 45 (6). **IR** (KBr): υ (cm^{-1}) 2952, 1656, 1483, 1437, 1281, 1135, 795.

Synthesis of *N*-[(*E*)-Hept-1-en-6-ynyl]pyrrolidine-2-thione (3e)



The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (6.4 mg, 0.02 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*octylphosphine (27 µL, 0.06 mmol) and 1,6-heptadiyne (229 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (11:1 mixture with the *Z*-isomer, 146.9 mg, 76%). **1H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.50 (d, *J* = 14.5 Hz, 1H, *H-4*), 5.30 (dt, *J* = 14.5, 7.3 Hz, 1H, *H-5*), 3.77 (t, *J* = 7.5 Hz, 2H, *H-3*), 3.03 (t, *J* = 8.0 Hz, 2H, *H-1*), 2.00-2.29 (m, 6H, *H-2*, *H-6*, *H-8*), 1.92 (t, *J* = 2.7 Hz, 1H, *H-10*), 1.53-1.68 (m, 2H, *H-7*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 199.4 (*C*=*S*), 127.2 (*C-4*), 117.7 (*C-5*), 83.7 (*C-9*), 68.7 (*C-10*), 52.3 (*C-3*), 45.1 (*C-1*), 28.9 (*C-6*), 28.3 (*C-8*), 19.3 (*C-2*), 17.7 (*C-7*) ppm. **EA** Calcd for $C_{11}H_{15}NS$: C, 68.35; H, 7.82; N, 7.25. Found: C, 68.47; H, 7.93; N, 7.21. **MS** (Ion trap, EI): *m/z* (%) = 193 (100, $[M^+]$), 165 (10), 166 (33), 140 (4), 126 (55). **IR** (KBr): υ (cm^{-1}) 3213, 2932, 1652, 1487, 1285, 962, 704.

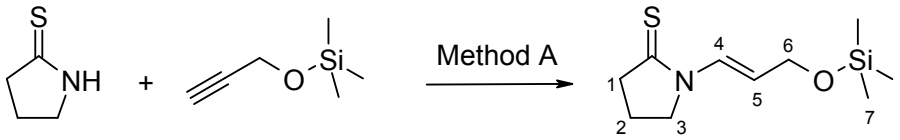
Synthesis of *N*-[(*E*)-3-Methoxy-propenyl]pyrrolidine-2-thione (3f)



The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (16 mg, 0.05 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol), 3-methoxy-1-propyne (169 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (11:1 mixture with the *Z*-isomer, 130.2 mg, 76%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.66 (d, *J* = 14.5 Hz, 1H, *H-4*), 5.37 (dt, *J* = 14.5, 6.7 Hz, 1H, *H-5*), 3.98 (d, *J* = 6.7 Hz, 2H, *H-6*), 3.79 (t, *J* =

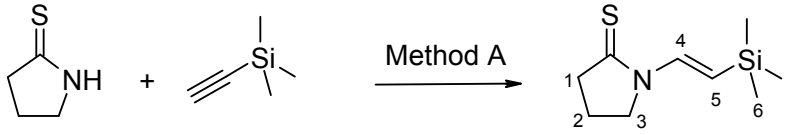
7.4 Hz, 2H, *H-3*), 3.29 (s, 3H, *H-7*), 3.04 (t, *J* = 7.8 Hz, 2H, *H-1*), 2.07-2.12 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 201.5 (*C=S*), 129.4 (*C-4*), 113.8 (*C-5*), 70.9 (*C-6*), 57.9 (*C-7*), 52.3 (*C-3*), 45.4 (*C-1*), 19.5 (*C-2*) ppm. **EA** Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18. Found: C, 56.29; H, 7.93; N, 7.87. **MS** (Ion trap, EI): *m/z* (%) = 171 (5, [M^+]), 140 (40), 126 (100), 85 (15), 45 (17). **IR** (KBr): υ (cm^{-1}) 2924, 2886, 1658, 1429, 1274, 1137, 1087, 954, 746.

Synthesis of *N*-[(*E*)-3-Trimethylsilanyloxypropenyl]pyrrolidine-2-thione (3g)



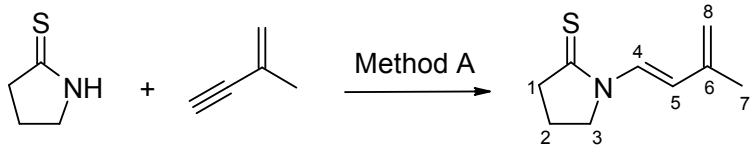
The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (6.4 mg, 0.02 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol) and trimethyl(propargyloxy)silane (308 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 3:2) to afford the title product as a yellow solid (19:1 mixture with the *Z*-isomer, 130.8 mg, 57%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.66 (d, *J* = 14.5 Hz, 1H, *H-4*), 5.41 (dt, *J* = 14.5, 6.2 Hz, 1H, *H-5*), 4.2 (d, *J* = 6.2 Hz, 2H, *H-6*), 3.79 (t, *J* = 7.4 Hz, 2H, *H-3*), 3.03 (t, *J* = 7.8 Hz, 2H, *H-1*), 2.06-2.11 (m, 2H, *H-2*), 0.10 (s, 9H, *H-7*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 201.1 (*C=S*), 127.8 (C-4), 116.8 (C-5), 61.4 (C-6), 52.3 (C-3), 45.4 (C-1), 19.5 (C-2), 0.3 (C-7) ppm. **EA** Calcd for $C_{10}H_{19}NOSSi$: C, 52.35; H, 8.35; N, 6.11. Found: C, 52.59; H, 8.56; N, 6.01. **MS** (Ion trap, EI): *m/z* (%) = 229 (3, [M^+]), 158 (10), 140 (10), 126 (100), 45 (9). **IR** (KBr): υ (cm^{-1}) 2924, 1658, 1506, 1482, 1460, 1418, 1274, 1137, 955, 845.

Synthesis of *N*-[(*E*)-Trimethylsilanyl-vinyl]pyrrolidine-2-thione (3h)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), molecular sieves (500 mg) and pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and trimethylsilylacetylene (282 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the title product as a white solid (1:1 mixture with the *Z*-isomer, 175.5 mg, 88%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.71 (d, *J* = 17.2 Hz, 1H, *H-4*), 5.20 (d, *J* = 17.2 Hz, 1H, *H-5*), 3.82 (t, *J* = 7.4 Hz, 2H, *H-3*), 3.06 (t, *J* = 7.8 Hz, 2H, *H-1*), 2.10 (m, 2H, *H-2*), 0.17 (s, 9H, *H-6*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 201.1 (*C=S*), 135.9 (*C-4*), 113.7 (*C-5*), 51.6 (*C-3*), 45.0 (*C-1*), 19.3 (*C-2*), 0.9 (*C-6*) ppm. **EA** Calcd for $C_{17}H_9NSSi$: C, 54.21; H, 8.59; N, 7.02. Found: C, 54.38; H, 8.50; N, 7.29. **MS** (Ion trap, EI): *m/z* (%) = 199 (3, [M^+]), 184 (12), 158 (8), 126 (100), 98 (11). **IR** (KBr): υ (cm^{-1}) 2954, 2851, 1537, 1490, 1449, 1289, 1114, 841, 788.

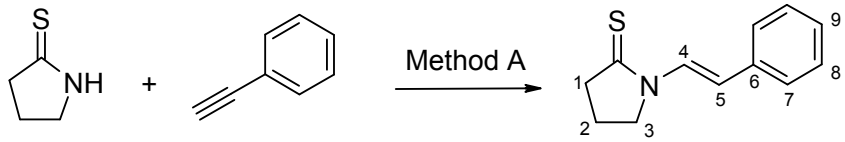
Synthesis of *N*-[(*E*)-3-Methyl-buta-1,3-dienyl]pyrrolidine-2-thione (3i)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol), 2-methyl-1-buten-3-yne (192 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellow solid (3:1 mixture with the *Z*-isomer, 118.8 mg, 71%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.70 (d, *J* = 14.7 Hz, 1H, *H-4*), 6.05 (d, *J* = 14.7 Hz, 1H, *H-5*), 5.03 (d, 2H, *H-8*), 3.87 (m, 2H, *H-3*), 3.11 (m,

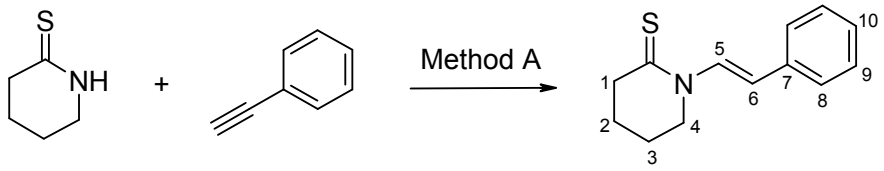
2H, *H-1*), 2.14 (m, 2H, *H-2*), 1.94 (s, 3H, *H-7*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 200.5 (*C=S*), 140.3 (*C-4*), 126.3 (*C-6*), 120.9 (*C-8*), 117.3 (*C-5*), 52.3 (*C-3*), 45.3 (*C-1*), 19.5 (*C-2*), 18.7 (*C-7*) ppm. **EA** Calcd for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37. Found: C, 64.43; H, 7.83; N, 7.55. **MS** (Ion trap, EI): *m/z* (%) = 167 (41, [M^+]), 134 (100), 126 (93), 98 (17), 58 (11). **IR** (KBr): υ (cm^{-1}) 2958, 2828, 1680, 1480, 1293, 1274, 1251, 1133, 948.

Synthesis of *N*-[(*E*)-2-Phenylvinyl]pyrrolidine-2-thione (3j)



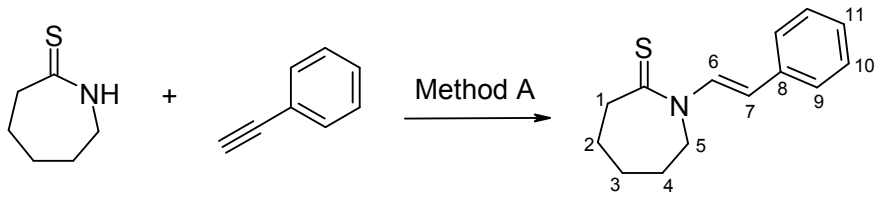
The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (6.4 mg, 0.02 mmol), molecular sieves (500 mg), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:4) to afford the product as a yellow solid (6:1 mixture with the *Z*-isomer, 197.29 mg, 97%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.24 (d, *J* = 14.9 Hz, 1H, *H-4*), 7.41 (m, 2H, *H-6*), 7.30 (m, 2H, *H-7*), 7.22 (m, 1H, *H-8*), 6.21 (d, *J* = 14.9 Hz, 1H, *H-5*), 3.91 (m, 2H, *H-3*), 3.09 (m, 2H, *H-1*), 2.13 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 200.5 (*C=S*), 135.2 (*C-4*), 128.6 (C_{arom}), 127.4 (C_{arom}), 126.1 (C_{arom}), 125.9 (*C-6*), 117.6 (*C-5*), 52.2 (*C-3*), 45.1 (*C-1*), 19.3 (*C-2*) ppm. **EA** Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.45; N, 6.89. Found: C, 71.02; H, 6.65; N, 6.57. **MS** (Ion trap, EI): *m/z* (%) = 203 (74, [M^+]), 174 (6), 126 (100), 77 (16), 44 (12). **IR** (KBr): υ (cm^{-1}) 2950, 2635, 1480, 1434, 1289, 1099, 735, 696, 571.

Synthesis of *N*-[(*E*)-2-Phenylvinyl]piperidine-2-thione (3k)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), molecular sieves (500 mg), piperidine-2-thione (115.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:9) to afford the product as a yellow solid (5:1 mixture with the *Z*-isomer, 193.4 mg, 89%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.87 (d, *J* = 14.9 Hz, 1H, *H-5*), 7.41 (d, 2H, *H-8*), 7.31 (t, 2H, *H-9*), 7.23 (d, 1H, *H-10*), 6.38 (d, *J* = 14.9 Hz, 1H, *H-6*), 3.72 (m, 2H, *H-4*), 3.14 (m, 2H, *H-1*), 2.00-2.04 (m, 2H, *H-3*), 1.76-1.80 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 201.1 (*C=S*), 131.9 (*C-5*), 128.8 (C_{arom}), 128.6 (C_{arom}), 127.5 (*C-7*), 126.4 (C_{arom}), 117.2 (*C-6*), 48.4 (*C-4*), 42.9 (*C-1*), 22.6 (*C-2*), 20.1 (*C-3*) ppm. **EA** Calcd for $C_{13}H_{15}NS$: C, 71.85; H, 6.96; N, 6.44. Found: C, 71.96; H, 7.26; N, 6.41. **MS** (Ion trap, EI): *m/z* (%) = 217 (54, [M^+]), 174 (6), 140 (100), 98 (11), 51 (16). **IR** (KBr): υ (cm^{-1}) 3058, 3023, 1635, 1449, 1385, 1103, 765, 692.

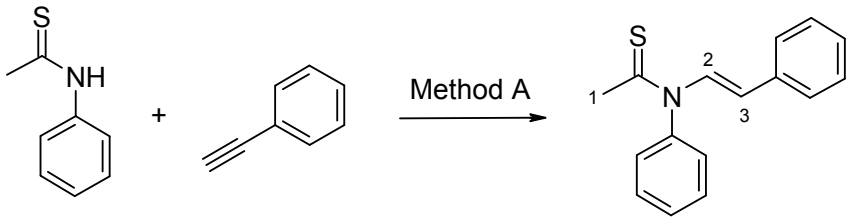
Synthesis of *N*-[(*E*)-2-Phenylvinyl]azepane-2-thione (3l)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), molecular sieves (500 mg), 2*H*-azepine-2-thione (129.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:4) to afford the product as a yellow solid (30:1 mixture with the *Z*-

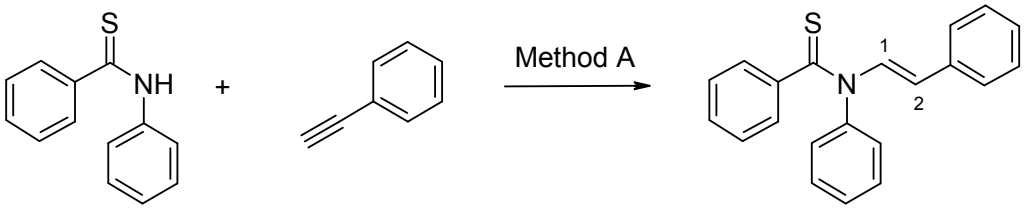
isomer, 194.3 mg, 84%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.59 (d, *J* = 14.7 Hz, 1H, *H-6*), 7.40 (d, 2H, *H-9*), 7.31 (t, 2H, *H-10*), 7.22 (t, 1H, *H-11*), 6.31 (d, *J* = 14.7 Hz, 1H, *H-7*), 4.02 (m, 2H, *H-5*), 3.28 (m, 2H, *H-1*), 1.78 (m, 6H, *H-2*, *H-3*, *H-4*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 206.3 (*C=S*), 135.7 (*C-6*), 132.8 (C_{arom}), 128.7 (C_{arom}), 127.4 (C_{arom}), 126.3 (C_{arom}), 117.1 (*C-7*), 50.5 (*C-5*), 47.5 (*C-1*), 28.6 (*C-4*), 26.6 (*C-2*), 25.0 (*C-3*) ppm. **EA** Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05. Found: C, 73.08; H, 7.28; N, 5.80. **MS** (Ion trap, EI): *m/z* (%) = 231 (68, [M^+]), 154 (100), 96 (31), 69 (12), 45 (9). **IR** (KBr): υ (cm^{-1}) 2923, 2848, 1630, 1495, 1446, 1414, 1337, 1069.

Synthesis of *N*-Phenyl-*N*-[(*E*)-2-phenylvinyl]thioacetamide (3m)



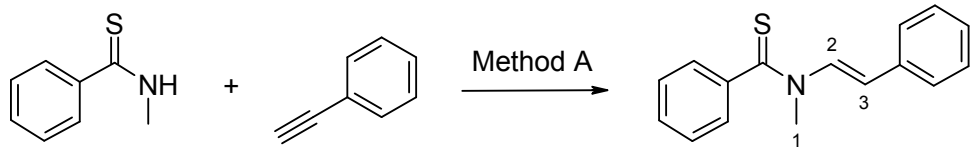
The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (16 mg, 0.05 mmol), molecular sieves (500 mg), *N*-phenyl-thioacetamide (151.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:4) to afford the product as a yellow solid (30:1 mixture with the *Z*-isomer, 248.3 mg, 98%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 9.01 (d, *J* = 14.67 Hz, 1H, *H-2*), 7.50-7.57 (m, 3H, H_{arom}), 7.16-7.29 (m, 7H, H_{arom}), 5.56 (d, *J* = 14.67 Hz, 1H, *H-3*), 2.39 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 200.4 (*C=S*), 141.2 (C_{arom}), 135.6 (*C-2*), 133.2 (C_{arom}), 130.2 (C_{arom}), 129.2 (C_{arom}), 128.6 (C_{arom}), 127.5 (C_{arom}), 127.4 (C_{arom}), 126.3 (C_{arom}), 120.1 (*C-3*), 35.0 (*C-1*) ppm. **EA** Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53. Found: C, 76.07; H, 6.23; N, 5.66. **MS** (Ion trap, EI): *m/z* (%) = 253(18, [M^+]), 176 (5), 118 (100), 77 (14), 59 (10). **IR** (KBr): υ (cm^{-1}) 3061, 3027, 1631, 1594, 1491, 1297, 1263, 1092, 750, 715, 692.

Synthesis of *N*-Phenyl-*N*-[(*E*)-2-phenylvinyl]thiobenzamide (3n)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (6.4 mg, 0.02 mmol), molecular sieves (500 mg), *N*-phenyl-thiobenzamide (231.3 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellow solid (30:1 mixture with the *Z*-isomer, 306.0 mg, 97%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.23-7.33 (m, 16H, *H-1*, H_{arom}), 5.87 (d, 1H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 201.6 (*C*=*S*), 143.5 (C_{arom}), 142.3 (C_{arom}), 135.5 (*C-1*), 133.8 (C_{arom}), 129.4 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.4 (C_{arom}), 128.2 (C_{arom}), 127.9 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 126.2 (*C-2*) ppm. **EA** Calcd for $C_{21}H_{17}NS$: C, 79.96; H, 5.43; N, 4.44. Found: C, 79.67; H, 5.31; N, 4.44. **MS** (Ion trap, EI): *m/z* (%) = 315 (10, [M^+]), 180 (100), 121 (29), 77 (23), 51 (12). **IR** (KBr): υ (cm^{-1}) 2958, 2928, 2871, 1658, 1594, 1495, 1445, 1320, 1271, 757, 715, 696.

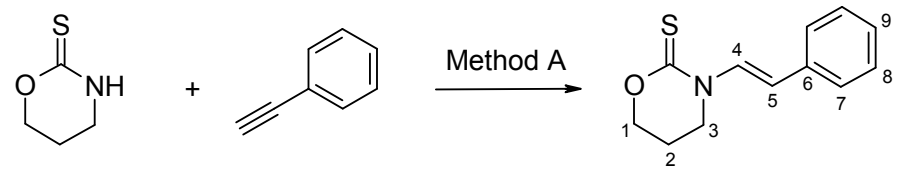
Synthesis of *N*-Methyl-*N*-[(*E*)-2-phenylvinyl]thiobenzamide (3o)



The compound was prepared according to method A, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), molecular sieves (500 mg), *N*-methyl-thiobenzamide (151.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:4) to afford the product as a yellow

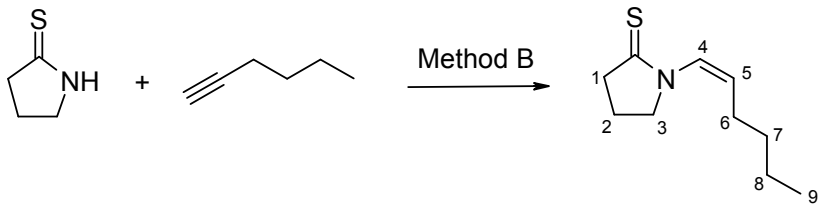
solid (15:1 mixture with the *Z*-isomer, 230.6 mg, 91%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.12-7.52 (m, 11H, *H-2*, H_{arom}), 6.25 (d, 1H, *H-3*), 3.97 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 201.5 (*C*=*S*), 142.9 (C_{arom}), 135.4 (*C-2*), 131.3 (C_{arom}), 129.3 (C_{arom}), 128.8 (C_{arom}), 128.4 (C_{arom}), 127.3 (C_{arom}), 127.04 (C_{arom}), 125.8 (C_{arom}), 114.8 (*C-3*), 37.8 (*C-1*) ppm. **EA** Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53. Found: C, 76.12; H, 6.19; N, 5.63. **MS** (Ion trap, EI): *m/z* (%) = 253 (49, [M^+]), 176 (50), 121 (75), 118 (100), 77 (48). **IR** (KBr): υ (cm^{-1}) 3058, 1627, 1461, 1377, 1305, 1099, 929, 768, 696.

Synthesis of *N*-[(*E*)-2-Phenylvinyl]-1,3-oxazinane-2-thione (3p)



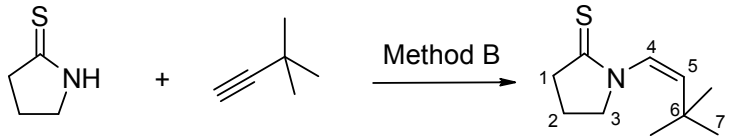
The compound was prepared according to method A, using the following amounts: $[Ru(cod)(met)_2]$ (16 mg, 0.05 mmol), molecular sieves (500 mg), 1,3-oxazinane-2-thione (117.2 mg, 1.00 mmol), tri-*n*-octylphosphine (67 µL, 0.15 mmol) and phenylacetylene (220 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellow solid (2:1 mixture with the *Z*-isomer, 92.1 mg, 42%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.05 (d, *J* = 15.0 Hz, 1H, *H-4*), 7.26-7.35 (m, 4H, *H-7*, *H-8*), 7.18 (t, 1H, *H-9*), 5.95 (d, *J* = 15.0 Hz, 1H, *H-5*), 3.71 (t, 2H, *H-1*), 3.10 (t, 2H, *H-3*), 2.33 (tt, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 164.6 (*C*=*S*), 136.4 (*C-4*), 128.7 (*C-7*), 127.3 (*C-6*), 126.7 (*C-9*), 125.9 (*C-8*), 110.7 (*C-5*), 45.8 (*C-1*), 28.3 (*C-3*), 23.8 (*C-2*) ppm. **EA** Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 66.08; H, 6.32; N, 6.27. **MS** (Ion trap, EI): *m/z* (%) = 219 (100, [M^+]), 191 (35), 130 (54), 103 (19), 77 (18). **IR** (KBr): υ (cm^{-1}) 2925, 2852, 1647, 1598, 1476, 1445, 1408, 1248, 1156, 952, 750, 692.

