Synthesis of propargylamines via catalytic alkynylation of (poly)halogenated imines

Proefschrift voorgelegd tot het behalen van

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Dankwoord

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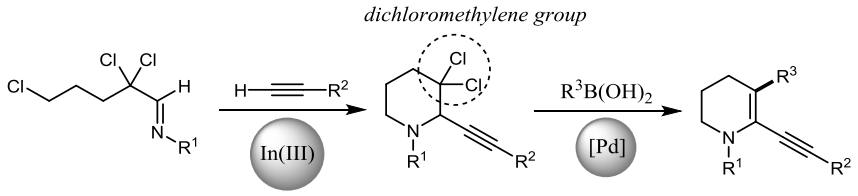
Summary

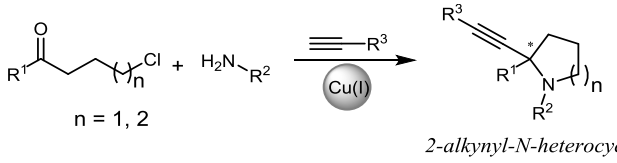
Propargylamines are an important class of organic molecules as they often serve as intermediate products in the synthesis of various nitrogen-containing heterocycles, which are of utmost importance in organic synthesis, because of their occurrence in natural products and applications in pharmaceuticals. Since the late '90s, propargylamines are synthesized via the one-pot, three-component, transition metal catalyzed coupling of amines, aldehydes and alkynes, and is often referred to as the A³ coupling.

In Chapter one, an overview of the literature about alkynylations on preformed imines on one side and the one-pot A³ coupling on the other side will be given, expanding a five year update since the 2012 review titled 'A walk around the A³ coupling' by Van der Eycken *et al*. Different methods based on new, homogeneous catalysts are presented, as well as the use of heterogeneous catalysts, that have received increased attention over the past few years, due to their possibility for re-use. Furthermore, a series of challenging replacements of one of the components in the A³ coupling are presented. Some special A³ couplings including decarboxylative, redox, and asymmetrical A³ couplings are discussed separately. At last, the synthetic utility of propargylamines as key intermediates in the synthesis of various *N*-heterocycles and methods, different from the A³ coupling, for the synthesis of propargylamines are discussed.

In Chapter two, we introduce polyhalogenated imines that possess enhanced electrophilicity compared to non-halogenated imines, as interesting coupling partners for alkynylation. The transition metal of choice for the alkynylations of α-chloro-, α,α-dichloro-, α,α,γ-trichloro- and α,α,δ-trichloro-aldimines, was found to be indium. Furthermore, the synthetic utility of the dichloromethylene group, often present in the synthesized propargylamines, will be exploited by making use of palladium-catalyzed cross-coupling reactions. This reactivity proved to be unique, since the reactivity of the dichloromethylene group in non-alkynylated 3,3-dichloropiperidines proved to be completely different. Finally, the application of the dichloromethylene group, as a coupling partner in the coupling with amines and alkynes in a so-called AHA (amine, haloalkane, and alkyne) coupling, was evaluated.

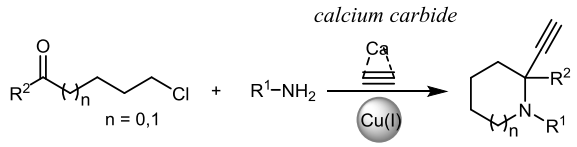


In Chapter three, we turned our attention to challenging A³ couplings and developed a copper(I)-catalyzed three-component coupling of ω-halogenated ketones, alkynes and amines, a so-called KA² coupling leading to interesting 2-alkynyl-*N*-heterocycles.

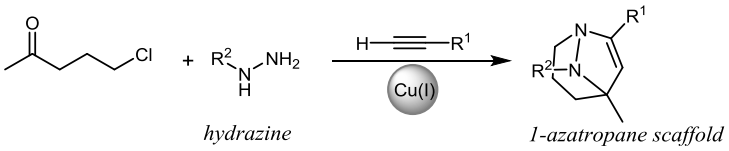


In Chapter four, calcium carbide, as a green and cheap but in organic synthesis underexplored acetylene source, was applied in a coupling of amines with challenging ketones. Calcium carbide can act as a C_2 synthon in alkynylation reactions that otherwise would make use of

TMS-protected acetylene, thereby avoiding a protection and deprotection step, and can thus be regarded as a cheaper and eco-friendlier alternative.



In the last chapter, we replaced the amine component in the KA² reaction developed in chapter three, by a hydrazine component. This replacement led to a change in reactivity, as no alkynylated, but alkenylated products, more specifically 1-azatropane products, were isolated.

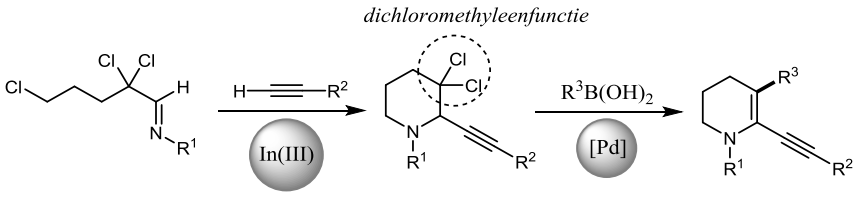


Samenvatting

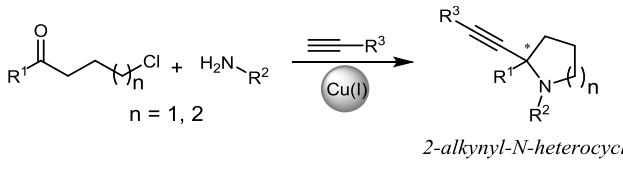
Propargylaminen zijn een belangrijke klasse van organische moleculen omdat ze dikwijls dienst doen als tussenproducten bij de synthese van verschillende stikstofhoudende heterocyclische moleculen, die zeer belangrijk zijn in organische synthese door hun veelvuldig voorkomen in natuurproducten en geneesmiddelen. Sinds het einde van de jaren '90, worden propargylaminen gesynthetiseerd via een één-pots, drie-componenten, transitiemetaal gekatalyseerde reactie van aminen, aldehyden en alkynen. Deze reactie staat beter bekend als de A³-koppeling.

In het eerste hoofdstuk wordt een overzicht van de literatuur gegeven omtrent alkynyleringen van op voorhand bereidde iminen enerzijds, en de één-pots A³-koppeling anderzijds waarbij wordt voortgebouwd op de review getiteld '*A walk around the A³ coupling*', geschreven door Van der Eycken *et al.* in 2012. Verschillende nieuwe homogene katalysatoren, alsook heterogene katalysatoren, dewelke steeds belangrijker worden vermits ze eenvoudig hergebruikt kunnen worden, worden beschreven. Verder wordt het vervangen van een van de componenten in een A³ koppeling, hetgeen als zeer uitdagend wordt aanzien, en een aantal speciale A³ koppelingen, zoals de decarboxylatieve, de redox of de asymmetrische A³ koppeling besproken. Tenslotte wordt de bruikbaarheid van propargylaminen als belangrijke bouwstenen voor de synthese van stikstofhoudende moleculen en andere strategieën om propargylaminen te synthetiseren, besproken.

In hoofdstuk twee, introduceren we polygehalogeneerde iminen, die een groter elektrofiel karakter hebben dan niet-gehalogeneerde iminen, als interessante koppelingspartners voor alkynylering. Het transitiemetaal bij uitstek voor de alkynylering van α-chloor-, α,α-dichloor-, α,α,γ-trichloor- en α,α,δ-trichlooriminen bleek indium te zijn. Voorts werden de synthetische mogelijkheden van de dichloormethyleenfunctie geëxploiteerd in palladium-gekatalyseerde koppelingsreacties. Hierbij bleek de reactiviteit van de dichloormethyleenfunctie uniek te zijn daar voor niet-gealkynyleerde substraten een andere reactiviteit werd waargenomen. Tot slot werd de dichloormethyleenfunctie als koppelingspartner gecombineerd met aminen en alkynen in een zogeheten AHA (amine, haloalkaan, alkyn) koppeling.



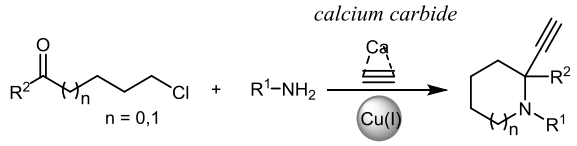
In hoofdstuk drie werd een meer uitdagende koper(I)-gekatalyseerde drie-componentskoppeling van ω-gehalogeneerde ketonen, alkynen en aminen, bestudeerd. Deze zogenaamde KA² koppeling leidde tot interessante 2-alkynyl-*N*-heterocyclische verbindingen.



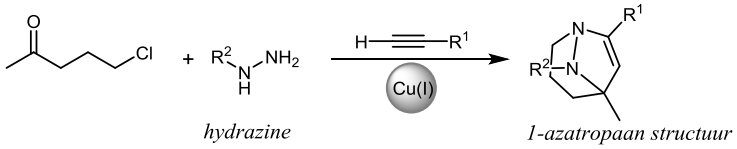
2-alkynyl-N-heterocyclische verbindingen

In het vierde hoofdstuk wordt gebruik gemaakt van calciumcarbide, als een groene en goedkope, maar in de organische synthese weinig gebruikte bron van acetyleen, voor de

koppeling met ketonen en aminen. Calciumcarbide treedt hierbij op als C_2-synthon bij alkynyleringen, die anders gebruik zouden moeten maken van TMS-beschermd acetyleen, waardoor een bescherming- en ontschermingsstap vermeden kan worden en deze strategie dus als goedkoper en duurzamer kan aanzien worden.



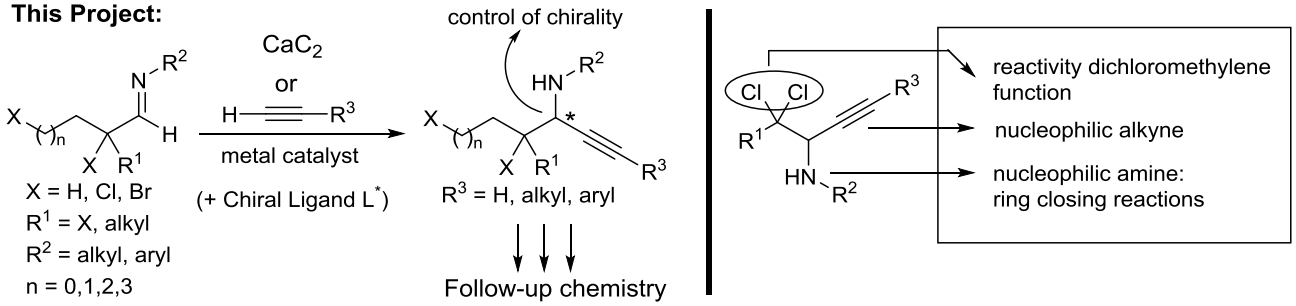
In het laatste hoofdstuk werd de amine component uit de KA² koppeling, ontwikkeld in hoofdstuk drie, vervangen door een hydrazine component. Deze vervanging leidde tot een drastische verandering in reactiviteit vermits hier geen gealkynyleerde producten, maar wel bijzondere en weinig voorkomende 1-azatropaan verbindingen werden geïsoleerd.



Preface

In this thesis it was our goal to investigate alkynylation reactions on polyhalogenated imines derived from polyhalogenated aldehydes and/or ketones to form functionalized propargylamines which offer extra opportunities for conversions to other molecules. Preferentially, this reaction would take place in a three-component reaction of (polyhalogenated) aldehydes, amines and alkynes in a so-called A^3 coupling. As this approach proved impossible for polyhalogenated aldehydes, the required polyhalogenated imines were prepared in a separate step before alkynylation. The presence of halogen atoms should not only render the imine more electrophilic, but also creates a chance for further functionalization. To achieve these goals an overview of closely related literature will be given in the first chapter.

The necessity of α-halogen atoms on aldehydes and more challenging ketones that could be used in A^3 couplings will be investigated. As a bonus, imines might not have to be prepared in a separate step and the ω-halogen atom in these substrates offers the opportunity for an extra ring-closing reaction, making the synthesis of azaheterocyclic compounds possible. At the start of this PhD, calcium carbide was an underexplored reagent in organic synthesis, and thus we envisioned this reagent as alternative acetylene source for alkynylations.



Separate numbering of molecules and references in each chapter will start from **1**. After each chapter the experimental details and reference list can be found. NMR-spectra can be found in a separate appendix to this thesis.

Outlook

1 Alkynylation reactions of imines and the A³ coupling

Since the 2012 landmark review by Van der Eycken *et al.* about synthetic methodologies for the synthesis of propargylamines via the one-pot coupling of amines, aldehydes and alkynes (abbreviated as A³ coupling), not much more work was invested in new methods for A³ couplings. Method generation and optimization was done in the past and only few challenges remain.

In recent years more emphasis was put on the use of heterogeneous catalysts in A³ couplings, with the aim of recycling this catalyst in view of developing greener and more environmentally friendly syntheses, thus generating less waste. Many of these catalysts are made via deposition of traditional A³-coupling transition metal catalysts, based on Cu(I)-, Cu(II)-, Au(I)-, Ag(I)-, Fe(II)-, Fe(III)-salts, onto different heterogeneous 'carriers'.

Expansion of the substrate scope and functional group tolerance for A³ couplings remains a domain of interest and is reviewed according to the replacement or expansion of one of the three A³ components. One example of this can be found in recent advances concerning the replacement of the aldehyde component by a more challenging ketone component, described as KA² couplings, and will be discussed separately in Chapter 3. Decarboxylative and redox-A³ couplings have gained interest over the last years and are thus included in this chapter. For asymmetric A³ couplings, one new class of ligands has been introduced, next to well-established chiral ligands.

In situ generation of imines is not always possible, and therefore imines sometimes must be synthesized in a separate step prior to alkynylation. Alkynylation methods for these special types of imines will also be discussed.

Next, the popularity of the A³ coupling is underlined by the overwhelming attention that the synthetic utility of propargylamines has received. Many examples exist of coupling reactions of propargylamines with other compounds (isocyanides, isothiocyanates, carbon dioxide, …) to form, among others, *N*-heterocycles, and underlining the importance the synthesis of propargylamines.

Lastly, methods for the generation of propargylamines other than A³ coupling will be discussed.

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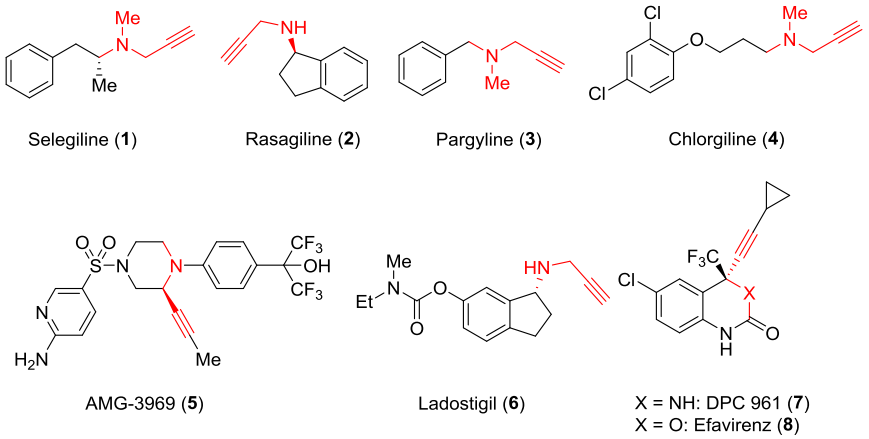
1.1 Introduction

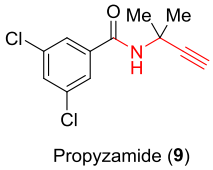
1.1.1 Propargylamines

Propargylamines, that are alkynes bearing an amine function on the propargylic position – indicated in red in molecules **1-11**, are very important building blocks for organic synthesis. Propargylamines as such can be found in therapeutics such as the selective Monoamine Oxidase B (MAO-B) inhibitors selegiline (Eldepryl®, **1**), rasagiline (Azilect®, **2**), pargyline (Eutonyl®, **3**) and the Monoamine Oxidase A (MAO-A) inhibitor chlorgiline (**4**, never marketed), which are used to treat Parkinson's disease.[1] AMG-3969 (**5**) is a compound that disrupts the glucokinase-glucokinase regulatory protein interaction, and is important for the treatment of diabetes.[2] Ladostigil (**6**) is a combined MAO-B inhibitor, reversible acetylcholinesterase and butyrylcholinesterase inhibitor, and is used to treat Alzheimer's, Parkinson's and Lewy body disease.[3] Another example is dihydroquinazoline DPC 961 (**7**), a 2nd generation HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) that is an analogue of Efavirenz (**8**) (Scheme 1-1).[4]



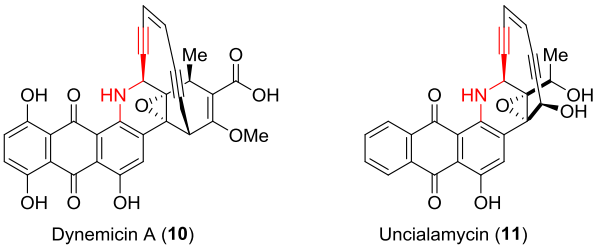
Scheme 1-1 Examples of therapeutics containing a propargylamine moiety.

The propargyl moiety can also be found in the herbicide Propyzamide (**9**) (Scheme 1-2).[5]



Scheme 1-2 The herbicide Propyzamide.

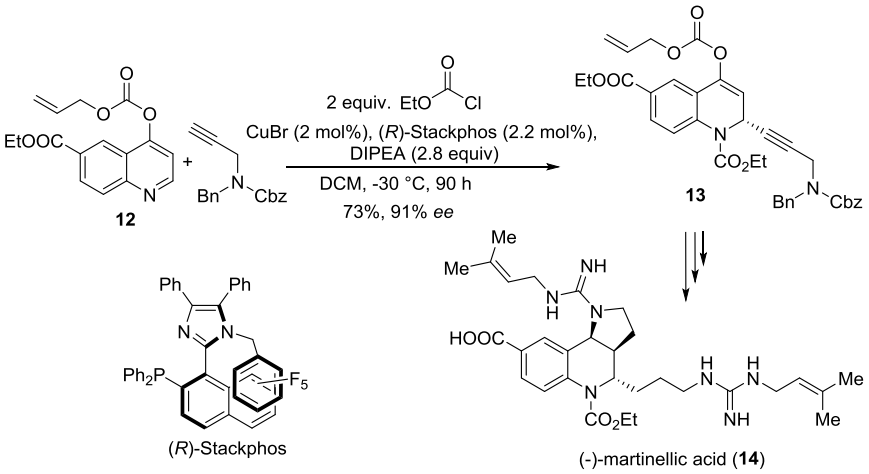
Propargylamines are rarely found as such in natural products, and rare examples are Dynemicin A (**10**), which is isolated from *Micromonospora chersina* and has antibiotic properties,[6] and Uncialamycin (**11**), which is isolated from *Cladonia uncialis* and also shows antibiotic activity (Scheme 1-3). Unsurprisingly, the two molecules are thought to be synthesized via similar biosynthetic pathways.[7]



Scheme 1-3 Natural products Dynemicin A and Uncialamycin.

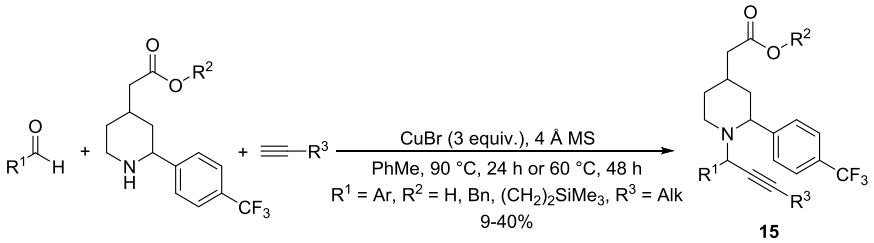
1.1.2 Synthetic utility

More important, besides their occurrence in nature and pharmacy, is that propargylamines often serve as precursors for the synthesis of other *N*-containing structures such as allylamines, pyrrolidines, oxazoles, pyrroles, and so on, as will be described *in extenso* in §1.4. Propargylamines are therefore also often intermediates in the total synthesis of biologically interesting molecules. Scheme 1-4 shows the total synthesis of (-)-martinellic acid, a compound isolated from the root bark extracts of *Martinella iquitoensis*, starts with enantioselective alkynylation of a quinoline derivative **12**, leading to propargylamine **13**, which can be further converted to (-)-martinellic acid (**14**).[8]



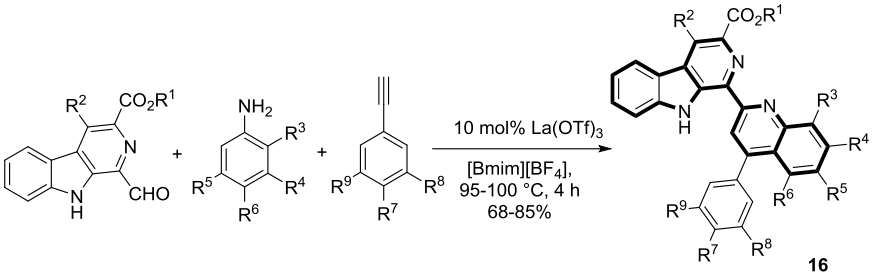
Scheme 1-4 The total synthesis of (-)-martinellic acid goes via a propargylamine intermediate.

In general, multicomponent reactions are preferred reactions in Diversity Oriented Syntheses (DOS). By varying the starting materials, different substituted scaffolds can be generated quickly, leading to libraries of potentially biologically interesting molecules. A³ couplings are excellent late-stage reactions for generating these libraries.
The synthesis of highly potent acidic γ-secretase modulators, equipped with photosensitive moieties for photoaffinity labeling is important in the research area of Alzheimer's disease. The synthesis of these modulators is done via an A³ coupling, yielding propargylamines **15**, which all showed some biological activity (Scheme 1-5).[9]



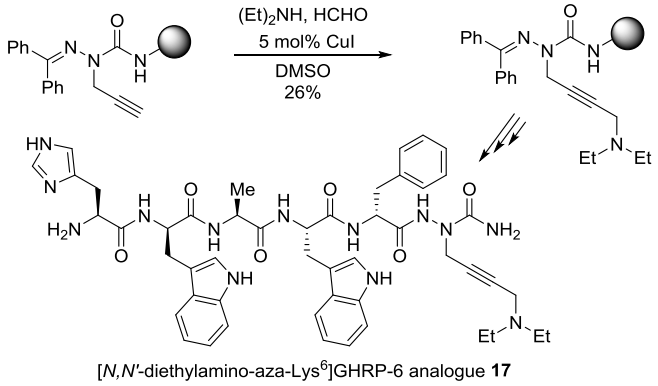
Scheme 1-5 A³ coupling for the synthesis of γ-secretase modulators.

The A³ coupling can also be used for example to synthesize Nitramarine analogues **16** in a straightforward fashion via a $La(OTf)_3$ catalyzed A³ coupling in an ionic liquid (Scheme 1-6).[10] In this way, the A³ coupling can be used to generate complex and versatile products from simple starting materials in a diversity-oriented synthesis (DOS) strategy.



Scheme 1-6 Nitramarine scaffold (in bold) synthesis via A³ coupling; a DOS strategy approach.

Propargylamines are also often found in peptide chemistry. Lubell and co-workers for example used an A³ coupling in the synthesis of azapeptide **17** (Scheme 1-7).[11]



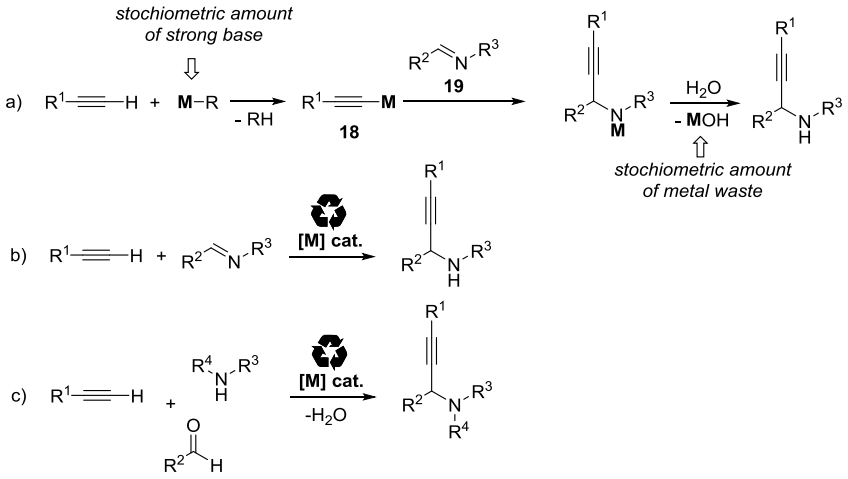
Scheme 1-7 A³ coupling used in peptide chemistry.

The introduction of alkynes in peptide chemistry has a very specific reason. Since the synthesis of peptides often includes a high number of individual reaction steps, the yield of these individual reactions must be very high to allow for an acceptable overall yield. Therefore, peptide chemistry often uses quick and high yielding reactions such as the [3+2] cycloaddition of azides and alkynes leading to triazoles to 'click' two fragments on to each other.

All these examples highlight the importance of the synthesis of propargylamines. In what follows, methods for the generation of propargylamines will be discussed.

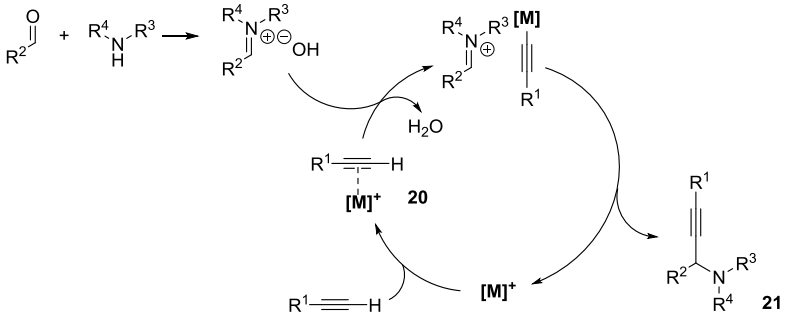
1.2 Methods for the generation of propargylamines: from classical approaches to the A³ coupling

Classically, propargylamines are made by the addition of a metal acetylide **18** to an imine **19** (Scheme 1-8a). The generation of the metal acetylide usually needs strong bases to deprotonate the relatively weakly acidic proton of the alkyne (pK_a around 25-30). Strong bases such as *n*-BuLi, LDA or organomagnesium compounds are not compatible with functionalized imines, and therefore the metal acetylides must be synthesized in a separate step. Next to this extra step, this strategy also causes stoichiometric amounts of metal waste, something that modern day organic chemists try to avoid as much as possible. Organic chemists thus came up with a procedure that could make the metal acetylide *in situ* from a terminal alkyne, a transition metal catalyst (often Cu(I)-, Cu(II), B(III)-, Ag(I)-, Zn(II)-, Zr(IV)-, Fe(III)-, Ni(II)-, Au(I)-, Au(III)-, In(III)- or Ir-complexes) and a weak base such as an amine (Scheme 1-8b). In this way the atom economy of the transformation is improved, generating less waste. The imine or iminium ion could then also be formed *in situ* from a condensation of aldehyde and amine; subsequent alkynylation would lead to propargylamines with only one equivalent of water as the sole by-product. This approach can be considered as the birth of the A³ (aldehyde, amine, alkyne) coupling (Scheme 1-8c).



Scheme 1-8 Different pathways for the generation of propargylamines (a) Classical pathway for the generation of propargylamines (b) catalytic pathway for the generation of propargylamines (c) A³ coupling.

Scheme 1-9 shows the mechanism of the A³ coupling that starts with C-H activation of the alkyne by the metal catalyst, forming a metal-π-alkyne complex **20**. This renders the C-H bond more acidic so that it can be deprotonated by any weak base present in the reaction medium (starting amine, intermediate imine/iminium, or final propargylamine). The formed metal acetylide reacts with the imine/iminium ion to form the propargylamine **21** and hereby regenerates the active catalyst.



Scheme 1-9 General mechanism of the A³ coupling.

Earliest reports of A³ couplings date from the middle of the 20th century where a copper-catalyzed Mannich reaction of trioxane, a secondary amine and a terminal propargyl alcohol was described to form propargyl amino ethers.[12] In 1998 Dax and coworkers described a solid-phase synthesis of propargylamines via the coupling of aldehydes, alkynes and secondary amines, promoted by two equivalents of CuCl.[13] Later that year, Dyatkin and Rivero described similar couplings of aldehydes, alkynes and secondary amines, using a catalytic amount (10 mol%) of CuCl.[14] This synthesis meets all criteria of an A³ coupling and can thus be seen as the first reported A³ coupling.
Since then, the A³ coupling became a popular tool to synthesize propargylamines and the scope of the reaction was largely expanded by different research groups. Some five years ago, Van der Eycken *et al.* wrote a landmark review titled 'A walk around the A³-coupling'[15], describing the literature since Dyatkin and Rivero's first report. Herein, they did not only describe different A³ coupling methods, but also the synthetic utility, asymmetric A³ couplings, modifications of A³ couplings and tandem reactions involving A³ couplings. They rightly mentioned that most method optimization was done for A³ couplings that use anilines or secondary amines, and the possibility for method generation that use primary amines was left open. It is our aim to make an update since this review-article.

1.3 A³ coupling since 2012

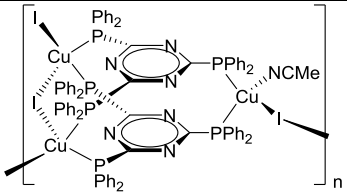
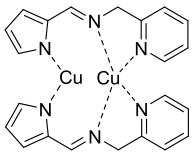
Since 2012, the main focus in the research that concerns A³ couplings has shifted from method optimization to the use of new catalysts, either as homogeneous or preferentially as heterogeneous catalysts. Together with further method development to extend the scope of the A³ coupling, replacement of one of the coupling partners to generate slightly different A³ couplings has led to research topics such as the KA² coupling (ketone instead of aldehyde), AHA coupling (haloalkane instead of aldehyde), decarboxylative A³ (mostly using carboxylated alkynes) and redox A³ (related to cross dehydrogenative couplings). Lastly, the search for new and more selective ligands in the asymmetric A³ or AA³ coupling will remain a topic of interest.

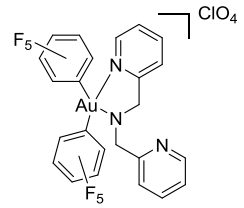
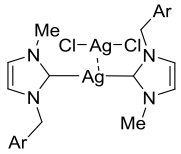
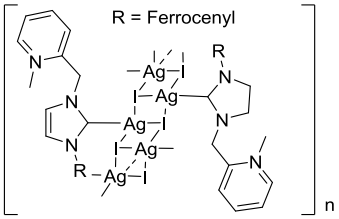
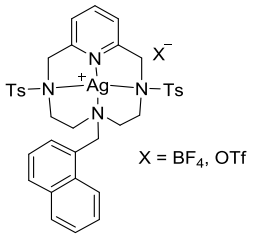
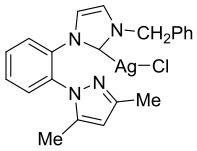
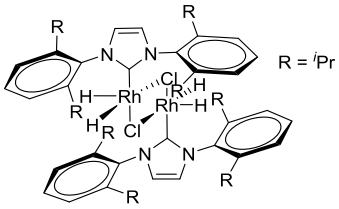
1.3.1 Homogeneous catalysts

The most popular catalysts in A³ coupling remain group 11 transition metals or 'coinage metals' such as Cu(I), Cu(II), Ag(I), Au(I) and Au(III). Therefore, it is not surprising that most new methods make use of these metal cations in combination with new counter ions and/or ligands to fine-tune the reactivity of the complex. In Table 1-1, an overview of new homogeneous catalysts developed for A³ couplings since 2012 is presented. Entry 1 shows a Cu(I) complex that was made via reaction of 2,4,6-tris(diphenylphosphino)-1,3,5-triazine with Cu(I)-salts. When CuI was used, the complexes exhibited a polymeric structure. This complex was used in simple A³ couplings, *i.e.* coupling of aldehydes, secondary amines and alkynes,

with a catalyst loading as low as 0.1 mol% and resulted in high yields. Entry 2 shows a dinuclear Cu(I) complex, comprising of two Cu(I) cations and two (2-picolyliminomethyl)pyrrole anions. The dimeric structure is stable in solution, and able to efficiently catalyze simple A³ couplings. Entry 3 describes a Cu(I) complex made from an equimolar ratio of CuCl and *tert*-butyldiallylphosphine and has a cubane-like structure. This catalyst can be used in low catalyst loading (0.5 mol%) to catalyze simple A³ couplings under mild reactions conditions. Entry 4 shows a Au(I) catalyst, which shows decent reactivity towards A³ coupling, even in very low (0.05 mol%) catalyst loadings. The complex is special in a way that in the solid state the ligand coordinates with one nitrogen atom to the gold atom, whereas in solution a rapid exchange between the two pyridine sites occurs, providing fluxional behavior. This complex also shows important cytotoxic activity against human tumor cell lines. Entries 5-8 describe Ag(I)-NHC complexes, which are used in simple A³ couplings. Entry 9 describes a Rh-NHC complex that can catalyze A³ couplings of aliphatic aldehydes, anilines and silylated alkynes. In 2012, Larsen and co-workers described a $Cu(OTf)_2$ catalyzed A³ coupling with primary amines and aliphatic/aromatic aldehydes/alkynes, also a single example of KA² coupling was shown. Experiments showed that the reaction rate was dependent on $Cu(OTf)_2$, and that by adding CuBr or CuI no increase in rate could be observed (Entry 10). While most method development focuses on increasing yield, Van der Eycken *et al.* were more interested in developing greener reaction conditions for the A³ coupling, describing the use of a $CuCl/CuCl_2$ catalytic system with water as eco-friendly solvent (Entry 11). Entry 12 shows the catalytic activity of some Cu(I)-Buchwald-type phosphane ligands, which lead to very high yields in simple A³ couplings. Entry 13 describes a Cu(II) complex coordinating with benzotriazole coordinating compounds for simple A³ couplings. Entry 14 describes $MnCl_2$ as efficient catalyst for A³ couplings. Also, a special type of amine, (*S*)-azidomethylpyrrolidine is used, resulting in A³ coupling, followed by intramolecular azide-alkyne 'click' reaction.

Table 1-1 Different homogeneous catalysts used in A³ couplings.

Entry	Catalyst	Reaction conditions	Yields	Ref.
1		0.1% catalyst, wet MeCN, MW, 100 °C, 5 min. Aryl/alkyl acetylenes, secondary amines and formaldehyde.	76-95%	[16]
2		0.4% catalyst, toluene, 110 °C, 2 h. Aryl/alkyl aldehydes and acetylenes, secondary amines.	81-99%	[17]
3	$[CuCl(^tBu\text{-}P(CH_2CH{=}CH_2)_2)]_4$	0.5% catalyst, neat, 50 °C, 6 h. Aryl/alkyl aldehydes/acetylenes, secondary amines.	15-99%	[18]

4		0.05-1% catalyst, neat, 40 °C, 24 h. Aryl aldehydes and acetylenes, secondary amines.	30-99%	[19]
5		3% catalyst, different solvents, 80 °C, 8 h. Phenylacetylene, alkyl/aryl aldehydes, secondary amines.	12-88%	[20]
6		0.5-3% catalyst, DMF, 80 °C. Aliphatic aldehydes or formaldehyde, phenylacetylene, secondary amines.	69-96%	[21]
7		3% catalyst, toluene, 150 °C, MW, 10 min. Aliphatic/aromatic aldehydes and alkynes, secondary amines. 3 examples of KA².	24-96%	[22]
8		1.5-3% catalyst, dioxane, 80 °C. Aliphatic/aromatic aldehyde, phenylacetylene, secondary amines.	13-97%	[23]
9		5% catalyst, benzene-d_6, 80 °C, 5-48 h. Aliphatic aldehydes, anilines, silylated alkynes.	36-98%	[24]
10	$Cu(OTf)_2$	10% catalyst, toluene, 2-72 h, 60-100 °C. Aliphatic/aromatic aldehydes and alkynes, primary amines. A single KA² example.	70-97%	[25]
11	$CuCl/CuCl_2$	10/10% catalyst, 110 °C, MW, water, 25 min. Aliphatic/aromatic aldehydes and alkynes, primary amines.	41-96%	[26]
12	Cu(I) complexes with Buchwald-type phosphane ligands	6% catalyst, toluene/water, 50 °C, 0.2-24 h. Formaldehyde, aliphatic/aromatic alkynes, pyrrolidine.	>90%	[27]

13	$[Cu(L^1)_2(CF_3SO_3)_2]$ L^1 = 1,2-bis((1*H*-benzo[*d*][1,2,3]triazol-1-yl)-methyl)benzene	2% catalyst, Aliphatic/aromatic aldehydes/alkynes and secondary amines.	57-100%	[28]
14	$MnCl_2$	10% catalyst, neat, 90 °C, 12 h. Aliphatic/aromatic aldehydes/alkynes and secondary amines.	65-98%	[29]

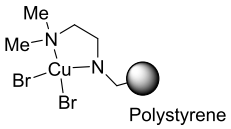
1.3.2 Heterogeneous catalysts

The use of heterogeneous catalysts has, in general, a few advantages over the use of homogeneous catalysts (Table 1-2). Heterogeneous catalysts are mostly easy recoverable by simple filtration of the resulting reaction mixture or by magnetic recovery if the catalyst/support has magnetic properties. The recovery of the catalysts allows the catalyst to be reused (several times), until eventually the catalyst loses catalytic activity due to catalyst inhibition or poisoning (degradation). From an environmental point of view this recovery is very important, since it limits hazardous metal waste. On the other hand, expensive metals can be reused, lowering the cost price of the catalyst in the synthesis. Although heterogeneous catalysts only seem to have advantages over homogeneous catalyst, this is not entirely true. Homogeneous catalysts have, in general, higher TON and TOF values, because of a better contact (fine dispersion) in the liquid phase. For A^3 couplings, popular homogeneous catalysts like group 11 transition metals (Cu, Ag, Au), are often deposited on so-called 'supports' or supporting materials.

In 2012 Yus *et al.* described the use of oxidized copper nanoparticles (CuNP's) on TiO_2 as an efficient catalyst for simple A^3 and KA^2 couplings (entry 1). A comparison between their catalyst and classical Cu(I) and Cu(II) salts showed enhanced catalytic activity for the CuNP's. The reusability of the catalyst was checked for four cycles with considerable loss of activity (98% → 79%). In entry 2, porous Cu/Al nanocomposites can catalyze simple A^3 couplings, with virtually no loss of activity after five cycles (yields remain >90%). Entry 3 described a catalytic system of monodispersed CuNP's on silica-support. The catalyst was used for A^3 couplings and TON's between 891 and 1032 were obtained. However, the reusability of the catalyst was not investigated, and only a small scope with six examples was presented. Entry 4 describes a Cu(0) supported on montmorillonite catalyst for simple A^3 couplings. Yields are slightly decreasing after new catalytic cycles from 94% to 88% over three cycles. Entry 5 shows a polystyrene-supported Cu(II) complex which is used for simple A^3 couplings. However, a leaching loss of 6% is observed after five cycles, decreasing the yield similarly by 5%. Entry 6 shows a tetra-nuclear macrocyclic Cu(II) complex, made from $Cu(OAc)_2.H_2O$, *N*-acetyl-L-phenylalanine and 4,4-bipyridine. This is an atypical heterogeneous catalyst since it has no support but is, nevertheless a rather stable macrocyclic complex. The complex can be recycled and reused in consecutive catalytic cycles with virtually no loss of activity. Entry 7 describes a catalytic system where $CuCl_2$ is deposited on graphene oxide, treated with 3-aminopropyltriethoxysilane, and this catalyst is used for simple A^3 couplings. Atomic absorption spectroscopy (AAS) experiments proved that the copper content in the resulting propargylamines is far lower (0.006 wt%) than when a homogeneous copper source is used (3.26 wt%). Furthermore, leaching was considered not significant since yields after five cycles only reduced slightly (96-88%). Entry 8 described CuI supported on amberlyst A-21, which possesses dimethylbenzylamine end groups that chelate with the copper ion. Consistent performance was seen over the first five recycling cycles, after which

the performance starts to drop considerably. Entry 9 describes a Cu@PMO-IL complex that is copper supported on periodic mesoporous organosilica, made from hydrolysis and polymerization of ionic liquid precursors. The decrease of the catalytic activity only led to a loss of yield of 6% after seven cycles. Entry 10 describes Cu(II) nanoparticles deposited on graphene nanosheets for simple A^3 couplings. TON values lie between 75-140. Reuse was tested, and no loss of yield was seen in the first five cycles. Entry 11 describes a magnetically separable CuO nanoparticles supported on graphene oxide catalyst for simple A^3 couplings. Recovery of the catalyst is easily done by applying an external magnet. After washing and air-drying, the catalyst can be reused in a next experiment. No significant loss of yield is observed after four cycles. Entry 12 describes the formation of CuO NP's from $CuCl_2$ and aqueous plant extracts from *Anthemis nobilis*. Recycling of the catalyst was done by centrifugation and does not lead to significant lowering of the yield. Different Cu-based heterogeneous catalysts have been discussed, and more information can be found in the 2016 review concerning the synthesis and applications of Cu-based NP's by Varma *et al.*[30] Entry 13 shows the polystyrene-supported *N*-phenylpiperazine-$CuBr_2$ complex that is used in KA^2 couplings of cyclic ketones. The reaction yield decreases by 8% after five consecutive cycles. Entry 14 shows the catalyst Cu(II)-carboxymethylcellulose made from sodium carboxymethylcellulose via exchange of the sodium ions for copper ions. The catalyst can catalyze simple A^3 couplings and slightly more difficult A^3 couplings with anilines, albeit in low yields. The catalyst can be reused and after four cycles the yield only drops from 88 to 79%. Entry 15 describes Cu(II) on hydromagnesite as catalyst for A^3, decarboxylative A^3 and KA^2 couplings. The catalyst is easily made from hydromagnesite and $CuCl_2$. A hot filter experiment, where the catalyst was filtered off 'hot' at half conversion, revealed no further conversion, thus proving that there is no leaching of copper into the reaction mixture. The reasoning for the very low catalyst loading and high yields was explained by the synergistic effect of both Cu^{2+} and Mg^{2+}, present in the hydromagnesite support. Entry 16 describes the use of Cu(II) on starch, prepared from $Cu(OAc)_2.H_2O$, starch micro particles and sodium borohydride. The structure is stable, with negligible leaching for temperatures up to 300 °C, and this was confirmed by recycling experiments, where only 10% yield is lost after five cycles. Entry 17 describes a copper complex containing decavanadate nanocluster, prepared from $Cu(NO_3)_2.4H_2O$ and NH_4VO_3. It can be used in A^3 and azide-alkyne cycloadditions. Recycling experiments, however, are missing. Entry 18 describes a catalyst where copper nanoparticles are deposited on nanoporous carbon, metal-organic framework. High yields were obtained for simple A^3 couplings; however, no information is given about reuse of the catalyst. Entry 19 describes a hierarchically porous sphere-like copper oxide catalyst used for A^3 coupling and tandem reactions. Recovery experiments show that no catalytic activity is lost over the first five cycles.

Table 1-2 Overview of heterogeneous copper catalysts used in A³ couplings.

Entry	Catalyst	Reactions conditions	Yield	Ref.
1	Cu_2O on TiO_2	0.5 mol%, neat, 70 °C, 4-24 h. Aliphatic/aromatic aldehydes and alkynes, secondary amines. Two examples of KA².	52-99%	[31]
2	Cu/Al nanocomposites	0.12 mol%, toluene, 100 °C, 22 h. Aliphatic/aromatic aldehydes/alkynes, secondary amines.	81-96%	[32]
3	$Cu@SiO_2$	50 mg catalyst/mmol, toluene, 110 °C, 5-6 h. Aromatic aldehydes, phenylacetylene, secondary amines.	82-95%	[33]
4	Cu^0@montmorillonite	0.05 mol%, toluene, 110 °C, 3-5 h. Aromatic aldehydes, aliphatic/aromatic alkynes, secondary amines.	82-94%	[34]
5		0.03 mol%, toluene, 110 °C, 6 h. Aromatic aldehydes, phenylacetylene, secondary amines.	64-95%	[35]
6	Macrocyclic $C_{92}H_{96}Cu_4N_{12}O_{29}$	0.05 mol%, dioxane, 80-120 °C, 12 h. Aliphatic/aromatic aldehydes/alkynes, secondary amines.	14-99%[a]	[36]
7	$CuCl_2$ on graphene oxide	0.6 mol%, 90 °C, MW, 20 min. Aromatic aldehydes/formaldehyde, aliphatic/aromatic alkynes, secondary amines.	85-96%	[37]
8	CuI on Amberlyst A-21	10 mol%, neat, 100 °C, Aromatic/aliphatic aldehydes/alkynes, secondary amines.	70-98%	[38]
9	Cu@PMO-IL	0.15 mol%, chloroform, 24 h. Aromatic/aliphatic aldehydes, phenylacetylene, secondary amines.	82-99%	[39]
10	CuO NP's on graphene nanosheets	0.7 mol%, MeCN, 82 °C, 3-12 h. Aromatic aldehydes/alkynes, secondary amines.	52-98%	[40]
11	Fe_3O_4NP's/GO-CuONP's	20 mg, EtOH, 90 °C, 24 h. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	50-88%	[41]
12	CuO NP's/plant extract	8 mol%, 90 °C, toluene, 5 h. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	72-87%	[42]
13	*N*-phenylpiperazine-$CuBr_2$ on PS	0.2 mol%, 110 °C, 6 h. Cyclic ketones, aliphatic/aromatic alkynes and secondary amines in KA² couplings.	75-98%	[43]
14	Cu(II)-carboxymethylcellulose	5 mol%, neat, 100 °C. Aromatic/aliphatic aldehydes/alkynes and secondary amines or anilines.	20-88%	[44]
15	Cu(II) on hydromagnesite	0.013 mol%, neat, 110 °C. Cyclic ketones or aldehydes, aromatic/aliphatic and carboxylated alkynes and secondary amines.	63-95%	[45]
16	Cu(II) on starch	0.3 mol%, THF, 60°C, 20 h. Aromatic/aliphatic aldehydes, phenylacetylene and secondary amines.	88-96%	[46]

17	$Na_2[Cu(H_2O)_6]_2(V_{10}O_{28}).4H_2O$	0.7 mol%, toluene, 100 °C, 12 h. Aromatic aldehydes, aliphatic/aromatic alkynes and secondary amines.	42-90%	[47]
18	Cu@MOF-5-C	20 mg, toluene, 110 °C, 6 h. Aliphatic/aromatic aldehydes/alkynes and secondary amines.	75-99%	[48]
19	HS-CuO	4 mg, neat, 110 °C, < 2 h. Aromatic aldehydes, aliphatic alkynes and secondary amines.	60-95%	[49]

[a] Conversion instead of yield.

Table 1-3 gives an overview of heterogeneous catalysts for A³ couplings based on more than one transition metal. Entry 1 describes the use of gold nanoparticles deposited on ZnO. Direct excitation of metallic nanoparticles (or Plasmon Mediated Catalysis) can be achieved by using LED light (ν = 530 nm) to catalyze the A³ coupling. In this way, simple A³ couplings can be achieved in short times at room temperature. In some cases, significant amounts of Glazer-homocoupling product, that is Cu-catalyzed homocoupling of alkynes in the presence of oxygen, are obtained. Entry 2 describes the use of nano copper(I)oxide and zinc oxide. The catalyst can be easily reused by centrifugation of the catalyst from the reaction mixture. Reusing the catalyst ten times is possible, without any loss of activity. Hot filtration experiments also showed no leaching of the heterogeneous catalyst. It is noteworthy that the catalyst is easily prepared by standard lab techniques assuring its general use. Entry 3 shows the use of Cu_2O/nano-$CuFe_2O_4$ as magnetically recoverable catalyst for A³ and KA² coupling. The catalyst did not show any form of leaching, and the catalytic performance did not change over five cycles. Entry 4 describes the use of copper(I) deposited on Fe_3O_4 nanoparticles, functionalized by bisimidazole ligands as a catalyst for simple A³ couplings. Other, similar catalysts (Cu(II), Ni(II) and Co(II)) were also able to catalyze A³ couplings, but Cu(I) gave the best result yield-wise. Entry 5 shows the use of Cu_2O deposited on nano Fe_3O_4@TiO_2, which is magnetically recoverable, for simple A³ and KA² couplings. The catalyst can be easily recovered with an external magnet and reused without apparent loss of activity. Entry 6 describes the use of Fe(III) deposited on TiO_2 nanoparticles. The use of this catalyst in a neat and microwave-promoted A³ coupling was reported. Recycling experiments were done and proved that the catalyst did not lose its catalytic activity over five cycles. Entry 7 describes magnetic Fe_3O_4 on TiO_2 core-shell hollow spheres, doped with nano-Ag as catalyst for simple A³ and KA² couplings. The catalyst can be easily recovered with an external magnet and reused without significant loss of activity. Entry 8 describes the use of a catalyst consisting of Au^{3+} ions and Au^0 NP's deposited on a chromium(III) terephthalate MOF, treated with ethylenediamine and salicylaldehyde. With a leaching percentage of 5%, leaching of the catalyst is an issue. Also, the use of toxic chromium might be problematic for certain applications. Next to these disadvantages, reactions require a quite high catalyst loading, making this method less favorable. Entry 9 shows a similar MOF containing chromium and treated with sulfoterephthalic acid, and further doped with a Ag(I) catalyst, used for A³ couplings. The catalysts can be easily recovered by centrifugation and reused without significant loss of catalytic activity.

Table 1-3 Heterogeneous mixed metal catalysts for A³ coupling.

Entry	Catalyst	Reaction conditions	Yields	Ref.
1	AuNP@ZnO	1 mol%, dry MeCN, LED light (ν = 530 nm), RT, 2 h. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	50-95%	[50]
2	Nano Cu_2O/ZnO	~3-4 mol%, neat, 100 °C, 1-2 h. Aromatic/aliphatic aldehydes, cyclic ketones, aromatic alkynes, secondary amines.	80-95%	[51]
3	Cu_2O on nano-$CuFe_2O_4$	1.5 mol%, neat, 90 °C, 1-3 h. Aromatic/aliphatic aldehydes or cyclic ketones, aromatic alkynes and secondary amines.	60-96%	[52]
4	MNPs@BiimCu(I)	0.85 mol%, water, 100 °C, 1.5 h. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	80-99%	[53]
5	Nano-Fe_3O_4@TiO_2/Cu_2O	1.5 mol%, 100 °C, 1 h. Aliphatic/aromatic aldehydes or cyclic ketones, aromatic alkynes, secondary amines.	65-96%	[54]
6	Fe/TiO_2 nanoparticles	1.5 mol%, neat, MW, 245 W, 15 min. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	82-94%	[55]
7	Nano Ag-doped Fe_3O_4@ mesoporous TiO_2	2.1 mol%, neat, 100 °C, 0.5-3 h. Aliphatic/aromatic aldehydes, cyclic ketones, aromatic alkynes, secondary amines.	60-95%	[56]
8	Au@MIL-101-ED-SA	~15 mol% Au, 120 °C, dioxane, 0.5-4 h. Aliphatic/aromatic aldehydes/alkynes, secondary amines.	9-95%	[57]
9	MIL-101(Cr)-SO_3Ag	0.15 mol% Ag, neat, 100 °C, 4-8 h. Aliphatic aldehydes, aromatic/aliphatic alkynes and secondary amines.	92-98%	[58]

In Table 1-4, heterogeneous catalysts based on gold will be discussed. Entry 1 shows gold nanoparticles on periodic mesoporous organosilica with an alkylimidazolium framework. This catalyst can catalyze simple A³ couplings and can be recovered and reused for several times with slowly decreasing activity, but leaching is considered negligible. Entry 2 describes the synthesis of two alkoxysilyl-modified ionic liquids, grafted onto mesoporous silica (MCM-41) and used for dispersing $AuCl_3$. Unfortunately, the catalyst suffers from considerable leaching (32 – 65%), limiting the use in applications for this catalyst. Entry 3 describes a Au^0 nanoparticles on modified montmorillonite catalyst for simple A³ couplings. Recycling and reusing can be easily done without the loss of catalytic activity. Entry 4 describes a gold nanoparticles catalyst supported on graphene oxide with ionic liquid framework for oxidative A³ coupling of aliphatic alcohols, aliphatic/aromatic alkynes and secondary amines. Recovery reactions proved the stability of the catalyst over five cycles. Entry 5 describes gold nanoparticles supported on soil fungus *Aspergillus japonicus*. The fungus reduces Au(III) to Au^0 NP's, with a small quantity of Au(I), and the nanoparticles are finely divided on the

fungal mycelia. The catalyst can be recovered via centrifugation, but after three cycles, the yield of the reaction was halved. This was explained by leaching of gold into the reaction medium, making this method less useful. Entry 6 describes a Au(III) catalyst supported on a thermoresponsive hydrogel, which is a polymer made from *N*-isopropylacrylamide and 4-vinylpyridine and exhibits a temperature-dependent phase transition with a low critical solution temperature. The recovery of the catalyst was nicely illustrated by ten recovery cycles, with variable yields between 93 and 90%, illustrating the excellent recyclability of the catalyst. Entry 7 describes the use of phosphine/phenylacetylide ligated gold clusters, supported on titania. Recovery experiments indicate no loss of catalytic activity over the first three cycles. Interestingly, the catalytic activity for aliphatic aldehydes lies much lower than for aromatic aldehydes. Entry 8 describes a gold nanoparticle catalyst, made from $HAuCl_4$, reduced by $NaBH_4$ and deposited on mercaptoethanol functionalized MCM-41, made from MCM-chloride and mercaptoethanol. Recovery experiments revealed that after five cycles only a 5% loss of yield occurred (95→90%), indicating a minimal amount of leaching. Entry 9 describes the use of a quantum-sized gold nanocluster. Recovery of these systems shows considerable loss of catalytic activity (30% after three cycles). In this case, aliphatic alkynes are worse coupling partners than aromatic alkynes. TON numbers of 250 and more underline the good catalytic activity of the catalyst.

Table 1-4 Heterogeneous gold A³ catalysts.

Entry	Catalyst	Reaction conditions	Yields	Ref.
1	Au-PMO-IL	0.2 mol% Au, chloroform, 60 °C, 7-20 h. Aliphatic/aromatic aldehydes, aromatic alkynes, secondary amines.	75-88	[59]
2	$AuCl_3$ on MCM41	Benzaldehyde, phenylacetylene, piperidine, 80 °C, 12 h.	98%	[60]
3	Au NP's on montmorillonite	0.05 mol% Au, toluene, 100 °C, 3 h. Aliphatic/aromatic aldehydes/alkynes, secondary amines.	82-94%	[61]
4	Au@GO-IL	1 mol% Au, water, 18 h, 100 °C, under air. Aliphatic alcohols, aliphatic/aromatic alkynes and secondary amines.	64-98%	[62]
5	Au NP's on soil fungus	40 mg catalyst/mmol SM, 80 °C, THF, 24 h. Aromatic aldehydes, phenylacetylene, piperidine	80-89%	[63]
6	Au(III) on thermoresponsive hydrogel	6.75 mol%, water, 60 °C, 1-15 h. Aromatic/aliphatic aldehydes, aromatic alkynes, secondary amines.	80-100%	[64]
7	$Au_{25}(PPh_3)_{10}(C{\equiv}CPh)_5X_2/TiO_2$	0.01% Au, water, 100 °C, 18 h. Aromatic/aliphatic aldehydes, aromatic alkynes, secondary amines.	30-99%[a]	[65]
8	Au NP's on mercaptoethanol bound MCM-41	2 mol% Au, water, 80 °C, 24 h. Aromatic aldehydes/alkynes, secondary amines.	73-96%	[66]

9	$Au_{38}(SC_2H_4Ph)_{24}$ nanocluster	0.01 mol% Au, 80 °C, neat, 5 h. Aromatic aldehydes, aliphatic/aromatic alkynes and secondary amines.	31-100%	[67]

[a] Conversion instead of yield.

Table 1-5 describes the use of various metals in heterogeneous catalysts for A³ couplings. Entry 1 describes the use of a Ag(I)- exchanged K10-montmorillonite clay as catalyst for A³ couplings. The use of this catalyst allows the reactions to be run under mild conditions in water, at room temperature. Recovery of the catalyst was tested and found to be very good as there was only a slight decrease in yield of 6% over six cycles. Entry two describes the use of a nitrogen rich porous covalent imine network material (CIN-1), made from melamine and 1,4-piparazinedicarbaldehyde and grafted with silver nanoparticles. Under mild conditions, simple A³ couplings can be achieved. The catalyst can be reused, and it was proven that the catalyst does not lose catalytic activity over the first five cycles. Entry 3 describes a similar silver nanoparticles deposited on montmorillonite clay catalyst such as in entry 1. The differences being pretreatment (boiling in HCl) of the montmorillonite and an extra reduction step with $NaBH_4$ of this catalyst, steps which were not included in the synthesis of the catalyst in entry 1. Easy recovery of the catalyst can be done by simple filtration and reuse of the catalyst shows only slightly diminished catalytic activity (~5% over the first four cycles). N_2 adsorption-desorption experiments also show a decrease in specific surface area of the catalyst from 276 to 238 and 212 m²/g over three runs. The synthesis of the catalyst in entry 4 starts with the amination of polyacrylonitrile fibers, while imidazolium salts are formed from imidazoles with methyl chloroacetate, and then reaction with Ag_2O yields Ag-NHC which is then coupled to the fiber in a simple transesterification process. The catalyst can be easily recovered via filtration, and can be reused for at least ten cycles, while the activity remained virtually unchanged. The silver content in filtrates was found to be less than 1.0 ppm Ag. The catalyst was also used in flow and produced excellent results with production of propargylamine in 90% yield with a productivity of 100 mmol/hour. Entry 5 describes the use of $Ag_2(NHC)(PPh_3)_2OTf$ as heterogeneous catalyst for A³ couplings. Although the catalytic system does not appear to be homogeneous at first due to the absence of a heterogeneous supporting material, it can easily be precipitated from the reaction mixture by adding hexane to it, recovery experiments show that the yield of the reaction only drops slightly (99→96%) over five cycles. Entry 6 describes the magnetically recoverable Fe(II, III)oxide deposited on graphene oxide. The advantage of this catalyst is that it can be easily recovered with the aid of a small magnet. The catalyst can also be reused and does not tend to lose activity for at least eight cycles. Entry 7 describes the magnetically recoverable Fe(II, III)oxide deposited on mesoporous SBA-15 as a catalyst for simple A³ couplings. Recycling experiments show no loss of activity over the first five cycles. Entry 8 describes a similar catalyst as entry 6, and only the method of making is different. This catalyst is made from directly from Fe_3O_4 and graphene oxide, whereas the catalyst in entry 6 is made from $Fe(CO)_5$. While in entry 6 only aliphatic aldehydes can be used, here also aromatic aldehydes could be used, but yields were still low. Recovery experiments showed gradual decrease of catalytic activity (from 93 to 71% over twelve cycles). Entry 9 describes a particular example of an indium on silica catalyst, made from $InCl_3$ and tetraethylorthosilicate. Next to a conventional heating method, the authors also developed a MW-assisted method, lowering reaction times greatly. Recovery experiments showed that the catalyst could be recovered for four consecutive times without losing catalytic activity. Entry 10 describes the use of zinc *N*,*N*-bis(2-hydroxyphenyl)pyridine-2,6-dicarboxamide as what seems to be a homogeneous catalyst, but the authors declare that the catalyst could be easily recovered and reused by simple filtration.

Recovery experiments show however, that the catalyst cannot be recovered completely, because every cycle a small part (~2%) remains in solution, resulting in lowered yields for consecutive recovery cycles.

Table 1-5 Various transition metal based heterogeneous catalysts for A³ couplings.

Entry	Catalyst	Reaction conditions	Yields	Ref.
1	Ag(I)-exchanged K10 Montmorillonite	~2 mol% Ag, water or neat, RT or 100 °C, 8-12 h. Aliphatic/aromatic aldehydes/alkynes and secondary amines.	75-92%	[68]
2	Ag NP's on covalent imine network material	50 mg catalyst/mmol SM, water, 40 °C, 3 h. Aromatic/aliphatic aldehydes, aromatic alkynes and secondary amines.	31-98%	[69]
3	Ag NP's on K10 Montmorillonite	0.82 mol% Ag, toluene, 100 °C, 2 h. Aliphatic/aromatic aldehydes/alkynes and secondary amines.	83-95%	[70]
4	Ag-NHC supported by Polyacrylonitrile fiber	1 mol% Ag, 60 °C, MeCN, 1 h. Aromatic/aliphatic aldehydes, aromatic alkynes and secondary amines.	71-92%	[71]
5	$Ag_2(NHC)(PPh_3)_2$ OTf	0.2-1 mol% Ag_2, DCM, 35 °C, 0.25-3.8 h. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	90-99%	[72]
6	Fe_3O_4 on graphene oxide	0.05 mol%, MeCN, 80 °C, 24 h. Aliphatic aldehydes, aromatic alkynes and secondary amines.	65-92%	[73]
7	Fe_3O_4 on SBA-15	5 mol%, toluene, 110 °C, 6-8 h. Aliphatic/aromatic aldehydes/alkynes, secondary amines.	45-93%	[74]
8	Fe_3O_4 on graphene oxide	0.3 mol%, neat, 90 °C, 16 h. Aliphatic/aromatic aldehydes, aromatic alkynes and secondary amines.	37-93%	[75]
9	In/SiO_2	10 mol%, neat, 70 °C, 12 h or 10 min under MW irradiation. Aliphatic/aromatic aldehydes, phenylacetylene, secondary amines.	58-97%	[76]
10	Zinc *N*,*N*-bis(2-hydroxyphenyl) pyridine-2,6-dicarboxamide	2 mol%, water, 70 °C, 1.5-10 h. Aromatic/aliphatic aldehydes, aromatic alkynes and secondary amines.	70-95%	[77]

In general, many different heterogeneous catalysts have been developed in the last few years. Group 11 transition metal ions (Cu^{1+}, Cu^{2+}, Ag^{1+}, Au^{1+} and Au^{3+}) remain the most effective catalysts, but also other catalysts (Fe^{2+}, Fe^{3+}, In^{3+}, Zn^{2+}) have been used to a lesser extent for A³ coupling reactions. Copper remains the most widely used catalyst because of its low price in comparison to silver or gold, the respective chlorides have prices of approximately € 700/mol (CuCl), € 2500/mol (AgCl) and € 50000/mol (AuCl).[78] The price of these metals is undoubtedly related to their earth's abundance and ease for mining. Copper is, for instance, present in the earth's crust at a 68 ppm level, while silver is present at 80 ppb and gold at 4

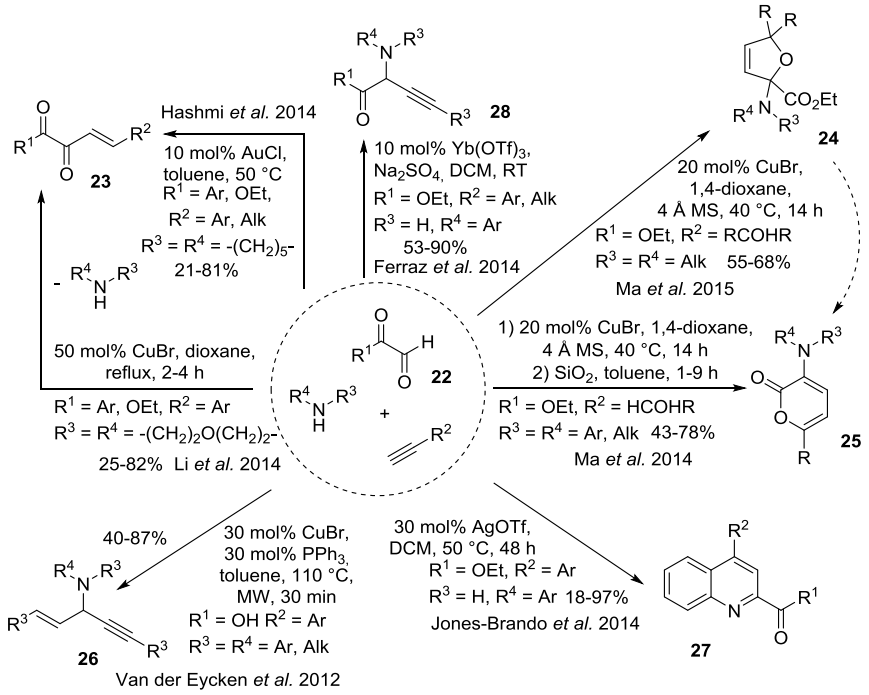
ppb.[79,80] Stockpiles for copper would only be finished in approximately five million years at current rate of extraction, but economical viable reserves will probably be finished in 25 to 60 years.[81] Although copper is a vital metal to our body, high concentrations of copper are considered 'toxic', and concentrations of 2 ppm in drinking water are considered the upper limit.[82] This is a quite high number, so that normally trace amounts of copper in pharmaceuticals do not pose a treat. Copper can, in general, be regarded as the most cost-effective and therefor most widely used transition metal in A³ couplings.

1.3.3 Replacement of components in A³ couplings

In order to widen the substrate scope of the A³ coupling, researchers have been using functionalized aldehydes, alkynes and amines or replacements for one of these coupling partners. Probably the best example, is the logical extension of using aldehydes to ketones. Ketones are generally less electrophilic and more sterically hindered than aldehydes and are thus more challenging substrates for A³ couplings. Whereas most of method optimization for A³ couplings has been done already, the method development for so-called KA² couplings (ketone, alkyne, and amine) is still ongoing. These KA² couplings will be discussed in detail in Chapter 3, together with our efforts in this domain. Another example is the substitution of the aldehyde component by a haloalkane, also known as the AHA (amine, haloalkane, and alkyne) coupling. This coupling will be discussed in detail in §2.6. Other replacements are less obvious, and often more functionalized aldehydes, amines or alkynes are used, where the extra functional groups provide opportunities for ring closure or other reactions. An overview of these reactions will be given here.