Synthesis of *N*-[(*Z*)-hex-1-enyl]pyrrolidine-2-thione (4a).



The compound was prepared according to method B, using the following amounts: $[Ru(cod)(met)_2]$ (16 mg, 0.05 mmol), KO*t*-Bu (5.6 mg, 0.04 mmol), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), bis(dicyclohexylphosphino)methane (12.3 mg, 0.06 mmol) and 1-hexyne (229 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (1:2 mixture with the *E*-isomer, 135 mg, 74%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 6.72 (d, *J* = 9.5 Hz, 1H, *H-4*), 5.08-5.24 (dt, *J* = 9.5 Hz, 1H, *H-5*), 3.97 (t, 2H, *H-3*), 3.00 (t, 2H, *H-1*), 2.02-2.21 (m, 4H, *H-2*, *H-6*), 1.24-1.44 (m, 4H, *H-7*, *H-8*), 0.87 (t, 3H, *H-9*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 202.3 (*C*=*S*), 125.8 (C-4), 123.3 (C-5), 56.2 (C-3), 44.3 (C-1), 31.7 (C-6), 27.2 (C-2), 22.2 (C-7), 21.1 (C-8), 13.8 (C-9) ppm. **EA** Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35; N, 7.64. Found: C, 65.49; H, 9.23; N, 7.68. **MS** (Ion trap, EI): *m/z* (%) = 183 (58, $[M^+]$), 126 (100), 98 (13), 85 (28), 45 (10). **IR** (KBr): υ (cm^{-1}) 2943, 2931, 2851, 1631, 1475, 1406, 1098, 935, 856.

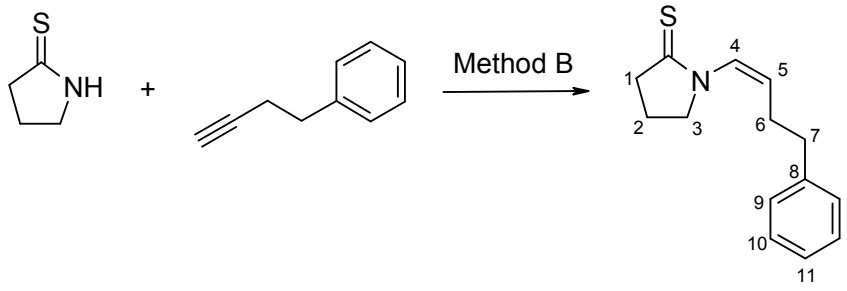
Synthesis of *N*-[(*Z*)-3,3-Dimethyl-but-1-enyl]pyrrolidine-2-thione (4b)



The compound was prepared according to method B, using the following amounts: $[Ru(cod)(met)_2]$ (16 mg, 0.05 mmol), KO*t*-Bu (5.6 mg, 0.04 mmol), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), bis(dicyclohexylphosphino)methane (12.3 mg, 0.06 mmol) and 3,3-dimethyl-1-butyne (246 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (1:8 mixture with the *E*-isomer, 128.32 mg, 70%). **^{1}H-NMR** (400 MHz, $CDCl_3$,

25 °C): δ = 5.77 (d, *J* = 9.4 Hz, 1H, *H-4*), 5.41 (d, *J* = 9.4 Hz, 1H, *H-5*), 3.72 (t, 2H, *H-3*), 2.94 (t, 2H, *H-1*), 2.05-2.11 (m, 2H, *H-2*), 1.05 (s, 9H, *H-7*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 203.1 (*C=S*), 141.4 (*C-4*), 123.1 (*C-5*), 58.3 (*C-3*), 44.5 (*C-1*), 33.5 (*C-6*), 29.2 (*C-7*), 20.7 (*C-2*) ppm. **EA** Calcd for $C_{10}H_{17}NS$: C, 65.52; H, 9.35; N, 7.64. Found: C, 65.27; H, 9.55; N, 7.65. **MS** (Ion trap, EI): *m/z* (%) = 183 (55, [M^+]), 134 (11), 128 (5), 127 (35), 126 (100). **IR** (KBr): υ (cm-1) 2962, 2932, 2863, 1639, 1414, 1293, 1263, 1099, 1027, 799.

Synthesis of *N*-[(*Z*)-4-Phenylbut-1-en-1-yl]pyrrolidine-2-thione (4c)



The compound was prepared according to method B, using the following amounts: [Ru(cod)(met)$_2$] (16 mg, 0.05 mmol), KO*t*-Bu (5.6 mg, 0.04 mmol), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), bis(dicyclohexylphosphino)methane (12.3 mg, 0.06 mmol) and 4-phenyl-1-butyne (281 µL, 2.0 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 2:3) to afford the product as a yellowish oil (1:2 mixture with the *E*-isomer, 128.3 mg, 64%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.33 (d, *J* = 7.6 Hz, 2H, *H-9*), 7.16-7.28 (m, 3H, *H10*, *H-11*), 6.82 (d, *J* = 9.5 Hz, 1H, *H-4*), 5.23-5.35 (dt, *J* = 9.5 Hz, 1H, *H-5*), 3.86 (t, 2H, *H-3*), 3.02 (t, 2H, *H-1*), 2.72-2.84 (m, 4H, *H-6*, *H-7*), 2.11 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 199.5 (*C=S*), 141.2 (*C-4*), 128.54 (C_{arom}), 128.50 (C_{arom}), 127.1 (C_{arom}), 126.1 (C_{arom}), 121.9 (*C-5*), 56.2 (*C-3*), 45.3 (*C-1*), 35.7 (*C-6*), 32.1 (*C-7*), 21.2 (*C-2*) ppm. **EA** Calcd for $C_{14}H_{17}NS$: C, 72.68; H, 7.41; N, 6.05. Found: C, 72.78; H, 7.52; N, 5.95. **MS** (Ion trap, EI): *m/z* (%) = 231 (22, [M^+]), 126 (100), 98 (8), 58 (5), 45 (10). **IR** (KBr): υ (cm^{-1}) 2925, 1655, 1480, 1457, 1415, 1275, 1134, 952, 746, 700.

5.3 Anti-Markovnikov addition of primary amides to alkynes

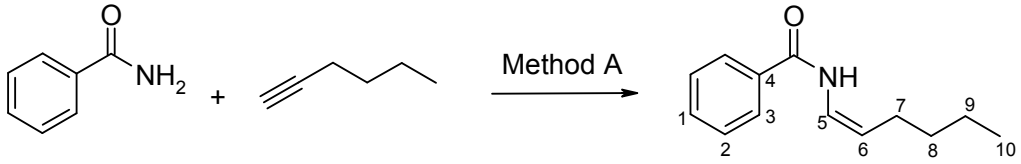
5.3.1 General methods

Method A: An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [Ru(cod)(met)$_2$] (16.0 mg, 0.05 mmol), primary amide (1.00 mmol), 1,4-bis(dicyclohexylphosphino)butane (27.0 mg, 0.06 mmol), and ytterbium triflate (24.8 mg, 0.04 mmol) and flushed with nitrogen. Subsequently, dry DMF (3.0 mL), alkyne (2.00 mmol), and water (108 μL, 6.00 mmol) were added via syringe. The resulting solution was stirred for 6 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the *Z*-secondary enamide. The identity and purity of the products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, mass spectroscopy and elemental analysis.

Method B: After the completion of the reaction following method A, 500 mg of 3 Å molecular sieves and 200 μL triethylamine were added into the reaction flask, and the reaction mixture was stirred for 24 h at 110 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the *E*-secondary enamide. The identity and purity of the products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, mass spectroscopy and elemental analysis.

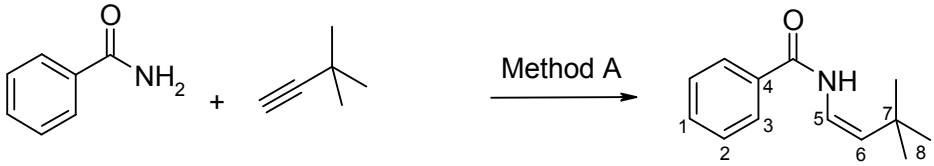
5.3.2 Synthesis of secondary enamides

Synthesis of *N*-((*Z*)-hex-1-en-1-yl)benzamide (6a)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a yellowish oil (18:1 mixture with the *E*-isomer, 191.1 mg, 94%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.78 (d, *J* = 7.2 Hz, 2H, *H-3*), 7.64 (d, *J* = 8.4 Hz, 1H, *N-H*), 7.52 (t, *J* = 7.4 Hz, 1H, *H-1*), 7.45 (t, *J* = 7.6 Hz, 2H, *H-2*), 6.90 (dd, *J* = 10.8, 9.2 Hz, 1H, *H-5*), 4.83-4.88 (m, 1H, *H-6*), 2.08 (qd, *J* = 7.3, 1.5 Hz, 2H, *H-7*), 1.40-1.44 (m, 2H, *H-8*), 1.34-1.39 (m, 2H, *H-9*), 0.92 (t, *J* = 7.2 Hz, 3H, *H-10*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.3 (*C=O*), 134.0 (*C-4*), 131.9 (*C-1*), 128.7 (*C-2*), 127.0 (*C-3*), 121.1 (*C-5*), 112.3 (*C-6*), 31.4 (*C-7*), 25.5 (*C-8*), 22.3 (*C-9*), 14.0 (*C-10*) ppm. **EA** Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.73; H, 8.49; N, 6.88. **MS** (Ion trap, EI): *m/z* (%) = 203 (8, [M^+]), 160 (10), 122 (27), 105 (100), 77 (39), 51 (11).

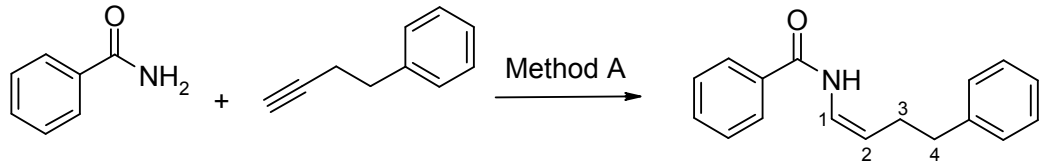
Synthesis of *N*-[(*Z*)-3,3-dimethyl-but-1-en-1-yl]benzamide (6b)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 3,3-dimethyl-1-butyne (246 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (>40:1 mixture with the *E*-isomer, 185.0 mg, 91%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.02 (d, *J* = 9.3 Hz, 1H, *N-H*), 7.75 (d, *J* = 7.1 Hz, 2H, *H-3*), 7.51 (t, *J*

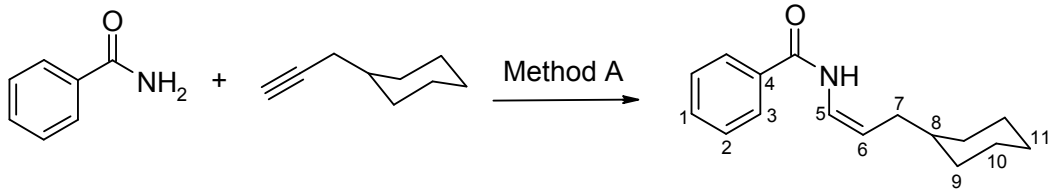
= 7.4 Hz, 1H, *H-1*), 7.44 (t, *J* = 7.6 Hz, 2H, *H-2*), 6.70-6.75 (m, 1H, *H-5*), 4.70 (d, *J* = 10.0 Hz, 1H, *H-6*), 1.21 (s, 9H, *H-8*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 163.7 (*C=O*), 133.8 (*C-4*), 131.9 (*C-1*), 128.7 (*C-2*), 126.7 (*C-3*), 121.5 (*C-5*), 118.7 (*C-6*), 32.6 (*C-7*), 30.9 (*C-8*) ppm. **EA** Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.49; H, 8.46; N, 6.72. **MS** (Ion trap, EI): *m/z* (%) = 203 (5, [M^+]), 188 (49), 146 (7), 105 (100), 77 (40), 51 (11).

Synthesis of *N*-[(*Z*)-4-phenyl-but-1-en-1-yl]benzamide (6c)



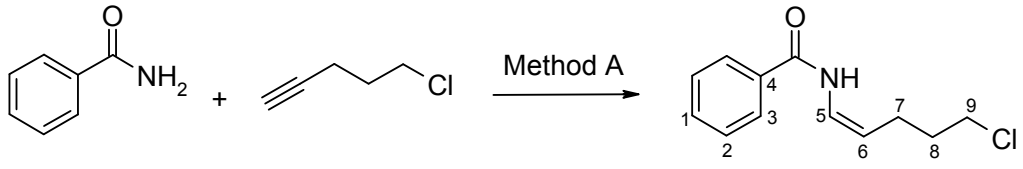
The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 4-phenyl-1-butyne (281 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (17:1 mixture with the *E*-isomer, 231.2 mg, 92%) **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.61 (d, *J* = 7.2 Hz, 2H, H_{arom}), 7.51 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.41 (t, *J* = 7.8 Hz, 2H, H_{arom}), 7.26-7.30 (m, 3H, H-11, *N-H*), 7.22-7.25 (m, 2H, H_{arom}), 7.16 (t, *J* = 7.3 Hz, 1H, H_{arom}), 6.89 (dd, *J* = 10.6, 9.1 Hz, 1H, *H-1*), 4.94 (q, *J* = 7.9 Hz, 1H, *H-2*), 2.76 (t, *J* = 7.3 Hz, 2H, *H-4*), 2.39-2.44 (m, 2H, *H-3*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.3 (*C=O*), 141.5 (C_{arom}), 133.7 (C_{arom}), 131.8 (C_{arom}), 128.53 (C_{arom}), 128.50 (C_{arom}), 128.4 (C_{arom}), 127.0 (C_{arom}), 126.2 (C_{arom}), 122.1 (*C-1*), 110.9 (*C-2*), 35.4 (*C-4*), 28.3 (*C-3*) ppm. **EA** Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.37; H, 6.78; N, 5.69. **MS** (Ion trap, EI): *m/z* (%) = 251 (4, [M^+]), 160 (47), 105 (100), 91 (27), 77 (37), 51 (11).

Synthesis of *N*-[(*Z*)-3-cyclohexyl-prop-1-en-1-yl]benzamide (6d)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 3-cyclohexyl-1-propyne (289 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (23:1 mixture with the *E*-isomer, 209.3 mg, 86%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.77 (d, *J* = 7.4 Hz, 2H, *H-3*), 7.67 (d, *J* = 9.7 Hz, 1H, *N-H*), 7.51 (t, *J* = 7.4 Hz, 1H, *H-1*), 7.44 (t, *J* = 7.6 Hz, 2H, *H-2*), 6.93 (dd, *J* = 10.7, 9.0 Hz, 1H, *H-5*), 4.87 (q, *J* = 7.8 Hz, 1H, *H-6*), 1.93-1.97 (m, 2H, *H-7*), 1.73-1.77 (m, 2H, H_{Cy}), 1.70 (dt, *J* = 13.0, 3.1 Hz, 2H, H_{Cy}), 1.63-1.67 (m, 1H, H_{Cy}), 1.36 (td, *J* = 7.1, 3.8 Hz, 1H, H_{Cy}), 1.18-1.26 (m, 2H, H_{Cy}), 1.10-1.17 (m, 1H, H_{Cy}), 0.90-0.97 (m, 2H, H_{Cy}) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.2 (*C=O*), 133.9 (*C-4*), 131.8 (*C-1*), 128.7 (*C-2*), 127.0 (*C-3*), 121.7 (*C-5*), 110.8 (*C-6*), 38.1 (*C-7*), 33.7 (*C-8*), 33.1 (*C-9*), 26.4 (*C-10*), 26.2 (*C-11*) ppm. **EA** Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.95; H, 8.73; N, 5.55. **MS** (Ion trap, EI): *m/z* (%) = 243 (17, [M^+]), 160 (23), 122 (26), 105 (100), 77 (31), 51 (7).

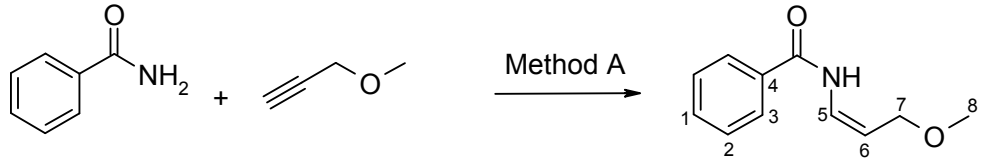
Synthesis of *N*-[(*Z*)-5-chloro-pent-1-en-1-yl]benzamide (6e)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 5-chloro-1-pentyne (210 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (31:1 mixture with the *E*-isomer, 203.6 mg, 91%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.95 (d, *J* = 9.0 Hz, 1H, *N-H*), 7.80-7.84 (m, 2H, *H-3*), 7.51 (t, *J* = 7.4

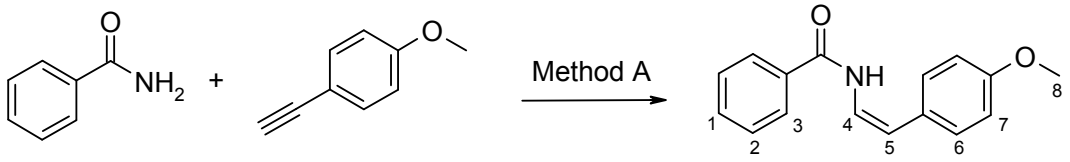
Hz, 1H, *H-1*), 7.44 (t, *J* = 7.6 Hz, 2H, *H-2*), 7.01 (dd, *J* = 10.6, 9.2 Hz, 1H, *H-5*), 4.78 (q, *J* = 8.3 Hz, 1H, *H-6*), 3.61-3.64 (m, 2H, *H-9*), 2.29-2.34 (m, 2H, *H-7*), 1.91 (dq, *J* = 6.5, 6.3 Hz, 2H, *H-8*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.5 (*C=O*), 133.6 (*C-4*), 131.9 (*C-1*), 128.7 (*C-2*), 127.1 (*C-3*), 123.3 (*C-5*), 109.4 (*C-6*), 44.5 (*C-9*), 31.3 (*C-7*), 22.3 (*C-8*) ppm. **EA** Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.10; H, 6.21; N, 5.98. **MS** (Ion trap, EI): *m/z* (%) = 223 (18, [M^+]), 188 (7), 160 (7), 105 (100), 77 (29), 51 (10).

Synthesis of *N*-[(*Z*)-3-methoxy-prop-1-en-1-yl]benzamide (6f)



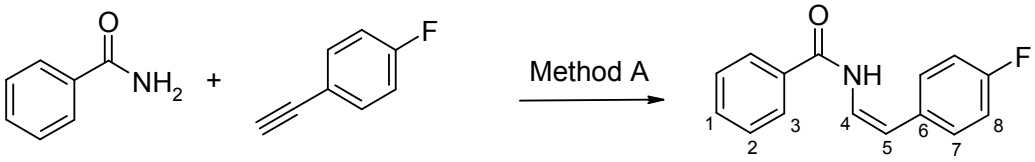
The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 3-methoxy-1-propyne (169 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a yellowish oil (15:1 mixture with the *E*-isomer, 80.0 mg, 42%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 9.58 (d, *J* = 7.83 Hz, 1H, *N-H*), 7.77 (d, *J* = 7.04 Hz, 2H, *H-3*), 7.40-7.52 (m, 3H, *H-1*, *H-2*), 7.04 (t, *J* = 9.78 Hz, 1H, *H-5*), 4.72-4.79 (m, 1H, *H-6*), 4.19 (d, *J* = 2.35 Hz, 2H, *H-7*), 3.44 (s, 3H, *H-8*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 163.7 (*C=O*), 133.7 (*C-4*), 131.8 (*C-1*), 128.6 (*C-2*), 127.0 (*C-3*), 124.4 (*C-5*), 105.3 (*C-6*), 71.1 (*C-7*), 58.6 (*C-8*) ppm. **EA** Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.80; H, 6.91; N, 6.98. **MS** (Ion trap, EI): *m/z* (%) = 191 (23, [M^+]), 176 (12), 160 (7), 105 (100), 77 (49), 51 (20).

Synthesis of *N*-[(*Z*)-2-(4-methoxyphenyl)vinyl]benzamide (6g)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 4-methoxy-phenylacetylene (259 µL, 2.00 mmol) and purified by column chromatography (1:8 ethyl acetate/hexane), yielding the product as a white solid (19:1 mixture with the *E*-isomer, 210.3 mg, 83%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.30 (d, *J* = 10.2 Hz, 1H, *N-H*), 7.75 (d, *J* = 7.4 Hz, 2H, *H-3*), 7.52 (t, *J* = 7.3 Hz, 1H, *H-1*), 7.44 (t, *J* = 7.7 Hz, 2H, *H-2*), 7.27 (d, *J* = 8.4 Hz, 2H, *H-6*), 7.12 (t, *J* = 10.2 Hz, 1H, *H-4*), 6.95 (d, *J* = 8.4 Hz, 2H, *H-7*), 5.83 (d, *J* = 9.2 Hz, 1H, *H-5*), 3.82 (s, 3H, *H-8*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.2 (*C=O*), 158.5 (C_{arom}), 133.4 (C_{arom}), 132.0 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 128.0 (C_{arom}), 127.0 (C_{arom}), 121.3 (*C-4*), 114.6 (C_{arom}), 110.7 (*C-5*), 55.3 (*C-8*) ppm. **EA** Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.59; H, 5.82; N, 5.31. **MS** (Ion trap, EI): *m/z* (%) = 253 (64, [M^+]), 150 (12), 133 (8), 105 (100), 77 (45), 51 (15).