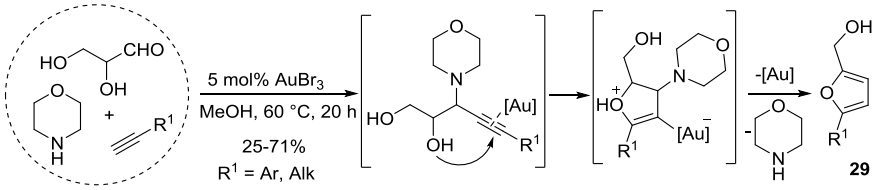
1.3.3.1 Aldehyde replacements

In the first place, functionalized aldehydes will be discussed. A first class of derived aldehydes is glyoxalates **22** (Scheme 1-10). In a first report, the A³ coupling leads to the formation of enones **23**, by a Au(III) catalyzed formation of propargylamines, followed by isomerization of the triple bond to form an allene and subsequent hydrolysis of the *in situ* formed enamine.[83] The same transformation can be achieved with a higher CuBr loading, but this leads to similar yields.[84] The use of ethyl glyoxylate, in combination with a specific propargyl alcohol and a secondary amine, leads under Cu(I) catalysis to 2,5-dihydrofurans **24**.[85] The reaction first forms a propargylamine, then the triple bond is isomerized to an allene moiety, and attacked by the hydroxyl group to form a 2,5-dihydrofuran **24**. In a follow-up paper, Ma *et al.* described the one-pot reaction leading to 3-amino-2-pyrones **25**. The *in situ* formed 2,5-dihydrofuran is then ring opened, forming an iminium. Esterification and aromatization leads to 3-amino-2-pyrones **25**.[86] Van der Eycken *et al.* reported the use of glyoxylic acid in an A³ coupling, catalyzed by CuBr and PPh_3, to generate 3-amino-1,4-enynes **26**. From a mechanistic point of view a decarboxylative A³ coupling occurs, followed by isomerization of the triple bond to form an allene, which is then attacked by a second molecule of copper acetylide to generate 3-amino-1,4-enynes **26**.[87] Jones-Brando and co-workers described an A³ coupling with ethyl glyoxylate, anilines and alkynes that forms quinolines **27**. The product can be formed via two pathways, in pathway one the A³ coupling product cyclizes, while in pathway two a Povarov-type [4+2] cycloaddition of the formed imine and the alkyne occur. Both pathways lead to quinolines **27**, which possess anti-toxoplasmosis activity.[88] The $Yb(OTf)_3$ catalyzed A³ coupling of ethyl glyoxylate, potassium alkyl/aryl ethynyl trifluoroborates and anilines leads to β-unsaturated α-amino esters **28**. The same strategy can be adopted for potassium alkenyl/allyl trifluoroborates, with the drawback that all these potassium trifluoroborates have to be synthesized upfront in a separate step.[89]



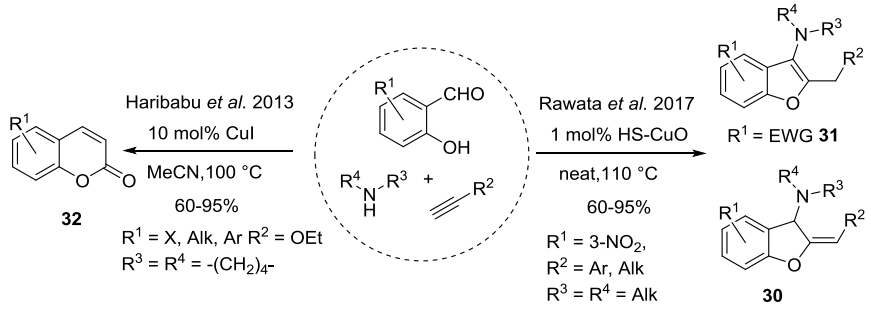
Scheme 1-10 Functionalized glyoxylates as aldehyde 'replacements' in A³ couplings.

A derivative of glyoxylates, glyceraldehyde, can also be used in A³ couplings with alkynes and sacrificial secondary amines. After the formation of the A³ adduct, a Au(III) catalyzed 5-*endo-dig* cyclization takes place. Loss of morpholine takes place upon aromatization towards furfuryl alcohols **29** (Scheme 1-11).[90]



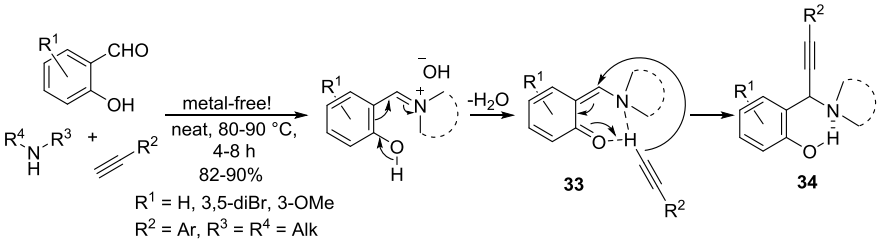
Scheme 1-11 Usage of glyceraldehyde in A³ couplings with a sacrificial secondary amine.

The use of specific *ortho*-hydroxylated benzaldehydes or salicylaldehydes, leads in two cases to different products (Scheme 1-12). In a first report, salicylaldehydes undergo A³ coupling with aromatic alkynes and secondary amines. The alkyne moiety in the A³ coupling product is then attacked by the nucleophilic hydroxyl group leading to dihydrobenzofurans **30**. Isomerization of the double bond only occurs for electron-deficient salicylaldehydes and leads to benzofurans **31**.[91] In a second report, the A³ coupling of salicylaldehydes, ethoxyacetylene and pyrrolidine leads to coumarins **32**. Pyrrolidine acts as an organocatalyst here, as it is only used in 25 mol%. After formation of the A³ product, the alkyne undergoes nucleophilic attack by the hydroxyl group in a 6-*endo-dig* fashion, subsequent hydrolysis and loss of ethanol leads to coumarins **32**.[92]



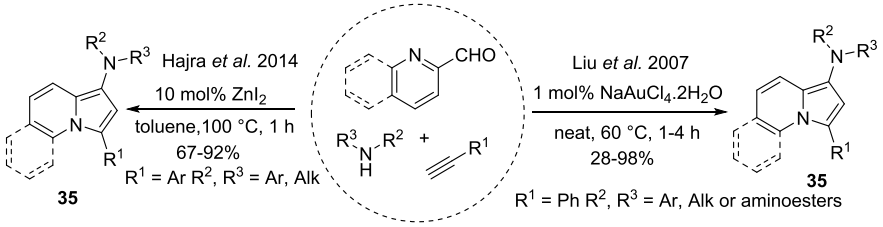
Scheme 1-12 Salicylaldehydes in A³ couplings.

The use of salicylaldehydes also enables a metal-free A³ coupling with secondary amines and alkynes (Scheme 1-13). The presence of the hydroxyl-group plays a crucial role in the proposed mechanism for this reaction. After formation of the iminium species, the aromaticity is broken to form an *o*-quinonoid intermediate **33** with the loss of water. The *o*-quinonoid then activates the C-H bond of the alkyne, to form the A³-coupling product **34**.[93]



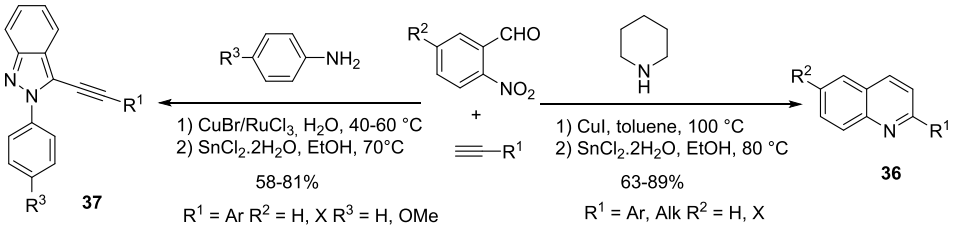
Scheme 1-13 Metal-free A³ coupling involving salicylaldehydes.

Scheme 1-14 shows the A³ coupling involving pyridine-2- and quinoline-2-carboxaldehydes, secondary amines and alkynes. The presence of this extra nitrogen atom, allows for intramolecular hydroamination, leading to aminoindolizines **35**. Two different methods, using either 10 mol% ZnI_2[94] or 1 mol% $NaAuCl_4.2H_2O$[95] are reported.



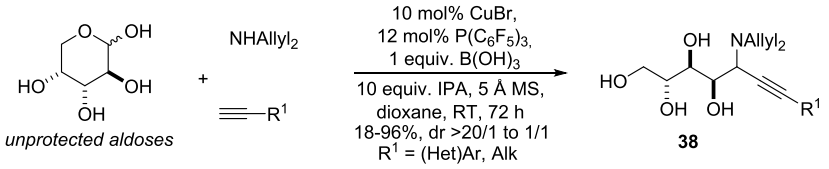
Scheme 1-14 A³ coupling with pyridine-2- and quinoline-2-carboxaldehydes, leading to aminoindolizines.

In Scheme 1-15, A³ couplings, followed by reductive cyclizations are presented. Therefore, an *o*-nitrobenzaldehyde is needed in combination with alkynes and secondary amines or anilines. A³ coupling occurs as usual, followed by the reduction of the nitro-group to an amino group, hydroamination and expulsion of the piperidine moiety to aromatize to quinolines **36** occur in case of piperidine. In case of anilines, the secondary propargylamine attacks the nitro group, aromatization with the loss of water, leads to indazoles **37**.[96]



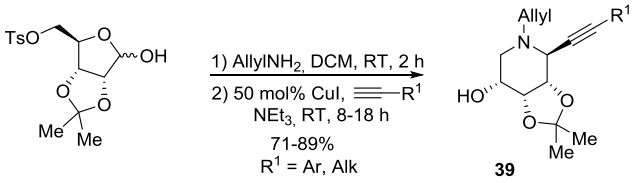
Scheme 1-15 A³ coupling involving *o*-nitrobenzaldehydes, leading to quinolines.

Scheme 1-16 shows the use of unprotected aldoses in A³ coupling under CuBr catalysis with perfluorinated triphenylphosphine and boric acid as additives. Boric acid plays an important role in complexating the free hydroxyl groups, while the phosphine acts as a ligand for the *in situ* generated copper acetylide species. The aldehyde component can be an unprotected aldose (pentose or hexose), or a disaccharide. In general, the diastereoselectivities are low, usually around 1/1 with exceptions going to >20/1. Nevertheless, this is a valuable method for A³ coupling, yielding highly functional propargylamines **38**.[97]



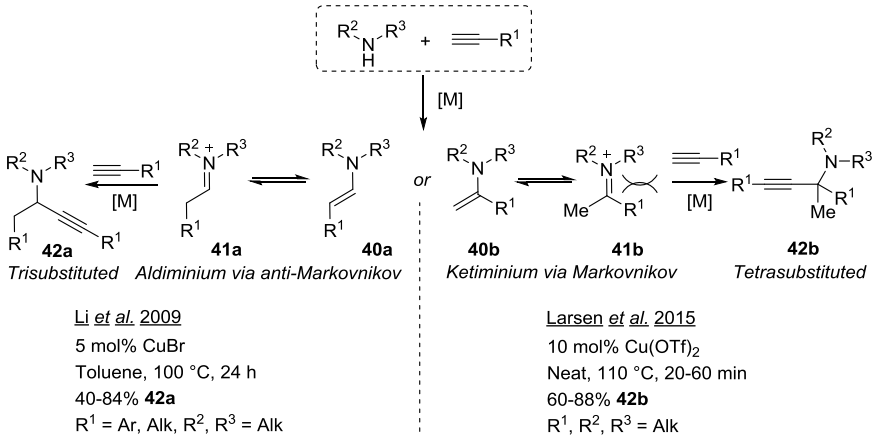
Scheme 1-16 A³ coupling involving aldoses.

Scheme 1-17 shows a similar coupling starting from a protected aldose, D-ribose tosylate. In a first step this aldose is reacted with allylamine and after two hours, CuI, triethylamine and alkyne are added to generate iminosugars **39**. Interestingly, here a high degree of stereoselectivity is claimed, addressing yields only for one diastereomer.[98]



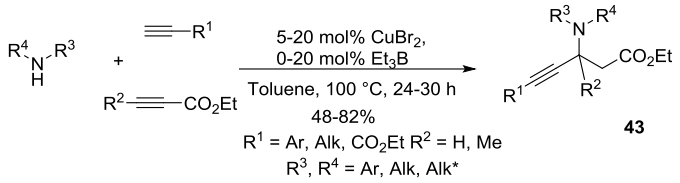
Scheme 1-17 Alkynylation of D-ribose tosylate produces iminosugars.

The aldehyde component can also be replaced by another alkyne (Scheme 1-18). In this way hydroamination of one alkyne leads to the formation of an enamine **40a** or **40b**. Depending on the regioselectivity of this hydroamination, either an aldiminium **41a** or ketiminium **41b** regioisomer can be obtained. The aldiminium isomer **41a** is formed by anti-Markovnikov hydroamination while the ketiminium **41b** isomer is formed by Markovnikov hydroamination. Addition of a second molecule of alkyne eventually generates trisubstituted propargylamines **42a** or tetrasubstituted propargylamines **42b**. The type of hydroamination seems to be dependent on the catalyst, since copper(I) salts in combination with aromatic alkynes give products **42a**[99] while copper(II) salts in combination with aliphatic alkynes give products **42b**.[100] However, when more steric hindrance is present in aliphatic alkynes, the reaction shifts towards the formation of **42a**.



Scheme 1-18 Aldehyde replaced by the same alkyne as used for alkynylation.

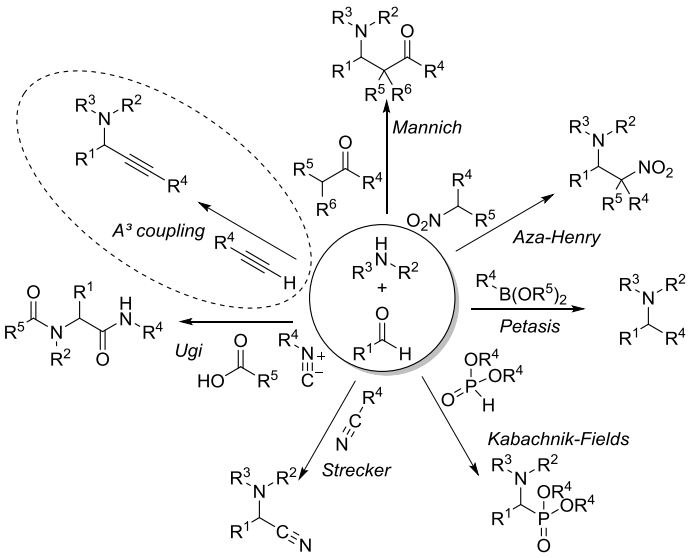
Interestingly, a few examples of internal alkynes, generating *in situ* ketiminium species, gave rise to β-aminoesters **43** (Scheme 1-19). The use of proline-derivatives as secondary amines resulted in high diastereomeric ratio of products **43**, underlining the importance of this method.[101]



Scheme 1-19 Aldehyde replaced by another alkyne, leading to interesting β-aminoester.

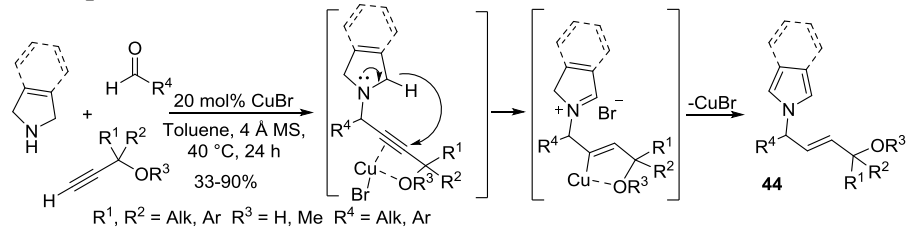
1.3.3.2 Alkyne replacements: Mannich-type reactions

Replacements of the alkyne by another nucleophile are the most encountered reactions (Scheme 1-20). Examples are the Mannich reaction (addition of an enolizable carbonyl compound), the Aza-Henry reaction (addition of nitroalkanes), also known as the nitro-Mannich reaction, the borono-acid Mannich or Petasis reaction (addition of a boronic acid or boronate ester), the Kabachnik-Fields reaction (addition of a dialkyl phosphonate), the Strecker reaction (addition of a cyanide). The Ugi four component reaction also fits this row, because it starts from a carbonyl compound, an amine and adds an isocyanide and carboxylic acid to the imine. Mentioning these reactions as alkyne replacements is vital to the structure of this story, but detailed discussion would lead us way too far and is beyond the goal of this thesis.



Scheme 1-20 Alkyne replacements are well-known Mannich-type reactions.

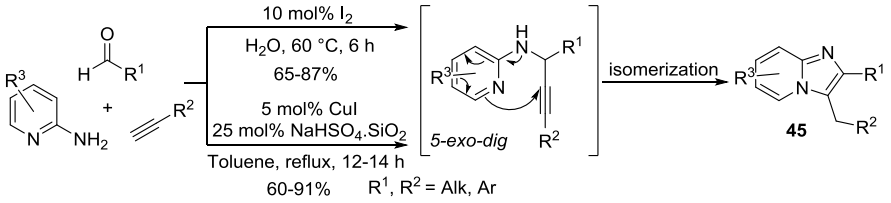
1.3.3.3 Amine replacements



Scheme 1-21 The use of 3-pyrrolines in A³ coupling leads to *N*-allylpyrroles.

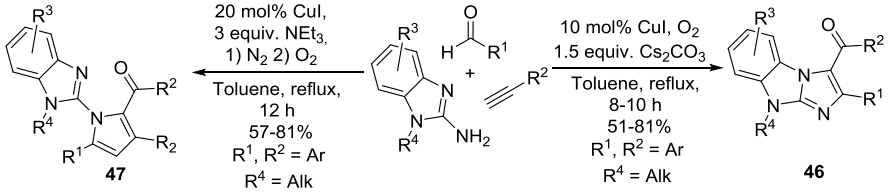
Scheme 1-21 shows the use of 3-pyrroline or isoindoline as special amines. Reaction with specific propargyl alcohols or ethers and aldehydes yields in the first place the A³ adduct, which can undergo a [1,5]-hydride shift. Deprotonation and aromatization leads to *N*-allylpyrroles **44**. The reaction works well for aromatic alkynes, but for aliphatic alkynes 20 mol% of CuCl is added and the solvent had to be changed to dioxane. The formed stereocenter can also be controlled by using chiral (*R,R*)- or (*R,S*)-*N*-PINAP ligand with excellent enantioselectivity.[102]

As with aldehydes, the presence of an extra nitrogen atom α to the amine nitrogen can lead to ring closure reactions. The use of 2-aminopyridines for example leads to the A³ adduct, which immediately undergoes 5-*exo*-*dig* cyclization. Isomerization leads to imidazo-[1,2-*a*]pyridines **45** (Scheme 1-22).[103] The same reaction can also be catalyzed by molecular iodine in water, in a transition metal-free A³ coupling. With 10 mol% I_2, products **34** can be generated in 6 hours at 60 °C. Iodine is believed to be mild Lewis-acidic in this case, complexating the imine nitrogen.[104]



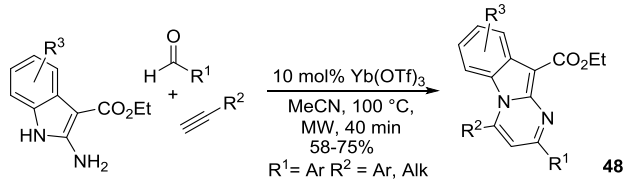
Scheme 1-22 The use of 2-aminopyridines allows for an extra cyclization.

The use of 2-aminobenzimidazoles can lead to two different products, depending on the reaction conditions (Scheme 1-23). In the first example, the A³ adduct undergoes a 5-*exo-dig* cyclization, followed by addition of oxygen and aromatization leading to benzoimidazolo[1,2-*a*]imidazolones **46**.[105] Switching the base from cesium carbonate to triethylamine leads to the A³ adduct, which undergoes 6-*endo-dig* cyclization in the absence of oxygen. The formed enamine undergoes a second alkynylation, and in the presence of oxygen the A³ adduct rearranges to form benzimidazole-linked pyrroles **47**.[106]



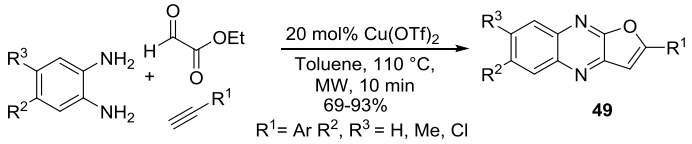
Scheme 1-23 A³ coupling with 2-aminobenzimidazoles leads to different products, depending on reaction conditions.

The use of 2-aminoindoles leads to interesting α-carbolines **48** (Scheme 1-24). Ytterbium triflate catalyzed A³ reaction leads to the A³ adduct, which then undergoes a 6-*endo-dig* cyclization, followed by aromatization, leading to structures **48**.[107]



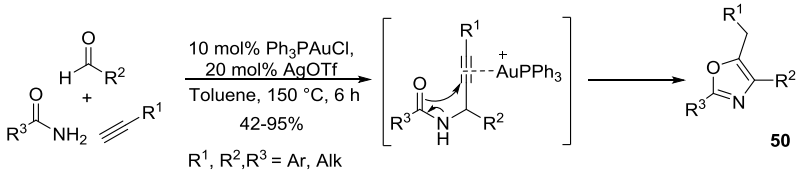
Scheme 1-24 The use of 2-aminoindoles leads to interesting α-carbolines.

Diamines, such as *o*-phenylenediamine, can also be used in A³ couplings with alkynes and glyoxylates (Scheme 1-25). After formation of the A³ adduct, the second amine moiety reacts with the ester moiety to form an amide. The amide oxygen then attacks the alkyne in a 5-*endo-dig* cyclization, followed by oxidation to obtain aromatic furoquinoxalines **49**. Reactions are performed under microwave irradiation with short reaction times, making this an extremely fast and high yielding method for the generation of compounds **49**.[108]



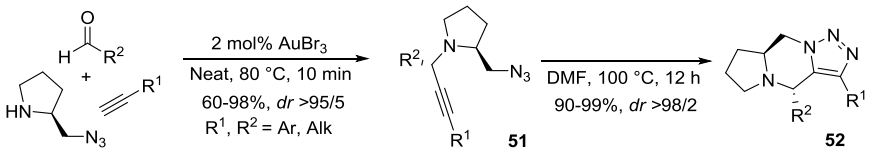
Scheme 1-25 Using *o*-phenylenediamines, furoquinoxalines **49** can be prepared.

A very important replacement of amines could be amides. In 2015, Li and co-workers used benzamides in a three-component coupling with aldehydes and alkynes, in the generation of oxazoles **50** (Scheme 1-26). Firstly, the amide and the aldehydes condense to form an imide, which is attacked by the gold acetylide to form A³ adduct. Attack of the amide oxygen onto the alkyne in a 5-*exo*-*dig* cyclization leads to fully substituted oxazoles **50**.[109]



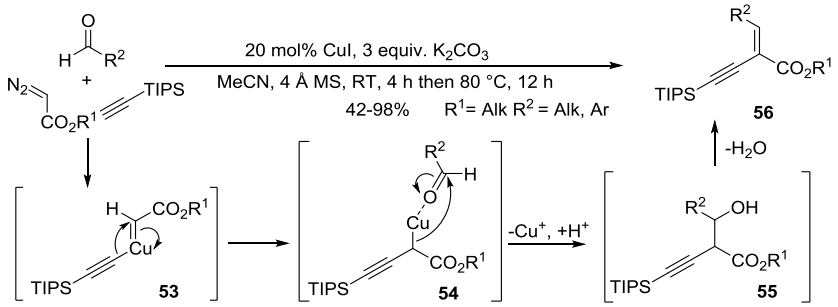
Scheme 1-26 A³ coupling involving amides, generating fully decorated oxazoles.

The use of azide-substituted amines allows, after A³ coupling, for an intramolecular [3+2] cycloaddition (Scheme 1-27). Generally, this alkyne-azide 'click' reaction is Cu-catalyzed (CuAAC), which is also a great metal for A³ couplings. This could be problematic, as A³ coupling has to occur first. Lee *et al.* reported a Au(III) catalyzed A³ coupling between enantiomeric pure β-azido-pyrrolidines, derived from L-proline, aldehydes and alkynes to generate β-azido-propargylamines **51** in excellent diastereomeric ratios. Intramolecular azide-alkyne click reaction occurs in DMF, without the addition of a transition metal catalyst to form interesting triazole-derivatives **52**.[110]



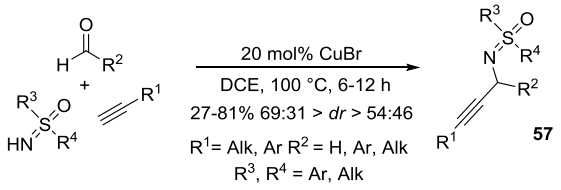
Scheme 1-27 Formation of β-azido-propargylamines and [3+2] cycloaddition to form triazole-derivatives.

Amines can also be replaced by diazoesters, in a specific coupling with silylated terminal alkynes and aldehydes (Scheme 1-28). Reaction of the *in situ* formed copper acetylide with diazoester generates a Cu(I)-carbene **53**. From **53**, migratory insertion of the alkynyl group generates Cu(I) species **54**. Nucleophilic addition of **54** to the aldehyde affords **55**, which eliminates water to generate 1,3-enyne **56** with an *E*/*Z*-ratio of >20/1.[111]



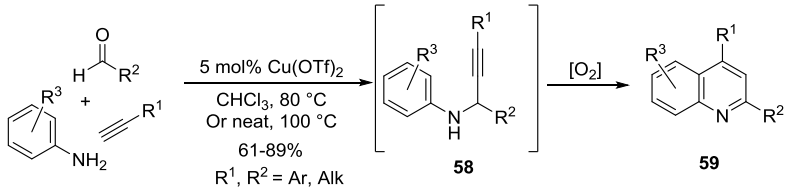
Scheme 1-28 Diazoesters as amine replacement in A³ coupling.

Another replacement for amines could be *N*H-sulfoximines (Scheme 1-29). *N*H-Sulfoximines react with aldehydes to form sulfoximinium intermediates, which can be alkynylated by *in situ* formed copper acetylides, yielding *N*-propargylsulfoximines **57**.[112]



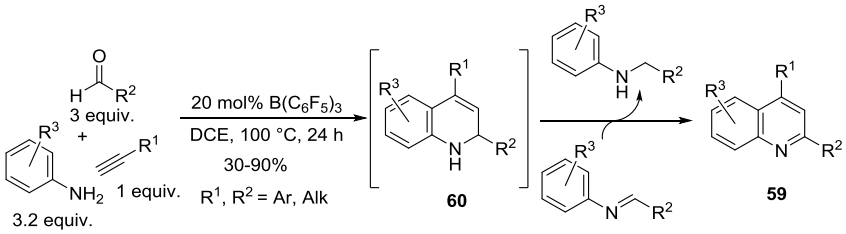
Scheme 1-29 *N*H-sulfoximines as amine replacements in A³ couplings.

The use of aromatic amines or anilines allows for a further ring closing reaction for the synthesis of quinoline derivatives **59** (Scheme 1-30). These quinoline derivatives are compounds known to be synthesized via [4+2] Povarov-type reactions of *N*-arylimines and alkynes, followed by *in situ* oxidation of dihydroquinolines. In a first example, an extension of the aldehyde scope is made, since also alkyl aldehydes can be used. Two methods are presented for the synthesis of quinolines **59**. Firstly, reactions involving aryl aldehydes were conducted at 80 °C in chloroform. When alkyl aldehydes were used, the reaction only yielded A³ intermediate **58**. When the reaction was run without solvent, at 100 °C, quinolines derived from alkyl aldehydes were obtained. The reactions have to be conducted under ambient atmosphere, to allow *in situ* formed dihydroquinolines to oxidize to quinolines **59**.[113]



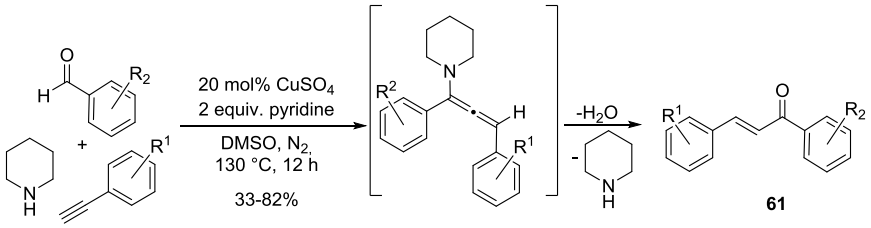
Scheme 1-30 A³ coupling with anilines leads to quinolines.

The formation of similar quinolines **59** could also be catalyzed by a triarylborane catalyst (Scheme 1-31). Reactions are run in sealed vials, minimizing the use of oxygen for the oxidation of dihydroquinolines **60** to quinolines **59**. By using three equivalents of both anilines and aldehydes, the *in situ* formed imines act as oxidants, and as a result are being reduced to secondary amines.[114]



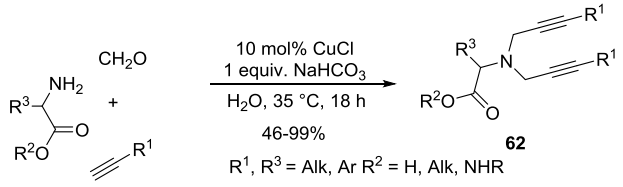
Scheme 1-31 Triarylborane catalyzed A³ coupling, leading to quinolines.

The addition of an external base next to the A³ catalyst allows propargylamines to undergo isomerization reactions, since α-deprotonation is easier due to the presence of the electrophilic alkyne moiety (Scheme 1-32). The formed enamine undergoes hydrolysis to yield chalcones **61**.[115]



Scheme 1-32 Formation of α,β-unsaturated ketones via one-pot A³ coupling.

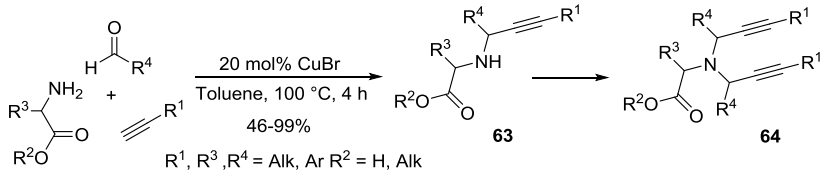
Amino acids can be used as special amines in A³ couplings. However, when copper is used as a catalyst, decarboxylation often occurs easily, leading to decarboxylative A³ couplings (Scheme 1-33). By carefully tuning the reaction conditions decarboxylation can be avoided. A protocol for using amino acids and amino esters in a CuCl catalyzed A³ coupling with formaldehyde and alkynes in water was developed for the generation of bispropargylated products **62**.[116]



Scheme 1-33 A³ coupling with amino acids or amino esters giving dipropargylated amines.

The formation of bispropargylated products is not surprising since the propargylamine formed after a first alkynylation is a secondary amine that can form an iminium species with a carbonyl compound. In general, the formed iminium is more electrophilic than an imine, explaining the easy formation of dipropargylated products **62**.

Amino esters can also be used in a similar procedure with aliphatic and aromatic aldehydes to form mono- **63** or bispropargylated amines **64**, depending on the number of equivalents of aldehyde and alkyne used (Scheme 1-34). The procedure can also be used to synthesize unsymmetrical dipropargylic amines, by adding other aldehydes and alkynes after a first alkynylation.[117]



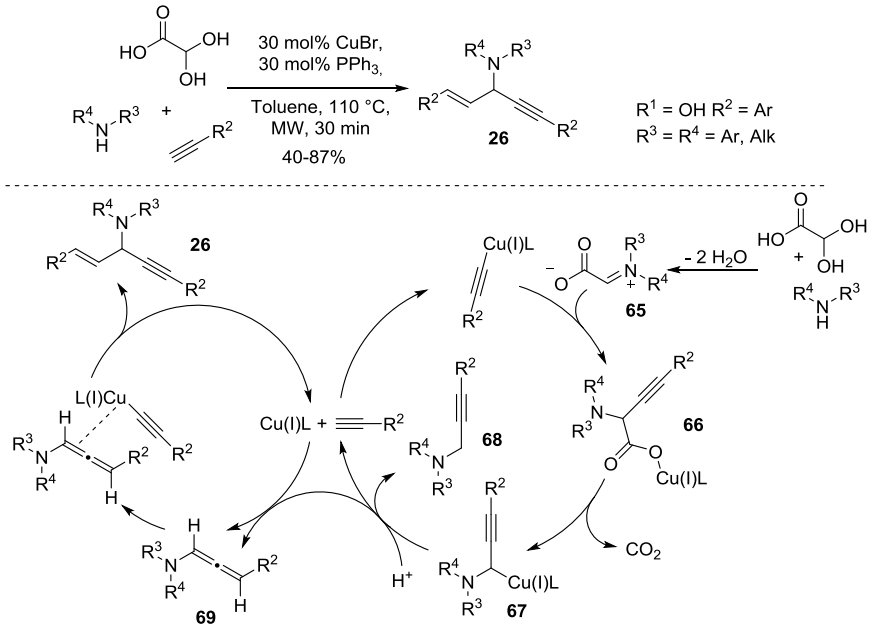
Scheme 1-34 Formation of mono- and dipropargylic amines from amino esters.

1.3.4 Decarboxylative A³ coupling

Decarboxylative A³ couplings are A³ couplings in which somewhere along the reaction process one molecule of carbon dioxide is lost. The carboxylic acid group can either be a part of the aldehyde, the amine or the alkyne component.

1.3.4.1 Glyoxylic acid as carboxylic acid derived aldehyde

A first example consists of glyoxylic acid, amines and alkynes, and was already discussed in the previous paragraph as an aldehyde replacement.[87] Here, we will focus on the mechanism of the decarboxylative A³ coupling (Scheme 1-35). Iminium salt **65** is formed via condensation of glyoxylic acid with secondary amines and with loss of two molecules water. Addition of *in situ* formed copper acetylide gives intermediate **66**, which upon decarboxylation forms copper species **67**. Protonation of the copper species **67** either yields propargylamine **68** or allene **69**. Allene **69** has an enamine structure, which can be attacked by a second molecule of copper acetylide to form 1,4-enyne **26**.[87]

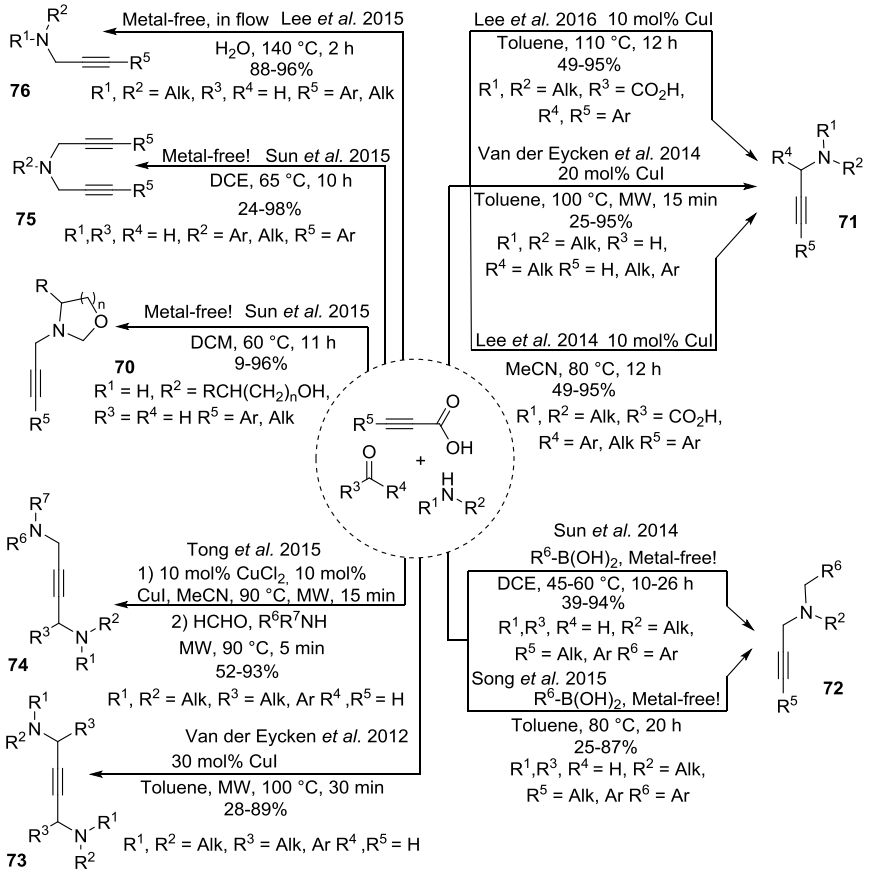


Scheme 1-35 Tandem carboxylative A³ coupling.

1.3.4.2 Propiolic acid derivatives as carboxylic acid derived alkynes

In the majority of decarboxylative reactions the carboxylic acid is attached to the alkyne moiety (Scheme 1-36). The synthesis of *N*-propargyl heterocycles **70** can be achieved via decarboxylative A³ coupling starting from aminoalcohols, formaldehyde and propiolic acids. The amino alcohol reacts firstly with formaldehyde to form an iminium, which is then attacked by the alcohol group to form oxazolidines or oxazinanes. The secondary amine formed in this way then undergoes a metal-free decarboxylative A³ coupling, yielding *N*-propargyl heterocycles **70**.[118] A second entry describes a double decarboxylative A³ coupling that starts from propiolic acids, glyoxylic acids and amines. From mechanistic study experiments it was shown that decarboxylation of glyoxylic acid occurs first, even in the absence of copper, and an iminium species is formed with the secondary amine. Afterwards, decarboxylative A³ coupling occurs with propiolic acid to generate propargylamines **71**.[119] A CuI catalyzed decarboxylative, microwave-assisted A³ coupling between aliphatic aldehydes, secondary amines and aryl/alkyl-substituted terminal propiolic acids is presented. In the proposed reaction mechanism, CuI reacts with propiolic acids and causes decarboxylation, forming copper acetylide which undergoes normal A³ coupling to generate propargylamines **71**.[120] Similar reaction conditions were described in the same year also using a CuI catalyst but reactions were run in acetonitrile instead of toluene, and at lower temperatures, giving similar yields of products **71**.[121] The use of an extra arylboronic acid with primary amines, formaldehyde, and propiolic acid allows for a Petasis reaction, followed by decarboxylative

A^3 coupling in one pot, without the use of a transition metal catalyst. Here, the Petasis reaction is used ingeniously to generate *in situ* a secondary amine. Decarboxylation only occurs after the addition of the propiolic acid to the iminium and generates propargylamines **72**.[122] The use of propiolic acid, secondary amines and aldehydes, designated as a PA^2 coupling by Van der Eycken *et al.* allows for a double alkynylation, *i.e.* a decarboxylative A^3 followed by a normal A^3 coupling, where the intermediate acts as alkyne. Two possible mechanistic pathways are proposed, depending on when carboxylation takes place; before or after addition to the iminium. The products of these couplings are symmetrical 1,4-diamino-2-butynes **73**.[123] Unsymmetrical 1,4-diamino-2-butynes **74** can be formed in a similar way, by sequential addition of formaldehyde and diisopropylamine after a first microwave-assisted PA^2 coupling. Unfortunately, this coupling is only possible if there is a minimum of sterical hindrance in the second formed iminium.[124] The formation of bispropargylic amines **75** can be achieved from primary amines, formaldehyde and propiolic acid derivatives in a metal-free decarboxylative A^3/A^3 coupling sequence. It was proposed that decarboxylation occurs prior to addition of the alkynyl species to the iminium.[125] A last protocol used flow-chemistry to do a decarboxylative A^3 coupling of propiolic acid derivatives with formaldehyde and secondary amines in water. The yield of the reaction is compared to the yield of the same reactions in batch and yields for products **76** are generally 5-10% lower for batch reactions.[126]

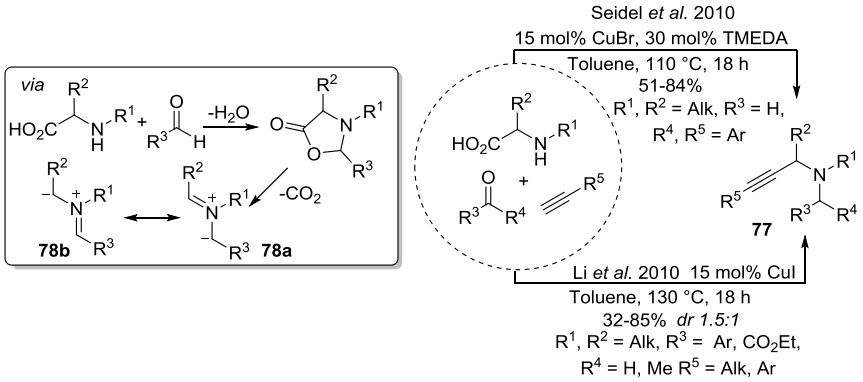


Scheme 1-36 Overview of decarboxylative A^3 couplings involving propiolic acid derivatives.

1.3.4.3 α-Amino acid derivatives as carboxylic acid derived amines

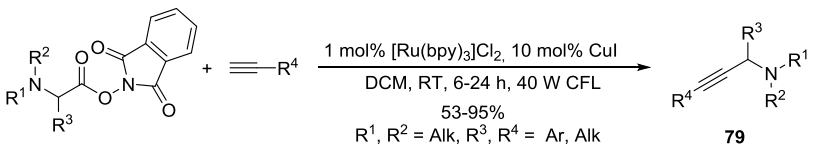
The carboxylic acid moiety can also be present in the amine component (Scheme 1-37). α-Amino acids are very important compounds, as they are building blocks for proteins. Most α-amino acids have primary amine functions, except proline, which has a secondary amine

function. Most α-amino acids possess a chiral center, but chirality regrettably will be lost when decarboxylation occurs. A first example describes the use of proline, pipecolic acid or sarcosine as α-amino acids with aromatic aldehydes and alkynes in a copper catalyzed decarboxylative A³ coupling to generate propargylamines **77**. Interestingly, aldehydes are added via a syringe pump over time to avoid that *in situ* formed azomethine ylides **78** undergo [3+2] cycloaddition with aldehydes. *In situ* formed azomethine ylides **78** exist in two resonance forms **78a** or **78b**, when proline or pipecolic acid are used, resonance form **78a** is protonated and alkynylated, while when sarcosine (R^1 = Me, R^2 = H) is used resonance form **78b** is protonated and alkynylated. This regioselectivity could be explained by the stability of intermediate iminiums.[127] Similar reactions conditions and outcome were observed by Li *et al.*, who expanded the scope to the use of other alkylated amino acids, while also aliphatic alkynes and ethyl glyoxylates or ethyl pyruvates as ketone equivalents were possible coupling partners. They conducted a series of calculations to explain the observed regioselectivity and showed that azomethine ylide **78a** has lower energy than intermediate **78b**, thus reaction is more likely to go via intermediate **78a**. If there is no α-substituent present (R^2 = H), then energy levels of **78a** and **78b** are similar, and protonation of these azomethine ylides lead to iminiums. The iminium formed from **78a** however is less stable than iminium formed from **78b**, explaining the regioselectivity obtained.[128]



Scheme 1-37 Decarboxylative A³ couplings with α-amino acids.

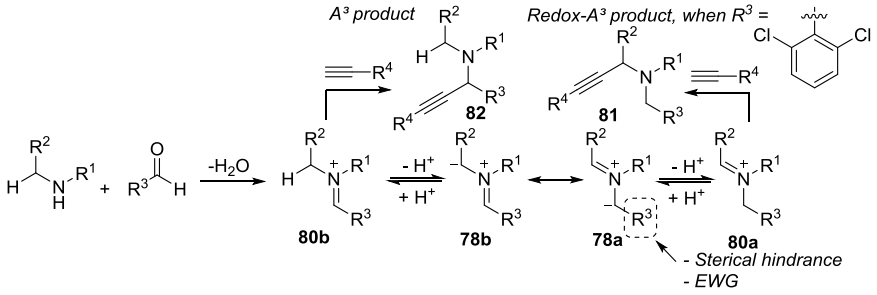
A last example is *stricto sensu* no decarboxylative A³ coupling, since there are only two components (Scheme 1-38). A photoredox reaction and decarboxylation of *N*-(acetoxy)phthalimides of α-amino acids produce *in situ* iminium species, which are alkynylated with terminal alkynes to produce propargylamines **79**. Mild reaction conditions characterize this transformation, since it could be run at room temperature in the presence of visible light.[129]



Scheme 1-38 Merging photoredox catalysis with decarboxylative alkynylation.

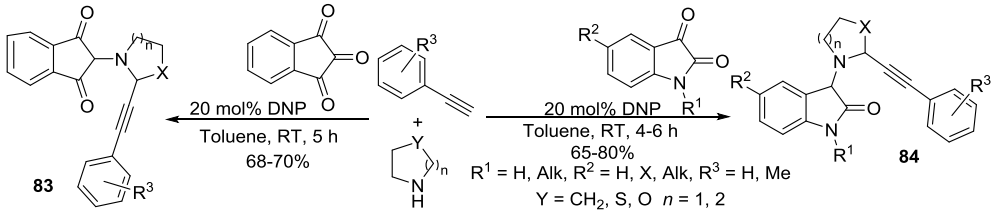
1.3.5 Redox-A³

Redox-A³ couplings are a special kind of cross-dehydrogenative couplings or CDC reactions.[130] CDC reactions generally use an external oxidant to couple two C-H bonds to generate a new C-C bond. Redox A³ reactions[131] use an internal oxidant to couple two C-H bonds for the generation of a new C-C bond. The redox-A³ coupling is an A³ coupling where an isomerization of the *in situ* formed iminium occurs[132], leading to α-alkynylation of the imine (Scheme 1-39). This isomerization, which is likely going via azomethine ylide intermediates **78a** and **78b**, only occurs when a more stable iminium species can be formed, posing certain requirements for coupling partners. Since a similar isomerization of iminium ions occurs in decarboxylative A³ couplings, they could also be regarded as redox-A³ couplings. The reaction is said to be 'redox-neutral' since a reductive *N*-alkylation and oxidative C-H bond functionalization take place. The key for making redox-A³ couplings work is either destabilization of the iminium **80b** or azomethine ylide **78b** or otherwise stabilization of isomerized iminium **80a** or azomethine ylide **78a**. The (de)stabilization could be obtained in general via two adaptations of either aldehyde- or amine-coupling partner. For the adaptation of aldehydes, aldehydes have to become more sterically hindered and electron-withdrawing. Sterical hindrance (R^3 is bulky) complicates direct alkynylation of iminium **80b** to form propargylamine **82**, while electron-withdrawing properties tend to stabilize azomethine ylide **78a**, thus forming iminium **80a** and redox-A³ product **81**. These two conditions limit the scope of used aldehydes greatly, and the best results (regioselectivities of 25:1 **81**:**82**) are obtained with 2,6-dichlorobenzaldehyde.[133]



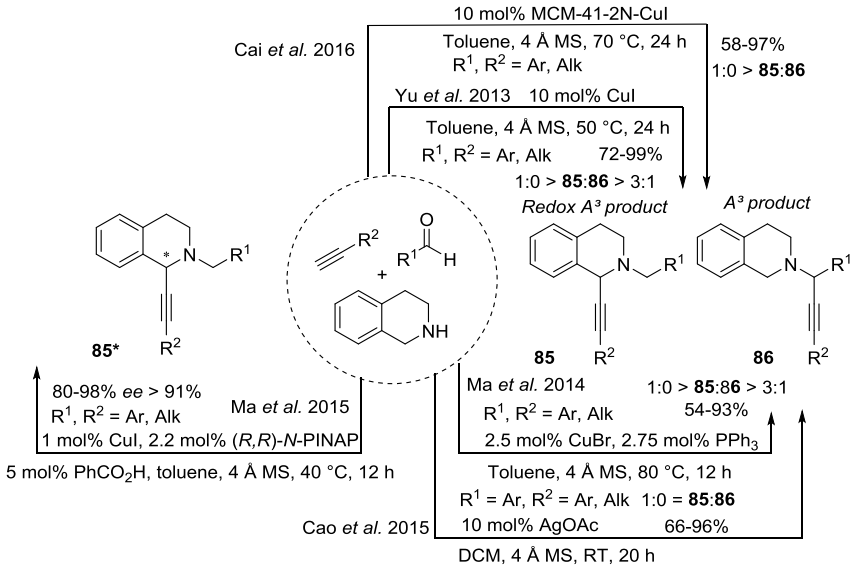
Scheme 1-39 Classical versus Redox-A³ coupling.

A second way to drive isomerization towards **80a** is by substituting the aldehyde by a ketone.[134] This substitution makes iminium **80b** harder to alkynylate since ketiminium ions are more sterically hindered and less electrophilic than aldiminiums. Chimni *et al.* used indoline-2,3-dione or 1*H*-indene-1,2,3-trione as special ketone derivatives in combination with secondary amines and aryl alkynes and a catalytic amount of 2,4-dinitrophenol in a metal-free redox A³ coupling to generate redox-A³ products **83** and **84** (Scheme 1-40). The catalyst 2,4-dinitrophenol is probably acting as a nucleophile that adds to the formed ketiminium, followed by generation of azomethine ylides that isomerize and form aldiminium species.



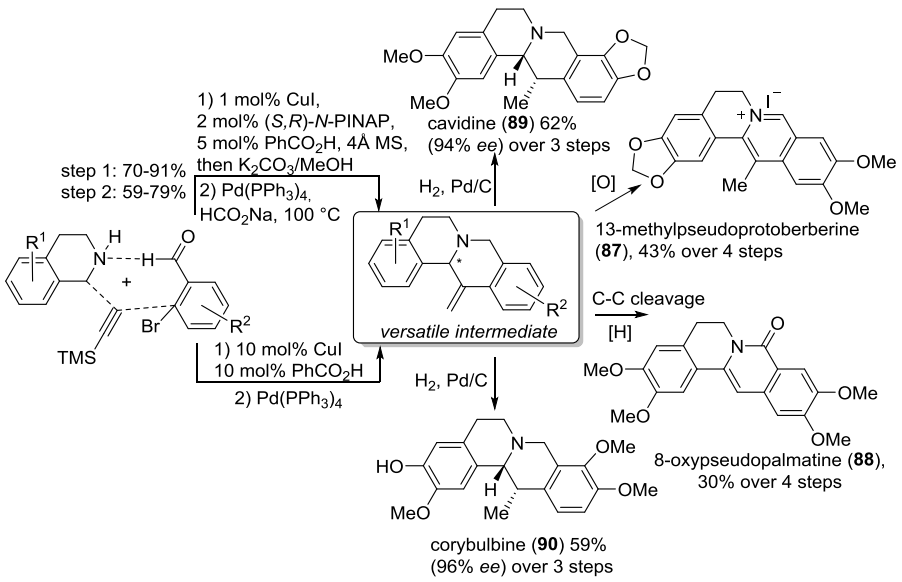
Scheme 1-40 Redox A³ coupling using ketone derivatives.

The second adaptation that could be made is to stabilize iminiums **80a** by using an unsaturated amine that is conjugated with newly formed iminium bond in **80a**. Tetrahydroquinolines (THIQ's) proved to be excellent for this purpose (Scheme 1-41). The groups of Yu[135] and Ma[136] independently described the use of THIQ's in combination with aldehydes and alkynes for the generation of 1-alkynyl isoquinolines **85**. Interestingly, the choice of catalyst and catalyst loading plays an important role for the regioselectivity of the reaction. Especially the choice of the copper-counter ion is of utmost importance; CuBr tends to give A³ product **86** while CuI or $CuBr/PPh_3$ gives redox-A³ product **85**. Lower catalyst loading favor redox-A³ over A³, since slower addition of copper acetylide results in more time for isomerization to occur. Similar reaction conditions proposed by Yu and Ma result in similar yields and regioselectivities. In 2016, Cai *et al.* reported on the use of a heterogeneous 3-(2-aminoethylamino)propyl-functionalized MCM-41-supported copper(I) complex, for the synthesis of 1-alkynyl isoquinolines **85** in comparable yields.[137] Interestingly, Ma and co-workers also found a set of conditions to allow for the stereoselective synthesis of **85***. By using a well-known (*R,R*)-*N*-PINAP ligand, used in asymmetric A³ couplings, and adding benzoic acid as co-catalyst they were able to produce 1-alkynyl isoquinolines **85*** in excellent yields and enantiomeric excesses. A last method describes the use of AgOAc as a catalyst for the redox A³ coupling of THIQ's, aromatic aldehydes and alkynes.[138] The reaction proceeds at room temperature with complete regioselectivity, however the scope of aldehydes is limited to aromatic aldehydes, since aliphatic aldehydes give A³ product **86**. The authors acknowledged structures **85** as interesting structures for the generation of THIQ-derived drugs and natural products.



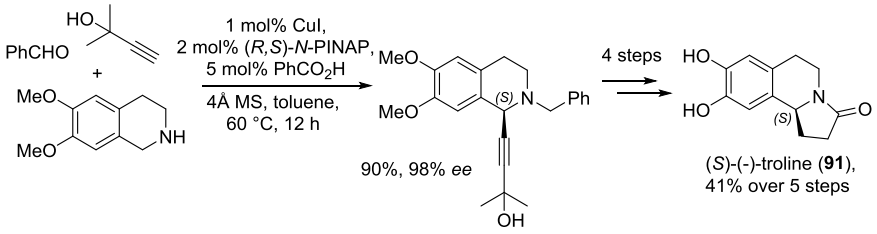
Scheme 1-41 Redox-A³ coupling with THIQ's.

Research interest is now focused on the applications of redox-A³ using THIQ's (Scheme 1-42). Tong *et al.* described a redox-A³ coupling of THIQ's using a CuI and benzoic acid catalytic system which after desilylation and carbocyclization led to a versatile intermediate, from which over fifty protoberberine (*e.g.* **87** and **88**) alkaloids in four to eight steps could be synthesized.[139] By addition of a chiral (*R,S*)-*N*-PINAP ligand they could turn this synthesis stereoselective, producing natural and unnatural occurring tetrahydroberberines (*e.g.* **89** and **90**).



Scheme 1-42 Redox-A³ using THIQ's for the generation of protoberberine derivatives.

Ma *et al.* reported on the synthesis of a pair of enantiomeric alkaloids (*S*)-(-)-troline (**91**) and (*R*)-(+)-oleracein E in five steps, starting with a redox-A³ coupling of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, benzaldehyde and 2-methyl-3-butyn-2-ol (Scheme 1-43).[140] Depending on which chiral ligand is used the stereoselectivity of redox-A³ product can be controlled.

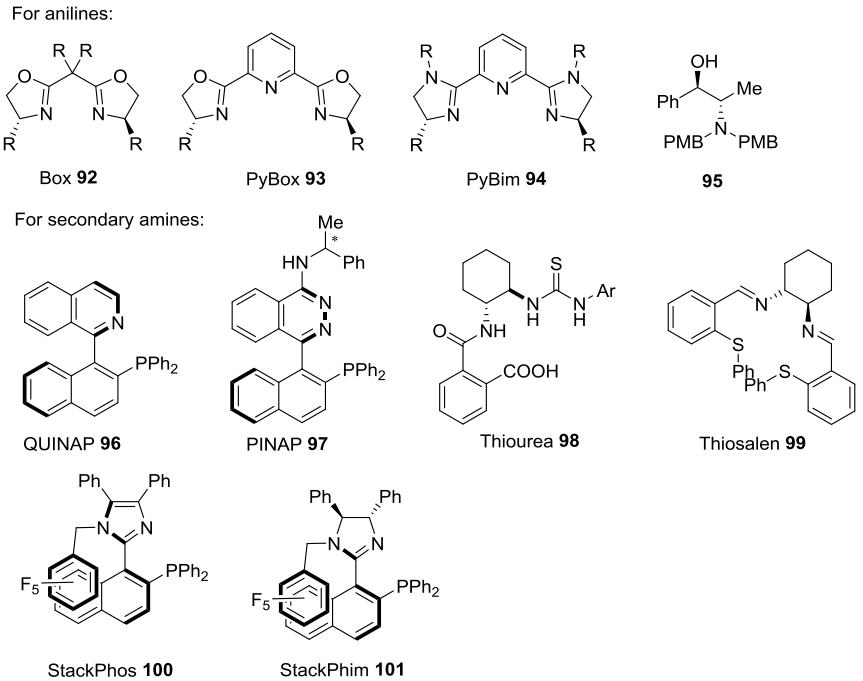


Scheme 1-43 Total synthesis of (*S*)-(-)-troline (**91**), starting with a redox A³ coupling.

1.3.6 Asymmetric A³ coupling

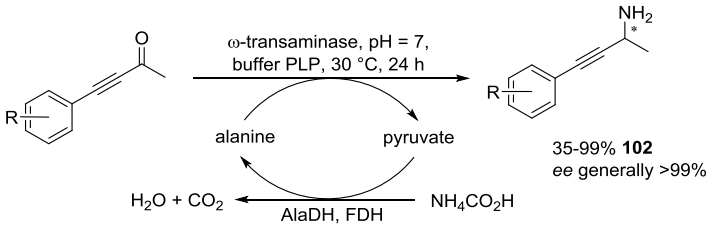
Asymmetric A³ couplings (AA³) use chiral ligands to form chiral metal-ligand complexes that can catalyze asymmetric A³ couplings (Scheme 1-44). The first report dates from 2002, when Li and co-workers introduced bidentate bis-oxazoline (Box) **92** and tridentate pyridine bis-oxazoline (PyBox) ligands **93** in combination with Cu(I) salts.[141] In 2010, Nakamura *et al.* described asymmetric A³ couplings with slightly modified tridentate pyridine bis(imidazoline) (PyBim) ligands **94**.[142] Bolm *et al.* described a norephedrine derived β-amino alcohol ligand **95** that in combination with superstochiometric amounts of dimethylzinc proved to be an excellent catalyst for A³ couplings.[143] These four classes of ligands are excellent ligands for A³ couplings with anilines. For the AA³ coupling of secondary amines, Knochel *et al.* introduced bidentate *P,N*-ligand QUINAP **96** in 2002.[144] The downside of this ligand is that it was very expensive. Therefore, Carreira *et al.* came up with a similar *P,N*-ligand PINAP **97**.[145] The advantage of this ligand being the fact that it produces separable diastereomers. In 2013, Ma *et al.* expanded the scope of the AA³ reaction with PINAP ligands **97** to aromatic aldehydes while also using propargylic alcohols, which are easily deprotectable to generate terminal propargylamines.[146] In 2015, Su and co-workers used a previously described PyBox

ligand **93** in combination with $Cu(OTf)_2$ and silica to do AA³ couplings with anilines, accelerated by ball-milling.[147] The authors also claimed to easily recover the catalytic system and reuse it for at least five cycles without significant loss of activity. In 2015, Seidel *et al.* reported on the use of a thiourea ligand **98** for the coupling of secondary amines, aromatic aldehydes and aliphatic or aromatic alkynes in good to excellent yields and enantiomeric excesses.[148] Moradian *et al.* described the use of a thiosalen ligand **99** for the coupling of secondary amines with aromatic aldehydes and alkynes. In combination with Cu(I) and triphenylphosphine A³ products were formed in excellent yields, but with moderate enantiomeric excesses and after long reaction times.[149] In 2013, Aponick and co-workers introduced a new chiral *P*,*N*-ligand, which was later named StackPhos **100**.[150] The idea was to create a ligand with enhanced rotation barrier as compared to QUINAP or PINAP ligands. With an increased rotation barrier, atropisomers are less susceptible to interconversion, which normally leads to loss of stereoselectivity. Before, this was accomplished by introducing large *ortho*-substituents. However, this could also be achieved by stabilizing the chiral ground-state conformation by π-stacking. The racemic ligand is easily synthesized in a straight-forward 6-step synthesis in 33% overall yield. Deracemization could be obtained by treating the racemic mixture with a chiral Pd-complex that generates a single diastereomeric complex, which upon treatment with another ligand, generates the free ligand in excellent enantiomeric excess. Comparison for an A³ coupling of butyraldehyde, TMS-acetylene and dibenzylamine with QUINAP **96** and with StackPhos **100** showed that the formation of A³ product with StackPhos is faster (97% yield after 24 h compared to 88% after 120 h with QUINAP). The presence of the fluorine atoms is of great importance for π-stacking, since absence of the fluorine atoms destabilizes the π-stacking considerably. The use of StackPhos as chiral ligand was further exploited in the synthesis of amino skipped diynes.[151] In 2017, Aponick and co-workers introduced a slightly modified StackPhim **101** ligand that is an analogue of known phosphinooxazolidines (PHOX) or phosphinoimidazoline (PHIM) ligands.[152] This ligand was particularly good for AA³ coupling with propargylic alcohols, giving good yields and excellent ee's. This ligand was also invented independently by Guiry and Rokade, and used in similar AA³ couplings.[153]



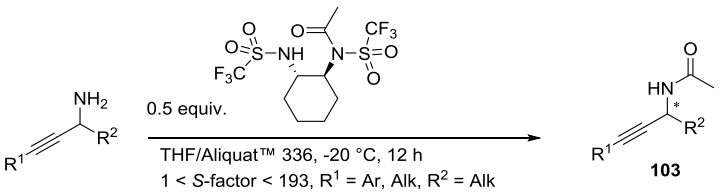
Scheme 1-44 Different ligands used in asymmetric A³ couplings.

An interesting way for the stereoselective synthesis of propargylamines **102** is reported in 2015 by Kroutil and co-workers (Scheme 1-45).[154] Although this method is not related to the A³ coupling, it could be a very valuable method, since it produces propargylamines in very high enantiomeric excesses (usually >99/1). The synthesis starts from prochiral aromatic propargyl ketones and uses ω-transaminases to do an asymmetric reductive bio-amination. Different ω-transaminases give rise to different enantiomers, either (*R*)- or (*S*)-selective.



Scheme 1-45 Biocatalytic pathway for the generation of optically pure aromatic propargylamines.

A second method for the generation of enantiopure propargylamines was reported in 2012 by Cossy and co-workers (Scheme 1-46). A non-enzymatic kinetic resolution of primary propargylamines with selective acetyl transfer using a bis trifluorsulfonamide and Aliquat™ 336 (*N*-methyl-*N*,*N*,*N*-trioctylammonium chloride) give rise to *N*-acetylated propargylamines **103**.[155] Yields are not reported, only conversions are reported, which are all around 50%, as the initial product is a racemic mixture. *S*-factors determine the efficiency of the reaction and this factor is the ratio between the reaction rate constants of both enantiomers. The higher these numbers, the better stereoselectivity can be obtained. Overall, conversions are excellent and *S*-factors are high, only in a few cases low *S*-factors were obtained.



Scheme 1-46 Kinetic resolution of primary propargylamines.

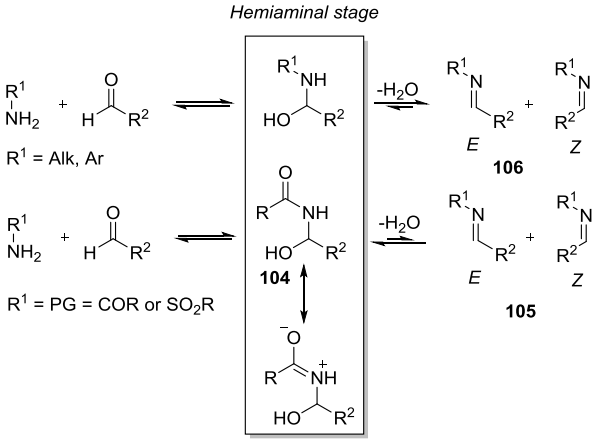
1.3.7 Alkynylation on imines and related species

The direct addition of alkynes to imines has been a topic of interest for the past decades. However, the last review dates from 2006 when Zani and Bolm described direct additions of alkynes to imines and related C=N electrophiles.[156] Since then, most scientific attention went to the one-pot A³ coupling. However, sometimes it is necessary to preform imines, before addition of the alkyne moiety. Reasons for this are variable but mostly include the incompatibility of different functional groups on either of the components in an A³ coupling, along with the presence of the formed water from the condensation of aldehyde and amine or generally sluggish formation of the imine due to the presence of electron-withdrawing groups on the amine component. In the next paragraphs, the direct addition of alkynes to aldimines, ketimines, iminium species and *N*,*O*-acetals will be discussed including asymmetric syntheses.

1.3.7.1 Alkynylation on aldimines

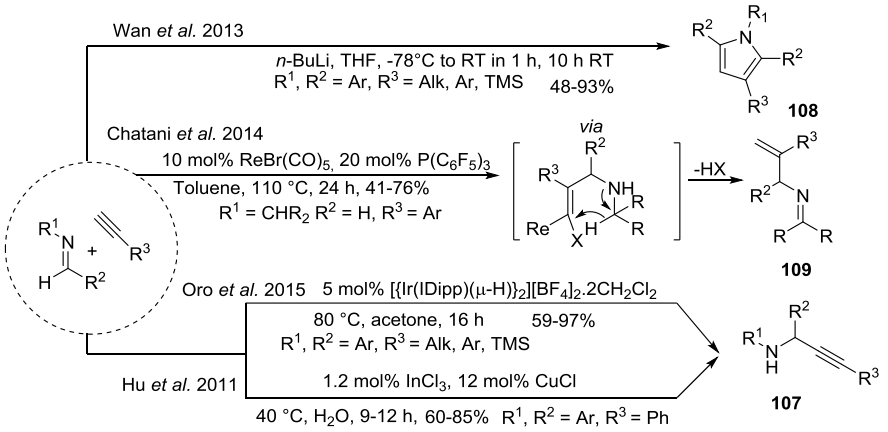
Aldimines, *i.e.* the imines generated from aldehydes, are usually more electrophilic than ketimines and are thus the most reactive electrophiles for alkynylation. The aldimines under

this topic are generally not easily prepared, otherwise A³ coupling would be an easier method to make the corresponding propargylamines. The here discussed aldimine often bear a protecting group on the nitrogen atom. Due to the presence of this protecting group (Cbz, Boc, Fmoc, Ts, Ac), the nucleophilic properties of the amine are reduced, making it a less good nucleophile for the generation of imines. Therefore, reactions of protected amines with aldehydes often remain in the hemiaminal stage **104** (Scheme 1-47). *N*-acyl imines **105** are more electrophilic than *N*-alkyl imines **106** and are thus more easily alkynylated. Therefore, the generation is often a more difficult step than alkynylation of *N*-acyl imines. For imines, the *E* and the *Z* isomer are shown. Depending on the steric hindrance of both substituents R^1 and R^2 the *E/Z* ratio could be altered, but in general the *E*-isomer is the more stable isomer.