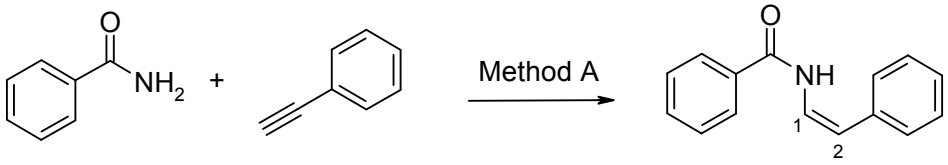
Synthesis of *N*-[(*Z*)-2-(4-fluoro -phenyl)-vinyl]benzamide (6h)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 1-ethynyl-4-fluorobenzene (229 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (20:1 mixture with the *E*-isomer, 238.9 mg, 99%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.24 (d, *J* = 10.0 Hz, 1H, *N-H*), 7.72-7.75 (m, 2H, *H-3*), 7.51-7.55 (m, 1H, *H-1*), 7.45 (t, *J* = 7.7 Hz, 2H, *H-2*), 7.29-7.33 (m, 2H, *H-7*), 7.17 (dd, *J* = 11.0, 9.7 Hz, 1H, *H-4*), 7.09-7.13 (m, 2H, *H-8*), 5.84 (d, *J* = 9.5 Hz, 1H, *H-5*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 163.3 (d, ^{2}J = 301 Hz, *C-F*), 160.7 (*C=O*), 133.2 (C_{arom}), 132.2

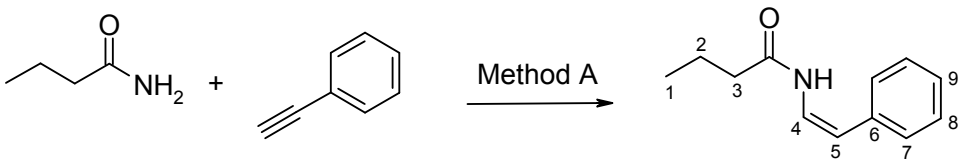
(C_{arom}), 131.7 (d, ^5J = 2.8 Hz, *C-6*), 129.5 (d, ^4J = 8.4 Hz, *C-7*), 128.8 (C_{arom}), 127.0 (C_{arom}), 122.4 (*C-4*), 116.2 (d, ^3J = 22.2 Hz, *C-8*), 109.9 (*C-5*) ppm. **EA** Calcd for $C_{15}H_{12}FNO$: C, 74.68; H, 5.01; N, 5.81. Found: C, 74.42; H, 4.98; N, 5.68. **MS** (Ion trap, EI): *m/z* (%) = 241 (56, [M^+]), 135 (3), 109 (6), 105 (100), 77 (37), 51 (12).

Synthesis of *N*-[(*Z*)-2-phenyl-vinyl]benzamide (6i)



The compound was prepared according to method A, using the following amounts: benzamide (121.1 mg, 1.00 mmol), and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (18:1 mixture with the *E*-isomer, 216.6 mg, 97%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.38 (d, *J* = 9.7 Hz, 1H, *N-H*), 7.75 (d, *J* = 7.2 Hz, 2H, H_{arom}), 7.53 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.44 (dt, *J* = 14.9, 7.5 Hz, 4H, H_{arom}), 7.35 (d, *J* = 7.4 Hz, 2H, H_{arom}), 7.28 (t, *J* = 7.3 Hz, 1H, H_{arom}), 7.20 (dd, *J* = 10.8, 9.7 Hz, 1H, *H-1*), 5.89 (d, *J* = 9.5 Hz, 1H, *H-2*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.3 (*C=O*), 135.7 (C_{arom}), 133.3 (C_{arom}), 132.1 (C_{arom}), 129.2 (C_{arom}), 128.8 (C_{arom}), 127.8 (C_{arom}), 127.0 (C_{arom}), 122.3 (*C-1*), 110.9 (*C-2*) ppm. **EA** Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.36; H, 5.84; N, 6.06. **MS** (Ion trap, EI): *m/z* (%) = 223 (54, [M^+]), 117 (5), 105 (100), 91 (5), 77 (46), 51 (14).

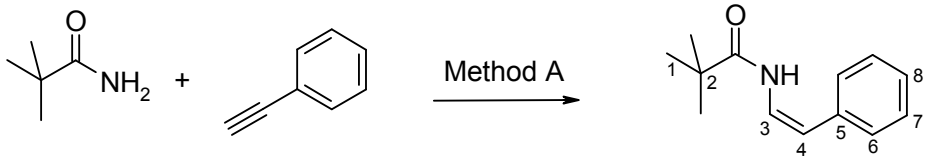
Synthesis of *N*-[(*Z*)-2-phenylvinyl]butyramide (6j)



The compound was prepared according to method A, using the following amounts: butyramide (87.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a

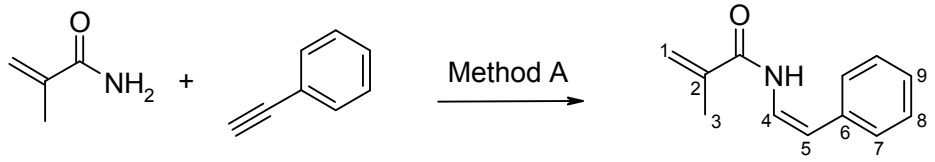
yellowish oil (14:1 mixture with the *E*-isomer,160.9 mg, 85%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.61 (d, *J* = 7.9 Hz, 1H, *N-H*), 7.39 (t, *J* = 7.7 Hz, 2H, *H-6*), 7.23-7.28 (m, 3H, *H-7*, *H-8*), 6.98 (dd, *J* = 11.0, 9.7 Hz, 1H, *H-4*), 5.73 (d, *J* = 9.5 Hz, 1H, *H-5*), 2.22 (t, *J* = 7.4 Hz, 2H, *H-3*), 1.65-1.72 (m, 2H, *H-2*), 0.97 (t, *J* = 7.3 Hz, 3H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 170.4 (*C=O*), 135.7 (*C-6*), 129.0 (*C-7*), 127.8 (*C-8*), 126.8 (*C-9*), 122.0 (*C-4*), 109.5 (*C-5*), 38.6 (*C-3*), 18.7 (*C-2*), 13.7 (*C-1*) ppm. **EA** Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.83; H, 7.92; N, 6.89. **MS** (Ion trap, EI): *m/z* (%) = 189 (50, [M^+]), 119 (100), 104 (2), 65 (4), 51 (2), 41 (8).

Synthesis of 2,2-dimethyl-*N*-[(*Z*)-2-phenylvinyl]propanamide (6k)



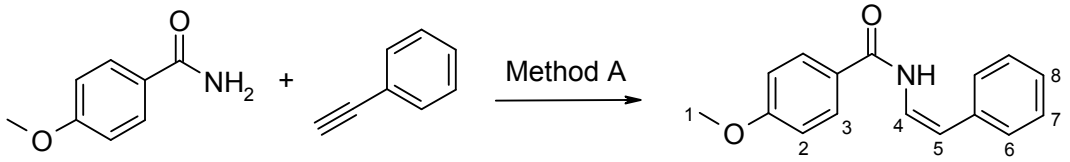
The compound was prepared according to method A, using the following amounts: 2,2-dimethylpropionamide (101.2 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (10:1 mixture with the *E*-isomer, 178.9 mg, 88%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (s, 1H, *N-H*), 7.35-7.45 (m, 2H, *H-5*), 7.21-7.31 (m, 3H, *H-6*, *H-7*), 6.99 (dd, *J* = 10.9, 9.7 Hz, 1H, *H-3*), 5.75 (d, *J* = 9.6 Hz, 1H, *H-4*), 1.22 (s, 9H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 175.6 (*C=O*), 135.8 (*C-5*), 129.1 (*C-6*), 127.6 (*C-7*), 126.8 (*C-8*), 122.4 (*C-3*), 109.7 (*C-4*), 38.8 (*C-2*), 27.2 (*C-1*) ppm. **EA** Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.81; H, 8.49; N, 6.75. **MS** (Ion trap, EI): *m/z* (%) = 203 (100, [M^+]), 160 (3), 119 (32), 91 (6), 65 (3), 57 (29).

Synthesis of 2-methyl-*N*-[(*Z*)-2-phenylvinyl]acrylamide (6l)



The compound was prepared according to method A, using the following amounts: 2-methyl-acrylamide (85.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a yellowish oil (19:1 mixture with the *E*-isomer, 168.5 mg, 90%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.06 (d, *J* = 7.4 Hz, 1H, *N-H*), 7.39 (t, *J* = 7.8 Hz, 2H, *H-7*), 7.28 (d, *J* = 7.2 Hz, 2H, *H-8*), 7.24 (t, *J* = 7.4 Hz, 1H, *H-9*), 7.03 (dd, *J* = 11.1, 9.6 Hz, 1H, *H-4*), 5.80 (d, *J* = 9.7 Hz, 1H, *H-5*), 5.72 (s, 1H, *H-1*), 5.43 (s, 1H, *H-1*), 1.97 (s, 3H, H-3) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 165.1 (*C=O*), 139.2 (*C-2*), 135.7 (*C-6*), 129.1 (*C-7*), 127.7 (*C-8*), 126.9 (*C-9*), 122.1 (*C-1*), 121.0 (*C-4*), 110.5 (*C-5*), 18.4 (*C-3*) ppm. **EA** Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.02; N, 7.15. **MS** (Ion trap, EI): *m/z* (%) = 187 (100, [M^+]), 159 (85), 144 (25), 117 (24), 69 (77), 41 (58).

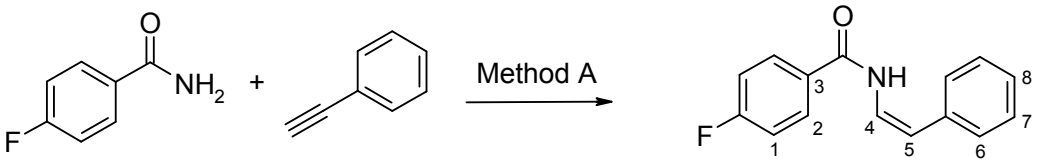
Synthesis of 4-methoxy-*N*-[(*Z*)-2-phenylvinyl]benzamide (6m)



The compound was prepared according to method A, using the following amounts: 4-methoxybenzamide (151.2 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:8 ethyl acetate/hexane), yielding the product as a white solid (18:1 mixture with the *E*-isomer, 243.2 mg, 96%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.31 (d, *J* = 10.5 Hz, 1H, *N-H*), 7.70-7.73 (m, 2H, *H-3*), 7.42 (t, *J* = 7.8 Hz, 2H, *H-6*), 7.34 (d, *J* = 7.2 Hz, 2H, *H-7*), 7.27 (t, *J* = 7.3 Hz, 1H, *H-8*), 7.16-7.21 (m, 1H, *H-4*), 6.91-6.94 (m, 2H, *H-2*), 5.85 (d, *J* = 9.5 Hz, 1H, *H-5*), 3.84 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 163.8 (*C=O*), 162.7 (C_{arom}), 135.9

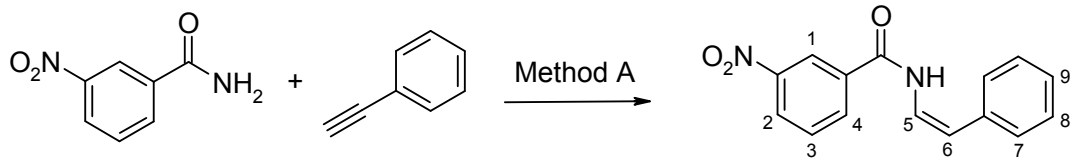
(C_{arom}), 129.2 (C_{arom}), 129.0 (C_{arom}), 127.8 (C_{arom}), 126.9 (C_{arom}), 125.5 (C_{arom}), 122.5 (*C-4*), 114.0 (C_{arom}), 110.2 (*C-5*), 55.4 (*C-1*) ppm. **EA** Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.97; H, 6.12; N, 5.43. **MS** (Ion trap, EI): *m/z* (%) = 253 (32, [M^+]), 135 (100), 107 (9), 92 (8), 77 (16), 63 (6).

Synthesis of 4-fluoro-*N*-[(*Z*)-2-phenylvinyl]benzamide (6n)



The compound was prepared according to method A, using the following amounts: 4-fluorobenzamide (139.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (19:1 mixture with the *E*-isomer, 224.4 mg, 93%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.24 (d, *J* = 10.6 Hz, 1H, *N-H*), 7.63-7.69 (m, 2H, H_{arom}), 7.33 (t, *J* = 7.7 Hz, 2H, H_{arom}), 7.22-7.27 (m, 2H, H_{arom}), 7.18 (t, *J* = 7.7 Hz, 1H, H_{arom}), 6.99-7.09 (m, 3H, H_{arom}, *H-4*), 5.79 (d, *J* = 9.5 Hz, 1H, *H-5*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 165.0 (d, ^2J = 253.4 Hz, *C-F*), 163.2 (*C=O*), 135.7 (C_{arom}), 129.6 (d, ^5J = 2.8 Hz, *C-3*), 129.4 (d, ^4J = 9.3 Hz, *C-2*), 129.2 (C_{arom}), 127.8 (C_{arom}), 127.1 (C_{arom}), 122.3 (*C-4*), 115.8 (d, ^3J = 22.2 Hz, *C-1*), 111.0 (*C-5*) ppm. **EA** Calcd for $C_{15}H_{12}FNO$: C, 74.68; H, 5.01; N, 5.81. Found: C, 74.67; H, 5.11; N, 5.66. **MS** (Ion trap, EI): *m/z* (%) = 242 (100, [M^{+1}]), 224 (6), 123 (100), 95 (21), 75 (7), 50 (3).

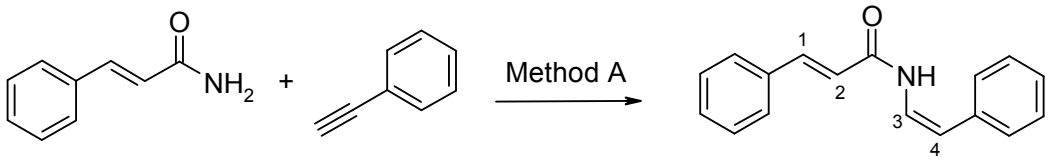
Synthesis of 3-nitro-*N*-[(*Z*)-2-phenylvinyl]benzamide (6o)



The compound was prepared according to method A, using the following amounts: 3-nitrobenzamide (168.2 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a

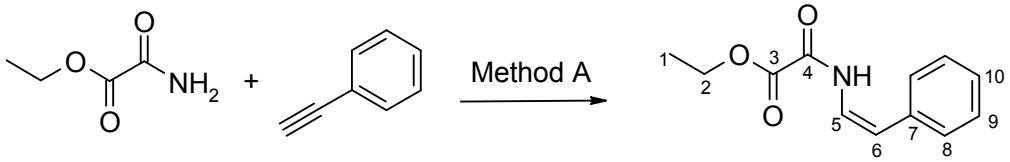
white solid (20:1 mixture with the *E*-isomer, 214.6 mg, 80%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.58 (d, *J* = 10.8 Hz, 1H, *N-H*), 8.54 (s, 1H, *H-1*), 8.30 (d, *J* = 8.2 Hz, 1H, *H-2*), 8.04 (d, *J* = 7.9 Hz, 1H, *H-4*), 7.62 (t, *J* = 7.9 Hz, 1H, *H-3*), 7.37 (t, *J* = 7.9 Hz, 2H, *H-8*), 7.32 (d, *J* = 7.2 Hz, 2H, *H-7*), 7.22 (t, *J* = 7.4 Hz, 1H, *H-9*), 7.08 (t, *J* = 10.5 Hz, 1H, *H-5*), 5.92 (d, *J* = 9.5 Hz, 1H, *H-6*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 162.1 (*C=O*), 148.0 (*C-NO$_2$*), 135.1 (C_{arom}), 134.8 (C_{arom}), 132.7 (C_{arom}), 129.8 (C_{arom}), 129.1 (C_{arom}), 127.8 (C_{arom}), 127.2 (C_{arom}), 126.3 (C_{arom}), 122.2 (C_{arom}), 121.7 (*C-5*), 112.5 (*C-6*) ppm. **EA** Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.15; H, 4.68; N, 10.52. **MS** (Ion trap, EI): *m/z* (%) = 268 (64, [M^+]), 150 (100), 120 (20), 104 (36), 76 (25), 50 (13).

Synthesis of (*E*)-3-phenyl-*N*-[(*Z*)-2-phenylvinyl]acrylamide (Lansiumamide A) (6p)



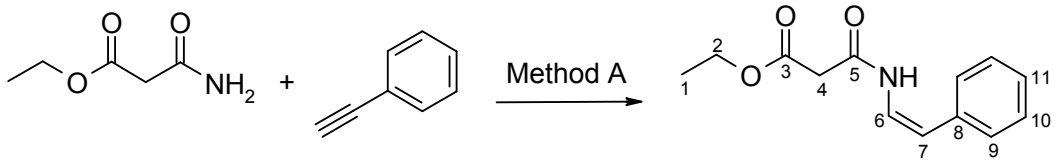
The compound was prepared according to method A, using the following amounts: 3-phenylacrylamide (147.2 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:8 ethyl acetate/hexane), yielding the product as a white solid (20:1 mixture with the *E*-isomer, 244.3 mg, 98%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.87 (d, *J* = 11.0 Hz, 1H, *N-H*), 7.71 (d, *J* = 15.6 Hz, 1H, *H-1*), 7.50 (dd, *J* = 6.5, 2.7 Hz, 2H, H_{arom}), 7.41 (t, *J* = 7.7 Hz, 2H, H_{arom}), 7.31-7.37 (m, 5H, H_{arom}), 7.27 (t, *J* = 7.4 Hz, 1H, H_{arom}), 7.12 (dd, *J* = 11.3, 9.7 Hz, 1H, *H-3*), 6.40 (d, *J* = 15.6 Hz, 1H, *H-2*), 5.82 (d, *J* = 9.5 Hz, 1H, *H-4*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 163.1 (*C=O*), 143.0 (*C-1*), 135.7 (C_{arom}), 134.4 (C_{arom}), 130.1 (C_{arom}), 129.1 (C_{arom}), 128.8 (C_{arom}), 128.0 (C_{arom}), 127.9 (C_{arom}), 127.0 (C_{arom}), 122.2 (C-3), 119.4 (*C-2*), 110.6 (*C-4*) ppm. **EA** Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.70; H, 6.05; N, 5.50. **MS** (Ion trap, EI): *m/z* (%) = 249 (44, [M^+]), 131 (100), 119 (35) 103 (50), 77 (23), 51 (10).

Synthesis of ethyl oxo{[*(Z)*-2-phenylvinyl]amino}acetate (6q)



The compound was prepared according to method A, using the following amounts: oxalamic acid ethyl ester (117.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) but owing to the high hydrolytic instability of the product, no water was added. Purification by column chromatography (1:7 ethyl acetate/hexane), yielded the product as a white solid (35:1 mixture with the *E*-isomer, 171.0 mg, 78%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 9.24 (d, *J* = 9.2 Hz, 1H, *N-H*), 7.41 (t, *J* = 7.7 Hz, 2H, *H-9*), 7.27-7.32 (m, 3H, *H-8*, *H-10*), 6.91 (dd, *J* = 11.8, 9.5 Hz, 1H, *H-5*), 5.98 (d, *J* = 9.5 Hz, 1H, *H-6*), 4.36 (q, *J* = 7.2 Hz, 2H, *H-2*), 1.38 (t, *J* = 7.2 Hz, 3H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 160.2 (*C-4*), 153.6 (*C-3*), 134.7 (*C-7*), 129.2 (*C-9*), 127.9 (*C-8*), 127.6 (*C-10*), 120.3 (*C-5*), 114.2 (*C-6*), 63.6 (*C-2*), 13.9 (*C-1*) ppm. **EA** Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.00; H, 5.99; N, 6.27. **MS** (Ion trap, EI): *m/z* (%) = 219 (100, [M^+]), 146 (3), 118 (10), 117 (11), 91 (2), 89 (3).

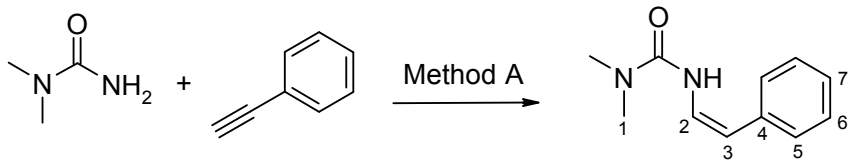
Synthesis of ethyl 3-oxo-3{[(*Z*)-2-phenylvinyl]amino}propanoate (6r)



The compound was prepared according to method A, using the following amounts: malonamic acid ethyl ester (131.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) but owing to the high hydrolytic instability of the product, no water was added. Purification by column chromatography (1:6 ethyl acetate/hexane), yielded the product as a white solid (19:1 mixture with the *E*-isomer, 165.6 mg, 71%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.34 (t, *J* = 7.6 Hz, 2H, *H-10*), 7.26-7.31 (m, 3H, *H-9*, *H-11*), 6.78 (d, *J* = 11.3 Hz, 1H, *H-6*), 6.50 (s, 1H, *H-4*), 6.35 (s, 1H, *H-4*), 5.95 (t, *J* = 10.9 Hz, 1H, *H-*

7), 4.43 (d, *J* = 10.5 Hz, 1H, *N-H*), 4.16-4.22 (m, 2H, *H-2*), 1.22-1.28 (m, 3H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 169.6 (*C-5*), 169.5 (*C-3*), 135.4 (*C-6*), 134.1 (*C-8*), 128.5 (*C-10*), 128.4 (*C-9*), 127.6 (*C-11*), 123.3 (*C-7*), 61.9 (*C-2*), 52.4 (*C-4*), 13.9 (*C-1*) ppm. **EA** Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.57; H, 6.17; N, 5.77. **MS** (Ion trap, EI): *m/z* (%) = 233 (6, [M^+]), 204 (100), 170 (41), 102 (72), 77 (12), 50 (25).

Synthesis of 1,1-dimethyl-3-[(*Z*)-2-phenylvinyl]urea (6s)



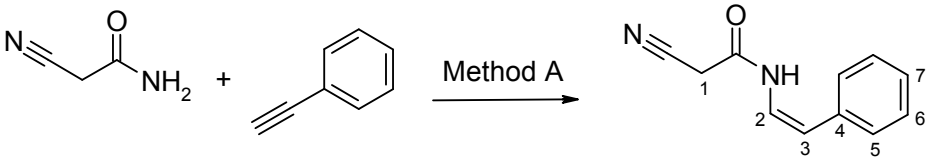
The compound was prepared according to method A, using the following amounts: 1,1-dimethylurea (88.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (30:1 mixture with the *E*-isomer, 87.6 mg, 46%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.37 (t, *J* = 7.8 Hz, 2H, *H-6*), 7.29 (d, *J* = 6.9 Hz, 2H, *H-5*), 7.21 (s, 1H, *H-7*), 7.08 (s, 1H, *N-H*), 6.97 (d, *J* = 9.7 Hz, 1H, *H-2*), 5.57 (d, *J* = 9.5 Hz, 1H, *H-3*), 2.95 (s, 6H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 154.8 (*C=O*), 136.7 (*C-4*), 129.1 (*C-6*), 127.5 (*C-5*), 126.3 (*C-7*), 124.7 (*C-2*), 106.0 (*C-3*), 36.2 (*C-1*) ppm. **EA** Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.56; H, 7.13; N, 14.75. **MS** (Ion trap, EI): *m/z* (%) = 190 (58, [M^+]), 145 (14), 117 (10), 89 (10), 72 (100), 44 (7).

Synthesis of 2-acetamido-*N*-[(*Z*)-2-phenylvinyl]acetamide (6t)

The compound was prepared according to method A, using the following amounts: 2-acetamidoacetamide (116.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:6 ethyl acetate/hexane), yielding the product

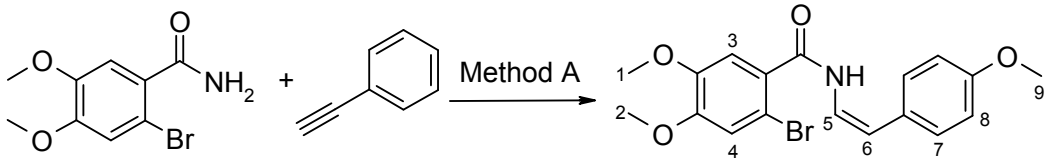
as a white solid (22:1 mixture with the *E*-isomer, 209.5 mg, 96%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.49 (d, *J* = 10.6 Hz, 1H, *N-H*), 7.36 (t, *J* = 7.5 Hz, 2H, *H-9*), 7.21-7.28 (m, 3H, *H-8*, *H-10*), 6.83 (dd, *J* = 11.1, 9.7 Hz, 1H, *H-5*), 6.62 (br, 1H, *N-H*), 5.76 (d, *J* = 9.9 Hz, 1H, *H-6*), 3.96 (s, 2H, *H-3*), 1.96 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 170.9 (*C-2*), 166.9 (*C-4*), 135.1 (*C-7*), 128.9 (*C-9*), 128.0 (*C-8*), 127.1 (*C-10*), 121.0 (*C-5*), 111.4 (*C-6*), 43.6 (*C-3*), 22.7 (*C-1*) ppm. **EA** Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.32; H, 6.57; N, 12.61. **MS** (Ion trap, EI): *m/z* (%) = 218 (9, [M^+]), 119 (100), 104 (4), 91 (10), 65 (4), 43 (11).

Synthesis of 2-cyano-*N*-[(*Z*)-2-phenylvinyl]acetamide (6u)



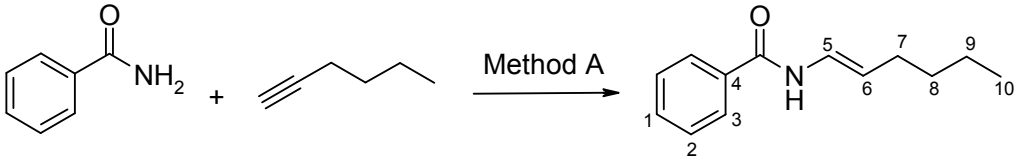
The compound was prepared according to method A, using the following amounts: 2-cyano-acetamide (84.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:6 ethyl acetate/hexane), yielding the product as a white solid (>40:1 mixture with the *E*-isomer, 57.7 mg, 31%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.24 (s, 1H, *N-H*), 7.41 (t, *J* = 7.7 Hz, 2H, H-6), 7.23-7.29 (m, 3H, *H-5*, *H-6*), 6.86-6.90 (m, 1H, *H-2*), 5.93 (d, *J* = 9.5 Hz, 1H, *H-3*), 3.40 (s, 2H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 158.4 (*C=O*), 134.5 (*C-4*), 129.3 (*C-6*), 127.8 (*C-5*), 127.6 (*C-7*), 120.7 (*C-2*), 113.9 (*C≡N*), 113.1 (*C-3*), 25.9 (C-2) ppm. **EA** Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.07; H, 5.12; N, 15.07. **MS** (Ion trap, EI): *m/z* (%) = 186 (100, [M^+]), 145 (13), 118 (53), 91 (52), 77 (7), 65 (12).

Synthesis of 2-bromo-4,5-dimethoxy-*N*-[(*Z*)-2-(4-methoxy-phenyl)vinyl]benzamide (6v)



The compound was prepared according to method A, using the following amounts: 2-bromo-4,5-dimethoxy-benzamide (260.1 mg, 1.00 mmol) and 4-methoxy-phenylacetylene (259 µL, 2.00 mmol) and purified by column chromatography (1:6 ethyl acetate/hexane), yielding the product as a white solid (>40:1 mixture with the *E*-isomer, 235.4 mg, 60%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.53 (d, *J* = 10.9 Hz, 1H, *N-H*), 7.33 (s, 1H, *H-3*), 7.28-7.32 (m, 2H, *H-7*), 7.08 (dd, *J* = 11.1, 9.7 Hz, 1H, *H-5*), 6.97 (s, 1H, *H-4*), 6.88-6.92 (m, 2H, *H-8*), 5.86 (d, *J* = 9.5 Hz, 1H, *H-6*), 3.88 (s, 6H, *H-1*, *H-2*), 3.80 (s, 3H, *H-9*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 163.7 (*C=O*), 158.6 (C_{arom}), 151.5 (C_{arom}), 148.6 (C_{arom}), 129.3 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 121.0 (*C-5*), 116.0 (C_{arom}), 114.4 (C_{arom}), 113.9 (C_{arom}), 111.3 (C_{arom}), 109.8 (*C-6*), 56.3 (*C-9*), 55.3 (*C-1*, *C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 391 (49, [M^+]), 393 (44, [M^+]), 245 (100), 132 (15), 104 (12), 77 (5).

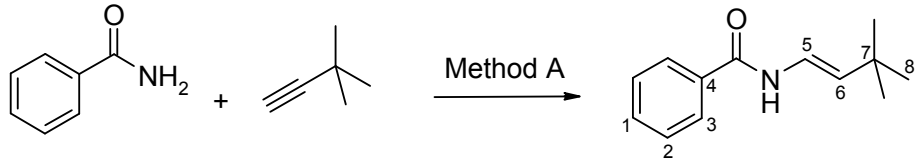
Synthesis of *N*-((*E*)-hex-1-en-1-yl)benzamide (7a)



The compound was prepared according to method B, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (1:4 mixture with the *Z*-isomer, 180.9 mg, 89%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.78 (d, *J* = 7.4 Hz, 2H, *H-3*), 7.69 (d, *J* = 8.4 Hz, 1H, *N-H*), 7.50 (t, *J* = 7.3 Hz, 1H, *H-1*), 7.43 (t, *J* = 7.7 Hz, 2H, *H-2*), 6.94 (dd, *J* = 14.0, 10.6 Hz, 1H, *H-5*), 5.30 (dt, *J* = 14.3, 7.2 Hz, 1H, *H-6*), 2.07 (q, *J* = 6.8 Hz, 2H, *H-7*), 1.30-1.38 (m, 4H, *H-8*, *H-9*), 0.89 (t, *J* =

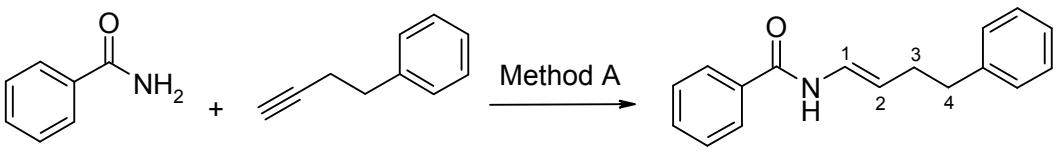
7.2 Hz, 3H, *H-10*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.3 (*C=O*), 133.9 (C-4), 131.9 (C_{arom}), 128.7 (C_{arom}), 127.0 (C_{arom}), 121.1 (*C-5*), 112.3 (*C-6*), 31.4 (*C-7*), 25.5 (*C-8*), 22.3 (*C-9*), 13.9 (*C-10*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 203 (17, [M^+]), 122 (26), 105 (100), 77 (41), 51 (12), 44 (15).

Synthesis of *N*-[(*E*)-3,3-dimethyl-but-1-en-1-yl]benzamide (7b)



The compound was prepared according to method B, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 3,3-dimethyl-1-butyne (246 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (1:20 mixture with the *Z*-isomer, 158.6 mg, 79%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.31 (d, *J* = 10.0 Hz, 1H, *N-H*), 7.78-7.81 (m, 2H, *H-3*), 7.44 (t, *J* = 7.4 Hz, 1H, *H-1*), 7.35 (t, *J* = 7.7 Hz, 2H, *H-2*), 6.88 (dd, *J* = 14.6, 10.2 Hz, 1H, *H-5*), 5.40 (d, *J* = 14.6 Hz, 1H, *H6*), 1.01 (s, 9H, *H-8*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.7 (*C=O*), 133.8 (*C-4*), 131.5 (*C-1*), 128.4 (*C-3*), 127.0 (*C-2*), 125.9 (*C-5*), 119.4 (*C-6*), 31.9 (*C-7*), 29.8 (*C-8*) ppm. **EA** Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.53; H, 8.46; N, 6.88. **MS** (Ion trap, EI): *m/z* (%) = 203 (10, [M^+]), 172 (45), 139 (58), 105 (77), 77 (45), 44 (100).

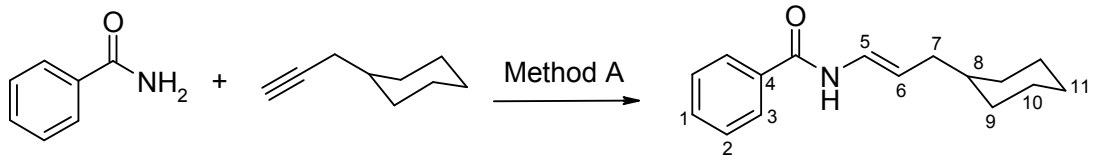
Synthesis of *N*-[(*E*)-4-phenyl-but-1-en-1-yl]benzamide (7c)



The compound was prepared according to method B, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 4-phenyl-1-butyne (281 µL, 2.00 mmol) and purified by column chromatography (1:8 ethyl acetate/hexane), yielding the product as a

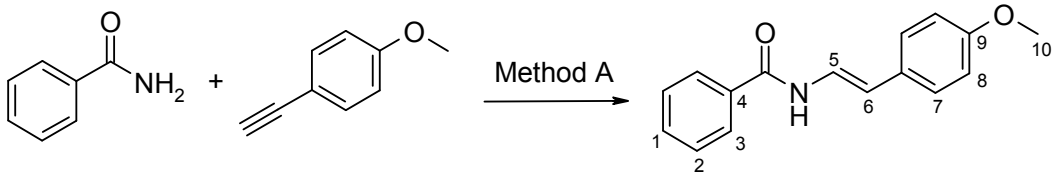
white solid (1:4 mixture with the *Z*-isomer, 213.6 mg, 85%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.03 (d, *J* = 10.2 Hz, 1H, *N-H*), 7.77-7.81 (m, 2H, H_{arom}), 7.46-7.52 (m, 1H, H_{arom}), 7.40 (t, *J* = 7.5 Hz, 2H, H_{arom}), 7.28 (t, *J* = 7.3 Hz, 2H, H_{arom}), 7.16-7.22 (m, 3H, H_{arom}), 7.00 (dd, *J* = 14.3, 10.6 Hz, 1H, *H-1*), 5.35 (dt, *J* = 14.3, 7.2 Hz, 1H, *H-2*), 2.67-2.73 (m, 2H, *H-3*), 2.39 (t, *J* = 7.2 Hz, 2H, *H-4*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 164.4 (*C=O*), 141.5 (C_{arom}), 133.8 (C_{arom}), 131.7 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 127.0 (C_{arom}), 125.9 (C_{arom}), 123.4 (*C-1*), 113.2 (*C-2*), 36.3 (*C-3*), 31.5 (*C-4*) ppm. **EA** Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.87; H, 6.88; N, 5.28. **MS** (Ion trap, EI): *m/z* (%) = 251 (12, [M^+]), 225 (25), 207 (52), 160 (47), 105 (100), 77 (36).

Synthesis of *N*-[(*E*)-3-cyclohexyl-prop-1-en-1-yl]benzamide (7d)



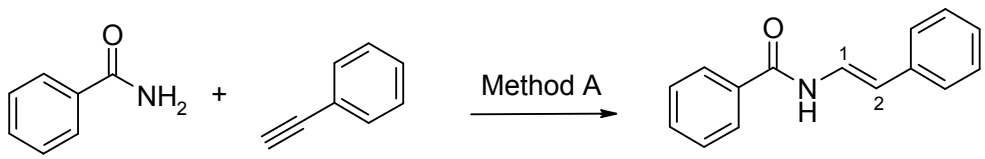
The compound was prepared according to method B, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and 3-cyclohexyl-1-propyne (289 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (1:4 mixture with the *Z*-isomer, 206.8 mg, 85%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.82 (d, *J* = 9.9 Hz, 1H, *N-H*), 7.75-7.80 (m, 2H, *H-3*), 7.46-7.51 (m, 1H, *H-1*), 7.41 (t, *J* = 7.5 Hz, 2H, *H-2*), 6.91 (dd, *J* = 14.3, 10.6 Hz, 1H, *H-5*), 5.29 (dt, *J* = 14.5, 7.3 Hz, 1H, *H-6*), 1.94 (dd, *J* = 7.2, 7.3 Hz, 2H, *H-7*), 1.62-1.72 (m, 6H, H_{Cy}), 1.15-1.26 (m, 3H, H_{Cy}), 0.83-0.94 (m, 2H, H_{Cy}) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 164.2 (*C=O*), 133.9 (*C-4*), 131.7 (*C-1*), 128.6 (*C-3*), 127.0 (*C-2*), 123.4 (*C-5*), 112.8 (*C-6*), 38.4 (*C-7*), 37.6 (*C-8*), 33.0 (*C-9*), 26.5 (*C-10*), 26.3 (*C-11*) ppm. **EA** Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.93; H, 8.72; N, 5.78. **MS** (Ion trap, EI): *m/z* (%) = 243 (12, [M^+]), 160 (23), 122 (27), 105 (100), 77 (33), 51 (9).

Synthesis of *N*-[(*E*)-2-(4-methoxyphenyl)vinyl]benzamide (Alatamide) (7g)



The compound was prepared according to method B, using the following amounts: benzamide (121.14 mg, 1.00 mmol) and 4-methoxy-phenylacetylene (259 µL, 2.00 mmol) and purified by column chromatography (1:7 ethyl acetate/hexane), yielding the product as a white solid (1:18 mixture with the *Z*-isomer, 200 mg, 79%). **^{1}H-NMR** (600 MHz, DMSO-d_6, 25 °C): δ = 10.53 (d, *J* = 9.7 Hz, 1H, *N-H*), 7.96 (d, *J* = 7.6 Hz, 2H, *H-3*), 7.58 (t, *J* = 7.6 Hz, 1H, *H-1*), 7.46-7.54 (m, 3H, *H-2*, *H-5*), 7.32 (d, *J* = 8.5 Hz, 2H, *H-7*), 6.88 (d, *J* = 8.5 Hz, 2H, *H-8*), 6.42 (d, *J* = 15.0 Hz, 1H, *H-6*), 3.73 (s, 3H, *H-10*) ppm. **^{13}C-NMR** (151 MHz, DMSO-d_6, 25 °C): δ = 163.8 (*C=O*), 158.0 (*C-9*), 133.5 (*C-4*), 131.8 (C_{arom}), 129.0 (C_{arom}), 128.4 (C_{arom}), 127.6 (*C-7*), 126.4 (C_{arom}), 122.3 (*C-5*), 114.2 (*C-8*), 112.8 (*C-6*), 55.1 (*C-10*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 253 (62, [M^+]), 150 (14), 133 (7), 105 (100), 77 (49), 51 (17).

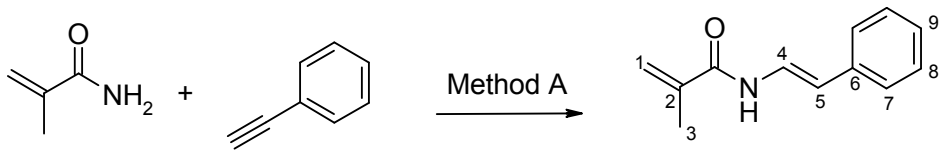
Synthesis of *N*-[(*E*)-2-phenyl-vinyl]benzamide (7i)



The compound was prepared according to method B, using the following amounts: benzamide (121.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:8 ethyl acetate/hexane), yielding the product as a white solid (1:18 mixture with the *Z*-isomer, 205.4 mg, 92%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.06 (d, *J* = 10.0 Hz, 1H, *N-H*), 7.84-7.86 (m, 2H, H_{arom}), 7.73 (dd, *J* = 14.6, 10.8 Hz, 1H, *H-1*), 7.52-7.56 (m, 1H, H_{arom}), 7.46 (t, *J* = 7.7 Hz, 2H, H_{arom}), 7.33-7.36 (m, 2H, H_{arom}), 7.29 (t, *J* = 7.7 Hz, 2H, H_{arom}), 7.19 (t, *J* = 7.3 Hz, 1H, H_{arom}), 6.27 (d, *J* = 14.6 Hz, 1H, *H-2*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 164.5 (*C=O*),

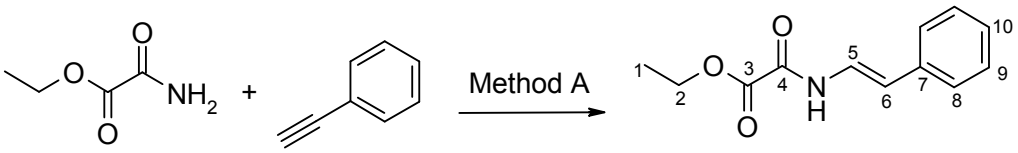
135.9 (C_{arom}), 133.4 (C_{arom}), 132.1 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 127.1 (C_{arom}), 126.8 (C_{arom}), 125.6 (C_{arom}), 123.0 (*C-1*), 113.6 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 223 (49, [M^+]), 105 (100), 91 (7), 77 (53), 51 (16), 44 (11).

Synthesis of 2-methyl-*N*-[(*E*)-2-phenylvinyl]acrylamide (7l)



The compound was prepared according to method B, using the following amounts: 2-methylacrylamide (85.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a white solid (1:17 mixture with the *Z*-isomer, 155.4 mg, 83%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.23 (d, *J* = 10.2 Hz, 1H, *N-H*), 7.60 (dd, *J* = 14.6, 10.9 Hz, 1H *H-4*), 7.23-7.32 (m, 4H, *H-7*, *H-8*), 7.16 (t, *J* = 7.2 Hz, 1H, *H-9*), 6.26 (d, *J* = 14.6 Hz, 1H, *H-5*), 5.84 (s, 1H, *H-1*), 5.46 (s, 1H, *H-1*), 2.03 (s, 3H, *H-3*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 165.6 (*C=O*), 139.4 (*C-2*), 136.1 (*C-6*), 128.6 (*C-7*), 126.6 (*C-9*), 125.5 (*C-8*), 122.9 (*C-4*), 120.7 (*C-5*), 113.7 (*C-1*), 18.5 (*C-3*) ppm. **EA** Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 75.27; H, 6.96; N, 7.21. **MS** (Ion trap, EI): *m/z* (%) = 187 (100, [M^+]), 159 (71), 144 (24), 117 (24), 69 (80), 41 (70).

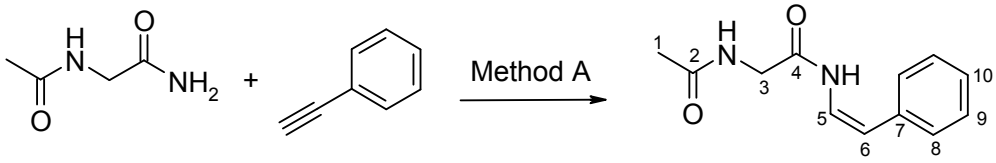
Synthesis of ethyl oxo{[(*E*)-2-phenylvinyl]amino}acetate (7q)



The compound was prepared according to method B, using the following amounts: oxalamic acid ethyl ester (117.1 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:7 ethyl acetate/hexane), yielding the product as a white solid (1:14 mixture with the *Z*-isomer, 149.1 mg, 68%). **^{1}H-NMR** (400

MHz, $CDCl_3$, 25 °C): δ = 9.00 (s, 1H, *N-H*), 7.47 (dd, *J* = 14.6, 10.9 Hz, 1H, *H-5*), 7.35-7.39 (d, *J* = 7.6 Hz, 2H, *H-8*), 7.32 (t, *J* = 7.7 Hz, 2H, *H-9*), 7.24 (t, *J* = 7.2 Hz, 1H, *H-10*), 6.42 (d, *J* = 14.6 Hz, 1H, H-6), 4.41 (q, *J* = 7.2 Hz, 2H, *H-2*), 1.42 (t, *J* = 7.2 Hz, 3H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 160.2 (*C-4*), 153.4 (*C-3*), 135.1 (*C-7*), 128.7 (*C-8*), 127.4 (*C-10*), 125.9 (*C-9*), 121.0 (*C-5*), 116.9 (*C-6*), 63.5 (*C-2*), 13.9 (*C-1*) ppm. **EA** Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.03; H, 5.95; N, 6.25. **MS** (Ion trap, EI): *m/z* (%) = 219 (100, [M^+]), 145 (39), 118 (26), 91 (13), 77 (5), 65 (4).

Synthesis of 2-acetamido-*N*-[(*E*)-2-phenylvinyl]acetamide (7t)



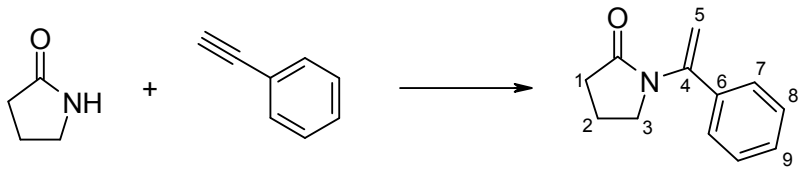
The compound was prepared according to method B, using the following amounts: 2-acetylamido-acetamide (116.12 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:5 ethyl acetate/hexane), yielding the product as a white solid (1:20 mixture with the *Z*-isomer, 168 mg, 77%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.47 (s, 1H, *N-H*), 7.42 (dd, *J* = 14.5, 10.6 Hz, 1H, *H-5*), 7.25-7.30 (m, 4H, *H-8*, *H-9*), 7.17 (t, *J* = 7.0 Hz, 1H, *H-10*), 6.44 (s, 1H, *N-H*), 6.20 (d, *J* = 14.6 Hz, 1H, *H-6*), 4.03 (d, *J* = 4.9 Hz, 2H, *H-3*), 2.08 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (151 MHz, DMSO-d_6, 25 °C): δ = 169.8 (*C-2*), 167.4 (*C-4*), 136.5 (*C-7*), 128.7 (*C-8*), 126.2 (*C-10*), 125.2 (*C-9*), 123.3 (*C-5*), 111.8 (*C-6*), 42.2 (*C-3*), 22.5 (*C-1*) ppm. **EA** Calcd for $C_{12}H_{13}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.79; H, 6.52; N, 12.54. **MS** (Ion trap, EI): *m/z* (%) = 218 (13, [M^+]), 119 (100), 91 (15), 77 (3), 65 (5), 43 (12).