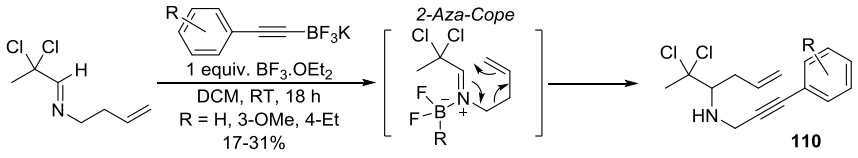
Scheme 1-47 For electron-poor amines, products remain in the hemiaminal stage.

In Scheme 1-48 an overview of methods for the direct alkynylation of imines will be given. In 2015, Oro *et al.* reported on a new dinuclear Ir-complex which was used to functionalize aromatic imines with aliphatic or aromatic alkynes.[157] Although the scope of the reaction is rather limited, and products could be obtained via classical A³ methods, the use of Iridium in alkynylation reactions to synthesize propargylamines **107** is somewhat new. Based on DFT calculations, the authors claim that the first step in the reaction mechanism must be the oxidative addition of the alkyne C-H bond to one of the iridium centers, thus making an iridium acetylide species. In 2011, Hu and co-workers reported on the addition of phenylacetylene to aldimines by $InCl_3$/CuCl under Barbier-type conditions in water for the synthesis of similar propargylamines **107**.[158] In 2013, Wan and co-workers described the reaction of imines with alkynes via deprotonation with a strong base butyllithium.[159] Addition of lithium acetylide to the imine generates a lithium propargylamide, which upon isomerization attacks a second molecule of imine. Loss of primary amine and aromatization leads to pyrroles **108**. In 2014, Chatani and co-workers used a Re(I) catalyst to do alkynylations on formaldehyde-derived imines.[160] Strangely, not the terminal alkynyl carbon adds to the imine, but rather the β-carbon atom to form a rhenium-vinylidene complex, which reorganizes via a [1,5]-hydride shift to allylimine **109**. Product yields are only moderate, and in the absence of either In or Cu-catalyst, the reaction is even more sluggish.



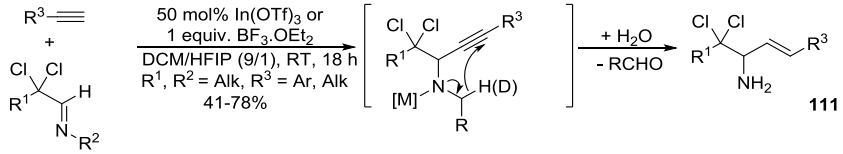
Scheme 1-48 Methods for direct alkynylation of imines.

In recent years, our group also made a contribution to the field of alkynylations on imines. The used imines are derived from polyhalogenated aldehydes, and the presence of extra halogen atoms near the imidoyl carbon causes this atom to be more electrophilic. The use of these polyhalogenated aldehydes impedes the use of these components in A^3 couplings since the halogen-atoms often interfere with Lewis-acid catalysts, leading to unwanted side-reactions. In 2008, the addition of alkynyl trifluoroborates to *N*-homoallylaldimines was reported to give unintended propargylamines **110** (Scheme 1-49).[161] Homoallylimine starting material undergoes a 2-aza-Cope rearrangement to form an isomerized homoallylimine, which undergoes alkynylation with alkynyl trifluoroborates in low yields.



Scheme 1-49 *In situ* 2-aza-Cope rearrangement, followed by alkynylation with alkynyl trifluoroborates.

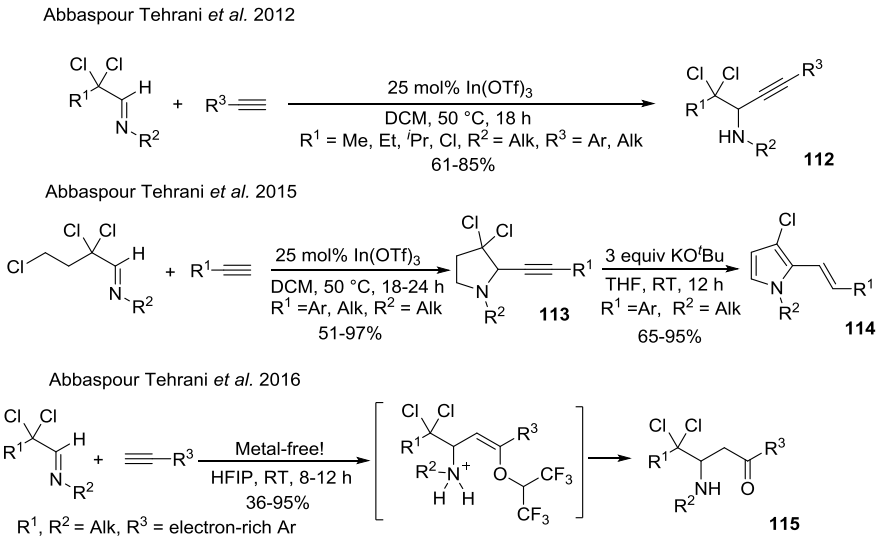
Later in 2013, it was reported that similar α,α-dichloroaldimines undergo alkynylation with alkynes under borontrifluoride or indium triflate catalysis (Scheme 1-50).[162] However, not the intended propargylamines were isolated, but primary β,β-dichloro allylamines **111** were isolated as products from [1,5]-hydride transfer and subsequent hydrolysis of the formed iminium species. Calculations showed two possible pathways. For arylacetylenes a stepwise mechanism was postulated, whereas for alkylacetylenes a concerted pathway is followed.



Scheme 1-50 Synthesis of β,β-dichloro allylamines from α,α-dichloroimines with alkynes.

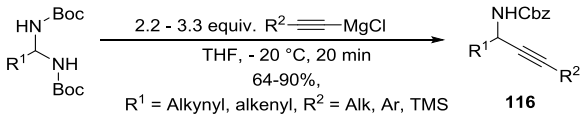
The first alkynylation reaction on α,α-dichloroaldimines leading to propargylamines **112** was reported in 2012 (Scheme 1-51). Interestingly, no column chromatography is necessary for the isolation of products **112**, since simple acid-base extraction yielded products **112** in good yields and high purity.[163] in 2015, an extension of the scope was made using α,α,γ-trichloroaldimines. After alkynylation and *in situ* ring closure with elimination of

hydrochloric acid, 1-alkynyl pyrrolidines **113** could be formed in good to excellent yields.[164] Upon treatment with potassium *tert*-butoxide pyrroles **114** could be formed. Later, in 2016 the metal-free reaction of α,α-dichloroaldimines in pure hexafluoroisopropanol yielded β-aminoketones **115**.[165] DFT calculations were performed to get a better understanding of the reaction mechanism. Firstly, HFIP protonates the imine, then addition of an electron-rich arylacetylene gives rise to an allenyl cation, which is attacked by a molecule of HFIP. Hydrolysis eventually leads to the formation of β-aminoketone **115**.



Scheme 1-51 Alkynylation reactions on α,α-dichloroaldimines.

Aldimines can also be generated *in situ* from, for example, *N*-Boc aminals. Alkynylation with alkynyl-Grignard reagents leads to the formation of aldimines, which are subsequently alkynylated with a second equivalent of Grignard alkynyl reagent to give propargylamines **116** (Scheme 1-52).[166]

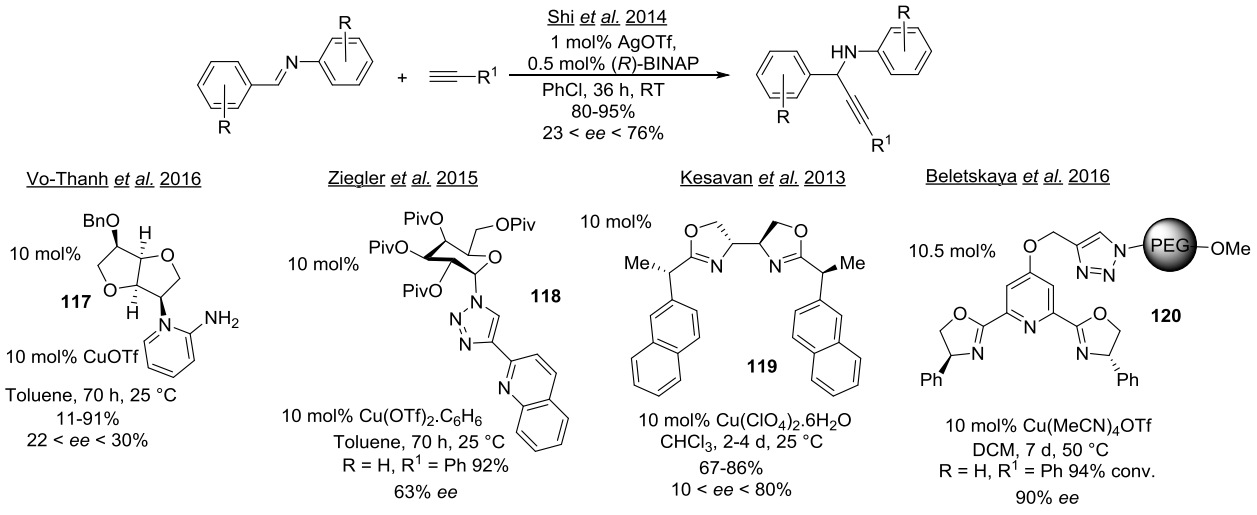


Scheme 1-52 Alkynylation of *N*-Boc aminals.

Asymmetric versions of alkynylations on imines are the next topic of interest. The main way to generate propargylamines stereoselectivily, is the addition of chiral metal-complexating ligands. It should not be surprising that the ligands used for this are the same or closely resemble ligands used in A³ couplings such as (Py)Box or bis-naphthalene derived ligands. Next to these ligands, other methods to generate stereoselectivity might be the use of chiral counter ions[167] or using chiral protecting groups to induce diastereoselectivity. The last review of the field, titled 'To catalytic asymmetric 1,2-alkynylation' was published in 2012, and contains a chapter dedicated to alkynylation of imines.[168] Here, we will give a five year update of this field.

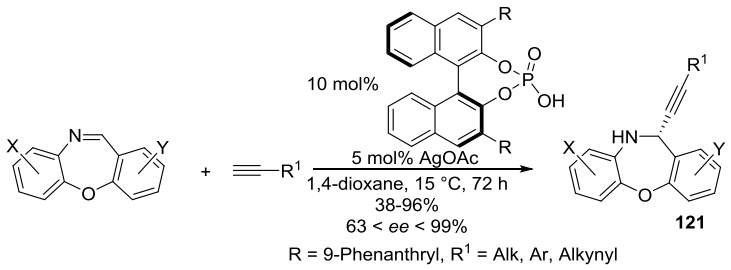
In 2014, Shi *et al.* reported on the use of a combination of AgOTf and BINAP for the direct alkynylation of imines at room temperature (Scheme 1-53).[169] Reported yields are high, but enantiomeric excesses are only moderate, making this method less useful. In 2016, Vo-Thanh

and co-workers described the combination of a copper(I) salt in combination with a diamine ligand **117** for alkynylation of imines.[170] Since only a few examples are given, and some giving rise to very low yields and *ee's* this method can be considered as not-useful. In 2015, Ziegler *et al.* reported on the use of sugar-derived triazole ligands, inspired by the Box and PyBox ligand-class, for the synthesis of propargylamines from imines and alkynes.[171] The main target of the authors was to synthesize different ligands, starting from different sugar derivatives. The best result was obtained with particular ligand **118**, although the enantiomeric excess is still moderate (63%). In 2013, Kesavan and co-workers prepared a number of Box-type ligand with an extra stereocenter in order to mitigate the poor chirality transfer.[172] Reactions are generally high-yielding and enantiomeric excesses are reasonably good, making this ligand **119** a recommended ligand, especially since the synthesis starts from easy accessible tartrate derivatives. Since chiral ligands are often expensive, reusability is a major topic of interest. Generation of heterogeneous ligand-metal complexes can be a solution to this problem, allowing easy recovery. In 2016, Beletskaya *et al.* described the use of poly(ethylene glycol)-supported PyBox **120** in combination with copper(I) salts for asymmetric alkynylation of simple aldimines.[173] Recycling experiments showed that the catalyst could be reused without loss of activity.



Scheme 1-53 Different ligands used for the alkynylation of aromatic aldimines.

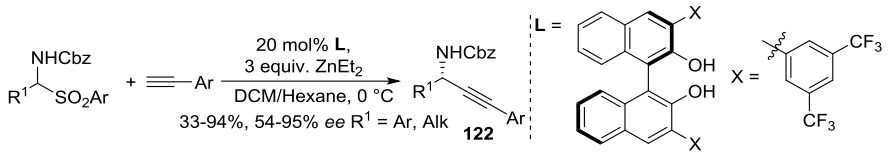
In 2014, Liu and co-workers described the use of a AgOAc/phosphoric acid catalytic system for the alkynylation of cyclic aldimines (Scheme 1-54).[174] Although reaction times are long (3 days), excellent yields and enantiomeric excesses can be achieved for the synthesis of heterocyclic propargylamines **121**. Here, the combination of the silver salt and phosphoric acid creates a new chiral silver salt, which enables stereoselective alkynylation. Reaction conditions are closely related to conditions described by Rueping in 2007 for the enantioselective alkynylation of *N*-PMP-imino esters.[175]



Scheme 1-54 Phosphoric acid as a catalyst for enantioselective alkynylation on cyclic aldimines.

Since chiral ligands are often expensive, reusability is a major topic of interest. Generation of heterogeneous ligand-metal complexes can be a solution to this problem, allowing easy recovery.

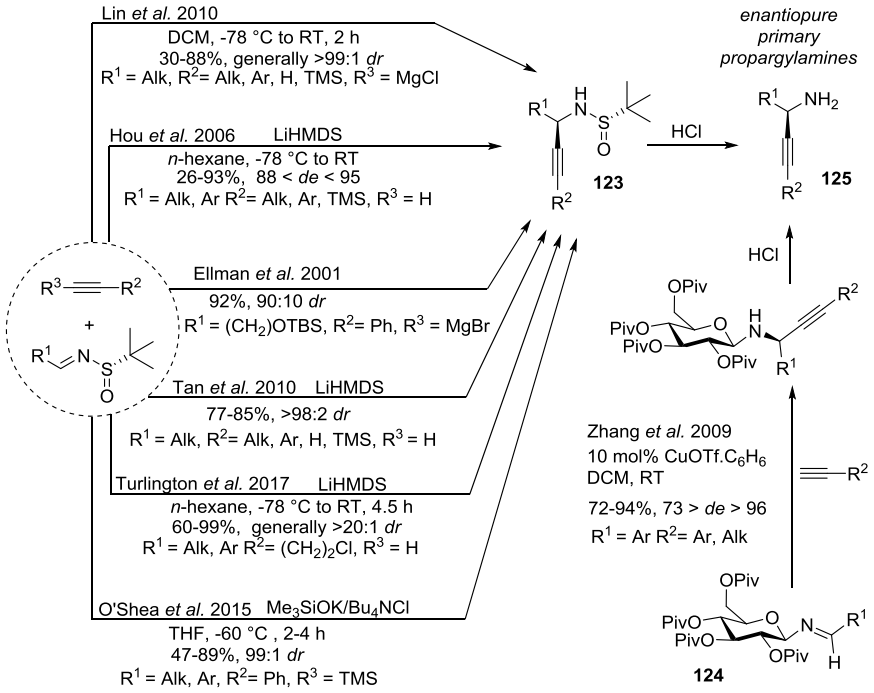
It is worth mentioning that aldimines can also be formed *in situ* from α-amido sulfones. Enantioselective alkynylation with a zinc/BINOL system leads to *N*-protected propargylamines **122** (Scheme 1-55).[176]



Scheme 1-55 Enantioselective alkynylation of α-amido sulfones.

Next to the use of chiral ligands for asymmetric alkynylation, there is also a possibility to obtain stereoselectivity via diastereoselective alkynylation on already chiral starting materials (Scheme 1-56). The best example of such a chiral starting material are *N*-sulfinylimines, introduced by Ellman in 1999.[177] Alkynylation is usually accomplished by using strong bases[178] to deprotonate alkynes or by using alkynyl Grignard reagents[179] and then direct addition at low temperatures to allow for excellent diastereoselectivities of products **123**. The sulfinylgroup can be removed by treatment with acid, yielding primary propargylamine **125**.

Similarly, other chiral imines could be used, such as chiral imine **124** derived from glucose.[180] In this example the alkynylation can be done in a catalytic way using a Cu(I) salt. At room temperature diastereomeric ratios are slightly lower than those obtained via *N*-sulfinylimines. Acid-treatment of the product generates again primary propargylamine **125**.

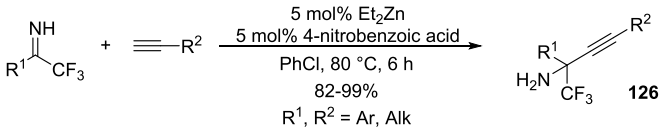


Scheme 1-56 Overview of methods of alkynylation on imines derived from chiral amines to yield enantiopure propargylamines.

1.3.7.2 Alkynylation on ketimines

In recent years the interest of organic chemists in the field of alkynylation of ketimines has mainly been focused on asymmetrical alkynylations. For years alkynylations on ketimines (and aldimines) have mainly been carried out with the use of stoichiometric amounts of metal reagents, such as dialkylzinc and alkyllithium compounds. However, from an environmental point of view it is better to avoid stoichiometric amounts of metal, because this creates hazardous metal waste. Preferentially catalytic amounts of transition metals are thus used.

Ketimines are less electrophilic than aldimines due to the presence of an extra electron-donating alkyl substituent. Furthermore, this substituent increases the sterical hindrance around the carbonyl. Since there is a big difference in sterical hindrance between an alkyl or aryl-group and a hydrogen atom, aldimines exclusively adopt *E*-configurations around the imine bond. Due to smaller differences in sterical hindrance between ketone side-chains in ketimines, ketimines usually do not have exclusively *E*-configurations, but rather *E*/*Z*-mixtures are obtained. Alkynylation on these substrates is thus more difficult, which is underlined by the fact that only in recent years KA² couplings can be performed where a ketone component replaces an aldehyde component (see more in Chapter 3). With KA² couplings possible nowadays, research interest is mainly focused on difficult substrates, often bearing protecting groups on the nitrogen atom. These protecting groups often have to be removed in a later stage of synthesis. To overcome this problem, Ohshima and colleagues published conditions for non-asymmetric alkynylation of *N*-unprotected trifluormethylketimines (Scheme 1-57) giving primary propargylamines **126**.[181] The use of dimethylzinc, before often used as a (super)stoichiometric catalyst, is here used in catalytic amounts in combination with 4-nitrobenzoic acid to obtain tetrasubstituted propargylamines. Interesting is the fact that alkynylation of *N*-unsubstituted ketimines takes place chemoselectively in the presence of *N*-protected aldimines. From a mechanistic point of view probably a (alkynyl)(carboxylato)-zinc(II) species is formed, this is supported by the higher enantioselectivity upon addition of a chiral phosporic acid salt.



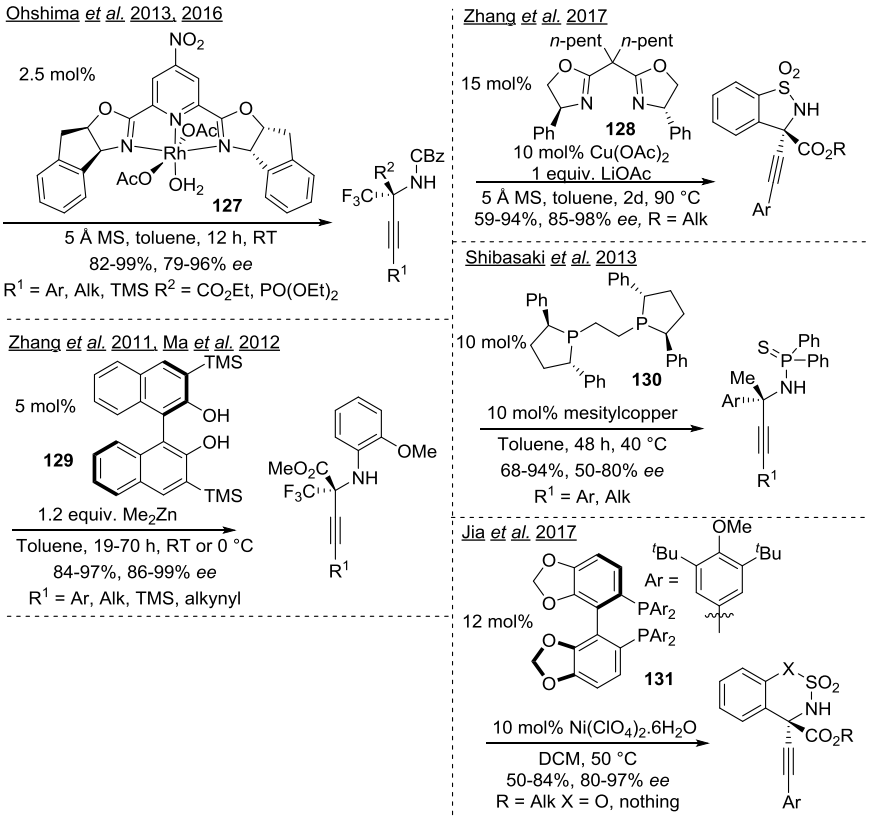
Scheme 1-57 Alkynylation of *N*-unsubstituted ketimines.

The field of asymmetric alkynylation reactions on ketimines has received a lot of attention in the last years, and this is underlined by a special review titled 'Recent advances in Catalytic Asymmetric C-C Bond-Forming Reactions to Ketimines Promoted by Metal-Based Catalysts', written by Kumagai and Shibasaki in 2015.[182] Here, we will discuss various methods for this alkynylation (Scheme 1-58).

Three types of ligands seem to play an important role in this field. In the first place, Box-derived ligands could be used, just as with aldimines. In 2013, Ohshima *et al.* described the use of a special PyBox ligand **127**, named PheBox in combination with rhodium, which allowed them to do alkynylation reactions on *N*-protected α-ketiminoesters.[183] Later, in 2016 they expanded the substrate scope so that also aliphatic and TMS-substituted alkynes could be used, meanwhile they also elucidated the reaction mechanism.[184] In 2017, Zhang and colleagues published an optimized Cu/Box **128** system for the enantioselective alkynylation of cyclic *N*-sulfonylketimines.[185] Yields and enantiomeric excesses are excellent. This is striking, given the fact that the reaction requires heating at 90 °C, which is quite high for asymmetric alkynylations.

In the second place, BINOL-ligands **129** are giving excellent results in combination with (super)stoichiometric amounts of dialkylzinc as described by Zhang in 2011.[186] In 2012, Ma *et al.* described very similar reactions conditions, using the same metal and ligand **129** but with diynes and carried out at 0 °C instead of room temperature.[187] Later in 2013, Zhang further expanded the scope of this Zn/BINOL catalyzed reaction to the use of α-aryl α-ketiminoester instead of α,α,α-trifluoromethyl α-ketiminoesters, however yields and enantiomeric excesses were low.[188] Therefore, they reoptimized the system and it turned out that the substitution on the 3- and 3'-positions of BINOL were of great importance. With the more electron-deficient Tf group on positions 3 and 3', excellent yields and enantiomeric excesses could be obtained again. Furthermore, the enantioselectivity was very sensitive to the reaction temperature. Room temperature was the best, with lower or higher temperatures leading to a decrease in enantioselectivity.

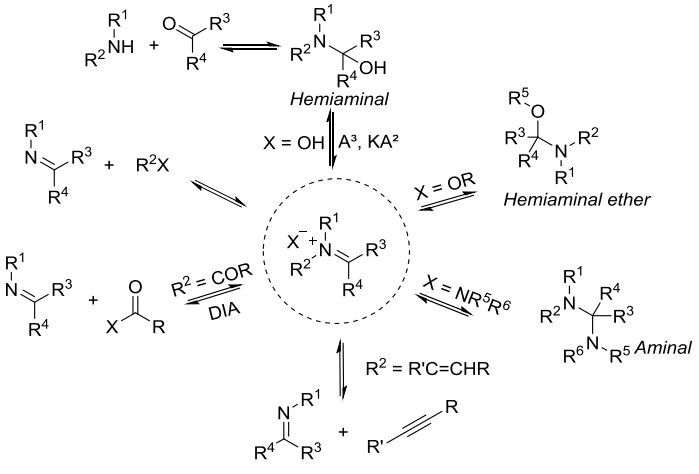
A third type of ligands, are different phosphine ligands. In 2013, Shibasaki and co-workers used a (*S,S*)-Ph-BPE bisphosphine ligand **130** in combination with mesitylcopper for alkynylation of *N*-thiophosphinoylketimines.[189] Yields were very good, but enantioselectivities are only moderate. The same group used this catalytic system in 2015 for the total synthesis of KAE609, which was at that time a clinical phase II antimalarial drug.[190] In 2017, Jia and co-workers published on the use of a Ni/(*R*)-DTBM-SegPhos **131** catalytic system for the alkynylation of cyclic *N*-sulfonyl α-ketiminoesters with excellent yields and enantiomeric excesses.[191]



Scheme 1-58 Different systems used for asymmetric alkynylation of ketimines.

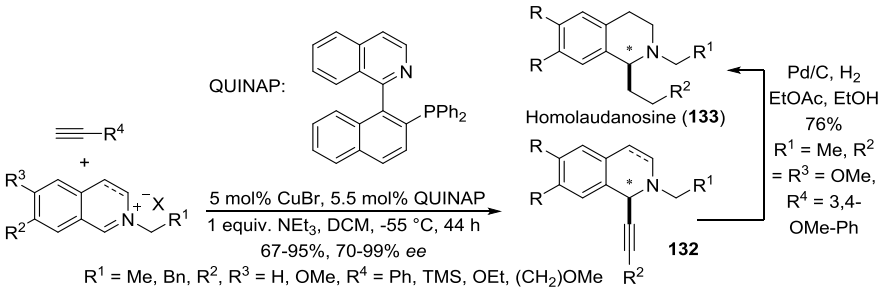
1.3.7.3 Alkynylation on iminium species

Alkynylation reactions on iminium species generally occur more easily than alkynylation reactions on imines. Due to the positive charge on nitrogen, the iminium species has a more electrophilic nature than an imine. Since this electrophilic nature often makes iminium species unstable, iminium species are often formed *in situ* and trapped by a nucleophile. Iminium species can be formed via a variety of ways *in situ* by the condensation of an aldehyde/ketone and a secondary amine via an intermediate hemiaminal (*i.e.* in A³ coupling) or via intermediate hemiaminal ethers, formally known as *N,O*-acetals (Scheme 1-59). In another way, iminium species are formed from imines by direct alkylation with alkyl halides, hydroamination with alkynes or acylation with acid chlorides via what is called a Direct Imine Acylation (DIA) reaction.



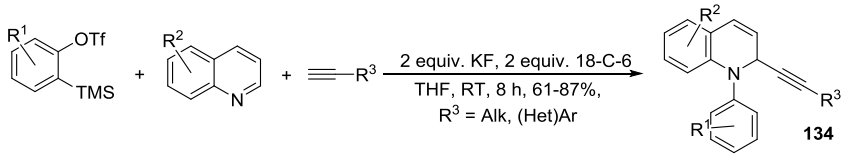
Scheme 1-59 Different pathways to generate iminium species.

A first example of direct iminium alkynylation is the enantioselective alkynylation on isolated isoquinolinium species (Scheme 1-60). The isoquinolinium species are formed from isoquinolines with alkyl halides in a separate step. At -55 °C, stereoselective alkynylation occurs with the help of the chiral ligand QUINAP to form propargylamines **132**.[192] This methodology is used in the synthesis of (*S*)-(-)-homolaudanosine (**133**), an alkaloid with neurologic activity, which is easily made via hydrogenation of **132**.



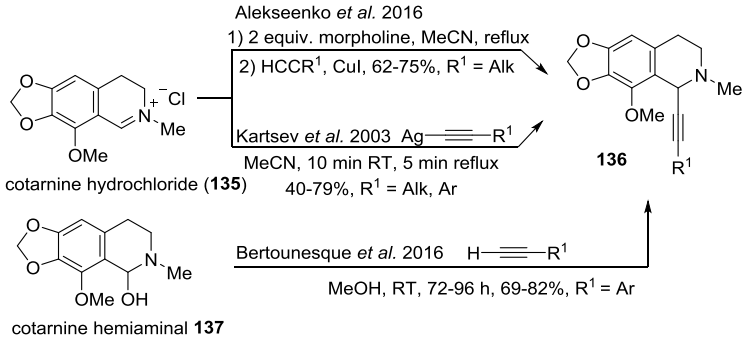
Scheme 1-60 Stereoselective alkynylation of isoquinolinium salts.

Direct alkynylation of quinolinium salts, *in situ* formed from quinolines and benzynes, is possible with KF and 18-crown-6 and gives propargylamines **134** (Scheme 1-61).[193]



Scheme 1-61 Alkynylation on *in situ* formed quinolinium salts.

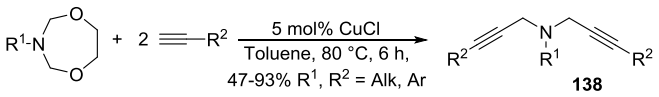
The alkynylation of cotarnine hydrochloride (**135**), a decomposition product of narcotine, leads to 1-alkynyl cotarnine derivatives **136** (Scheme 1-62). The first method describes the alkynylation with preformed silver acetylides.[194] A second method used morpholine to generate *in situ* aminal, which can be alkynylated with a stoichiometric amount of CuI.[195] A third method starts from cotarnine hemiaminal **137**, and leads to product **136** via a direct metal-free alkynylation in methanol.[196]



Scheme 1-62 Alkynylation of cotarnine hydrochloride.

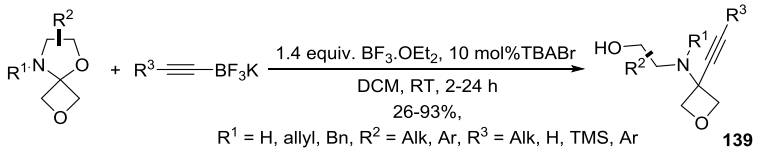
Alkynylation on *N,O*-acetals generates *in situ* iminium species, without loss of water, but with the loss of an alcohol. A first example describes the alkynylation on *N*-substituted 1,5,3-dioxazepanes, which is a formaldehyde-derived surrogate (Scheme 1-63). Double

alkynylation with two equivalents of alkyne, in the presence of catalytic copper chloride, leads to bispropargylamines **138**.[197]



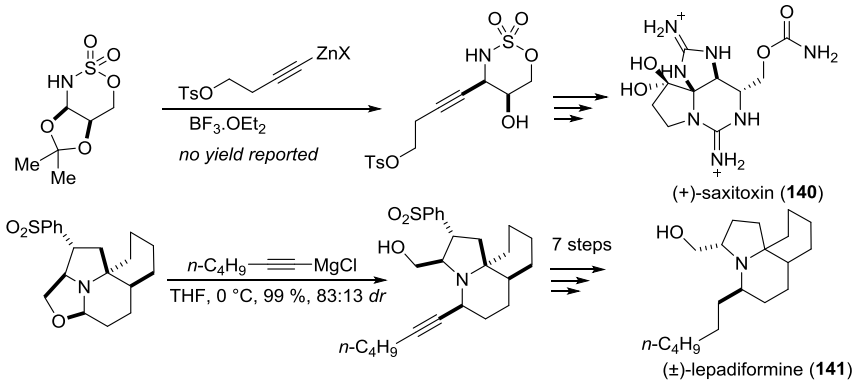
Scheme 1-63 Double alkynylation on *N,O*-acetals.

N,O-Acetals, derived from 3-oxetanone and 1,2-amino alcohols undergo addition with alkynylpotassium trifluoroborates (but also with allyl-, allenyl- and vinylpotassium trifluoroborates) in a Petasis or Borono-Mannich-like reaction (Scheme 1-64).[198] In the presence of superstochiometric amounts of boron trifluoride and catalytic tetrabutyl ammonium bromide, alkynylation occurs to form special propargylamines **139**.



Scheme 1-64 Addition of alkynylpotassium trifluoroborates to *N,O*-acetals.