5.4 Markovnikov addition of secondary amides to alkynes

5.4.1 Phosphine-catalyzed hydroamidation of phenylacetylenes

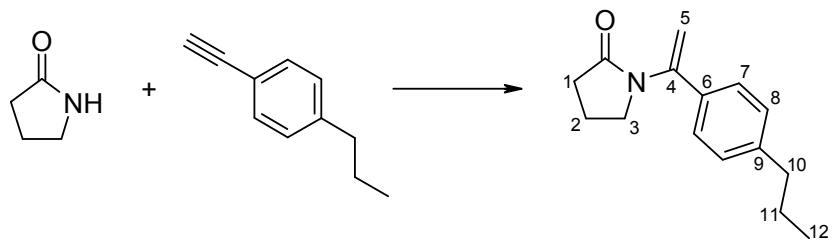
General method: An oven-dried flask was flushed with nitrogen and charged with dry toluene (1.0 mL), tri-*n*-butylphosphine (23 µL, 0.09 mmol), amide (1 mmol) and alkyne (2.00 mmol) via syringe. The resulting solution was stirred for 15 h at 100 °C, and then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the enamide. The identity and purity of the products were confirmed by ^{1}H and ^{13}C NMR spectroscopy, mass spectroscopy, and elemental analysis.

Synthesis of 1-(1-phenylvinyl)pyrrolidin-2-one (10a) (CAS NO.: 66373-96-4)



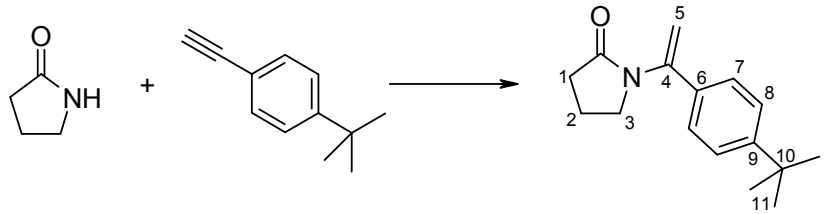
The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a colorless oil (159.0 mg, 85%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.25-7.29 (m, 5H, *H-7*, *H-8*, *H-9*), 5.33 (s, 1H, *H-5*), 5.23 (s, 1H, *H-5*), 3.47 (t, *J* = 7.0 Hz, 2H, *H-3*), 2.49 (t, *J* = 8.1 Hz, 2H, *H-1*), 2.04 (dt, *J* = 7.2, 7.9, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 174.2 (*C=O*), 143.2 (*C-4*), 135.9 (*C-9*), 128.08 (*C-6*), 128.04 (*C-7*), 126.0 (*C-8*), 108.9 (*C-5*), 49.2 (*C-3*), 31.5 (*C-1*), 18.2 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 187 (100, [M^+]), 159 (22), 132 (39), 77 (9), 51 (7).

Synthesis of 1-(1-(4-propylphenyl)vinyl)pyrrolidin-2-one (10b)



The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and 4-*n*-propylphenylacetylene (317 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a colorless oil (96.0 mg, 42%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.23 (d, *J* = 8.3 Hz, 2H, *H-7*) 7.11-7.16 (m, 2H, *H-8*) 5.37 (s, 1H, *H-5*) 5.23 (s, 1H, *H-5*) 3.52 (t, *J* = 7.0 Hz, 2H, *H-3*) 2.56 (t, *J* = 8.3 Hz, 4H, *H-1*, *H-10*) 2.07-2.12 (m, 2H, *H-2*) 1.60-1.66 (m, 2H, *H-11*) 0.92 (td, *J* = 7.3, 2.7 Hz, 3H, *H-12*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 174.5 (*C=O*), 143.4 (*C-9*), 143.1 (*C-4*), 133.3 (*C-6*), 128.5 (*C-7*), 126.1 (*C-8*), 108.8 (*C-5*), 49.6 (*C-3*), 37.7 (*C-10*), 31.9 (*C-1*), 24.3 (*C-11*), 18.6 (*C-2*), 13.8 (*C-12*) ppm. **EA** Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.39; H, 8.42; N, 6.24. **MS** (Ion trap, EI): *m/z* (%) = 229 (100, [M^+]), 200 (47), 186 (78), 145 (26), 115 (39).

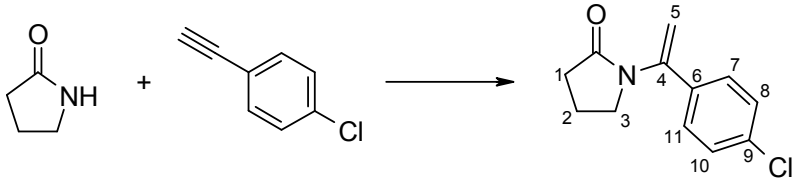
Synthesis of 1-(1-(4-tert-butylphenyl)vinyl)pyrrolidin-2-one (10c)



The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and 4-*tert*-butylphenylacetylene (356 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a white solid (97.0 mg, 40%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.31-7.37 (m, 2H, *H-7*), 7.22-7.30 (m, 2H, *H-8*), 5.38 (s, 1H, *H-5*), 5.23 (s, 1H, *H-5*),

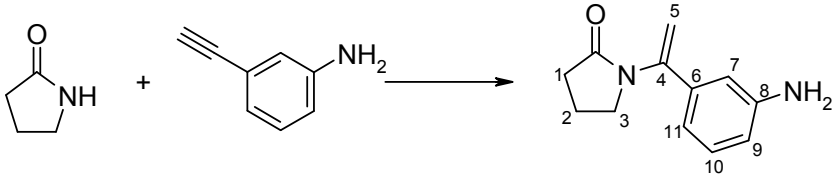
3.53 (t, *J* = 7.0 Hz, 2H, *H-3*), 2.51-2.58 (m, 2H, *H-1*), 2.07-2.12 (m, 2H, *H-2*), 1.28-1.34 (m, 9H, *H-11*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 174.5 (*C=O*), 143.3 (*C-4*), 133.3 (*C-6*), 128.2 (*C-9*), 125.9 (*C-7*), 125.3 (*C-8*), 108.8 (*C-5*), 49.7 (*C-3*), 34.6 (*C-10*), 31.9 (*C-1*), 31.2 (*C-11*), 18.6 (*C-2*) ppm. **EA** Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.79; H, 8.52; N, 6.01. **MS** (Ion trap, EI): *m/z* (%) = 243 (100, [M^+]), 200 (30), 143 (43), 115 (25), 86 (77).

Synthesis of 1-(1-(4-chlorophenyl)vinyl)pyrrolidin-2-one (10d) (CAS NO.: 750634-67-4)



The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and 4-chlorophenylacetylene (238 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (180.0 mg, 81%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.57 (d, *J* = 14.7 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.24-7.34 (m, 1H), 7.17 (t, *J* = 7.58 Hz, 1H), 7.08 (td, *J* = 7.6, 1.5 Hz, 1H), 6.18 (d, *J* = 14.9 Hz, 1H), 3.65 (t, *J* = 7.2 Hz, 2H, *H-3*), 2.52 (t, *J* = 8.2 Hz, 2H, *H-1*), 2.13 (dq, *J* = 7.8, 7.7 Hz, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 173.5 (*C=O*), 134.3, 132.3, 129.5, 127.4, 126.9, 125.5, 125.3, 107.6, 45.1, 31.1, 17.3 ppm. **MS** (Ion trap, EI): *m/z* (%) = 221 (87, [M^+]), 186 (100), 166 (14), 130 (60), 103 (9).

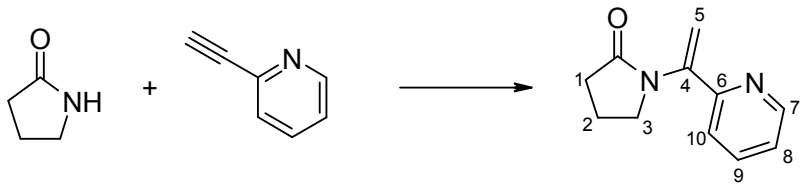
Synthesis of 1-(1-(3-aminophenyl)vinyl)pyrrolidin-2-one (10e)



The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and 3-aminophenylacetylene (225 µL, 2.00

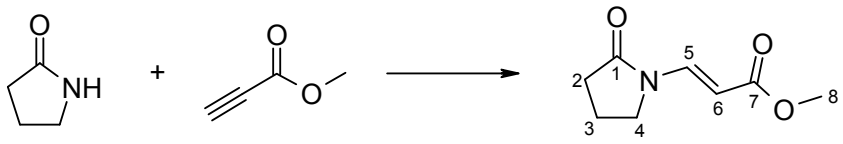
mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (155.0 mg, 77%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.05 (t, *J* = 7.7 Hz, 1H, *H-10*), 6.72 (d, *J* = 10.0 Hz, 1H, *H-5*), 6.54 (d, *J* = 7.8 Hz, 2H, *H-9*, *H-11*), 6.47 (s, 1H, *H-7*), 5.88 (d, *J* = 10.0 Hz, 1H, *H-5*), 3.65 (br, 2H, *NH_2*), 3.23 (t, *J* = 7.0 Hz, 2H, *H-3*), 2.37 (t, *J* = 7.9 Hz, 2H, *H-1*), 1.86-1.94 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 175.5 (*C=O*), 145.8 (*C-4*), 137.2 (*C_{arom}*), 128.6 (*C_{arom}*), 123.5 (*C_{arom}*), 119.5 (*C_{arom}*), 115.6 (*C_{arom}*), 113.9 (*C_{arom}*), 113.6 (*C-5*), 47.9 (*C-4*), 30.3 (*C-1*), 18.8 (*C-2*) ppm. **EA** Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.36; H, 7.28; N, 13.57. **MS** (Ion trap, EI): *m/z* (%) = 202 (100, [M^+]), 173 (8), 145 (20), 119 (45), 91 (13).

Synthesis of 1-(1-(pyridine-2-yl)vinyl)pyrrolidin-2-one (10f)



The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and 2-ethynylpyridine (202 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a colorless oil (105.2 mg, 56%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.55 (d, *J* = 4.8 Hz, 1H, *H-7*), 7.65 (td, *J* = 7.8, 1.9 Hz, 1H, *H-9*), 7.33 (d, *J* = 8.0 Hz, 1H, *H-10*), 7.19 (dd, *J* = 7.6, 3.8 Hz, 1H, *H-8*), 5.71 (s, 1H, *H-5*), 5.35 (s, 1H, *H-5*), 3.63-3.70 (m, 2H, *H-3*), 2.52 (t, *J* = 8.1 Hz, 2H, *H-1*), 2.10-2.19 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 174.6 (*C=O*), 154.1 (*C-6*), 149.2 (*C-7*), 143.5 (*C-4*), 136.5 (*C-9*), 122.9 (*C-10*), 121.0 (*C-8*), 111.1 (*C-5*), 49.5 (*C-3*), 31.6 (*C-1*), 18.5 (*C-2*) ppm. **EA** Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.98; H, 6.52; N, 14.81. **MS** (Ion trap, EI): *m/z* (%) = 189 (100, [M^{+1}]), 160 (8), 132 (18), 104 (9), 78 (2).

Synthesis of (*E*)-methyl 3-(2-oxopyrrolidin-1-yl)acrylate (11a) (CAS NO.: 145294-78-6)

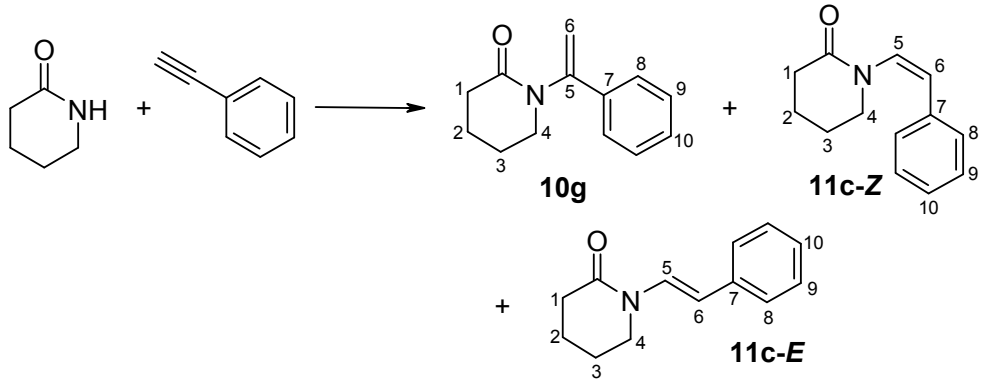


The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and methyl propiolate (179 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a colorless oil (147.0 mg, 87%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.06 (dd, *J* = 14.3, 2.9 Hz, 1H, *H-5*), 5.16 (dd, *J* = 14.3, 1.9 Hz, 1H, *H-6*), 3.69 (d, *J* = 2.5 Hz, 3H, *H-8*), 3.52 (t, *J* = 7.3 Hz, 2H, *H-4*), 2.48-2.54 (m, 2H, *H-2*) 2.10-2.19 (m, 2H, *H-3*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 174.2 (*C-1*), 167.6 (*C-7*), 137.3 (*C-5*), 100.1 (*C-6*), 51.3 (*C-8*), 44.8 (*C-4*), 30.8 (*C-2*), 17.3 (*C-3*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 169 (42, [M^+]), 138 (71), 110 (100), 82 (77), 55 (15).

Synthesis of 1-((*E*)-3-oxobut-1-enyl)pyrrolidin-2-one (11b) (CAS NO.: 145294-79-7)

The compound was prepared according to the general method, using the following amounts: 2-pyrrolidone (77 µL, 1.00 mmol) and 3-butyn-2-one (155 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a colorless oil (113.2 mg, 74%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.94 (d, *J* = 14.7 Hz, 1H, *H-5*), 5.49 (d, *J* = 14.4 Hz, 1H, *H-6*), 3.54 (t, *J* = 7.2 Hz, 2H, *H-4*), 2.54 (t, *J* = 8.2 Hz, 2H, *H-2*), 2.25 (s, 3H, *H-8*) 2.16 (dq, *J* = 7.8, 7.7 Hz, 2H, *H-3*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 197.7 (*C-7*), 174.5 (*C-1*), 137.0 (*C-5*), 111.2 (*C-6*), 44.9 (*C-4*), 30.9 (*C-2*), 26.6 (*C-8*), 17.4 (*C-3*) ppm **MS** (Ion trap, EI): *m/z* (%) = 153 (32, [M^+]), 138 (43), 110 (100), 82 (35), 70 (38).

Synthesis of 1-(1-phenylvinyl)piperidin-2-one (10g) (CAS NO.: 153392-52-0), 1-*((Z)*-2-styryl)piperidin-2-one (11c-*Z*) (CAS NO.: 24904-52-7), and, 1-*((E)*-2-styryl)piperidin-2-one (11c-*E*) (CAS NO.: 17179-93-0)



These compounds were prepared as a mixture according to the general method, using the following amounts: 2-piperidone (94 µL, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding:

10g as a colorless oil (30.2 mg, 15%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.36 (d, *J* = 7.9 Hz, 2H, *H-8*), 7.31 (t, *J* = 7.7 Hz, 2H, *H-9*), 7.26-7.28 (m, 1H, *H-10*), 5.68 (s, 1H, *H-6*), 5.22 (s, 1H, *H-6*), 3.45 (t, *J* = 5.9 Hz, 2H, *H-4*), 2.52 (t, *J* = 6.4 Hz, 2H, *H-1*), 1.86-1.91 (m, 4H, *H-2*, *H-3*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 169.7 (*C=O*), 147.9 (*C-5*), 135.5 (*C-7*), 128.5 (*C-9*), 128.3 (*C-10*), 125.3 (*C-10*), 111.8 (*C-6*), 50.3 (*C-4*), 32.6 (*C-1*), 23.3 (*C-3*), 21.4 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 201 (100, [M^+]), 172 (41), 130 (21), 103 (36), 77 (33).

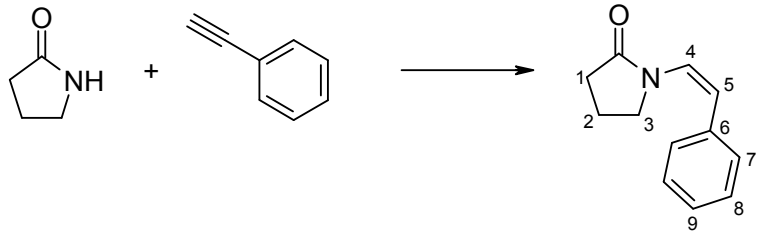
11c-*Z* as a colorless oil (24.5 mg, 12%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.29 (t, *J* = 7.6 Hz, 2H, *H-9*), 7.24 (d, *J* = 7.2 Hz, 2H, *H-8*), 7.20 (t, *J* = 7.2 Hz, 1H, *H-10*), 6.76 (d, *J* = 9.5 Hz, 1H, *H-5*), 6.07 (d, *J* = 9.5 Hz, 1H, *H-6*), 3.17 (t, *J* = 6.8 Hz, 2H, *H-4*), 2.48 (t, *J* = 6.8 Hz, 2H, *H-1*), 1.75-1.80 (m, 2H, *H-3*), 1.63-1.68 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 170.7 (*C=O*), 135.6 (*C-5*), 128.9 (*C-7*), 128.4 (*C-10*), 128.1 (*C-8*), 127.2 (*C-9*), 119.6 (*C-6*), 48.7 (*C-4*), 32.2 (*C-1*), 23.0 (*C-3*), 20.9 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 201 (100, [M^+]), 172 (48), 130 (24), 103 (29), 77 (29).

11c-*E* as a white solid (14.2 mg, 7%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 8.16 (d, *J* = 14.9 Hz, 1H, *H-5*), 7.37 (d, *J* = 7.2 Hz, 2H, *H-8*), 7.28 (t, *J* = 7.7 Hz, 2H, *H-9*), 7.16 (t, *J* = 7.3 Hz, 1H, *H-10*), 5.96 (d, *J* = 15.1 Hz, 1H, *H*-6), 3.54 (t, *J* = 6.1 Hz, 2H, *H-4*), 2.54 (t, *J* = 6.5 Hz, 2H, *H-1*), 1.92-1.96 (m, 2H, *H-3*), 1.81-1.85 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 168.7 (*C=O*), 136.8 (*C-5*), 128.6 (*C-8*), 127.0 (*C-7*), 126.4 (*C-10*), 125.7 (*C-9*), 110.8 (*C-6*), 45.3 (*C-4*), 33.0 (*C-1*), 22.6 (*C-3*), 20.5 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 201 (100, [M^+]), 172 (16), 130 (24), 103 (11), 77 (14).

5.4.2 Base-catalyzed hydroamidation of phenylacetylene

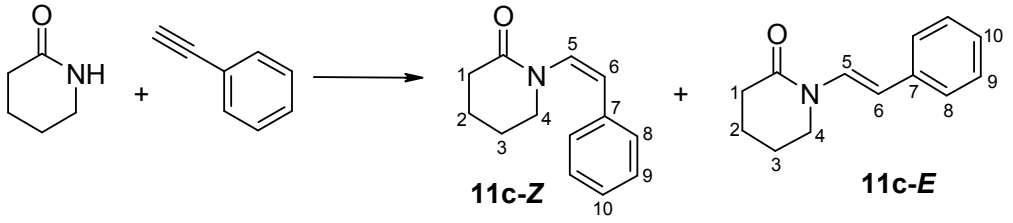
General method: An oven-dried flask was charged with potassium *tert*-butoxide (16.8 mg, 0.15 mmol) and flushed with nitrogen. Subsequently, dry DMF (2.0 mL), amide (1 mmol) and phenylacetylene (1.65 µL, 1.50 mmol) were added via syringe. The resulting solution was stirred for 24 h at 100 °C, and then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the enamide. The identity and purity of the products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, and mass spectroscopy.

Synthesis of 1-*((Z)*-2-styryl)pyrrolidin-2-one (11d-*Z*) (CAS NO.: 19883-35-3)



The compound was prepared according to the general method, using 2-pyrrolidone (77 µL, 1.00 mmol) and purified by column chromatography (1:4 ethyl acetate/hexane), yielding the product as a colorless oil (8:1 mixture with the *E*-isomer, 150 mg, 80%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.24-7.29 (m, 2H, *H-8*), 7.20 (t, *J* = 7.3 Hz, 1H, *H-9*), 7.15 (d, *J* = 7.2 Hz, 2H, *H-7*), 6.76 (d, *J* = 9.9 Hz, 1H, *H-4*), 5.95 (d, *J* = 9.9 Hz, 1H, *H-5*), 3.13-3.18 (m, 2H, *H-3*), 2.34-2.39 (m, 2H, *H-1*), 1.85-1.93 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 175.3 (*C=O*), 136.3 (*C-6*), 129.1 (C_{arom}), 127.7 (C_{arom}), 126.8 (C_{arom}), 113.7 (*C-5*), 47.9 (*C-3*), 30.2 (*C-1*), 18.7 (*C-2*) ppm **MS** (Ion trap, EI): *m/z* (%) = 187 (100, [M^+]), 158 (12), 132 (61), 103 (13), 77 (18).

Synthesis of 1-*((Z)*-2-styryl)piperidin-2-one (11c-*Z*), and, 1-*((E)*-2-styryl)piperidin-2-one (11c-*E*)



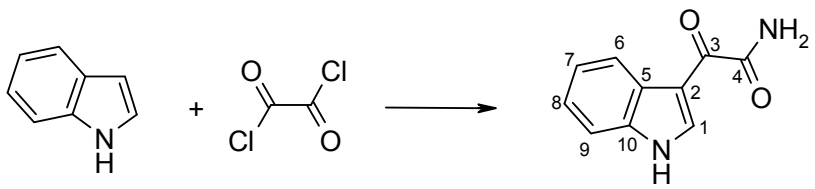
These compounds were prepared as a mixture according to the general method, using 2-piperidone (94 µL, 1.00 mmol) and purified by column chromatography (1:4 ethyl acetate/hexane), yielding the product (2:1 mixture of *Z*:*E*,110.6 mg, 55%):

11c-*Z* as a colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.27-7.32 (m, 2H, *H-9*), 7.19-7.26 (m, 3H, *H-8*, *H-10*), 6.77 (d, *J* = 9.5 Hz, 1H, *H-5*), 6.08 (d, *J* = 9.5 Hz, 1H, *H-6*), 3.18 (t, *J* = 6.8 Hz, 2H, *H-4*), 2.49 (t, *J* = 6.8 Hz, 2H, *H-1*), 1.77-1.82 (m, 2H, *H-3*), 1.64-1.69 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 170.7 (*C=O*), 135.9 (*C-5*), 129.0 (*C-7*), 128.6 (*C-10*), 128.2 (*C-8*), 127.2 (*C-9*), 119.5 (*C-6*), 48.8 (*C-4*), 32.2 (*C-1*), 23.1 (*C-3*), 20.9 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 201 (100, [M^+]), 172 (48), 130 (24), 103 (29), 77 (29).

11c-*E* as a white solid. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 8.16 (d, *J* = 15.0 Hz, 1H, *H-5*), 7.36 (d, *J* = 7.5 Hz, 2H, *H-8*), 7.24-7.31 (m, 2H, *H-9*), 7.16 (t, *J* = 7.2 Hz, 1H, *H-10*), 5.95 (d, *J* = 15.3 Hz, 1H, *H*-6), 3.53 (t, *J* = 6.5 Hz, 2H, *H-4*), 2.53 (t, *J* = 6.5 Hz, 2H, *H-1*), 1.89-1.96 (m, 2H, *H-3*), 1.77-1.86 (m, 2H, *H-2*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 168.5 (*C=O*), 136.9 (*C-5*), 128.6 (*C-8*), 127.2 (*C-7*), 126.4 (*C-10*), 125.8 (*C-9*), 110.8 (*C-6*), 45.3 (*C-4*), 33.0 (*C-1*), 22.7 (*C-3*), 20.5 (*C-2*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 201 (100, [M^+]), 172 (16), 130 (24), 103 (11), 77 (14).

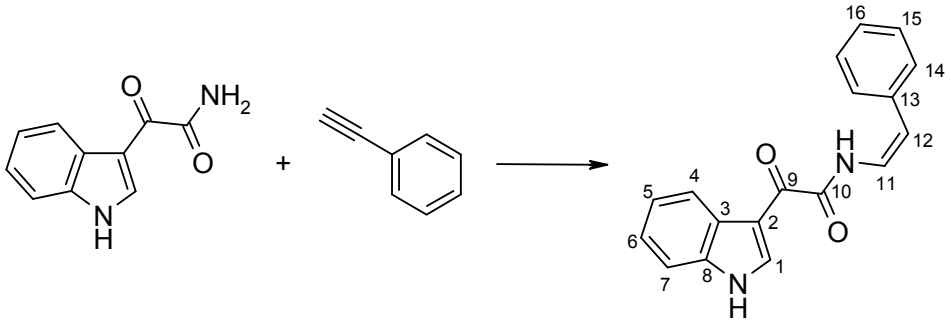
5.5 Synthesis of natural products

Synthesis of indole-3-glyoxylamide (17) (CAS NO.: 58117-28-5)



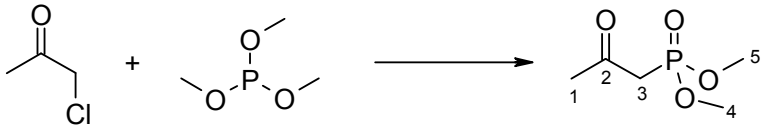
To a solution of indole (3.00 g, 25.6 mmol) in dry ether (100 mL) at 0 °C, oxallylchloride (2.82 mL, 29.7 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 3 h, and then allowed to warm to room temperature for 1 h. The resulting yellow crystals were collected by filtration under nitrogen, washed with cold ether (2 x 30 mL) and dried under vacuum. Gaseous ammonia was bubbled through a suspension of the previous crude in dry chloroform (40 mL) for 15 min. After stirring for 1 h, the solvent was pumped off. Addition of water (100 mL) was followed by extraction with ethyl acetate, the combined organic layers were dried, and evaporated. The crude was washed with cold ethyl acetate and dried to yield the product (3.35 g, 70%) which was used without further purification. **^{1}H-NMR** (400 MHz, DMSO-d_6, 25 °C): δ = 8.67 (s, 1H, *H-1*), 8.19-8.23 (m, 1H), 8.08 (s, 1H, *NH*), 7.70 (s, 1H, *NH*), 7.50-7.54 (m, 1H), 7.22-7.27 (m, 2H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6, 25 °C): δ = 182.8 (*C-3*), 166.0 (*C-4*), 138.1 (*C-1*), 136.2, 126.1, 123.3, 122.4, 121.2, 112.4, 112.1 ppm. **MS** (Ion trap, EI): *m/z* (%) = 188 (17, [M^+]), 144 (100), 116 (32), 89 (24), 63 (12).

Synthesis of 1*H*-indol-3-yl-*N*-[(*Z*)-2-phenylvinyl]glyoxylamide (18)



The compound was prepared according to method A for addition of primary amides to alkynes, using the following amounts: indole-3-glyoxylamide (188.0 mg, 1.00 mmol) and phenylacetylene (220 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (18:1 mixture with the *E*-isomer, 185.0 mg, 64%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 9.82 (d, *J* = 11.7 Hz, 1H, *NH-amide*), 9.28 (s, 1H, *NH-indole*), 9.06 (s, 1H, *H-1*), 8.41 (d, *J* = 7.4 Hz, 1H, *H-11*), 7.36-7.46 (m, 5H), 7.27-7.35 (m, 4H), 6.99 (dd, *J* = 11.9, 9.6 Hz, 1H), 5.99 (d, *J* = 9.4 Hz, 1H, *H-12*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 179.39 (*C-9*), 159.48 (*C-10*), 138.37, 135.74, 135.16, 129.20, 128.02, 127.34, 126.54, 124.38, 123.58, 122.39, 120.41, 113.73, 113.29, 111.71 ppm. **EA** Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.56; H, 5.05; N, 9.61. **MS** (Ion trap, EI): *m/z* (%) = 290 (49, [M^+]), 144 (100), 116 (28), 89 (24), 63 (9).

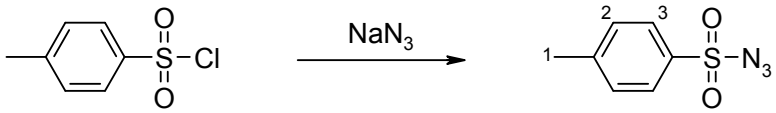
Synthesis of dimethyl 2-oxopropylphosphonate (22) (CAS NO.: 4202-14-6)



To a stirred suspension of potassium iodide (33.2 g, 200 mmol) in acetone (40mL) and MeCN (50 mL) was added chloroacetone (16.1 mL, 200 mmol). Stirring was continued for 1 h at r.t. Trimethyl phosphite (24.4 mL, 200 mmol) was slowly added. After 12 h at r.t., the mixture was heated to 50 °C to ensure complete conversion. Filtration through a pad of Celite and evaporation of the solvents under reduced pressure yielded the crude

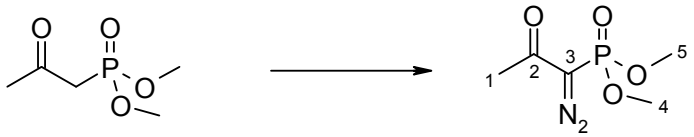
product. Distillation under vacuum (0.5 mbar) furnished the product as a colorless liquid (17.7 g, 53%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 3.74 (s, 3H, *H-4*), 3.72 (s, 3H, *H-5*), 3.05 (d, *J* = 22.9 Hz, 2H, *H-3*), 2.26 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 200.1, 52.6 (d, *J* = 6.5 Hz), 42.9, 41.3, 31.1. **MS** (Ion trap, EI): *m/z* (%) = 167 (100, [M^+]), 124 (61), 109 (46), 94 (53), 79 (48).

Synthesis of 4-toluenesulfonyl azide (23) (CAS NO.: 938-10-3)



To a stirred suspension of 4-toluenesulfonyl chloride (2.1 g, 11 mmol) in DCM (20 mL) was added tetrabutylammonium chloride (8.3 mg, 0.03 mmol), followed by a solution of sodium azide (0.813 g, 12.5 mmol) in H_2O (4 mL) (**CAUTION**: AZIDES CAN CAUSE EXPLOSIONS!). Stirring was continued at r.t.; two clear phases formed overnight. The organic layer was washed with water and brine, dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure. A colorless solid was obtained, which directly used without further purification (1.75 g (81%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.83 (d, *J* = 8.52 Hz, 2H, *H-3*), 7.40 (d, *J* = 8.17 Hz, 2H, *H-2*), 2.47 (s, 3H, *H-1*).

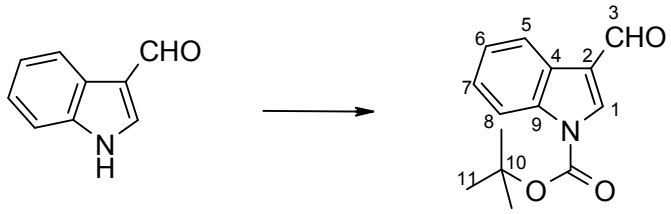
Synthesis of dimethyl 1-diazo-2-oxopropylphosphonate (24) (CAS NO.: 90965-06-3)



A 250 mL, three-necked flask was equipped with an overhead stirrer and an addition funnel. The flask was charged with phosphonate **22** (5.40 g, 32.5 mmol) in toluene (30 mL) and the solution cooled to 0 °C. NaH (1.40 g of 60% in paraffin; 35 mmol) was added in portions. After the gas evolution had ceased, a soln of azide **23** (6.51 g, 33 mmol) in THF (10 mL) was added dropwise; the highly viscous suspension slowly discolored to yellow-brown and stirring became easier. After 16 h the mixture was

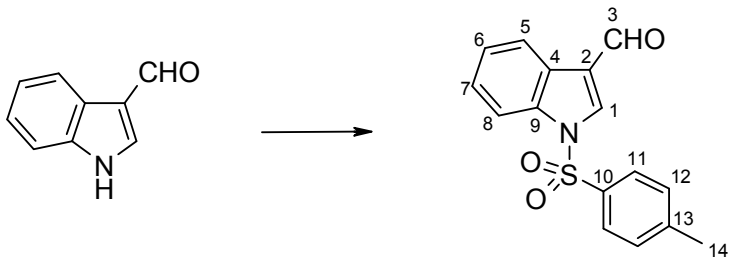
diluted with petroleum ether, filtered through a pad of Celite, rinsed thoroughly with ether, and the solvents removed under reduced pressure, yielding the crude of the product (5.1 g, 82%). For many applications the remaining slightly impure yellow oil can be directly used. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 3.82 (s, 3H, *H-4*), 3.79 (s, 3H, *H-5*), 2.23 (s, 3H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 189.8 (d, *J* = 13.0 Hz, *C=O*) 127.9 (d, *J* = 323.7 Hz, *C-3*), 53.54 (*C-4*), 53.48 (*C-5*).

Synthesis of *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate (25) (CAS NO.: 57476-50-3)



To a stirred solution of 3-formyl-indole (2.9 g, 20 mmol), THF (60 mL), and DMAP in a two-necked flask was added di-*tert*-butyl dicarbonate (6.62 mL, 30 mmol). Liberation of CO_2 was then observed. After 1.5 h, the mixture was extracted with ether (3 × 100 mL) and the organic layer was washed with water and brine, dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography (1:5 ethyl acetate/hexane), yielding the product as a colorless oil (1.84 g, 75%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 9.12 (s, 1H, *H-3*), 7.31 (d, *J* = 7.5 Hz, 1H), 7.25 (s, 1H), 7.16 (s, 1H), 6.41 (s, 2H), 0.73 (s, 9H, *H-11*) ppm.

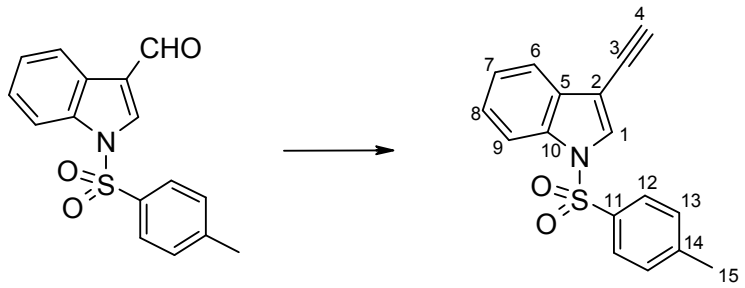
Synthesis of 1-tosyl-1*H*-indole-3-carbaldehyde (26) (CAS NO.: 50562-79-3)



A mixture of 3-formyl-indole (10 g, 68.9 mmol) and sodium hydroxide (6.06 g, 152 mmol) in DCM was stirred for 15 min, and the toluenesulfony chloride (15.8 g, 82.7

mmol) was added. The reaction mixture was heated to 35 °C and stirred for 15 h. The solution was quenched with ammonia solution (25%, 25 mL) and water (25 mL) and stirred for 2 h at 35 °C. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was washed with ethyl acetate, dried to afford the produc which was used without further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 10.08 (s, 1H, *H-3*), 8.20-8.26 (m, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.32-7.42 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 2.34 (s, 3H, *H-14*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 185.2 (*C-3*), 146.1, 136.1, 135.2, 134.4, 130.3, 127.2, 126.3, 126.2, 125.0, 122.5, 122.4, 113.2, 21.6 (*C-14*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 299 (86, [M^+]), 155 (77), 116 (22), 91 (100), 65 (25).

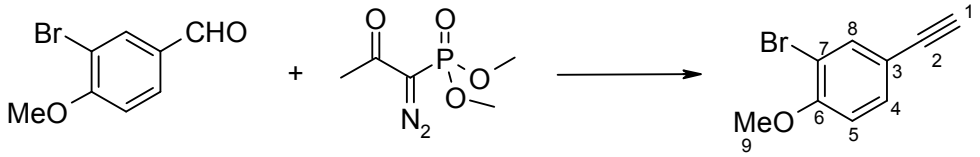
Synthesis of 3-ethynyl-1-tosyl-1*H*-indole (27) (CAS NO.: 765914-04-3)



Dimethyl 1-diazo-2-oxopropylphosphonate (9.48 mL, 60 mmol) was added to a solution of aldehyde **26** (15.80 g, 50 mmol), potassium carbonate (13.8, 100.0 mmol) and methanol (20.3 mL, 500 mmol) in THF (3 mL) and stirring was continued for 72 h. The resulting solution was poured into an aqueous sodium bicarbonate solution (200 mL), extracted repeatedly with 100 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (1:5 ethyl acetate/hexane), yielding the product as a white solid (8.85 g, 60%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.96 (d, *J* = 8.3 Hz, 1H, *H-12*), 7.75-7.79 (m, 3H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.0 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H, *H-13*), 3.25 (s, 1H, *H-4*), 2.33 (s, 3H, *H-15*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ

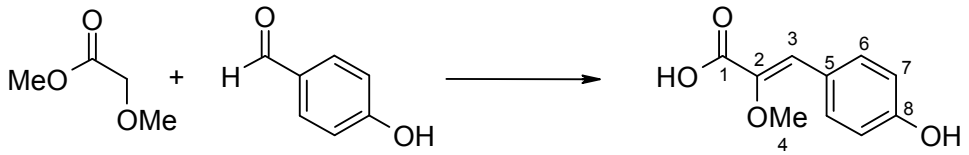
= 145.4, 135.1, 134.2, 130.8, 130.0, 130.0, 127.0, 125.5, 123.8, 120.5, 113.6, 104.1, 81.5 (*C-4*), 75.0 (*C-3*), 21.5 (*C-15*) ppm. **EA** Calcd for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.74. Found: C, 69.15; H, 4.39; N, 4.50. **MS** (Ion trap, EI): *m/z* (%) = 295 (100, [M^+]), 155 (30), 140 (51), 113 (22), 91 (43).

Synthesis of 2-bromo-4-ethynyl-anisole (29b) (CAS NO.: 859211-28-2)



Dimethyl-1-diazo-2-oxopropylphosphonate (2.377 g, 12 mmol) was added to a solution of 3-bromo-4-methoxybenzaldehyde (2.151 g, 10.0 mmol) and potassium carbonate (2.764 g, 20.0 mmol) in methanol (30 mL) and stirring was continued for 12 h. The reaction mixture was diluted with ether (150 mL), washed with an aq. solution of sodium bicarbonate (100 mL, 5%) and dried over magnesium sulfate, filtered, and the volatiles were removed in vacuo. The alkyne was obtained as a white solid (8.85 g, 60%) and remained in analytically pure form. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.67 (d, *J* = 2.0 Hz, 1H, *H-8*), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H, *H-4*), 6.81 (d, *J* = 8.5 Hz, 1H, *H-5*), 3.89 (s, 3H, *H-9*), 3.02 (s, 1H, *H-1*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 156.5 (*C-6*), 136.8 (*C-8*), 132.6 (*C-4*), 115.7 (*C-7*), 111.6 (*C-5*), 111.4 (*C-3*), 82.11 (*C-2*), 76.9 (*C-1*), 56.3 (*C-9*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 212 (100, [M^+]),210 (98, [M^+]), 197 (23), 169 (26), 116 (10), 88 (26).

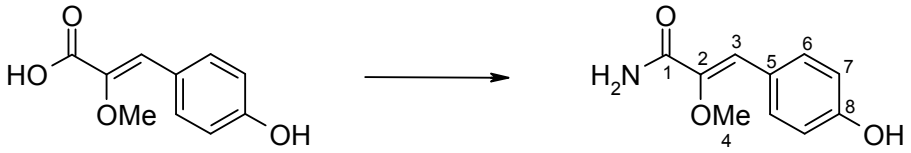
Synthesis of (*Z*)-3-(4-hydroxyphenyl)2-methoxyacrylic acid (30) (CAS NO.: 690258-63-0)



Methylmethoxyacetate (12 mL, 120 mmol) was added to 30% of a solution of sodium methoxide (13,5 g NaOMe + 40 mL MeOH) and stirred for 1 h. A solution of 4-

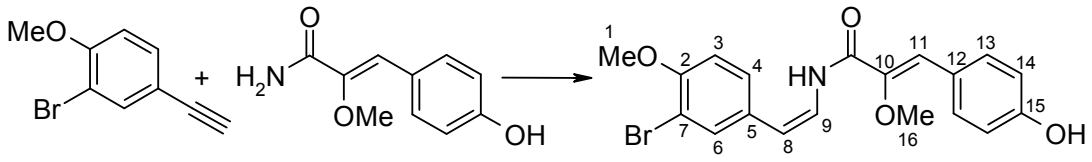
hydroxybenzaldehyde (4.88 g, 40 mmol) in MeOH (20 mL) was added, the mixture was refluxed for 6 h, followed by addition of water (100 mL) and acidified with conc. HCl until pH 2. After stirring for an hour, the precipitated was collected, yielding the product as a white solid (7.49 g, 96%) which was used without further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.17 (d, *J* = 8.7 Hz, 3H, *H-6*), 6.49 (s, 1H, *H-3*), 6.40 (d, *J* = 8.7 Hz, 2H, *H-7*), 3.32 (s, 3H, *H*-4) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 165.5 (*C=O*), 158.4 (*C-2*), 143.7, 131.8, 124.4, 123.1, 115.7, 58.44 (*C-4*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 194 (100, [M^+]), 151 (27), 123 (38), 95 (24), 77 (33).

Synthesis of (*Z*)-3-(4-hydroxyphenyl)-2-methoxyacrylamide (31)



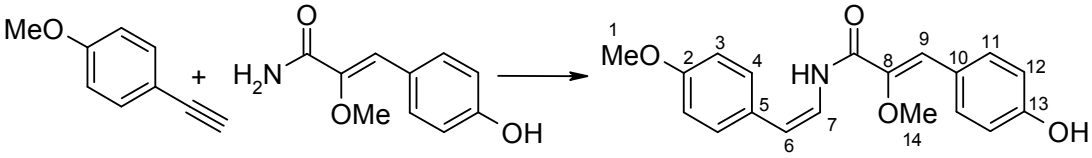
A solution of oxalylchloride (1.05 mL, 11 mmol) in dry DCM (5 mL) was added dropwise to a suspension of acid **30** (1.0 g, 5.15 mmol) in dry DCM (8 mL). The reaction mixture was stirred at r.t. for 1 h and then the volatile was removed vacuum. DCM (5 mL), was added and followed by dropwise addition of ammonia solution (6 mL, 25%) and the mixture was stirred for another hour. The resulting solution was poured into an aqueous sodium bicarbonate solution (20 mL), extracted repeatedly with 20 mL portions of DCM, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The crude was washed with ethyl acetated and dried, yielding the product as a white solid (753 mg, 70%) which was used without further purification. **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 9.78 (s, 1H, *H-3*), 7.57 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 2H, *H-6*), 7.30 (s, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.68 (s, 1H), 3.56 (s, 3H, *H-4*) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 165.62 (*C=O*), 157.76, 147.37, 131.20, 124.49, 118.55, 115.6, 58.5(*C-4*) ppm. **MS** (Ion trap, EI): *m/z* (%) = 193 (100, [M^+]), 161 (27), 122 (50), 107 (28), 77 (36).

Synthesis of (*Z*)-3-(4-hydroxyphenyl)-2-methoxy-*N*-[(*Z*)-2-(3-bromo-4-methoxy-phenyl)vinyl]-acrylamide (34)



The compound was prepared according to method A of addition of primary amides to alkynes, using the following amounts: amide **31** (193.0 mg, 1.00 mmol) and 2-bromo-4-ethynyl-anisole (422.0 mg, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (15:1 mixture with the *E*-isomer, 355.5 mg, 88%). **^{1}H-NMR** (400 MHz, DMSO-d_6, 25 °C): δ = 9.89 (s, 1H), 9.29 (d, *J* = 10.4 Hz, 1H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.38 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 6.86 (s, 1H), 6.78-6.84 (m, 3H), 5.78 (d, *J* = 9.6 Hz, 1H), 3.86 (s, 3H), 3.66 (s, 3H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6, 25 °C): δ = 161.6, 158.3, 154.1, 145.5, 132.2, 131.6, 129.6, 128.6, 123.8, 121.6, 120.5, 115.7, 112.9, 110.9, 110.1, 59.0, 56.28 ppm. **EA** Calcd for $C_{19}H_{18}BrNO_4$: C, 56.45; H, 4.49; N, 3,46. Found: C, 56.07; H, 4.78; N, 3.14.

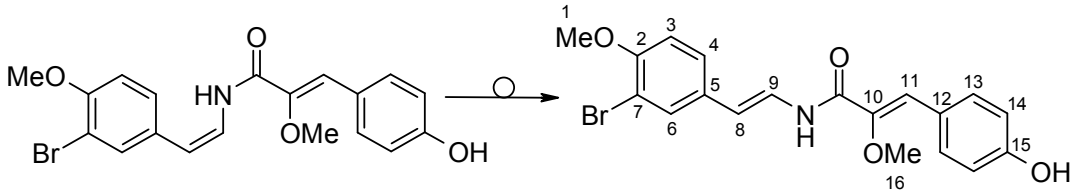
Synthesis of (*Z*)-3-(4-hydroxyphenyl)-2-methoxy-*N*-[(*Z*)-2-(4-methoxyphenyl)vinyl]-acrylamide (35)



The compound was prepared according to method A of addition of primary amides to alkynes, using the following amounts: amide **31** (193.0 mg, 1.00 mmol) and 4-methoxy-phenylacetylene (259 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (15:1 mixture with the *E*-isomer, 276.3 mg, 85%). **^{1}H-NMR** (200 MHz, DMSO-d_6, 25 °C): δ = 9.88 (s, 1H), 9.10 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.73-6.91 (m, 4H), 5.80 (d, *J* = 9.5 Hz, 1H), 3.69-3.81 (m, 3H), 3.63 (s, 3H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6, 25 °C): δ = 161.1, 158.1, 158.0, 145.4, 131.4, 128.9, 127.7, 123.6, 120.2,

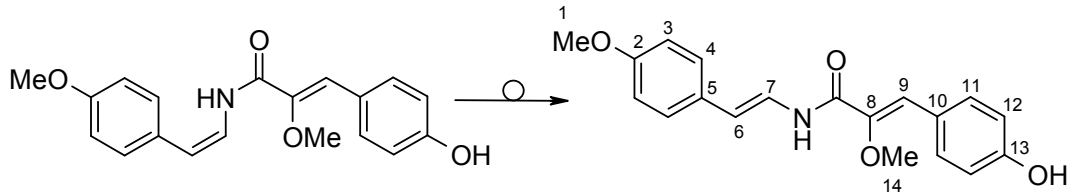
120.2, 115.5 114.3, 111.0, 58.9, 55.0 ppm. **EA** Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.94; H, 4.78; N, 4.32.