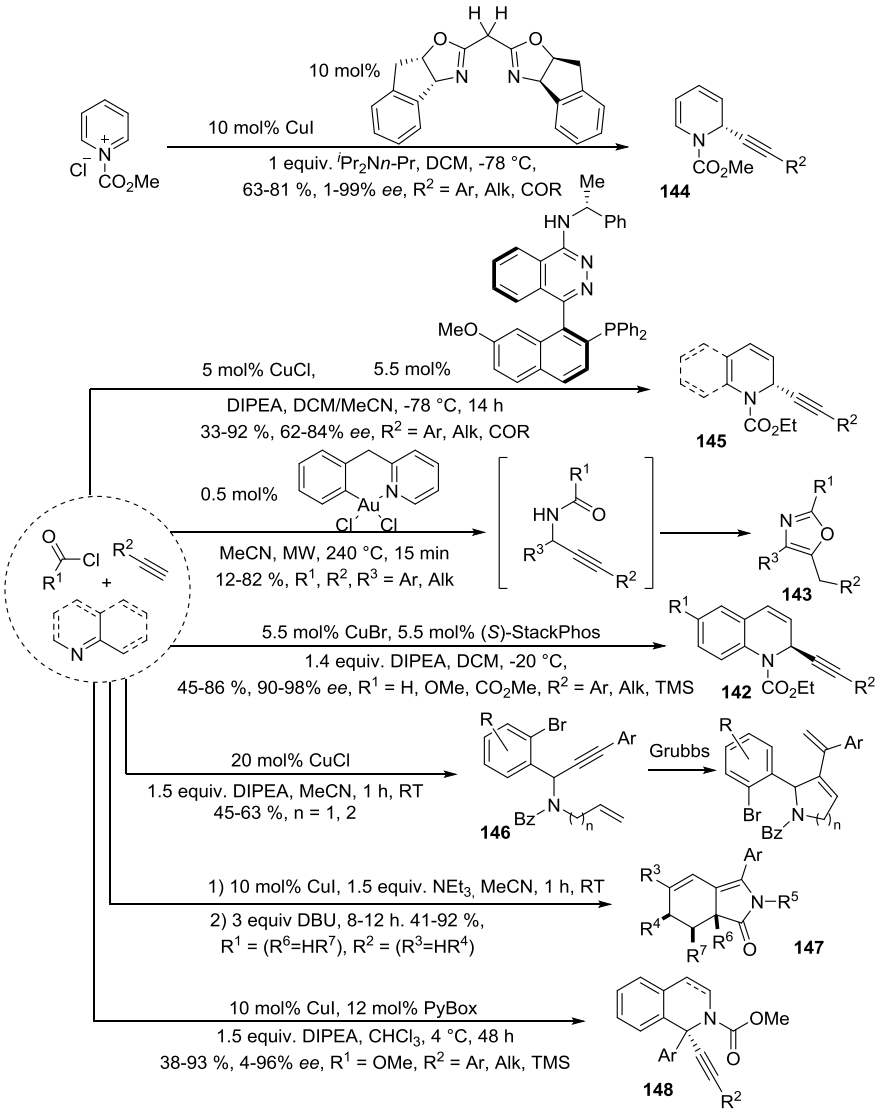
Alkynylation on *N,O*-acetals is also described in the synthesis of natural products (+)-saxitoxin (**140**)[199] and (±)-lepadiformine (**141**) using stoichiometric amounts of metal reagents (Scheme 1-65).[200]



Scheme 1-65 Examples of alkynylation of *N,O*-acetals in total synthesis.

Direct Imine Acylation (DIA) generates iminium species which can be trapped with a variety of nucleophiles, including acetylides (Scheme 1-66). In 2015, Aponick and co-workers reported on the enantioselective alkynylation of *in situ* generated quinolinium salts derived from quinolines and acyl chlorides by using a CuBr/StackPhos metal/ligand combination. Yields and enantiomeric excesses were generally very high, making this an excellent method for the generation of propargylamides **142**.[201] In 2015, Strand *et al.* reported on the use of a Au(III) complex that is able to catalyze the coupling of imines, acyl chlorides and alkynes to form oxazoles **143**. A low catalyst loading and short reaction times are advantages of this synthesis, yields however are variable from poor to good.[202] In 2007, Ma and co-workers reported on the enantioselective alkynylation of 1-acylpyridinium salts with CuI/Box catalytic system. Yields were generally high, and enantiomeric excesses are high for alkynylation with

propiolates, while alkynylation with aryl/alkyl substituted alkynes resulted in very low enantiomeric excesses of products **144**.[203] In 2008, Arndtsen and colleagues reported on the enantioselective alkynylation of pyridines and quinolines with chloroformates (R^1 = OR) and alkynes.[204] They used a CuI/PINAP-derivative catalytic system with decent yields and enantioselectivities of propargyl carbamates **145**. In 2013, Malinakova *et al.* reported the one pot three-component coupling of imines, acyl chlorides and alkynes to generate structures **146** via CuCl catalysis.[205] These enyne structures **146** could be further used in RCM reactions catalyzed by Grubbs catalyst. In 2010, Huang and co-workers published a three component coupling between 1,3-enynes, imines and α,β-unsaturated enoic acid chlorides.[206] From a mechanistic point of view, the reaction first forms the corresponding propargylamide, which undergoes a propargyl-allenyl isomerization, and the isomerized product undergoes a [4+2] cyclization toward product **147**. Product yields are quite high for a three-step tandem reaction. In 2016, Watson and colleagues published a method for the alkynylation of isoquinolines, which are in fact ketimines, catalyzed by CuI/PyBox in combination with methyl chloroformate and alkynes yielding 1-alkynyl isoquinolines **148**.[207] Yields and enantioselectivities are generally high, except when alkyl or TMS-substituted alkynes are used, then the enantioselectivity drops dramatically.



Scheme 1-66 Different methods for one pot alkynylation of *in situ* formed iminium species from imines and acyl chlorides.

1.4 Synthetic utility of propargylamines

The popularity of propargylamines originates from the nature of this class of molecules. Propargylamines possess a nucleophilic amine and an electrophilic alkyne moiety, leaving the molecules susceptible to reactions with other electrophiles/nucleophiles, and thereby often constructing *N*-heterocycles. It is our aim to give a brief, non-exhaustive overview of the different types of reactions possible with propargylamines as starting materials. Examples of highly substituted propargylamines undergoing intramolecular ring closing reactions were already included in the discussion in §1.3. In this section emphasis will be on intermolecular reactions with propargylamines. Only reactions specific for propargylamines will be discussed *in extenso* while other reactions which are general for either amines or alkynes will only be mentioned briefly. In 2014, Yunyun Liu published a review entitled 'Recent advances on diversity oriented heterocycle synthesis via multicomponent tandem reactions based on A^3 coupling', where the focus was mainly on substituted A^3 components, which were used in further intramolecular derivatization strategies. Only very briefly the coupling of more than the classical three components in A^3 couplings was discussed, leaving plenty of opportunity for this to be discussed here. After writing §1.4-1.5, Castagnolo *et al.* published a review entitled 'Synthesis and reactivity of propargylamines in organic chemistry' which discusses different A^3 couplings and C-H functionalization of alkynes for the synthesis of propargylamines and is sorted by transition metal catalysts. In a second part the reactivity of propargylamines is discussed and sorted by the different classes of reaction products that could be obtained.[208]

1.4.1 Classical amine- or alkyne-reactions involving propargylamines

In 2015, the book 'Modern Alkyne Chemistry: Catalytic and Atom-Economical Transformations' was published with editors Prof. B. M. Trost and Prof. C.-J. Li.[209] The book describes many of the actual work going on in alkyne chemistry, and can be regarded as a trustworthy reference work. Not surprisingly, a chapter is dedicated to the A^3 coupling. Classical reactions of alkynes and amines can be found in every good organic synthesis handbook. Examples of these reactions are the electrophilic fluorination on the triple bond of propargylamines which can be achieved via Au(I) catalysis and with HF.[210] Another example is the application of the amine moiety in primary propargylamines in Petasis reactions to generate secondary propargylamines.[211] A third example is the semi-hydrogenation of the triple bond of propargylamines, which is challenging, but was nevertheless accomplished with the help of heterogeneous Pd nanoparticles.[212]

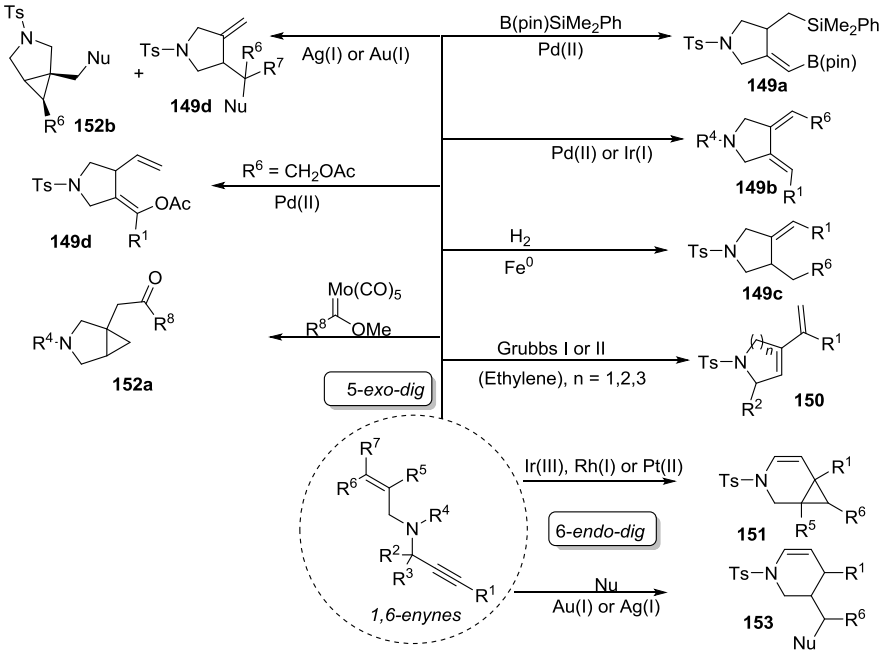
1.4.2 Intramolecular reactions of propargylamines

A classic reaction involving alkynes is the 'Click' reaction between alkynes and azides. Next to using A^3 components containing an azide moiety at one of the components, intermolecular reactions of propargylamines and azides could also lead to triazole-derivatives such as triazolo(benzo)diazepines.[213] Proline derivatives are frequent coupling partners in A^3 couplings, prolinols can be used for A^3 coupling, followed by oxidation of the alcohol to an aldehyde moiety, condensation with hydroxylamine and ring closure leads to fused isoxazolo[3,4]-pyrrolizines.[214] 2-Alkynylindoles are formal propargylamines and can undergo a variety of cyclizations towards annulated indoles.[215] Propargylamines can undergo hydroarylation reactions with indole moieties,[216] present on the propargylamine structure, forming annulated indoline structures or with the acetylene moiety forming 3-benzazepine structures.[217] Ring expansions of propargylamines with nitrogen incorporated in a six membered ring and the alkyne function exocyclic, can be achieved using a Au(I) complex and pyridine *N*-oxide to form azepine scaffolds,[218] using chloroethyl fluoride and trimethylaluminium to form 10-membered lactams,[219] or by addition of propiolic acids to 1-

alkynyl tetrahydroisoquinolines, yielding benzazecines via [3,3]-sigmatropic rearrangement.[220]

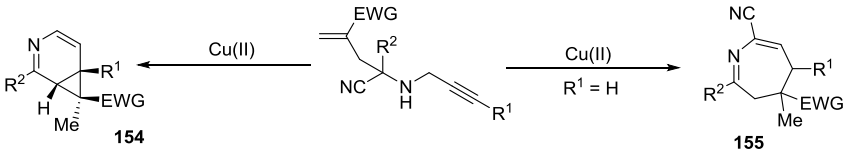
There is one very important subclass of propargylamines that has received a good amount of attention due their applicability in metathesis reactions. These propargylamines contain a double bond and are better known as enynes. Depending on the position of the alkyne and alkene moiety relative to each other, they are named 1,*n*-enynes. The field of metathesis is considered to be very valuable for the synthesis of heterocycles. This is underlined by the fact that Chauvin, Grubbs and Schrock have received the Noble Prize in Chemistry in 2005 for their work in this field. It should not be surprising that many publications in this field, led to a variety of reviews concerning this topic.[221] For propargylamines ring-closing enyne metathesis (RCEYM) is the most abundant form of metathesis. Catalysts used for this process are Mo, W or Ta complexes (Schrock-carbenes) or Ru-complexes (Grubbs, Hoveyda, Hermann), but also Pd(II), Pt(II), Pt(IV), Ir(I), Rh(I), Au(I) or Fe^0 complexes can be used for RCEYM.

Scheme 1-67 gives an overview of reactions of 1,6-enynes. Pd(II)-catalyzed silaborative carbocyclization,[222] normal carbocyclization[223], Fe^0-catalyzed reductive cyclization[224] or Ir(I)-catalyzed cyclization[225] lead to *exo*-methylenepyrrolidines **149**, while Grubbs I (Ru-carbene) catalyzed[226] and ethylene assisted cyclization[227], Grubbs II-catalyzed[178c] or Pd(II)- catalyzed *trans*-acetoxypalladation and cyclization[228] lead to 3-vinylpyrrolines **150**. The use of an Ir(III) [229], a Rh(I)[230] or Pt(II)[231] catalyst leads to cyclopropyl annulated tetrahydropiperidines **151**. In the early days, Mo-carbenes were used as stoichiometric reagents for the synthesis of cyclopropylpyrrolidines **152**.[232] In 2008, Echavarren and co-workers nicely illustrated the broad range of products arising from RCEYM. With one catalyst, they have produced two product classes **149d**/**152b** (via 5-*exo-dig* cyclization) and **153** (via 6-*endo-dig* cyclization) just depending on the substitution pattern of the starting materials.[233] The difficulty of metathesis reactions lies in the choice of catalyst for the selective synthesis of one product, since often more than one product can be formed.



Scheme 1-67 Ring Closing Enyne Metathesis of 1,6-enynes, bearing a propargyl moiety.

1,5-Enynes give rise to the formation of pyrrolidines via Au(I) catalysis[233] or pyrroles via silver trifluoroacetate catalysis, although this last reaction is not a metathesis reaction.[234] 1,7-enynes give rise to either cyclopropyldihydropyridines **154** or 4,5-dihydro-3*H*-azepines **155** via [2+2] cycloadditions (Scheme 1-68).[235]



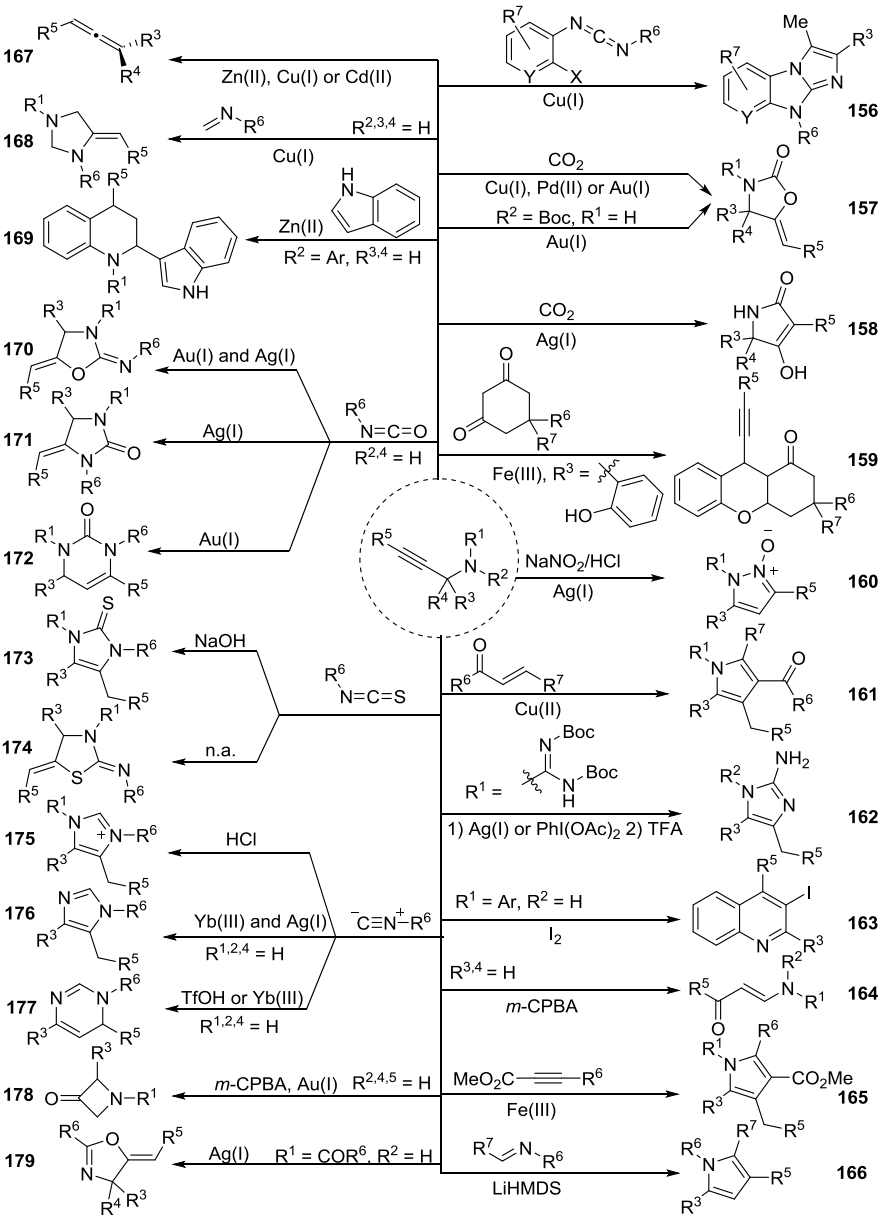
Scheme 1-68 1,7-enynes in Cu(II)-catalyzed ring closing reactions.

1.4.3 Propargylamines in follow-up chemistry

In Scheme 1-69 an overview of different methods for the functionalization of propargylamines is presented. Synthesis of imidazobenzimidazoles **156** is possible via a copper/proline catalyzed domino addition/cycloisomerization/coupling process of propargylamines and carbodiimides.[236] A recent review from Ghorbani-Kalhor *et al.* in 2017 describes reactions of propargylamines with carbon disulfide or isothiocyanates and ringclosing reactions of propargyl thioamides, for the construction of thiazole cores.[237] 'Upgrading carbon dioxide by incorporation into heterocycles', was the title of the 2015 review by Yu and He,[238] that included reactions of propargylamines with carbon dioxide yielding oxazolidinones **157**. This can be done via a four ($KA^2 + CO_2$) component reaction catalyzed by $CuI/SnCl_2$,[239] directly by addition of CO_2 and an aryl iodide, catalyzed by a Pd(II)complex[240], or by a dendritic Au(I)-NHC complex[241]. The same molecules **157** can also be generated from *N*-Boc propargylamines with the help of Au(I).[242] Incorporation of CO_2 also leads to tetramic acids **158** when catalyzed by Ag(I)/DBU.[243]

Iron(III) catalyzed reaction of propargylamines with 1,3-diones leads to xanthenone derivatives **159** with the loss of amine.[244] The electrophilicity of the alkyne can be exploited by a number of reactions. For instance, the use of sodium nitrite leads to the formation of pyrazole *N*-oxides **160**.[245] Reaction of propargylamines with α,β-unsaturated ketones leads to the formation of 3-acylpyrroles **161** under Cu(II) catalysis.[246] Guanylation of propargylamines or combination of propargylamines with thiourea, and subsequent ring closure and deprotection leads to 2-aminoimidazoles **162**.[247] Building quinolines **163** from propargylamines can be done in a variety of ways,[248] but the simplest would probably be via iodocyclization.[249] Propargylamines can be oxidized *in situ* to form isoxazoles, which then rearrange to enaminones **164**.[250] Propargylamines can form pyrroles **165** via a reaction with an extra alkyne,[251] or pyrroles **166** via reaction with an extra imine moiety.[252] The formation of allenes **167** from propargylamines via [1,5]-hydride shift with the loss of the amine moiety, also known is the ATA (allenylation of terminal alkynes) reaction can be achieved via a variety of ways using Zn(II)-,[253] Cu(I)-[254] or Cd(II)-salts[255], including the one pot A^3 coupling/allene formation.[256] Imidazolidines **168** can be formed from propargylamines via reaction with an extra equivalent of imine.[257] Intramolecular hydroarylation and cross-dehydrogenative coupling of *N*-propargylanilines with indoles leads to 2-indolyltetrahydroquinolines **169** under Zn(II) catalysis.[258] The reaction of propargylamines with isocyanates can give a number of molecules. Depending on the choice of catalyst and reaction conditions, either oxazolidin-2-imines **170**, imidazolidin-2-ones **171** or dihydropyrimidin-2-ones **172** can be formed.[259] Isothiocyanates in combination with propargylamines however give rise to imidazole-2-thiones **173** in the presence of NaOH,[260] or thiazolidin-2-ylideneamines **174** with no additives.[261] The combination of propargylamines

and isocyanides gives under Brønsted acid catalysis rise to tetrasubstituted imidazolium salts **175**,[262] while under Lewis acid catalysis with Yb(III) and Ag(I) imidazoles **176** and with triflic acid or Yb(III) 1,6-dihydropyrimidines **177** are formed.[263] Terminal propargylamines can be oxidized to form azetidin-3-ones **178**.[264] The formation of oxazolines **179** from propargylamides is mediated by Ag(I) salts.[265]



Scheme 1-69 Overview of propargylamines in follow-up chemistry.

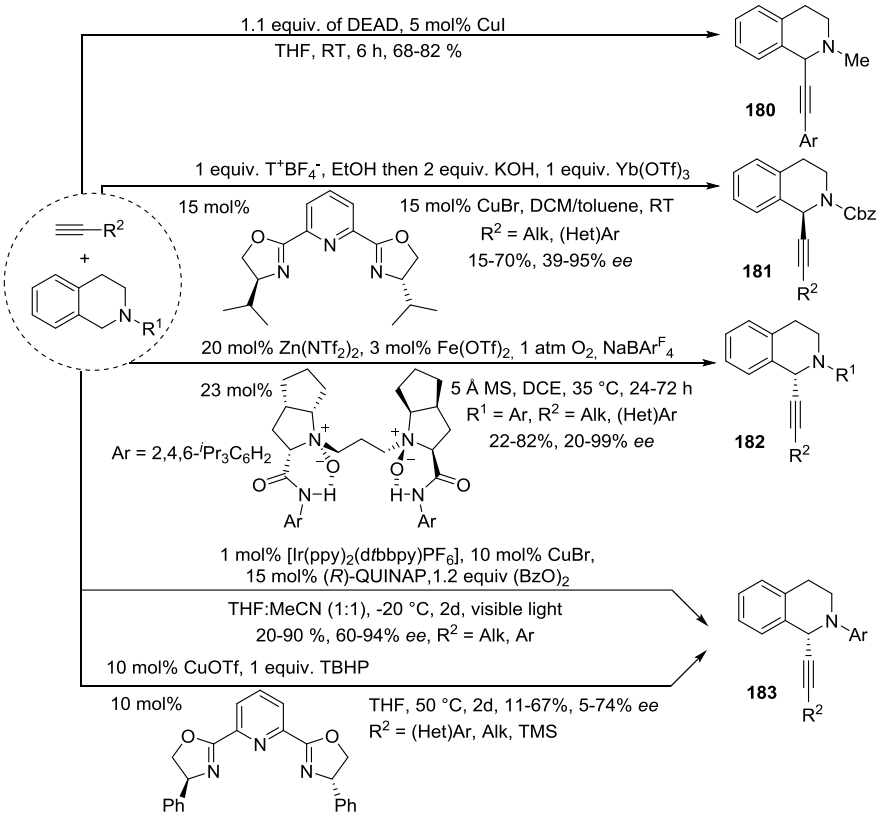
1.5 Other methods for the generation of propargylamines

The A³ coupling, and by extension its closely related adaptations such as the KA², decarboxylative A³, redox A³, … remains, by far, the most widely-used reaction to generate propargylamines. However, there are a number of other reactions that could be used to generate propargylamines in a different way. Often, these methods are far less interesting, since they start from non-commercial starting materials, adding an extra starting material synthesis step.

1.5.1 CDC reactions

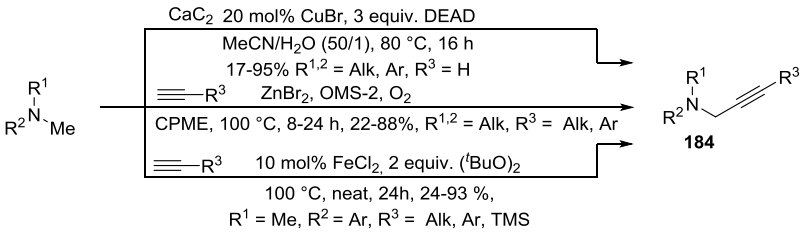
One type of reactions is very useful for the synthesis of propargylamines, and these are the cross-dehydrogenative couplings or CDC reactions. These reactions are not much different from A^3 couplings since they also use an amine and alkyne moiety, but the generation of imine/iminium occurs via oxidation of the amine with an external oxidant (often peroxides). This implies one limitation for the used amines; an α-hydrogen atom on the amine needs to be present. Since amines often have different α-hydrogen atoms, it helps when the formed imine/iminium is somehow stabilized. Therefore, this strategy is often used with tetrahydroisoquinolines (THIQ's), since the formed imine is stabilized by conjugation (Scheme 1-70).

In 2012, Singh and co-workers described the DEAD-assisted CDC reaction of methylisoquinolines with alkynes catalyzed by copper iodide.[266] Yields are reasonable, but the substrate scope regarding to alkynes is limited, since only aromatic alkynes can be used to generate *N*-methyl-1-alkynyltetrahydroisoquinolines **180**. In 2015, Liu and co-workers described the enantioselective CDC reaction of THIQ's with alkynes, assisted by the external oxidant trityl tetrafluoroborate and a Cu(I)/PyBox catalytic system.[267] Yields and enantiomeric excesses for products **181** were generally high, except in the case of aliphatic alkynes. In 2017, Feng *et al.* reported on the aerobic, enantioselective CDC reaction of THIQ's with alkynes.[268] Using molecular oxygen as oxidant is eco-friendly, Fe(II) is used as catalyst for this oxidation and Zn(II) is used as a catalyst for alkynylation to generate THIQ's **182**. Yields are moderate, but enantioselectivities are excellent for aromatic alkynes. For aliphatic alkynes, yields and *ee's* drop dramatically. In 2015, Li and co-workers reported an enantioselective CDC reaction of THIQ's with alkynes where the oxidation step is photocatalytically performed with the help of an iridium-complex and visible light.[269] CuBr/QUINAP is used for the actual alkynylation. Yields and *ee's* are moderate, especially for coupling with aliphatic alkynes. Similarly, 1-alkynyltetrahydroisoquinolines **183** were reported in 2006 by Li *et al.* to be formed from THIQ's and alkynes in a CDC reaction catalyzed by a Cu(I)/PyBox system and with TBHP as external oxidant.[270] Although this was the first enantioselective CDC reaction, yields and *ee's* are generally low, making this method less applicable.



Scheme 1-70 CDC reactions of THIQ's with alkynes, yielding propargylamines.

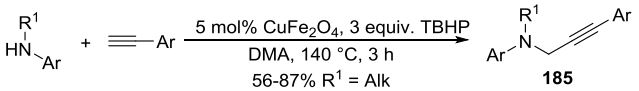
Cross-dehydrogenative couplings can also be done with other substrates than THIQ's, generating propargylamines **184** (Scheme 1-71). A first example uses DEAD in combination with tertiary methylamines and calcium carbide, under copper bromide catalysis.[271] Yields are generally high, and the reaction works particularly well for aliphatic amines. Remarkably, when tertiary dimethylamines are used, only one alkynylation reaction occurs, even in the presence of excess calcium carbide and DEAD present. A second example uses molecular oxygen in combination with similar tertiary methylamines and terminal alkynes for a $ZnBr_2$ and manganese oxide-based octahedral molecular sieve (OMS-2) – catalyzed CDC reaction.[272] Yields are generally high, except for aliphatic alkynes, where yields are low. A third example uses tertiary dimethylanilines with terminal alkynes in a CDC reaction catalyzed by $FeCl_2$ and with di-*tert*-butyl peroxide.[273] Yields are generally high.



Scheme 1-71 CDC reaction of tertiary methylamines with calcium carbide or terminal alkynes.

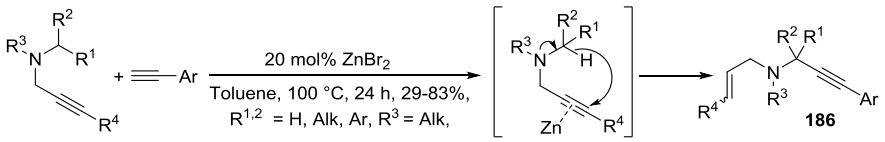
Similarly, the CDC reaction of *N*-alkyl anilines with aromatic alkynes is catalyzed by $CuFe_2O_4$ nanoparticles (Scheme 1-72). *Tert*-butylhydroperoxide is used as external oxidant and methylating agent.[274] The mechanism of the reaction is proposed as follows: homolytic

cleavage of the peroxide yields a *tert*-butoxy radical, which is further cleaved into a molecule of acetone and a methyl radical. The methyl radical is caught by the substrate and is further oxidized to generate an iminium species, which is then alkynylated to obtain the end product. A similar reaction was reported by the same research group and uses a MOF $Cu_2(BDC)_2(DABCO)$ with TBHP in DMA at 120 °C to generate the same structure **185** in 58-77% yield.[275]



Scheme 1-72 CDC reaction of secondary *N*-alkyl anilines with aromatic alkynes.

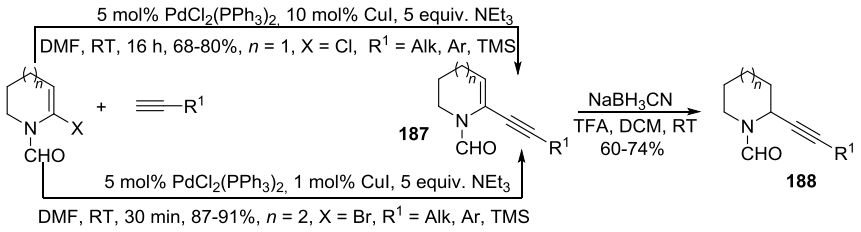
A slightly different CDC reaction uses the internal propargyl moiety as oxidant for coupling of propargylamine with alkyne, thus reducing the alkyne and generating 1,6-enyne **186** (Scheme 1-73).[276] Under Zn(II) catalysis the α-hydrogen atom undergoes a [1,5]-hydride shift, generating *in situ* an iminium species, which is trapped by the alkyne nucleophile to generate 1,6-enyne **186**. Although yields are variable, this synthesis is very atom-economical, since all atoms of the starting materials are incorporated in the end product.



Scheme 1-73 Internal CDC reaction of propargylamines to generate 1,6-enynes.

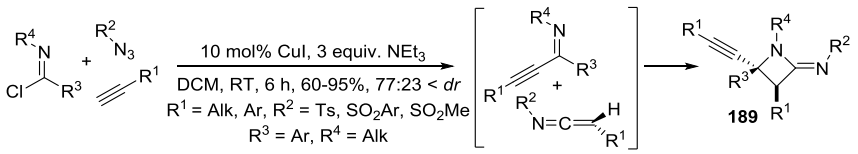
1.5.2 Cross-coupling reactions

Cross-coupling reactions of vinyl chloride[277] or bromide enamines[278] with alkynes in a Pd(II) and Cu(I) catalyzed Sonogashira reaction yields propargyl enamines **187** (Scheme 1-74). Selective reduction with sodium cyanoborohydride yields propargylamines **188**.



Scheme 1-74 Cross coupling of vinyl chlorides and bromides to yield propargyl enamines.

Alkynylation of imidoyl chlorides leads to alkynylimines, which are *in situ* used in a [2+2] cycloaddition with ketenimines to generate specific propargylamines **189** (Scheme 1-75).[279]

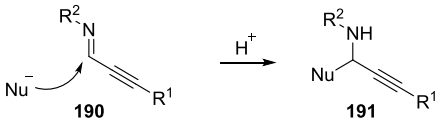


Scheme 1-75 Alkynylation on imidoyl chlorides.

1.5.3 Propargylamines from other propargylic substrates

1.5.3.1 Reduction of alkynylimines

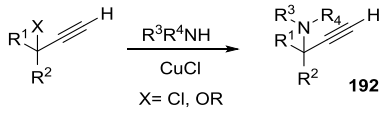
Reduction of alkynylimines **190** via hydrogenation or addition of another nucleophile generates propargylamines **191** (Scheme 1-76). Examples are the addition of an arylgroup in a Friedl-Crafts-type reaction[280], addition of diazoacetate to form α-alkynyl aziridines[281], addition of enolizable aldehydes yield β-aminoaldehydes[282], while enantioselective hydrogenation leads to enantiopure propargylamines.[283]



Scheme 1-76 Addition of a nucleophile to an alkynylimine leads to propargylamines.

1.5.3.2 Substitution of propargylic moieties

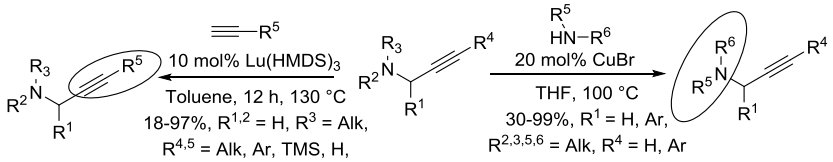
Propargylamines can be synthesized by nucleophilic substitution with amines of *tert*-acetylenic chlorides,[284] or propargyl esters,[285] both catalyzed by CuCl to generate terminal propargylamines **192** (Scheme 1-77).



Scheme 1-77 Substitution of propargyl esters and chlorides with amines.

1.5.3.3 From other propargylamines

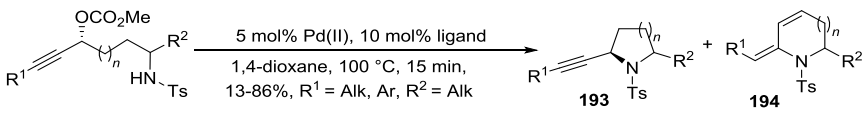
Propargylamines can be formed from other propargylamines by substitution of the acetylene group with another acetylene moiety or substitution of one amine function with another amine function (Scheme 1-78). The former is done in refluxing toluene with the assistance of lutetium(III)hexamethyldisilazane,[286] the latter can be done in THF and catalyzed by CuBr.[287]



Scheme 1-78 Synthesis of propargylamines from … propargylamines.