Synthesis of (*Z*)-3-(4-hydroxyphenyl)-2-methoxy-*N*-[(*E*)-2-(3-bromo-4-methoxy-phenyl)vinyl]-acrylamide (botryllamide C) (36) (CAS NO.: 163564-66-7)



The compound was prepared according to method B of addition of primary amides to alkynes, using the following amounts: amide **31** (193.0 mg, 1.00 mmol) and 2-bromo-4-ethynyl-anisole (422.0 mg, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (1:19 mixture with the *Z*-isomer, 250.5 mg, 62%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 10.32 (d, *J* = 10.2 Hz, 1H), 9.86 (s, 1H), 7.55-7.63 (m, 3H), 7.43 (dd, *J* = 14.7, 10.2 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.79-6.86 (m, 3H), 6.45 (d, *J* = 14.7 Hz, 1H), 3.83 (s, 3H), 3.62 (s, 3H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6, 25 °C): δ = 161.3, 158.0, 153.8, 146.12, 131.3, 130.9, 129.3, 125.5, 124.1, 123.2, 119.8, 115.5, 112.9, 111.5, 111.0, 58.82, 56.16 ppm. **EA** Calcd for $C_{19}H_{18}BrNO_4$: C, 56.45; H, 4.49; N, 3,46. Found: C, 56.15; H, 4.72; N, 3.18.

Synthesis of (*Z*)-3-(4-hydroxyphenyl)-2-methoxy-*N*-[(*E*)-2-(4-methoxyphenyl)vinyl]-acrylamide (botryllamide E) (37) (CAS NO.: 724434-03-1)

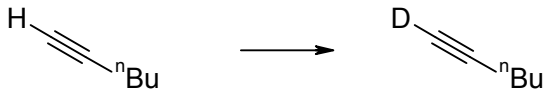


The compound was prepared according to method B of addition of primary amides to alkynes, using the following amounts: amide **31** (193.0 mg, 1.00 mmol) and 4-methoxy-

phenylacetylene (259 µL, 2.00 mmol) and purified by column chromatography (1:3 ethyl acetate/hexane), yielding the product as a greenish solid (1:19 mixture with the *Z*-isomer, 204.8 mg, 63%). **^{1}H-NMR** (400 MHz, DMSO-d_6, 25 °C): δ = 10.25 (d, *J* = 10.2 Hz, 1H), 9.97 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.78-6.89 (m, 6H), 6.49 (d, *J* = 14.7 Hz, 1H), 3.73 (s, 3H), 3.60 (s, 3H) ppm. **^{13}C-NMR** (101 MHz, DMSO-d_6, 25 °C): δ = 161.2, 158.1, 157.9, 146.2, 131.3, 129.1, 126.4, 124.1, 121.9, 119.7, 115.6, 114.2, 113.1, 58.9, 55.0 ppm. **EA** Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.22; H, 6.08; N, 4.44.

5.6 Mechanistic studies of catalytic addition of nucleophiles to alkynes

Synthesis of 1-hexyne-1-D (38) (CAS NO.: 7299-48-1)



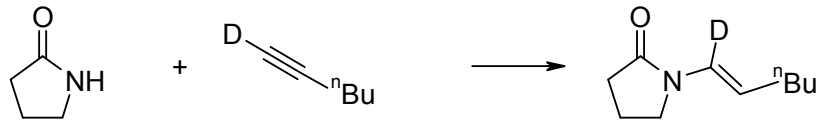
In a flame-dried, nitrogen-flushed flask, a small amount of sodium hydride (60% in mineral oil) (2.4 g, 60 mmol) was added while stirring to 99% D_2O (20 mL, 1 mol). The alkyne (5.78 mL, 50 mmol) was added, and the two-phase mixture was stirred for 24 h. The operation was repeated. The layers were separated under a nitrogen atmosphere. The organic layer was dried over molecular sieves, filtered, and distilled to afford the product (7.90 g, 95%; 98 incorporated deuterium). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 2.15 (t, *J* = 7.0 Hz, 2H) 1.32-1.55 (m, 4H) 0.88 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 84.0 (t, $^3J_{C\text{-}D}$ = 7.40 Hz) 67.7 (t, $^2J_{C\text{-}D}$ = 38 Hz) 30.6 (s) 21.8 (s) 18.0 (s) 13.4 (s) ppm.

5.6.1 Addition of 2-pyrrolidones to hexynes

Syntheses of *N*-D-2-pyrrolidone (41) (CAS NO.: 930-49-4)

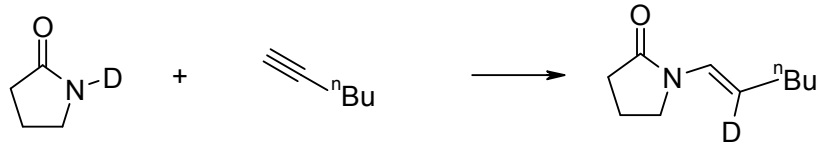
In a flame-dried, nitrogen-flushed flask, a mixture of 2-pyrrolidone (1.16 mL, 15 mmol) and 1-D-ethanol (8.64 mL, 150 mmol) was heated at 60 °C for 24 h. The operation was repeated. The solvent was evaporated under high pressure to afford the product (1.25 g, 98%; 85% incorporated deuterium). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 3.36 (td, *J* = 6.9, 2.2 Hz, 2H) 2.24-2.28 (m, 2H) 2.06-2.11 (m, 2H) ppm.

Synthesis of *N*-[1'-deutero-(*E*)-hex-1-en-1-yl]-2-pyrrolidone (39)



An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (6.4 mg, 0.02 mmol) and DMAP (4.99 mg, 0.04 mmol) and flushed with argon. Subsequently, tri-*n*-butylphosphine (15 µL, 0.06 mmol), 2-pyrrolidone (77 µL, 1 mmol), 1-D-hexyne (234 µL, 2.0 mmol), and dry toluene (3.0 mL) were added via syringe. The resulting green solution was stirred for 15 h at 100 °C and was then poured into aqueous $NaHCO_3$ solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:1), yielding the product as a colorless oil (155.7 mg, 93%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 4.83 (t, *J* = 7.0 Hz, 1H), 3.37-3.43 (m, 2H), 2.37 (t, *J* = 8.2 Hz, 2H), 1.94-2.03 (m, 4H), 1.19-1.30 (m, 4H), 0.80 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 172.4 (*C*=*O*), 123.2 (t, $J_{C\text{-}D}$ = 25.9 Hz), 112.0, 45.1, 32.1, 31.1, 29.5, 21.9, 17.3, 13.7 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 6.82 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{16}NOD$: C, 71.38; H, 9.58; N, 8.32. Found: C, 71.15; H, 9.79; N, 8.02. **MS** (Ion trap, EI): *m/z* (%) = 169 (66, $[M+1]^+$), 139 (7), 125 (100), 97 (43), 81 (3).

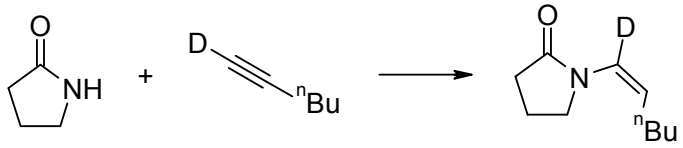
Synthesis of *N*-[2'-deutero-(*E*)-hex-1-en-1-yl]-2-pyrrolidone (40)



This compound was synthesized following the same method of compound **39**,using *N*-D-2-pyrrolidone (86.1 mg, 1.00 mmol) and 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography, yielding the product as a colorless oil (152.5 mg, 91%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 6.77 (s, 1H), 3.38-3.43 (m, 2H), 2.38 (t, *J* = 8.2 Hz,

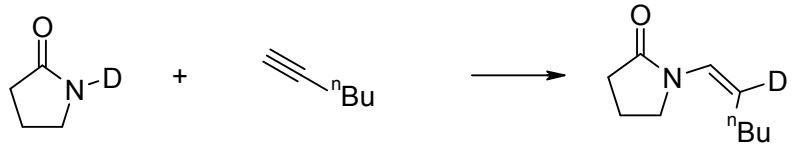
2H), 1.95-2.04 (m, 4H), 1.19-1.30 (m, 4H), 0.80 (t, J = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 172.4 (*C=O*), 123.4, 111.8 (t, $J_{C\text{-}D}$ = 23.1 Hz,), 45.1, 32.1, 31.1, 29.4, 21.9, 17.3, 13.7 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 4.91 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{16}NOD$: C, 71.38; H, 9.58; N, 8.32. Found: C, 71.19; H, 9.79; N, 7.97. **MS** (Ion trap, EI): *m/z* (%) = 169 (62, $[M+1]^+$), 139 (8), 125 (100), 97 (45), 81 (5).

Synthesis of *N*-[1'-deutero-(*Z*)-hex-1-en-1-yl]-2-pyrrolidone (42)



An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (6.4 mg, 0.02 mmol), bis(dicyclohexylphosphino)methane (12.3 mg, 0.03 mmol) and flushed with argon. Subsequently, 2-pyrrolidone (77 µL, 1 mmol), 1-D-hexyne (234 µL, 2.0 mmol), toluene (3.0 mL) and deoxygenated water (36 µL, 2 mmol) were added via syringe. The resulting green solution was stirred for 15 h at 100 °C and was then poured into aqueous $NaHCO_3$ solution (30 mL) and the resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate / hexane 3:1), yielding the product as a colorless oil (148. mg, 89%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 4.77-4.82 (m, 1H), 3.71 (td, J = 7.1, 2.1 Hz, 2H), 2.36 (t, J = 8.1 Hz, 2H), 2.13 (q, J = 7.5 Hz, 2H), 2.00-2.07 (m, 2H), 1.26-1.34 (m, 4H), 0.82-0.87 (m, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 174.5 (*C=O*), 121.8 (t, $J_{C\text{-}D}$ = 26.8 Hz), 116.5, 48.6, 32.3, 30.1, 26.8, 22.2, 18.5, 13.8 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 6.38 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{16}NOD$: C, 71.38; H, 9.58; N, 8.32. Found: C, 71.23; H, 9.75; N, 7.99. **MS** (Ion trap, EI): *m/z* (%) = 168 (10, $[M^+]$), 139 (27), 125 (100), 97 (50), 83 (39).

Synthesis of *N*-[2'-deutero-(*Z*)-hex-1-en-1-yl]-2-pyrrolidone (43)

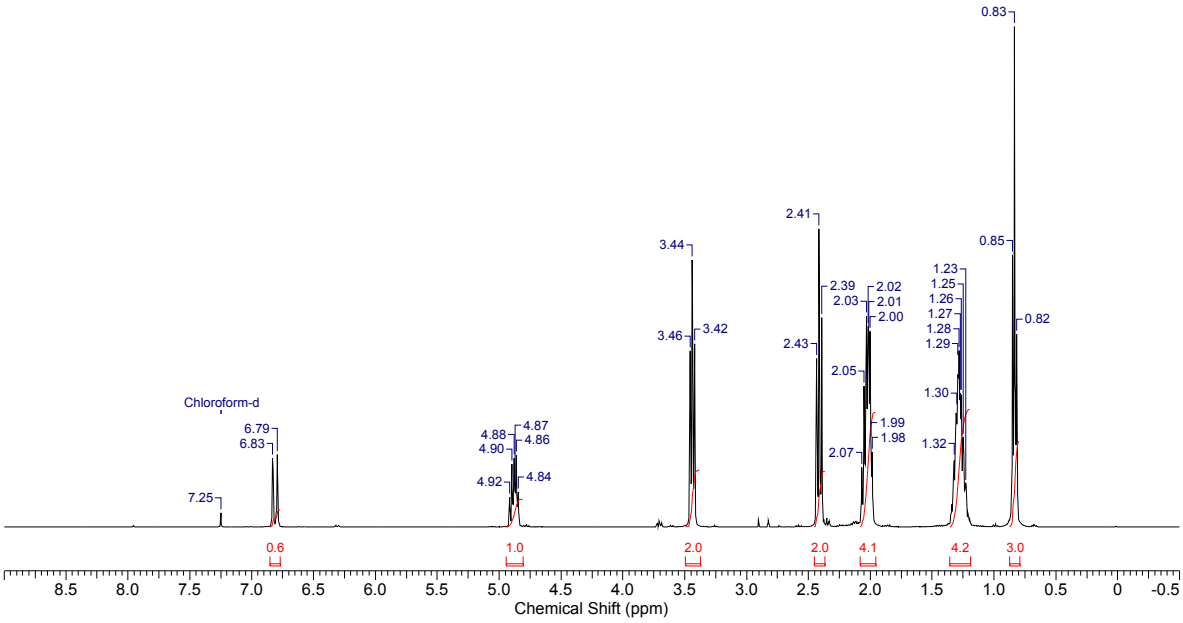


This compound was synthesized following the same method of compound **42**, using *N*-D-2-pyrrolidone (86.1 mg, 1.00 mmol) and 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography, yielding the product as a colorless oil (151.2 mg, 90%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 6.38 (s, 1H), 3.76-3.79 (m, 2H), 2.43 (t, *J* = 8.22 Hz, 2H), 2.19 (t, *J* = 7.13 Hz, 2H), 2.06-2.13 (m, 2H), 1.32-1.40 (m, 4H), 0.89-0.93 (m, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 174.5 (*C*=*O*), 122.1, 116.6 (t, $J_{C\text{-}D}$ = 23.5 Hz,), 48.6, 32.3, 30.3, 26.8, 22.3, 18.6, 13.9 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 4.86 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{16}NOD$: C, 71.38; H, 9.58; N, 8.32. Found: C, 71.15; H, 9.72; N, 7.95. **MS** (Ion trap, EI): *m/z* (%) = 168 (12, [M^+]), 139 (28), 125 (100), 97 (49), 81 (35).

Procedures for kinetic isotope effect for addition of 2-pyrrolidone

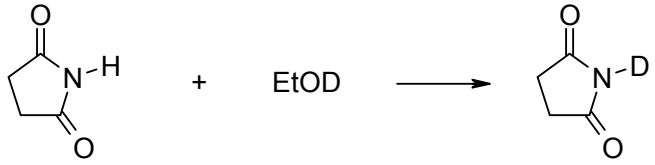
An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (6.4 mg, 0.02 mmol) and DMAP (4.99 mg, 0.04 mmol) and flushed with argon. Subsequently, tri-*n*-butylphosphine (15 µL, 0.06 mmol), 2-pyrrolidone (77 µL, 1 mmol), 1-hexyne (229 µL, 2.00 mmol), 1-D-hexyne (234 µL, 2.0 mmol) and dry toluene (3.0 mL) were added via syringe. The resulting green solution was stirred for 15 h at 100 °C and was then poured into aqueous $NaHCO_3$ solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:1). A kinetic isotope effect of 1.56 was confirmed by NMR.

$k_H/k_D = 1.56$



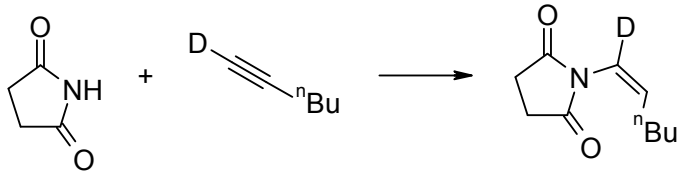
5.6.2 Addition of succinimdes to hexynes

Syntheses of *N*-D-succinimide (47) (CAS NO.: 60890-57-5)



In a flame-dried, nitrogen-flushed flask, a mixture of succinimide (1.49 g, 15 mmol) and 1-D-ethanol (8.64 mL, 150 mmol) was heated at 60 °C for 24 h. The operation was repeated. The solvent was evaporated under high pressure to afford the product (1.43 g, 96%; 85% incorporated deuterium). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 2.74 (s, 4H) ppm.

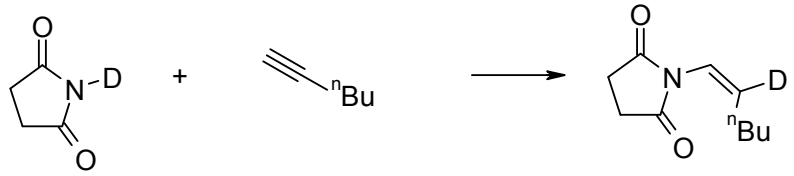
Synthesis of *N*-[1'-deutero-(*Z*)-hex-1-en-1-yl]succinimide (46) (CAS NO.: 919086-95-6)



An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (6.4 mg, 0.02 mmol), scandium triflate (19.7 mg, 0.04 mmol) and succinimide (99.1 mg, 1.0 mmol) and flushed with argon. Subsequently, tri-*n*-butylphosphine (15 µL, 0.06 mmol), 1-D-hexyne (234 µL, 2.0 mmol), and dry DMF (3.0 mL) were added via syringe. The resulting colorless solution was stirred for 15 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, and filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 3:1), yielding the product as a yellowish oil (169.5 mg, 94%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 5.67 (s, 1H), 2.73 (s, 4H), 1.85-1.91 (m, 2H), 1.23-1.36

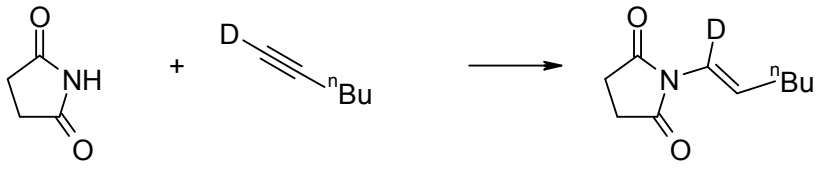
(m, 4H), 0.81 (t, J = 7.3 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 175.5 (*C*=*O*), 133.4, 116.4 (t, $J_{C\text{-}D}$ = 27.7 Hz), 30.6, 28.3, 27.6, 22.2, 13.7 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 5.87 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{14}NO_2D$: C, 65.91; H, 7.74; N, 7.69. Found: C, 65.81; H, 8.00; N, 7.49. **MS** (Ion trap, EI): *m/z* (%) = 183 (100, $[M+1]^+$), 139 (30), 111 (14), 83 (25), 57 (17).

Synthesis of *N*-[2'-deutero-(*Z*)-hex-1-en-1-yl]succinimide (48)



This compound was synthesized following the same method of compound **46**, using *N*-D-succinimide (100.1 mg, 1.00 mmol) and 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography, yielding the product as a yellowish oil (165.2 mg, 91%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 5.81 (s, 1H), 2.73 (s, 4H), 1.88 (t, J = 7.3 Hz, 2H), 1.23-1.35 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 175.5 (*C*=*O*), 133.3 (t, $J_{C\text{-}D}$ = 21.3 Hz), 116.6, 30.5, 28.3, 27.6, 22.2, 13.7 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 5.76 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{14}NO_2D$: C, 65.91; H, 7.74; N, 7.69. Found: C, 65.81; H, 8.00; N, 7.49. **MS** (Ion trap, EI): *m/z* (%) = 183 (100, $[M+1]^+$), 139 (30), 111 (14), 83 (25), 57 (17).

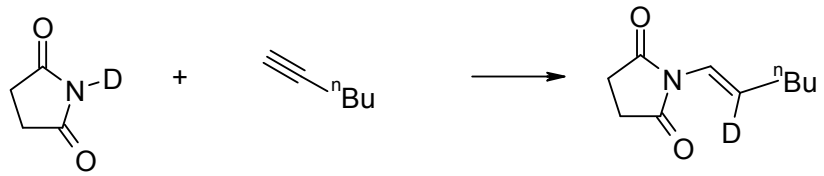
Synthesis of *N*-[1'-deutero-(*E*)-hex-1-en-1-yl]succinimide (50) (CAS NO.: 919083-08-2)



An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (16 mg, 0.05 mmol), scandium triflate (19.7 mg, 0.04 mmol) and succinimide (99.1 mg, 1.0 mmol) and flushed with argon. Subsequently, tri-isopropylphosphine (29 µL, 0.15

mmol), 1-D-hexyne (234 µL, 2.0 mmol) and DMF-d_7 (1.0 mL) were added via syringe. The resulting colorless solution was stirred for 15 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate and filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 3:1), yielding the product as a yellowish oil (136.0 mg, 75%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 6.53 (t, *J* = 7.3 Hz, 1H) 2.67 (s, 3H) 2.07 (td, *J* = 7.5 Hz, 2H) 1.22-1.43 (m, 4H) 0.85 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 175.3 (*C*=*O*), 124.3, 117.6 (t, $J_{C\text{-}D}$ = 27.1 Hz), 31.2, 30.4, 27.6, 21.9, 13.6 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 6.43 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{14}NO_2D$: C, 65.91; H, 7.74; N, 7.69. Found: C, 65.81; H, 8.00; N, 7.49. **MS** (Ion trap, EI): *m/z* (%) = 182 (8, [M^+]), 139 (83), 100 (93), 83 (100), 68 (65).

Synthesis of *N*-[2'-deutero-(*E*)-hex-1-en-1-yl]succinimide (51)

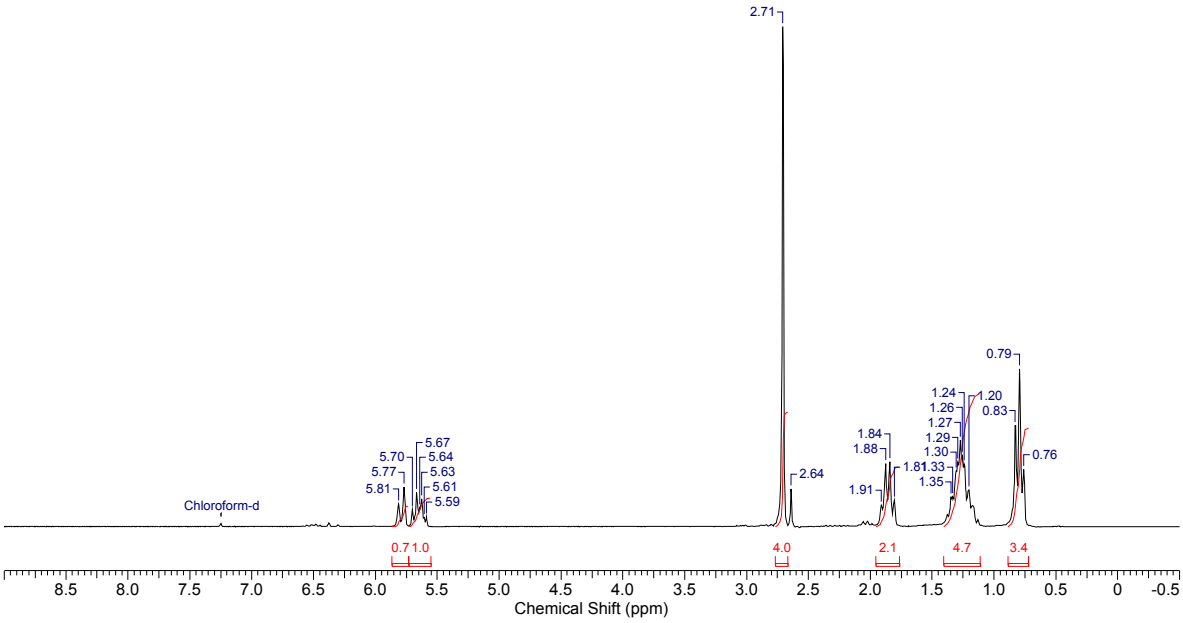


This compound was synthesized following the same method of compound **50**, using *N*-D-succinimide (100.1 mg, 1.00 mmol), 1-hexyne (229 µL, 2.00 mmol), and DMF (3 mL) and purified by column chromatography, yielding the product as a yellowish oil (131.0 mg, 72%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 6.39 (s, 1H), 2.69 (s, 4H), 2.08 (t, *J* = 7.34 Hz, 2H), 1.35-1.41 (m, 2H), 1.27-1.34 (m, 2H), 0.87 (t, *J* = 7.34 Hz, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 175.6 (*C*=*O*), 124.5 (t, $J_{C\text{-}D}$ = 24.5 Hz), 117.8, 31.3, 30.6, 27.8, 22.2, 13.9 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 6.61 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{14}NO_2D$: C, 65.91; H, 7.74; N, 7.69. Found: C, 65.71; H, 8.05; N, 7.40. **MS** (Ion trap, EI): *m/z* (%) = 182 (9, [M^+]), 139 (80), 100 (95), 83 (100), 68 (62).

Procedures for kinetic isotope effect for addition of succinimde

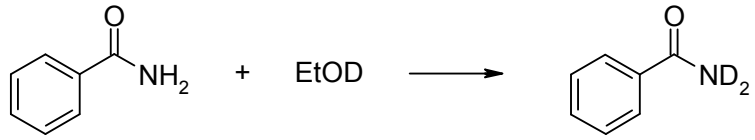
An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (6.4 mg, 0.02 mmol), scandium triflate (19.7 mg, 0.04 mmol) and succinimide (99.1 mg, 1.0 mmol) and flushed with argon. Subsequently, tri-*n*-butylphosphine (15 µL, 0.06 mmol), 1-hexyne (229 µL, 2.00 mmol), 1-D-hexyne (234 µL, 2.0 mmol) and dry DMF (3.0 mL) were added via syringe. The resulting colorless solution was stirred for 15 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, and filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 3:1). A kinetic isotope effect of 2.23 was confirmed by NMR.

$k_H/k_D = 2.23$



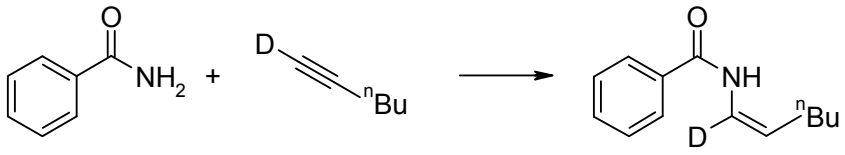
5.6.3 Addition of benzamides to hexynes

Synthesis of *N*,*N*-D_2-benzamide (54) (CAS NO.: 33093-38-8)



In a flame-dried, nitrogen-flushed flask, a mixture of benzamide (1.82 g, 15 mmol) and ethanol-1-D (8.64 mL, 150 mmol) was heated at 100 °C for 24 h. The operation was repeated. The solvent was evaporated under high pressure to afford the product (1.80 g, 99%; 80% incorporated deuterium). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.81 (d, *J* = 7.2 Hz, 2H) 7.52 (t, *J* = 7.3 Hz, 1H) 7.44 (t, *J* = 7.5 Hz, 2H) ppm.

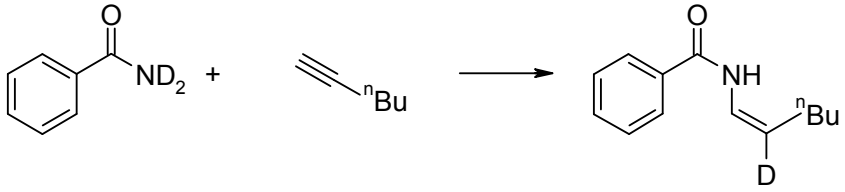
Synthesis of *N*-[1'-deutero-(*Z*)-hex-1-en-1-yl]benzamide (53) (CAS NO.: 1095320-68-5)



An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [Ru(cod)(met)$_2$] (16.0 mg, 0.05 mmol), benzamide (121.1 mg, 1.00 mmol), 1,4-bis(dicyclohexylphosphino)butane (27.0 mg, 0.06 mmol), and ytterbium triflate (24.8 mg, 0.04 mmol) and flushed with nitrogen. Subsequently, dry DMF (3.0 mL) and 1-D-hexyne (234 µL, 2.0 mmol) were added via syringe. The resulting solution was stirred for 6 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a yellowish oil (182.8 mg, 90%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.76 (d, *J* = 7.2 Hz, 3H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 4.38 (t, *J* = 7.2 Hz, 1H), 2.08 (q, *J* = 7.4 Hz, 2H),

1.31-1.43 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 164.3 (*C*=*O*), 134.0, 131.7, 128.6, 126.9, 120.9 (t, $J_{C\text{-}D}$ = 27.7 Hz), 112.1, 31.4, 25.4, 22.2, 13.8 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 6.96 (br, 1D) ppm. **EA** Calcd for $C_{13}H_{16}NOD$: C, 76.43; H, 7.89; N, 6.86. Found: C, 76.73; H, 8.60; N, 6.87. MS (Ion trap, EI): *m/z* (%) = 205 (67, [M^+]), 187 (24), 161 (3), 105 (100), 77 (2).

Synthesis of *N*-[2'-deutero-(*Z*)-hex-1-en-1-yl]benzamide (55) (CAS NO.: 1095320-67-4)

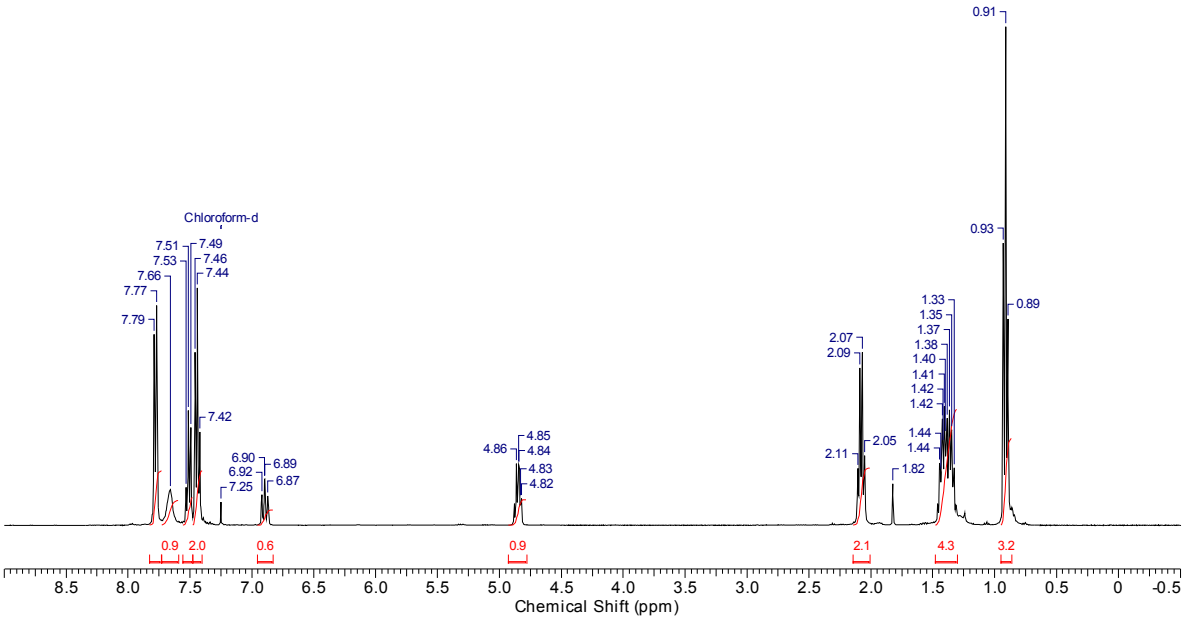


The compound was synthesized following the same method of compound **53**, using the following amounts: *N,N*-D_2-benzamide (123.2 mg, 1.00 mmol) and 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography (1:9 ethyl acetate/hexane), yielding the product as a yellowish oil (182.8 mg, 90%). **^{1}H-NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.81 (d, J = 7.2 Hz, 2H), 7.72 (s, 1H), 7.51-7.56 (m, 1H), 7.47 (t, J = 7.3 Hz, 2H), 6.92 (dd, J = 6.3, 4.6 Hz, 1H), 2.10 (t, J = 7.2 Hz, 2H), 1.35-1.47 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$, 25 °C): δ = 164.3 (*C*=*O*), 134.0, 131.8, 128.7, 127.0, 121.1, 112.1 (t, $J_{C\text{-}D}$ = 24.5 Hz), 31.4, 25.4, 22.3, 13.8 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 4.93 (br, 1D) ppm. **EA** Calcd for $C_{13}H_{16}NOD$: C, 76.43; H, 7.89; N, 6.86. Found: C, 76.73; H, 8.59; N, 6.87. **MS** (Ion trap, EI): *m/z* (%) = 205 (52, [M^+]), 187 (20), 161 (2), 105 (100), 77 (2).

Procedures for kinetic isotope effect for addition of benzamide

An oven-dried flask was charged with bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [Ru(cod)(met)$_2$] (16.0 mg, 0.05 mmol), benzamide (121.1 mg, 1.00 mmol), 1,4-bis(dicyclohexylphosphino)butane (27.0 mg, 0.06 mmol), and ytterbium triflate (24.8 mg, 0.04 mmol) and flushed with nitrogen. Subsequently, dry DMF (3.0 mL), 1-hexyne (229 µL, 2.00 mmol), and 1-D-hexyne (234 µL, 2.0 mmol) were added via syringe. The resulting solution was stirred for 6 h at 60 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (1:9 ethyl acetate/hexane). A kinetic isotope effect of 1.50 was confirmed by ^{1}H-NMR.

k_H/k_D = 1.50

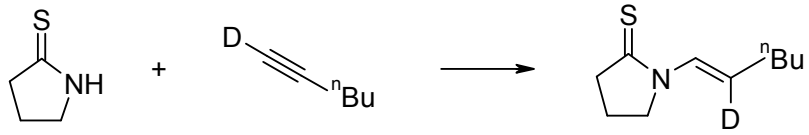


5.6.4 Addition of pyrrolidine-2-thiones to hexynes

Synthesis of 1-D-pyrrolidine-2-thione (59) (CAS NO.: 69362-77-2)

In a flame-dried, nitrogen-flushed flask, a mixture of pyrrolidine-2-thione (708 mg, 7 mmol) and 1-D-ethanol (4.03 mL, 70 mmol) was heated at 80 °C for 24 h. The operation was repeated. The solvent was evaporated under high pressure to afford the product (690 mg, 97%; 85% incorporated deuterium). ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.64 (t, *J* = 7.9 Hz, 2H) 2.89 (t, *J* = 7.9 Hz, 2H) 2.24-2.16 (m, 2H) ppm.

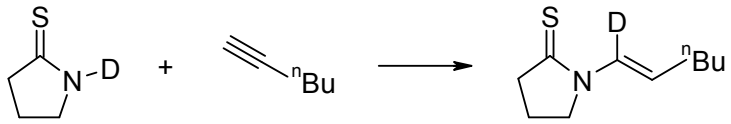
Synthesis of *N*-[2'-deutero-(*E*)-hex-1-en-1-yl] pyrrolidine-2-thione (56)



An oven-dried flask was charged with the bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) [Ru(cod)(met)$_2$] (6.4 mg, 0.02 mmol), pyrrolidine-2-thione (101.2 mg, 1.00 mmol), and molecular sieves (500 mg) and flushed with nitrogen. Subsequently, dry toluene (3.0 ml), tri-*n*-octylphosphine (27 µL, 0.06 mmol), and 1-D-hexyne (234 µL, 2.0 mmol) were added via syringe. The resulting solution was stirred for 15 h at 100 °C, then poured into an aqueous sodium bicarbonate solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried with magnesium sulfate, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (15:1 mixture with the *Z*-isomer, 174.0 mg, 95%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 7.43 (s, 1H) 3.73-3.77 (m, 2H) 3.01 (t, *J* = 7.9 Hz, 2H) 2.06 (tt, *J* = 14.9, 7.2 Hz, 4H) 1.31-1.36 (m, 2H) 1.23-1.30 (m, 2H) 0.83 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 198.8, 126.3, 118.9 (t, $J_{C\text{-}D}$ = 25.0 Hz), 52.3, 45.1, 31.6, 29.5, 22.0, 19.2, 13.7

ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 5.37 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{16}NSD$: C, 65.16; H, 8.75; N, 7.60. Found: C, 65.35; H, 9.00; N, 7.72.

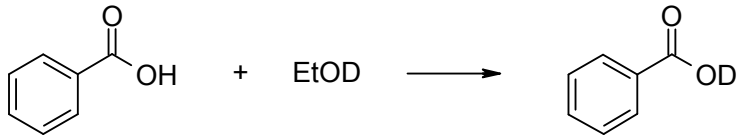
Synthesis of *N*-[1'-deutero-(*E*)-hex-1-en-1-yl] pyrrolidine-2-thione (57)



The compound was synthesized following the same method of compound **56**, using the following amounts: [Ru(cod)(met)$_2$] (6.4 mg, 0.02 mmol), molecular sieves (500 mg), *N*-D-pyrrolidine-2-thione (102.2 mg, 1.00 mmol), tri-*n*-octylphosphine (27 µL, 0.06 mmol), and 1-hexyne (229 µL, 2.00 mmol). The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:3) to afford the product as a yellowish oil (14:1 mixture with the *Z*-isomer, 174.0 mg, 95%). **^{1}H-NMR** (600 MHz, $CDCl_3$, 25 °C): δ = 5.33 (dt, *J* = 14.5, 7.2 Hz, 1H) 3.76-3.80 (m, 2H) 3.05 (t, *J* = 7.9 Hz, 2H) 2.06-2.14 (m, 4H) 1.34-1.40 (m, 2H) 1.27-1.33 (m, 2H) 0.87 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$, 25 °C): δ = 198.9, 126.5 (t, $J_{C\text{-}D}$ = 25.0 Hz), 119.3, 52.3, 45.1, 31.7, 29.7, 22.0, 19.3, 13.8 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$, 25 °C): δ = 7.54 (br, 1D) ppm. **EA** Calcd for $C_{10}H_{16}NSD$: C, 65.16; H, 8.75; N, 7.60. Found: C, 65.31; H, 8.92; N, 7.82.

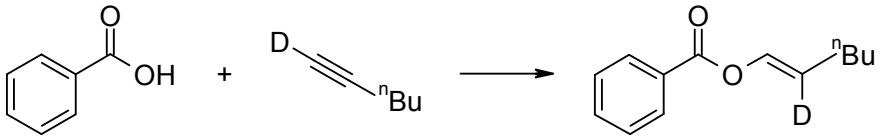
5.6.5 Addition of benzoic acids to hexynes

Synthesis of *O*-D-benzoic acid (67) (CAS NO.: 406679-59-2)



In a flame-dried, nitrogen-flushed flask, a mixture of benzoic acid (855 mg, 7 mmol) and 1-D-ethanol (4.03 mL, 70 mmol) was heated at 100 °C for 24 h. The operation was repeated. The solvent was evaporated under high pressure to afford the product (840 mg, 98%; 88% incorporated deuterium). ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.94 (d, *J* = 6.9 Hz, 2H) 7.61 (t, *J* = 6.9 Hz, 1H) 7.49 (t, *J* = 6.9 Hz, 2H) ppm.

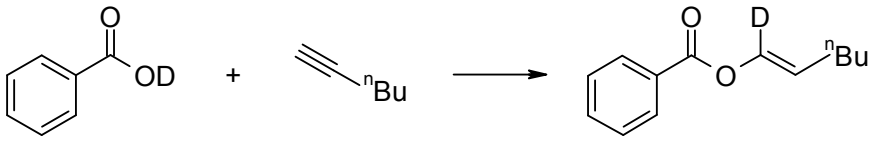
Synthesis of 2-deutero-(*Z*)-hex-1-en-1-yl] benzoate (65)



An oven-dried flask was charged with *p*-cymene ruthenium(II) chloride dimmer (6.4 mg, 0.01 mmol) tri-(4-chlorophenyl)phosphine (14.6 mg, 0.04 mmol), benzoic acid (122 mg, 1 mmol), and DMAP (4.89 mg, 0.04 mmol) and flushed with argon. Subsequently, dry toluene (2.0 mL) and 1-D-hexyne (234 µL, 2.0 mmol) were added via syringe. The resulting solution was stirred for 15 h at 60 °C and was then poured into aqueous $NaHCO_3$ solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:1), yielding the product as a colorless oil (170.0 mg, 83%). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.13-8.15 (m, 2H), 7.61-7.64 (m, 1H), 7.49-7.52 (m, 2H), 7.30 (br, 1H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.40-1.48 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 163.6, 134.1, 133.4, 129.8, 129.4, 128.5, 114.5 (t, $J_{C\text{-}D}$ = 25 Hz), 31.3, 24.3, 22.2, 13.9 ppm. **^{2}H-NMR**

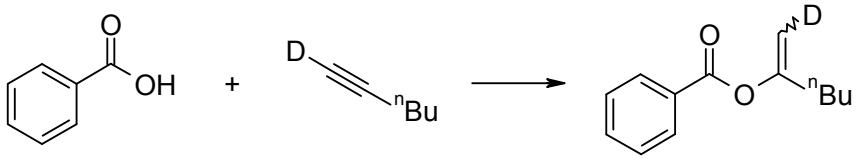
(61 MHz, $CHCl_3$): δ = 5.07 (br, 1D) ppm. **EA** Calcd for $C_{13}H_{15}O_2D$: C, 76.07; H, 7.37. Found: C, 75.85; H, 7.49. **MS** (Ion trap, EI): *m/z* (%) = 205 (1, [M^+]), 105 (100), 77 (11), 51 (4).

Synthesis of 1-deutero-(*Z*)-hex-1-en-1-yl] benzoate (66)



This compound was synthesized following the same method of compound **65**, using *O*-D-benzoic acid (122.2 mg, 1.00 mmol), 1-hexyne (229 µL, 2.00 mmol) and purified by column chromatography, yielding the product as a colorless oil (160.0 mg, 78%). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.11 (dd, *J*=8.3, 1.2 Hz, 2H), 7.61-7.64 (m, 1H), 7.49-7.52 (m, 2H), 8.11 (t, *J* = 7.4 Hz, 2H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.39-1.47 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 163.5, 134.1, 133.4, 129.8, 129.5, 128.6, 114.9, 31.4, 24.2, 22.3, 13.7 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$): δ = 7.37 (br, 1D) ppm. **EA** Calcd for $C_{13}H_{15}O_2D$: C, 76.07; H, 7.37. Found: C, 76.13; H, 7.30. **MS** (Ion trap, EI): *m/z* (%) = 205 (2, [M^+]), 105 (100), 77 (13), 51 (5).

Synthesis of 1-deutero-(*Z*)-hex-1-en-2-yl] benzoate (68)



An oven-dried flask was charged with *p*-cymene ruthenium(II) chloride dimmer (6.4 mg, 0.01 mmol) tri-(2-furyl)phosphine (9.3 mg, 0.04 mmol), benzoic acid (122 mg, 1 mmol), and sodium carbonate (4.2 mg, 0.04 mmol) and flushed with argon. Subsequently, dry toluene (2.0 mL) and 1-D-hexyne (234 µL, 2.0 mmol) were added via syringe. The resulting solution was stirred for 15 h at 60 °C and was then poured into aqueous

$NaHCO_3$ solution (30 mL). The resulting mixture was extracted repeatedly with 20 mL portions of ethyl acetate, the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:1), yielding the product as a colorless oil (150.0 mg, 73%). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 9.7 Hz, 2H), 7.58 (t, *J* = 6.8 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 4.83 (s, 1H), 2.33 (t, *J* = 7.7 Hz, 2H), 1.35-1.42 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (151 MHz, $CDCl_3$): δ = 164.8, 156.8, 133.2, 129.92, 129.90, 128.4, 101.0 (t, $J_{C\text{-}D}$ = 25 Hz), 33.1, 28.6, 22.1, 13.8 ppm. **^{2}H-NMR** (61 MHz, $CHCl_3$): δ = 4.89 (br, 1D) ppm. **EA** Calcd for $C_{13}H_{15}O_2D$: C, 76.07; H, 7.37. Found: C, 75.99; H, 7.54. **MS** (Ion trap, EI): *m/z* (%) = 205 (1, [M^+]), 105 (100), 77 (11), 51 (4).

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7 Curriculum vitae

Personal information

Name	Kifah S. M. Salih
Date and place of birth	September 2, 1976 in Baghdad
Marital status	Married with a baby "Dania"
Nationality	Iraqi

Education

09.2004	General certificate of secondary school, Iraq
10.1994-07.1998	BSc, chemistry, Al-Mustansiriyah university, Iraq
10.2001-06.2004	MSc, chemistry, the university of Jordan, Jordan Thesis title: Synthesis of some new coumarin derivatives Advisor: Prof. Dr. Mohammad S. Mubarak
10.2006-07.2010	PhD, organic chemistry, Technische Universität Kaiserslautern, Germany Dissertation title: Environmentally benign synthesis of enamides via waste-free catalytic addition of amides to terminal alkynes Advisor: Prof. Dr. Lukas J. Gooßen

Proffessional experience

10.2001-05.2004	Involved in teaching general chemistry and organic chemistry laboratories at the university of Jordan during the master study
05.2004-05.2006	Worked as a researcher on a project related to synthesis of new coumarin and coumarlic acid derivatives
2003-2006	Taught organic and general chemistry, as a tutor for undergraduates