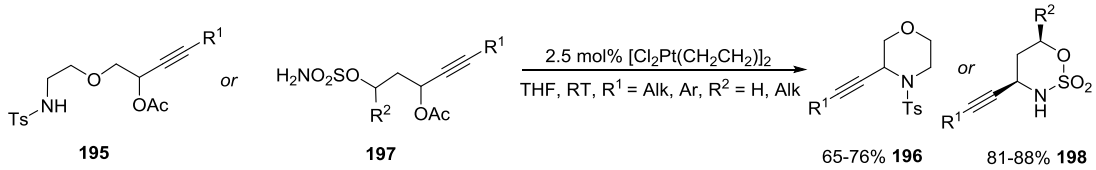
1.5.3.4 Via ring closing reactions

The propargyl moiety can be created when the alkyne and amine function are already present in the molecule, via a ring closing reaction (Scheme 1-79). The first reaction is a $Pd(OAc)_2$/DPEPhos catalyzed ring closing reaction of propargylic carbonates.[288] Depending on the choice of Pd(II) counter ion and ligand, propargylamine **193** (counter ion = OAc, L = DPEPhos) or enamine **194** (counter ion = dba, L = dppe) can be formed, with excellent regio- and enantioselectivity.



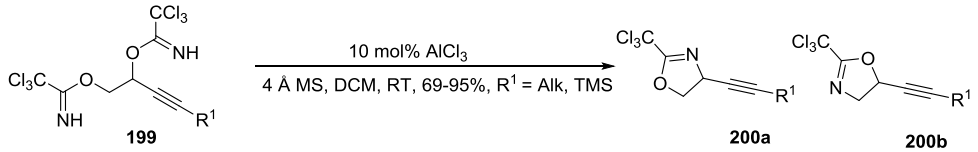
Scheme 1-79 Ring closing of propargyl carbonates yields propargylamines or enamines.

Similarly, propargyl carbonates **195** or **197** can be transformed to propargylamines **196** or **198** via a 6-*exo*-*tet* Pt(II) catalyzed ring-closing reaction (Scheme 1-80).[289]



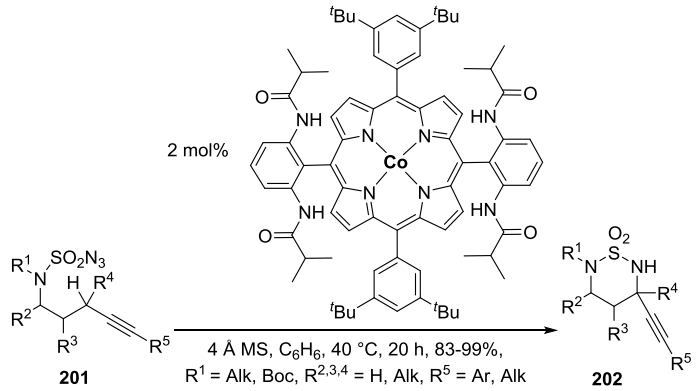
Scheme 1-80 Ring-closing reactions of propargyl carbonates lead to propargylamines.

Propargyl bis-imidates **199** can be transformed to oxazolines **200a** and **200b** with good regioselectivity by a number of Lewis acids, from which aluminium trichloride is overall the best (Scheme 1-81). Mechanistically, the reaction goes via a simple intramolecular mixed S_N1/S_N2 pathway, where one of the imidate groups acts as a leaving group.[290]



Scheme 1-81 Ring closing reactions of propargyl bis-imidates to oxazolines bearing a propargylamine moiety.

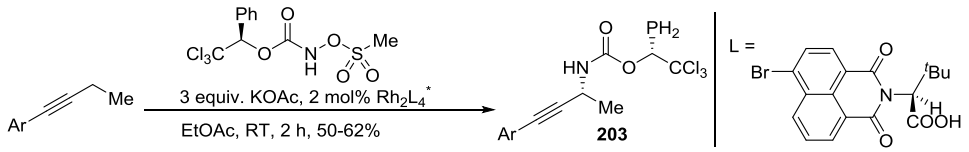
A slightly different ring-closing reaction of sulfamoyl azides **201** leads to propargylamines **202**, with the loss of N_2 (Scheme 1-82). From a mechanistic point of view, the Co(II) amination proceeds through a stepwise radical mechanism. Yields are very high, making this an excellent method for the synthesis of specific propargylamines **202**.[291]



Scheme 1-82 Ring-closing reaction of sulfamoyl azides leading to propargylamines.

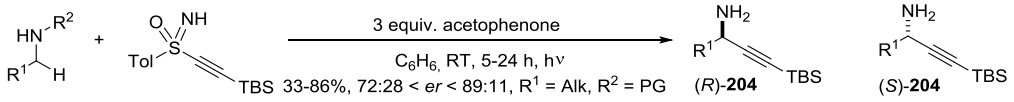
1.5.3.5 Various methods

A few other very specific methods for the generation of propargylamines will be discussed here. In a first example, an intermolecular propargylic C-H amination takes place under rhodium catalysis, with similarities to the previous cobalt-catalyzed example giving propargylamines **203** in a stereoselective way (Scheme 1-83).[292]



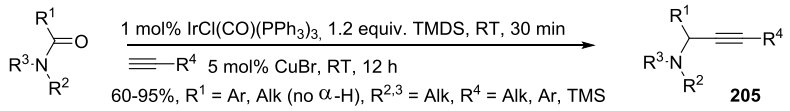
Scheme 1-83 Propargylic C-H amination.

Stereoselective production of propargylamines **204** was obtained via the coupling of amines with sulfoximines bearing an alkynyl moiety (Scheme 1-84). The transformation is catalyzed by acetophenone and visible light.[293]



Scheme 1-84 Stereoselective preparation of propargylamines from amines and chiral alkynyl-substituted sulfoximines.

Lastly, an example is showed, where an amide function is transformed into a propargylamine function (Scheme 1-85). Overall, a chemoselective reductive alkynylation occurs, catalyzed by Ir(I) and Cu(I). Ir(I) and TMDS generate *in situ* enamines, which are alkynylated with the help of Cu(I) to generate propargylamines **205**.[294]



Scheme 1-85 Chemoselective reductive alkynylation of tertiary amides.

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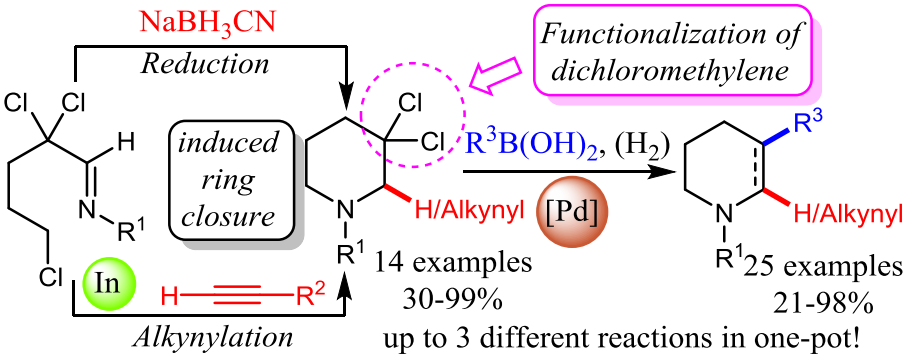
2 Alkynylation of polyhalogenated imines and functionalization of the dichloromethylene group

In this chapter our efforts towards alkynylation reactions on polyhalogenated imines will be discussed. A first topic discusses the alkynylation of α-chloroaldimines, the subsequent synthesis of 2-alkynylaziridines, and the existence of invertomers of these products. A second part describes the alkynylation of α,α,δ-trichloroaldimines for the synthesis of *N*-alkyl-2-alkynyl-3,3-dichloropiperidines.

A third part of this chapter is dedicated to the further elaboration of the dichloromethylene group, present in earlier synthesized *N*-alkyl-2-alkynyl-3,3-dichloropiperidines. The reactivity of this group in Pd-catalyzed cross-coupling reactions was investigated. The generality of these reactions was further investigated by applying similar cross-coupling reactions on non-alkynylated 3,3-dichloropiperidines.

Lastly, the possibility for the dichloromethylene group to be used as a dihaloalkane in a so-called AHA coupling, this is the coupling of an amine, a dihaloalkane and an alkyne moiety, for the generation of propargylamines, was examined.



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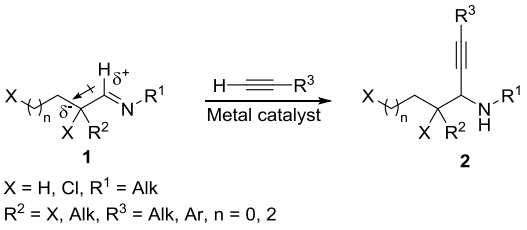
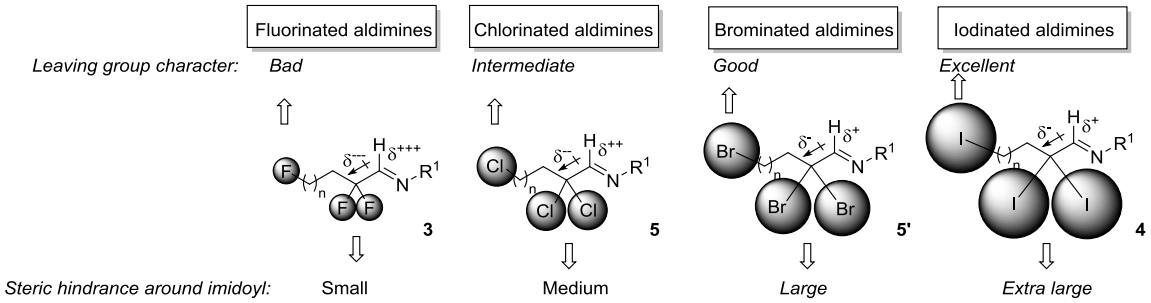
2.1 Introduction

The reason why polyhalogenated aldimines **1** are used in this chapter is because they have an enhanced electrophilic character around the carbonyl moiety compared to non-halogenated aldimines due to the presence of the halogen atoms that exhibit electron-withdrawing properties (Scheme 2-1), making addition of weak nucleophiles easier.



Scheme 2-1 Presence of halogen atoms leads to enhanced electrophilic character of the imine.

This enhanced electrophilicity effect is dependent on several factors. Firstly, the closer the halogen atom is to the carbonyl moiety the more pronounced the effect. Multiple halogen atoms will increase the effect over a single halogen atom, but the drawback is that with more halogen atoms present, sterical hindrance around the imidoyl moiety will increase, leading to less reactive aldimine systems. A third factor is the nature of the halogen atom (Scheme 2-2).

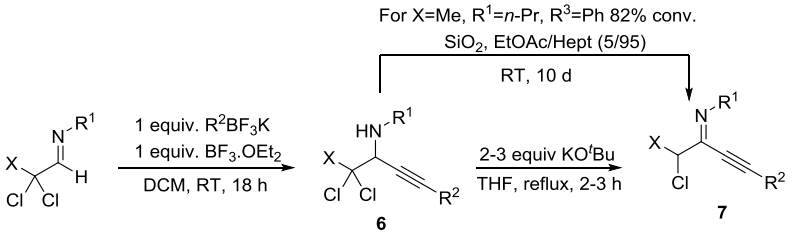


Scheme 2-2 Selection of the appropriate halogenated aldimine.

In the series fluorine, chlorine, bromine and iodine the electronegativity decreases towards iodine, while the size of the atom increases. From this point of view, fluorine decorated aldimines **3** would thus be the best choice as they would be the most electrophilic, but since we also would like to further functionalize the synthesized propargylamines via the halogen atoms, the halogen atom should also be a good leaving group. For this purpose, iodine would be the best atom, but α,α-diiodoaldimines are highly unstable and only one example of α-iodoaldimines is known.[1] These two conditions made us choose for an intermediate solution; aldimines will be decorated with chlorine atoms **5** rather than bromine atoms **5'** since they are smaller and generate less waste and brominated aldimines are too unstable.[2] Since the imidoyl carbon needs to be alkynylated, the best choice is to decorate that part of the molecule originating from the aldehyde with α-chlorine atoms, since they will be the closest to the carbonyl atom.

In recent years, our research group has used different polyhalogenated aldimines in different reactions. In 2007 for example, potassium organotrifluoroborates were used in addition reactions to α,α-dichloroaldimines, promoted by boron trifluoride (Scheme 2-3).[3] Potassium alkenyl and alkynyl trifluoroborates could be used in the generation of allylamines and

propargylamines **6**. The drawback of this approach is that the trifluoroborates need to be synthesized upfront from terminal alkynes.



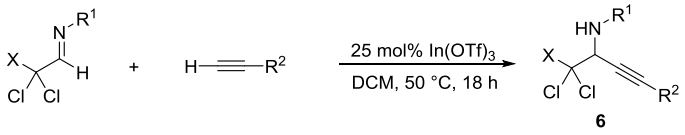
X = Me (Ref. 2):
R^1=Bn, R^2=Ph **6a** 81% crude, R^1=^{i}Pr, R^2=Ph **6b** 72% crude, R^1=*n*-Pr, R^2=Ph **6c** 78% crude, R^1=allyl, R^2=Ph **6d** 83% crude, R^1=Et, R^2=Ph **6e** 80% isolated, R^1=Me, R^2=Ph **6f** 20% crude, R^1=*n*-Pr, R^2=3-MeOC$_6$H$_4$ **6g** 88% isolated, R^1=*n*-Pr, R^2=4-EtC$_6$H$_4$ **6h** 90% isolated, R^1=*n*-Pr, R^2=MeOCH$_2$ **6i** 44% isolated.
X = Cl (Ref. 3):
R^1=^{t}Bu, R^2=Ph **6o** 76% crude, R^1=^{i}Pr, R^2=Ph **6p** 68% crude, R^1=*n*-Pr, R^2=Ph **6q** 68% crude, R^1=allyl, R^2=Ph **6r** 65% crude.

X=Cl, R^1=^{t}Bu, R^2=Ph **7a** 84% crude, X=Me, R^1=*n*-Pr, R^2=Ph **7b** 95% crude, X=Me, R^1=^{i}Pr, R^2=Ph **7c** 89% crude.

Scheme 2-3 Alkynylation of α,α-dichloroaldimines with potassium alkynyl trifluoroborates.

In 2009, the reaction scope was extended towards the use of α,α,α-trichloroaldimines, using the same potassium alkynyl trifluoroborates and boron trifluoride.[2a] Also, the reactivity of the end products **6** towards treatment with KO^{t}Bu was explored, giving alkynyl imines **7**. The products **7** could also be generated by treating **6** with silica in an ethyl acetate/heptane mixture.

In 2012, a first transition-metal catalyzed alkynylation on α,α-dichloroaldimines was reported (Scheme 2-4).[4] Different catalysts were screened, including Cu(I), Cu(II), Au(I), Zn(II), Fe(III) and In(III) catalysts, with In(OTf)$_3$ giving the best results. The scope of the reaction was examined with respect to different aromatic and aliphatic alkynes and aliphatic amine substituents. One major advantage of this reaction is that it creates secondary propargylamines **6** in a very selective way, so that an acid-base workup is sufficient to yield pure propargylamines **6**, thereby avoiding the use of column chromatography.

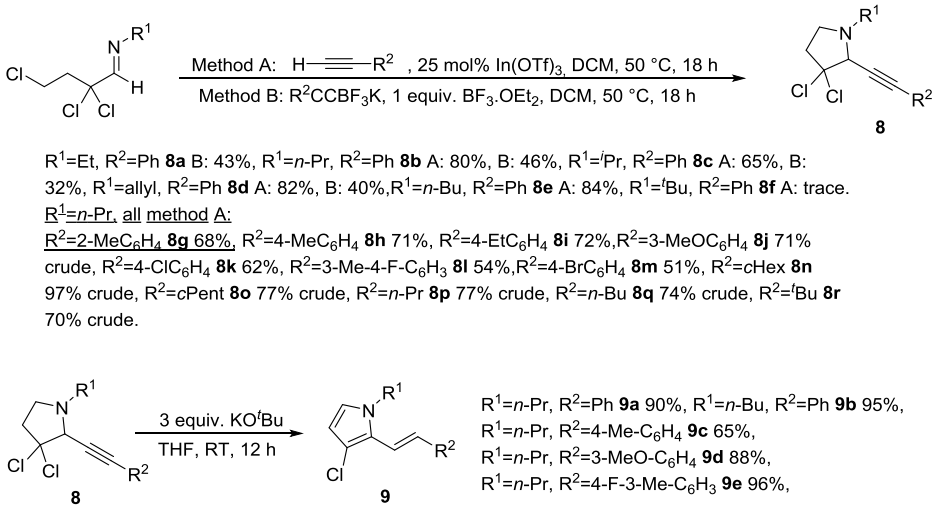


X = Me:
R^1=Bn, R^2=Ph **6a** 72%, R^1=^{i}Pr, R^2=Ph **6b** 83%, R^1=*n*-Pr, R^2=Ph **6c** 75% crude, R^1=allyl, R^2=Ph **6d** 66%, R^1=Et, R^2=Ph **6e** 65%, R^1=Me, R^2=Ph **6f** 20% crude, R^1=*n*-Pr, R^2=3-MeOC$_6$H$_4$ **6g** 71%, R^1=*n*-Pr, R^2=4-EtC$_6$H$_4$ **6h** 71%, R^1=*n*-Pr, R^2=2-MeC$_6$H$_4$ **6j** 67%, R^1=*n*-Pr, R^2=4-MeC$_6$H$_4$ **6k** 79%, R^1=*n*-Pr, R^2=4-^{t}BuC$_6$H$_4$ **6l** 65%, R^1=*n*-Pr, R^2=4-ClC$_6$H$_4$ **6m** 66%, R^1=*n*-Pr, R^2=3-Me-4-F-C$_6$H$_3$ **6n** 72%.
X = Cl, R^1=^{t}Bu, R^2=Ph **6o** 76%, X= Et, R^1=Et, R^2=Ph **6s** 62%, X= ^{i}Pr, R^1=Allyl, R^2=Ph **6t** 61%.

Scheme 2-4 In(OTf)$_3$ catalyzed alkynylation of α,α-dichloroaldimines.

Extension of the scope of aldimines to α,α,γ-trichloroaldimines was further elaborated and published in 2015 (Scheme 2-5).[5] The presence of an ω-chloro atom allows for the substitution reaction of chlorine by the *in situ* formed secondary amine moiety, giving access

to pyrrolidines **8** in one step. A comparison between the two previously reported alkynylations methods using either potassium alkynyl trifluoroborates (method B) or alkynes in combination with $In(OTf)_3$ (method A), was included. In general, method A is giving superior results. The behavior of pyrrolidines towards the use of the strong base potassium *tert*-butoxide causes elimination and migration of the triple bond for the generation of vinylpyrroles **9**.



R1=Et, R2=Ph **8a** B: 43%, R1=*n*-Pr, R2=Ph **8b** A: 80%, B: 46%, R1=*i*Pr, R2=Ph **8c** A: 65%, B: 32%, R1=allyl, R2=Ph **8d** A: 82%, B: 40%,R1=*n*-Bu, R2=Ph **8e** A: 84%, R1=*t*Bu, R2=Ph **8f** A: trace. R1=*n*-Pr, all method A: R2=2-MeC6H4 **8g** 68%, R2=4-MeC6H4 **8h** 71%, R2=4-EtC6H4 **8i** 72%,R2=3-MeOC6H4 **8j** 71% crude, R2=4-ClC6H4 **8k** 62%, R2=3-Me-4-F-C6H3 **8l** 54%,R2=4-BrC6H4 **8m** 51%, R2=*c*Hex **8n** 97% crude, R2=*c*Pent **8o** 77% crude, R2=*n*-Pr **8p** 77% crude, R2=*n*-Bu **8q** 74% crude, R2=*t*Bu **8r** 70% crude.

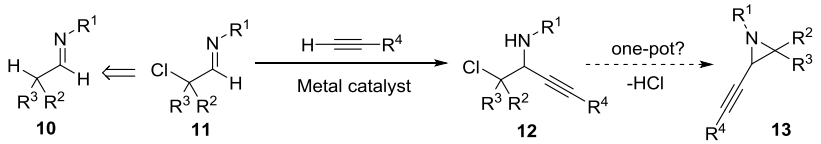
R1=*n*-Pr, R2=Ph **9a** 90%, R1=*n*-Bu, R2=Ph **9b** 95%, R1=*n*-Pr, R2=4-Me-C6H4 **9c** 65%, R1=*n*-Pr, R2=3-MeO-C6H4 **9d** 88%, R1=*n*-Pr, R2=4-F-3-Me-C6H3 **9e** 96%,

Scheme 2-5 Alkynylation of α,α,δ-trichloroaldimines.

2.2 Alkynylation on α-chloroaldimine systems

2.2.1 Starting material synthesis and optimization of reaction conditions

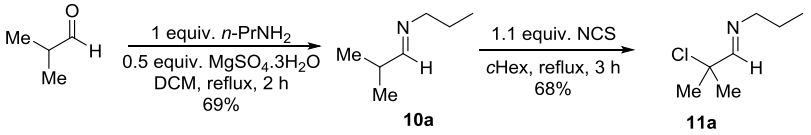
In a first expansion of the scope of alkynylations on polyhalogenated aldimines, we became interested in the alkynylation reactions on α-chloroaldimines **11**, derived from aldimines **10** (Scheme 2-6). Since alkynylation reactions of α,α,γ-trichloroaldimines yielded pyrrolidines **8**, via ring closing reaction of an intermediately formed amine, we expected a similar ring closing reaction after alkynylation of α-chloroaldimines to give 2-alkynylaziridines **13** from propargylamines **12**. In literature, a precedent reaction exists, using lithium alkynyl reagents and α-chloroketimines that yielded 2-alkynylaziridines in one-pot, proving the viability of this strategy.[6]



Scheme 2-6 Alkynylation on α-chloroaldimines might result in the formation of 2-alkynylaziridines.

In the literature, 2-alkynylaziridines are mostly made via intramolecular nucleophilic substitution of β-halo-amines,[7] β-hydroxy-amines,[8] or oxiranyl carbaldimines.[9] Other methods comprise the intermolecular substitution of 2-alkynyloxiranes with sodium azide,[10] the reaction of imines and allenylzinc carbenoids,[11] the stereoselective reaction of alkynyl imines with diazo compounds,[12] or the reaction of 1,3-enynes with amines and diacetoxyiodobenzene (PIDA).[13]

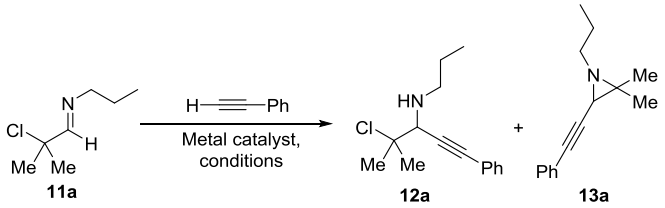
Firstly, the starting α-chloroaldimine **11a** had to be synthesized (Scheme 2-7). This could be easily accomplished by condensing an aldehyde and an amine to generate imine **10a**, followed by chlorination with *N*-chlorosuccinimide (NCS). To avoid unwanted side reactions, like aldol condensations, an aldehyde (isobutyraldehyde) was chosen that after chlorination did not possess any α-hydrogen atoms. α-Chloroaldimine **11a** was obtained almost pure, and was further purified via distillation.



Scheme 2-7 Synthesis of α-chloroaldimine **11a**.

With starting material **11a** in hands, the quest for optimal reaction conditions and catalyst was started for the coupling of phenylacetylene to this substrate (Table 2-1). In Entry 1 starting material **11a** and phenylacetylene were coupled under $In(OTf)_3$ catalysis in toluene, but only low yields of the resulting propargylamine **12a** and aziridine **13a** were observed. Increasing the temperature to 100 °C did not improve the outcome of the reaction (Entry 2), and at lower temperature almost no product was obtained (Entry 3). Changing the solvent from toluene to dichloromethane led to an improved yield, but mostly of non-ring closed propargylamine **12a** (Entry 4). Slight heating to 30 °C instead of room temperature, resulted in a diminished yield of propargylamine **12a** while the same amount of aziridine **13a** was present (Entry 5). The reaction in toluene at room temperature gave almost no product (Entry 5). Increasing the temperature led to better alkyne coupling and to more aziridine **13a** (Entries 6-8). Using different solvents such as a DCM/HFIP mixture, MeCN, EtOAc, $CHCl_3$ and cyclohexane did not improve the formation of the desired products (Entries 9-13). In case acetonitrile was used as a solvent, no products **12a** or **13a** were seen, but mass spectrometry showed traces of an aziridine and acetonitrile addition product. This probably originates from the [3+2] cycloaddition of aziridines, which are known to be 1,3-dipoles, and cyanides, and is a well-documented reaction in literature.[14] Due to very low yields, this product was, unfortunately, never isolated. Microwave experiments with $In(OTf)_3$ (Entry 14) or CuI (Entry 15) led mostly to the formation of propargylamine **12a**. Using two equivalents phenylacetylene (Entry 16) or addition of triethylamine (Entries 17-18) did not improve results. Screening other catalysts (Entries 19-25) did not lead to better results, although Zn(II) and Cu-salts were able to catalyze the coupling, albeit in low yields. Using an ionic liquid instead of a regular solvent gave a low yield of propargylamine **12a** (Entry 26). Eventually, by adding molecular sieves to the reaction mixture (Entries 28-31), product **13a** could be isolated as the sole product, albeit in a disappointing 39% yield.

Table 2-1 Optimization of reaction conditions for the synthesis of aziridine **13a**.

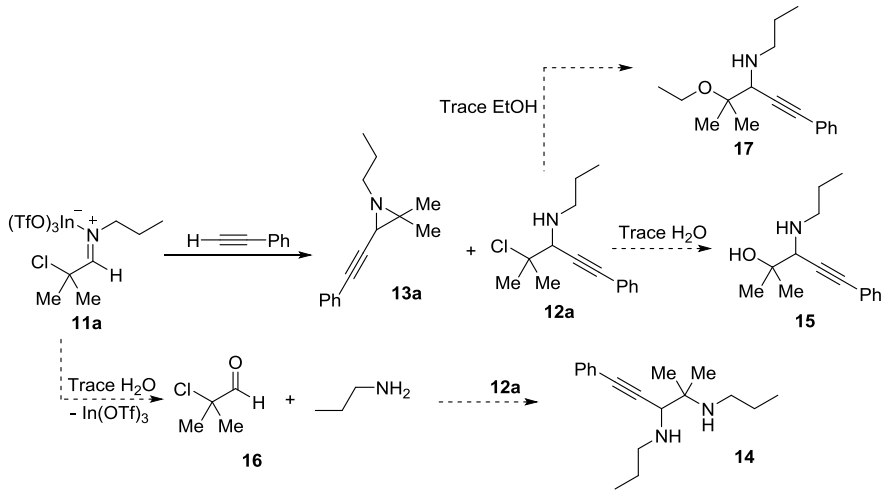


Entry	Catalyst (mol%)	T (°C)	Time (h)	Solvent	**12a** (%)	**13a** (%)
1	$In(OTf)_3$ (25)	80	20	Toluene	7	14
2	$In(OTf)_3$ (25)	100	20	Toluene	2	/
3	$In(OTf)_3$ (10)	RT	65	Toluene	< 1	/
4	$In(OTf)_3$ (10)	RT	65	DCM	21	4
5	$In(OTf)_3$ (10)	30	65	DCM	11	4
6	$In(OTf)_3$ (15)	50	65	DCM (5 mL)	3	8
7	$In(OTf)_3$ (10)	40	65	DCM	6	9
8	$In(OTf)_3$ (25)	70	24	DCM	21	17
9	$In(OTf)_3$ (25)	70	24	DCM/HFIP (9/1)	complex, 8	/
10	$In(OTf)_3$ (25)	70	24	MeCN	Different product	
11	$In(OTf)_3$ (25)	70	24	EtOAc	3	11
12	$In(OTf)_3$ (25)	70	24	$CHCl_3$	18	12
13[a]	$In(OTf)_3$ (25)	65	24	*c*Hex	/	13
14	$In(OTf)_3$ (25)	70	0.5 (MW)	DCM	25	8
15[b]	CuI (25)	100	25 min (MW)	Neat	33	/
16[c]	$In(OTf)_3$ (25)	70	24	DCM	19	5
17[d]	$In(OTf)_3$ (50)	70	24	DCM	10	/
18[d]	$In(OTf)_3$ (25)	70	24	DCM	2	/
19	$ZnCl_2$ (50)	70	24	DCM	/	3
20	$Zn(OTf)_2$ (50)	70	24	DCM	/	7
21[b]	Ag(OTf) (50)	70	24	DCM	/	/
22[b]	$AgBF_4$ (50)	70	24	DCM	/	/
23	$CeCl_3$ (100)	65	24	DCM	/	/
24[e]	$Sc(OTf)_3$ (50)	70	24	DCM	/	/

25	$Cu(OTf)_2$ (50)	70	24	DCM	/	6
26	$In(OTf)_3$ (25)	70	24	$[Bmim][BF_4]$	5	/
27[f,g]	**$In(OTf)_3$ (25)**	**65**	**24**	**DCM**	**/**	**39**
28[f,h]	$In(OTf)_3$ (25)	65	24	DCM	/	35
29[f]	$In(OTf)_3$ (25)	60	48	DCM	/	29
30[f]	$In(OTf)_3$ (25)	70	48	DCM	/	25

Conditions: Substrate **11a** (0.5 mmol), phenylacetylene (0.5 mmol), catalyst (x mol%), solvent (1.5 mL). Yields were calculated from the ^{1}H NMR spectrum with internal standard 1,3,5-trimethoxybenzene (TMB). [a] Formation of a 'black pellet' in the reaction tube instead of a homogeneous solution. [b] Starting material, no degradation. [c] 2 equivalents of phenylacetylene used. [d] 1 equivalent of triethylamine (TEA) used. [e] Complete degradation. [f] 150 mg 4 Å molecular sieves added. [g] 0.25 mL DCM used. [h] 1 mL DCM used.

Since the mass balance is often not correct, the purity of the starting material was evaluated. Phenylacetylene was checked via ^{1}H NMR and was found to be pure. The purity of the imine was tested by adding a known amount of TMB to a known amount of imine, the purity was found to be 86% with traces of non-chlorinated aldimine and aldehyde next to base-line impurities. The workup of the reaction did not have any influence on the reaction outcome; several reactions were worked up in different way, but yielded the same product ratios. The reaction outcome is not dependent on the concentration of sodium hydroxide used, or on the time of extraction. Direct column chromatography of the reaction mixture, without aqueous workup, gave a similar result.



Scheme 2-8 Formation of (side) products from alkynylation on α-chloroimine **11a**.

In some cases, side products were obtained and identified by NMR next to propargylamine **12a** and aziridine **13a** (Scheme 2-8). One of the products originates from hydrolysis of starting α-chloroimine, which liberates *n*-propylamine and 2-chloroisobutyraldehyde **16**. *N*-Propylamine substitutes the chloro atom in **12a** or ring opens the alkynylaziridine **13a** and generates diamine **14**. Another product originates from the direct substitution of the chloro-atom in **12a** by trace amounts of water to form β-hydroxylamine **15**. To test the hypothesis of hydrolysis, the reaction mixture was investigated with GC-MS to identify propylamine and 2-chloro-2-methylpropanal **16** as products in the reaction mixture. Next to products **12a**, **13a**,

14, **15** and unreacted phenylacetylene, indeed, *n*-propylamine and 2-chloro-2-methylpropanal **16** were found as products in the GC-trace. In a special case where chloroform was tested as reaction solvent, a third side product could be identified, namely 4-ethoxy-4-methyl-1-phenyl-*N*-propylpent-1-yn-3-amine (**17**), which is generated from propargylamine **12a** and ethanol. Ethanol is often added to chloroform as stabilizer, and this stabilizing effect is only present from concentrations of ethanol of ~1%.[15] This explains the formation of side product **17**.

As discussed before, the starting materials α-chloroaldimine **11a** and phenylacetylene did not contain any water which could explain the hydrolysis of the starting material. Solvents were always dried over activated 4 Å molecular sieves, and are thus also considered 'dry'. $In(OTf)_3$, however, is a substance known for its hygroscopic properties. Indeed, when a spatula tip of $In(OTf)_3$ is left in contact with air, it takes less than a minute to dissolve the spatula tip in water attracted from the air, resulting in the formation of a 'droplet' of dissolved $In(OTf)_3$. In literature[16] a method is presented to remove water from $In(OTf)_3$, via heating (180 °C – 1 h) under high vacuum. This method was tested, and indeed significant amounts of mass were lost during this process. For 0.125 mmol of $In(OTf)_3$, 6.2 mg of water (~0.35 mmol) could be lost during this drying process, which could explain the low yields of propargylamine **12a** and aziridine **13a**. However, when the reaction was run with this 'dry' $In(OTf)_3$, the outcome did not differ. Thermogravimetric analysis of an $In(OTf)_3$ sample showed that there are two steps with considerable loss of mass in the thermogram (Figure 2-1). If we assume that $In(OTf)_3$ contains up to 5 molecules of water, the total molecular mass becomes 652.08 g/mol. In step 1 8.37% of the total weight or around 54.57 g/mol is lost, this is very nearly the mass of three molecules of water (54.05 g/mol). In step 2, another 5.8% of the total weight or 37.93 g/mol is lost, this is also close to the mass of two molecules of water (36.03 g/mol). Although, one is not sure which molecule is lost in this thermogravimetric analysis, it appears that a considerable amount of water is only lost at temperatures above 200 °C.

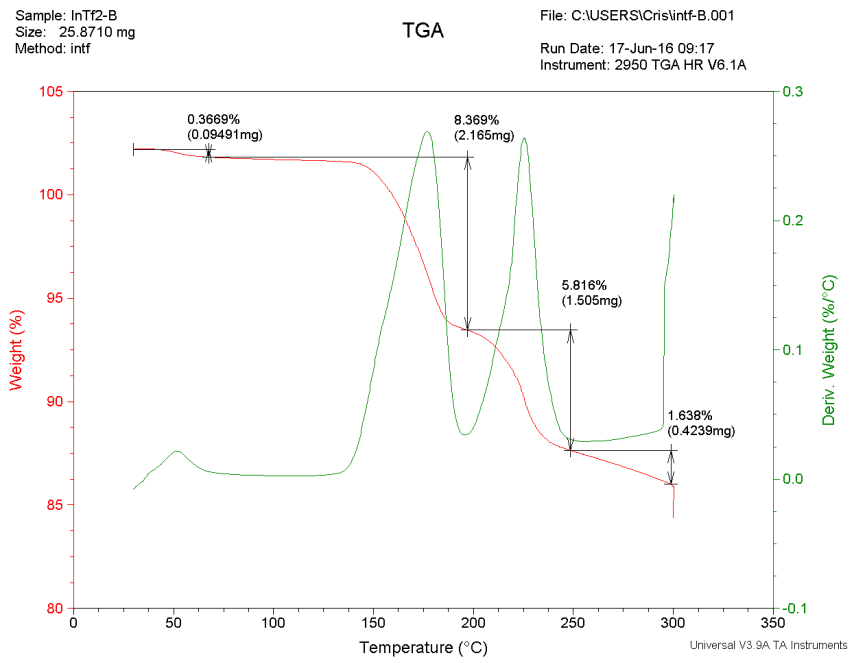


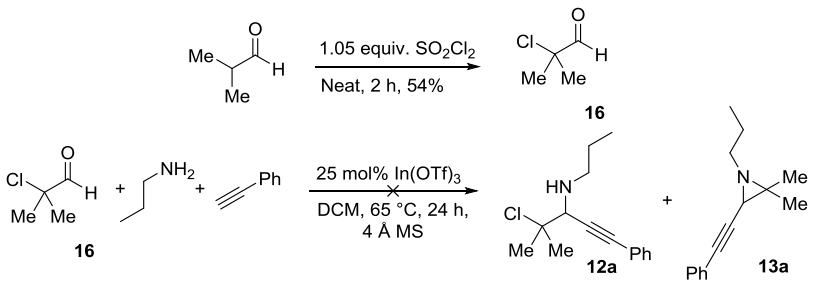
Figure 2-1 Thermogravimetric analysis of $In(OTf)_3$.

Other adaptations of the reaction conditions were tested, but did not improve the yield (Entries are not included in Table 2-1 for clarity reasons). 1) Addition of more equivalents of

starting material **11a** led to an increase in yield of side products **14** and **15**, but no improved yield of intended products **12a** or **13a**. 2) Flushing the reaction vessel with argon before closure instead of no flushing. 3) Weighing $In(OTf)_3$ in an inert atmosphere like the glove box, and addition of reactants and reagents via syringe. 4) Order of addition of the different coupling partners, catalyst and solvent had no influence on the outcome of the reaction. 5) The use of a more electron-rich alkylacetylene, cyclohexylacetylene, did not give a higher yield of intended propargylamine **12a** or aziridine **13a**. 6) Synthesis of α-bromoaldimine instead of α-chloroaldimine **11a** via similar reaction of imine **10a** with *N*-bromosuccinimide instead of *N*-chlorosuccinimide was tried, because there were indications that hydrolysis of the starting material was problematic. Since a bromine atom has lower electronegativity (EN = 2.96 on Pauling scale) than chlorine (EN = 3.16 on Pauling scale), and bromine is a bigger atom than chlorine, introducing more sterical hindrance, this adaptation should make the imine less electrophilic. However, in reaction with phenylacetylene, the enhanced leaving group character of the α-bromoaldimine becomes problematic generating more side products **14** and **15** than intended products **12a** and **13a**.

Eventually, 4 Å molecular sieves were added to the reaction mixture to trap water that is probably attached to $In(OTf)_3$. This resulted in the formation of aziridine **13a** in improved yields and in the absence of propargylamine **12a**. Molecular sieves are indeed known to 'catch' small molecules like water, but they are also able to trap hydrochloric acid, which leads to an increase in the rate of intramolecular substitution reaction that forms aziridine **13a**.[17]

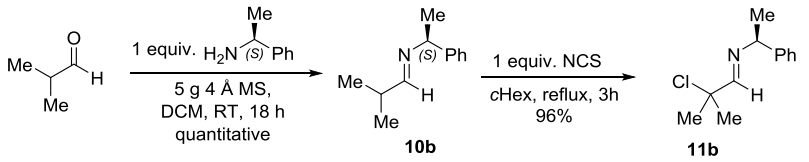
To test how much of a problem the hydrolysis is, the imine **11a** was stirred in a solution of 25 mol% $In(OTf)_3$ in dichloromethane. The reaction was followed by ^1H NMR and this revealed that under the reaction conditions, more than half of the starting imine is already hydrolyzed after three hours. From this experiment, we can conclude that hydrolysis is faster than alkynylation. Another test includes the synthesis of 2-methyl-2-chloropropanal (**16**) and application of this compound in an A³ coupling to generate propargylamine **12a** and aziridine **13a**. Product **16** is easily obtained via neat reaction of isobutyraldehyde and sulfuryl chloride (Scheme 2-9). The three-component reaction of 2-chloro-2-methylpropanal (**16**), *n*-propylamine and phenylacetylene, with catalytic $In(OTf)_3$ and 4 Å molecular sieves, did not result in the formation of propargylamine **12a** or aziridine **13a**, proving the problem of hydrolysis.



Scheme 2-9 Synthesis of 2-chloro-2-methylpropanal (**16**), and application in A³ coupling.

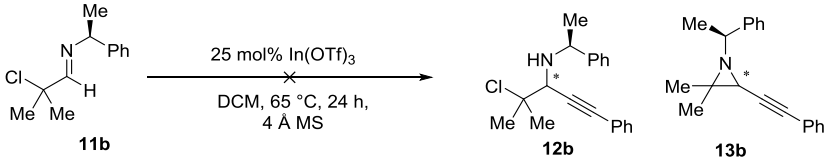
In order to avoid hydrolysis of the starting material, we envisioned that more sterical hindrance around the imine could lead to enhanced hydrolytic stability. On the other hand, more sterical hindrance would also mean more difficult alkynylation. Firstly, the use of a more sterically hindered amine, *i.e.* (*S*)-(-)-α-methylbenzylamine, was investigated. The starting material **11b** was synthesized in a similar way as before (Scheme 2-10). Moreover,

the use of a chiral amine could lead to diastereoselective alkynylation. This is interesting since the control of stereocentra in biological active molecules is of great importance.



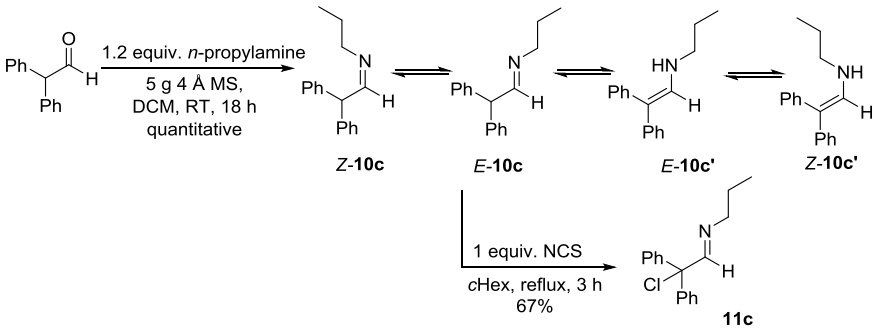
Scheme 2-10 Synthesis of alternative α-chloroaldimine starting material.

The use of this starting material **11b** in a coupling reaction with phenylacetylene under the optimized reaction conditions only yielded intended product **13b** in trace amounts, while hydrolysis products were, once again, predominantly present (Scheme 2-11).



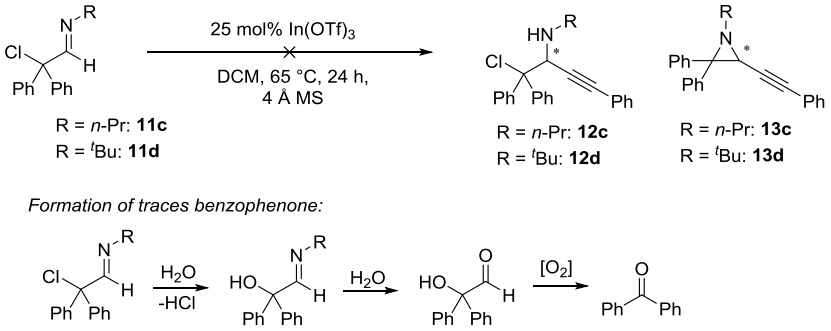
Scheme 2-11 Alternative starting material gives only trace amounts of intended products **12b** and **13b**.

Another starting material that was evaluated is derived from 2,2-diphenylacetaldehyde (Scheme 2-12). The synthesis of **11c** is not so straightforward, not only because of sterical hindrance, but also because the aldimine can easily isomerize to form an enamine that is in conjugation with the phenyl groups. Although the ^{1}H NMR spectrum of compound **10c** looks rather complicated, with up to 4 different isomers present (imine **10c** – enamine **10c'** tautomers and *E*/*Z* isomers), mass spectrometry suggests that condensation did occur, and thus this material was used as such in the chlorination step. After chlorination, only one isomer **11c** was present in the ^{1}H NMR spectrum, although a small amount of aldehyde suggests that this compound is also quite prone to hydrolysis.



Scheme 2-12 Synthesis of sterically hindered imine **11c**.

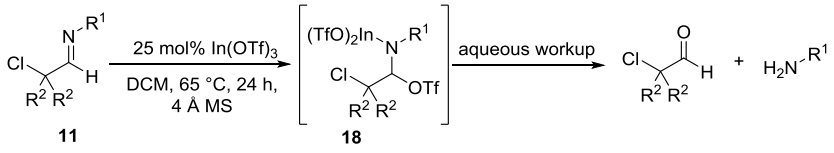
Using the same, optimized, reaction conditions only resulted in trace amounts of intended aziridine **13c** (Scheme 2-13). This can be explained by the augmented sterical hindrance surrounding the imine. Upon attempted purification of product **13** on column chromatography, benzophenone was isolated as the major product. Benzophenone was probably formed via aerobic oxidative cleavage from the hydroxylated hydrolysis product.[18]



Scheme 2-13 Alternative starting material gives only trace amounts of intended products **13c** or **13d**.

A similar outcome was seen for the reaction starting from *N*-(*tert*-butyl)-2-chloro-2-methylpropan-1-imine (**11d**) as benzophenone was again isolated. Since all the tested α-chloroaldimines have poor hydrolytic stability, we can conclude that hydrolysis will always be an issue with α-chloroaldimines. However, in the past reductions of α-chloroaldimines with $LiAlH_4$, $NaBH_4$ or borane-methyl sulfide could reduce the imine rather than to hydrolyze it.[19] This can be explained by the simple fact that these reducing agents are far more nucleophilic than the alkynylindium compounds in our research, and furthermore they are self-drying.

To conclude, it is clear that hydrolysis is a powerful side-reaction which is unavoidable under the current optimized reaction conditions using $In(OTf)_3$. The hydrolysis reaction takes place much easier than the alkynylation reaction and this results in overall low yields of the intended products. We feel that every precaution is taken to avoid attraction of water in this reaction, but that trace amounts of water will probably form a strong bond with $In(OTf)_3$, and are only released *in situ*.



Scheme 2-14 Formation of hemiaminal **18** from α-chloroaldimine **11** and $In(OTf)_3$.

On the other hand, $In(OTf)_3$ and α-chloroimine **11** could also form a hemiaminal structure **18** by nucleophilic attack of one of the triflate anions on the imine **11** (Scheme 2-14). This hemiaminal is then easily hydrolyzed in the aqueous workup after the reaction. Intermediate **18** was, however, never identified via NMR, although experiments were carried out in the absence of phenylacetylene in $CDCl_3$ to detect the presence of compound **18**. ^1H NMR only showed slightly different signals for $In(OTf)_3$-imine complex and imine **11**. Because of overall low yields, our efforts stopped here and no further scope investigation regarding the use of different acetylenes was done.

2.2.2 Aziridine invertomers

One interesting aspect of aziridine **13a** is that in the ^1H and ^{13}C NMR spectra two different isomers could be distinguished (Figure 2-2). Since the reaction is not stereoselective, one would expect a 50/50 mixture of enantiomers, which would show identical signals in the ^1H NMR spectrum. However in the actual ^1H NMR spectrum of **13a**, the ratio of the two isomers was not exactly 50/50 but rather 55/45. The literature teaches us that aziridines are subject to

slow pyramidal inversion of the nitrogen's lone pair (*N*-inversion).[20] When the interconversion is slow enough, two different invertomers can be observed. The rate of interconversion is dependent on the activation energy to interconvert between the two invertomers. When *N*-inversion occurs, the nitrogen atom becomes a stereocenter and together with the other stereocenter, the two isomers become diastereomers, characterized by different NMR spectra.

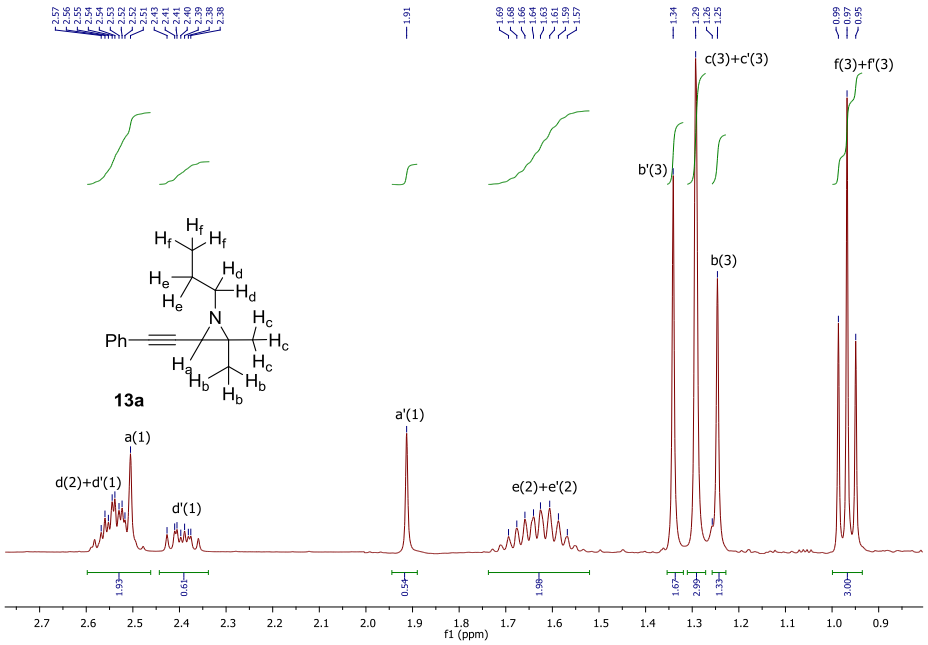
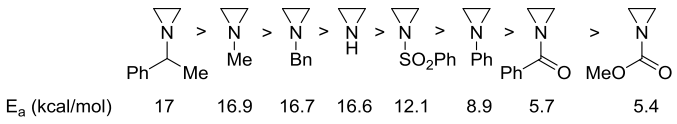


Figure 2-2 ^{1}H NMR spectrum of a 55/45 mixture of invertomers of **13a** ($CDCl_3$, 400 MHz).

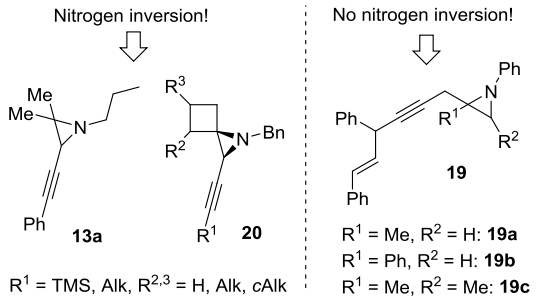
For normal trivalent amines the *N*-inversion activation barrier is calculated to be around 6-7 kcal/mol. For aziridines, because of ring strain, the barrier increases to 18-20 kcal/mol. At room temperature there is approximately 23 kcal/mol energy present so that *N*-inversion in trivalent amines happens relatively fast and for aziridines relatively slow.[21] When *N*-inversion activation energies transcend this limit of 23 kcal/mol, the nitrogen atom can become a chiral center and the different invertomers can be separated from each other at room temperature.[22] For aziridines, at least two factors influence this activation energy barrier. Addition of electron-withdrawing substituents on the aziridine carbon atoms enlarge the E_a,[21] while addition of electron-withdrawing groups on the aziridine nitrogen atom reduce the E_a (Scheme 2-15).[20a]



Scheme 2-15 *N*-inversion activation energies of a series of aziridines.

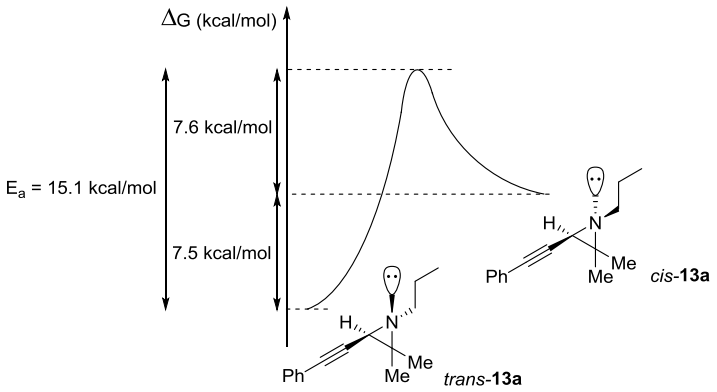
From these factors we can understand that for structures **19**, that closely resemble **13a** no invertomers were reported due to the presence of a phenyl group on the nitrogen atom,[23] while for structures **20** invertomers could indeed be distinguished in most cases (Scheme 2-16).[11d] The ratio of both invertomers is dependent on the relative energy of both invertomers; when

the ΔG between the two invertomers is similar, a 1/1 mixture will be obtained, but when the ΔG is substantial, a 1/x mixture will be obtained.



Scheme 2-16 Substituent dependence of aziridines on the *N*-inversion.

To prove that these molecules were indeed invertomers, the two invertomers and their interconversion was calculated[1] on the B3LYP-6-311G* level of theory with chloroform as solvent correction in the Polarizable Continuum model (PCM), using Gaussian (Scheme 2-17 and Figure 2-3).[24] The activation energy E_a to go from *trans*-**13a** to *cis*-**13a** was calculated to be 15.1 kcal/mol, while *trans*-**13a** was calculated to be 7.5 kcal/mol more stable than *cis*-**13a**. This last difference explains why there is no equimolar ratio of both invertomers. Although the calculated activation energy is lower than 23 kcal/mol (the energy present at room temperature), interconversion occurs rapidly, but slow enough to be seen on "the NMR-time scale".[25] On the other hand, whether two invertomers can be distinguished in a NMR spectrum is also dependent on how much chemical shift difference there is between the two forms; more difference will more rapidly result in distinguished invertomers.



Scheme 2-17 Relative energy differences between invertomers.

Variable temperature NMR measurements in DMSO were performed at room temperature, 30, 35, 50 and 80 °C. For the methyl singlets H_b and H_c, one can clearly see four different signals at room temperature, while at 80 °C these four signals become one big peak (accumulation of one invertomer) with a small shoulder (accumulation of the other invertomer), and further heating would probably lead to only one peak (Figure 2-4). A similar, but not so clear, effect is seen for the aziridine ring hydrogen H_a. In the ^{13}C NMR spectrum,

[1] Many thanks go out to Carl Mensch from the Research group Cryospectroscopy for these calculations.

the merging of peaks is less obvious as some peaks disappear in the noise of the spectrum (Figure 2-5).

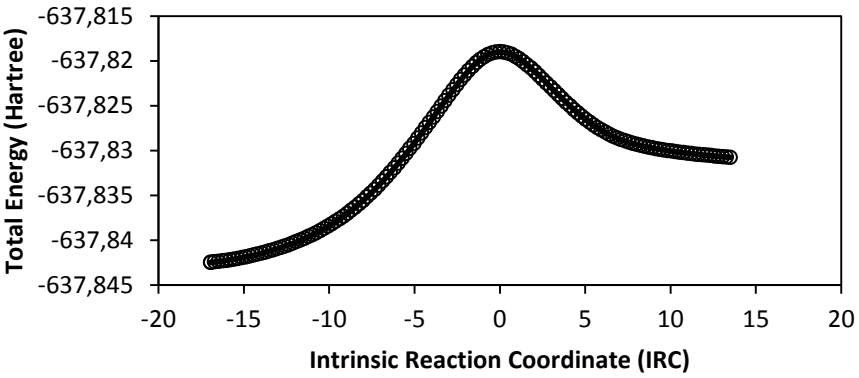
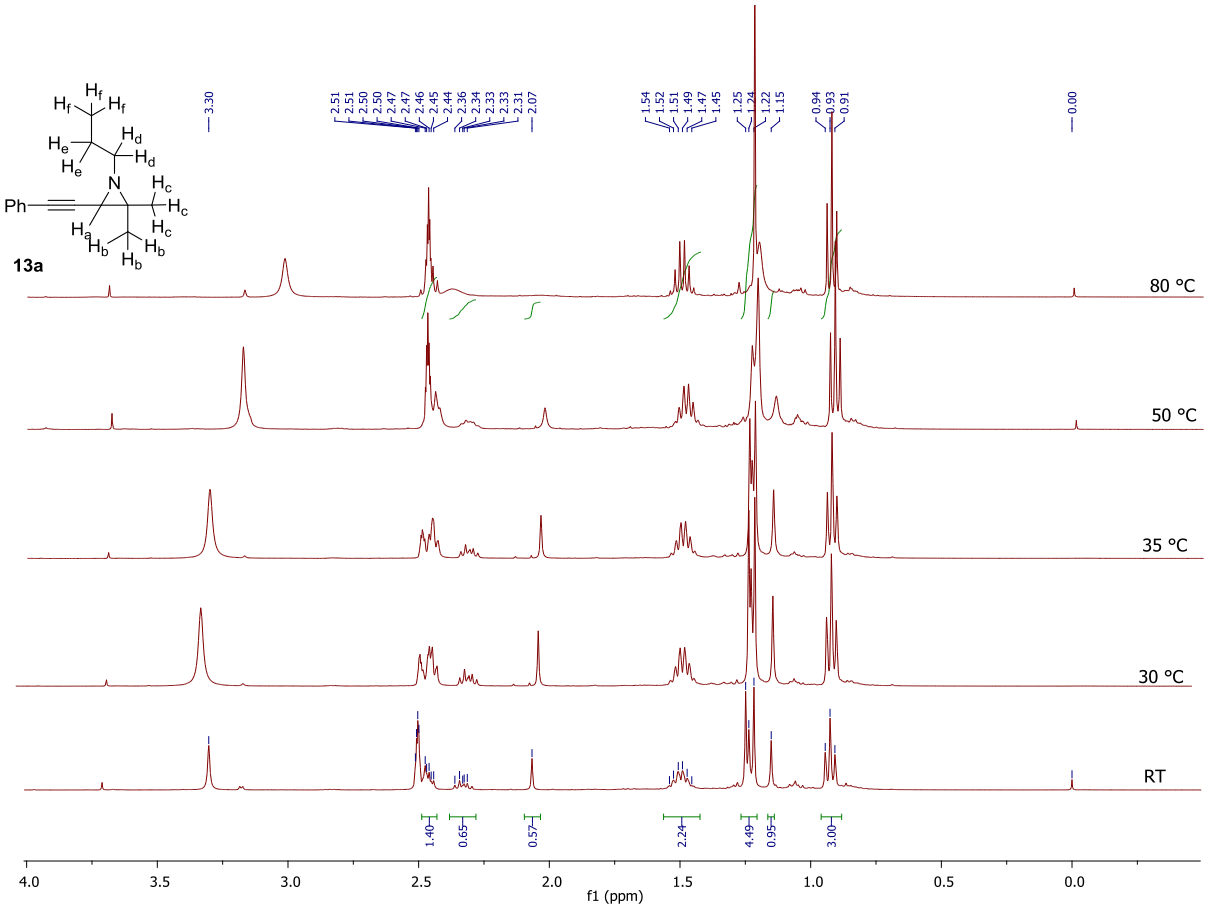


Figure 2-3 Total energy versus intrinsic reaction coordinate.



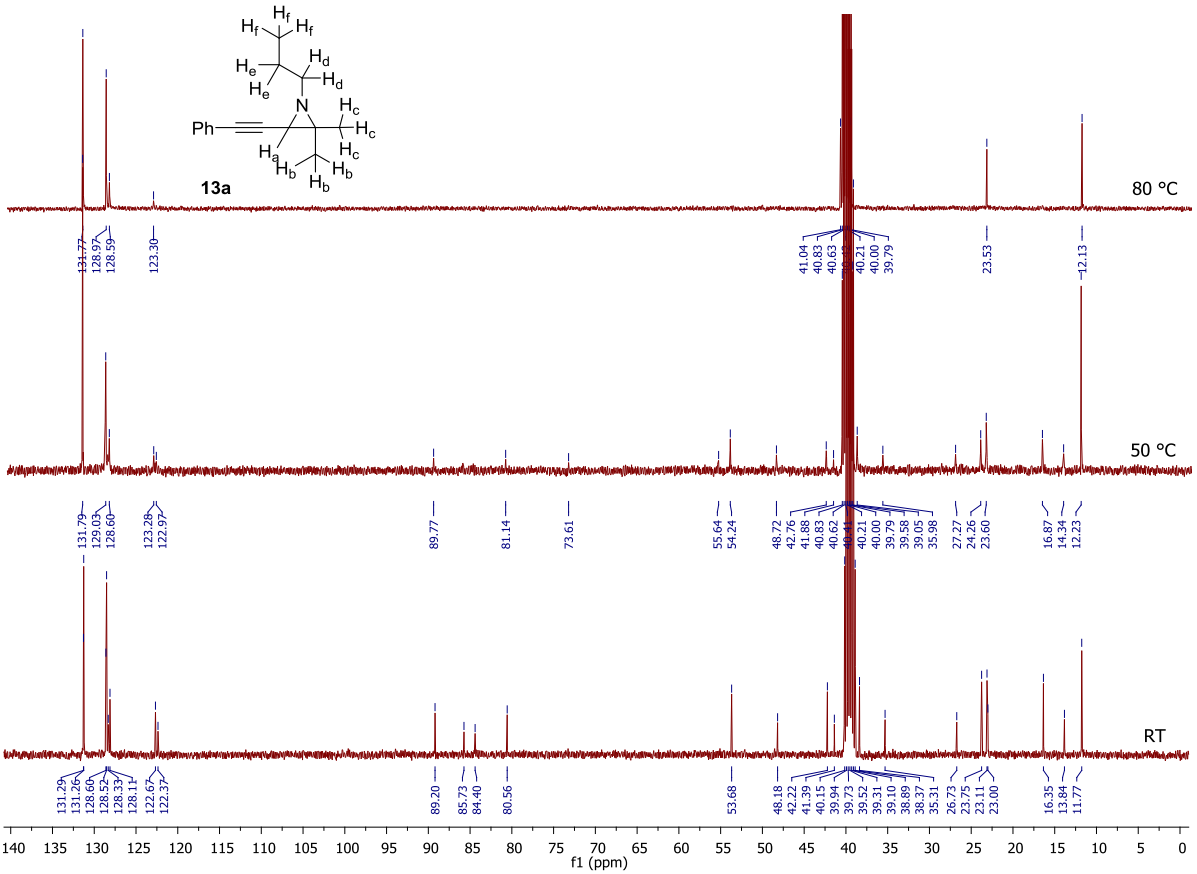
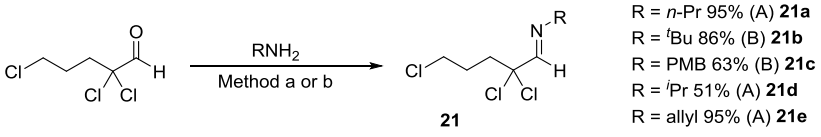


Figure 2-5 ^{13}C NMR spectra of **13a** at room temperature, 50 °C and 80 °C (DMSO-d_6, 100 MHz).

2.3 Alkynylation on α,α,δ-trichloroaldimine systems

2.3.1 Synthesis of starting materials and optimization of reaction conditions

α,α,δ-Trichloroaldimines **21** are easily prepared from a condensation reaction of α,α,δ-trichloroaldehydes, *i.e.* 2,2,4-trichloropentanal, and primary amines (Scheme 2-18). For non-sterically hindered primary amines (*e.g. n*-propylamine) the condensation is assisted by 4 Å molecular sieves as drying agent, while for more sterically-hindered amines (*e.g. tert*-butylamine), $TiCl_4$ is added in 0.5 equivalents to facilitate the condensation, generating TiO_2 as a side product.[3] In earlier reports the lithium aluminum hydride and sodium cyanoborohydride reduction of α,α,δ-trichloroaldimines **21** was already investigated, giving rise to 3-chloropiperidines and 3,3-dichloropiperidines respectively.[26]



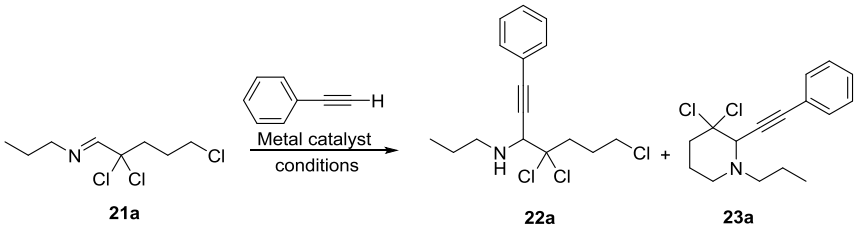
Method A: 1.3 equiv. RNH_2, 4 Å MS, toluene, 2 h, 60 °C
Method B: 1 equiv. RNH_2, 2 equiv. NEt_3, 0.6 equiv. $TiCl_4$, Et_2O, 3 h, 0 °C to RT

Scheme 2-18 Synthesis of α,α,δ-trichloroaldimines **21**.

With the starting material in hands, the optimization of reaction conditions for the reaction of α,α,δ-trichloroaldimine **21a** with phenylacetylene was started (Table 2-2).[5] Entry 1 uses the same reaction conditions as obtained for the synthesis for 3,3-dichloropyrrolidines **8**. Although product **23a** is obtained in a decent 59% yield, another 18% of propargylamine **22a** is still present in the reaction mixture. Using more equivalents of phenylacetylene (Entry 2) or

a higher loading of $In(OTf)_3$ (Entry 3) did not result in a higher yield of product **23a**. Since intramolecular ring closing reactions are relatively easier for five-membered rings than for six-membered rings, we expected that a higher reaction temperature would probably lead to increased yields of **23a**.[27] Indeed, Entry 4 applies a reaction temperature of 80 °C and toluene instead of DCM, resulting in a 71% yield of **23a**, with no starting material observed. Other solvents did not result in higher yields (Entries 5 and 9), while different other metal catalysts also resulted in trace amounts or no product **23a** at all (Entries 18-30). Only other In(III) salts and AgOTf were able to catalyze the coupling, albeit in lower yields than $In(OTf)_3$. The reaction time could be diminished to 3 hours without loss of yield (Entry 11). Using less (10 mol% - Entry 13) or more (50 mol% - Entry 14) catalyst also resulted in lower yields, and thus the optimized reaction conditions use 25 mol% $In(OTf)_3$, with toluene as solvent at 80 °C for 3 hours. Higher yields are probably hard to obtain for this reaction, since the reaction mixture becomes heterogeneous upon addition of $In(OTf)_3$, which forms a 'sticky lump' in the reaction vessel. Although this 'lump' catalyzes the reaction, it is also a source for degradation. Addition of water or 2-MeTHF as co-solvent resulted in dissolution of this 'lump', but this did not result in an augmented yield, and thus we ignored the formation of this 'lump'. The one-pot three-component coupling of 2,2,5-trichloropentanal, *n*-propylamine and phenylacetylene did not result in the formation of product **23a** under the optimized reaction conditions (toluene, 80 °C, 3 h). After workup, imine **21a** was the main product.

Table 2-2 Optimization of reaction conditions for the synthesis of piperidine **23a**.



Entry	Catalyst (mol%)	Solvent	T (°C)/ t (h)	Yield **22a** (%)	Yield **23a** (%)
1	$In(OTf)_3$ (25)	CH_2Cl_2	50/18	18[a]	59[a]
2[e]	$In(OTf)_3$ (25)	CH_2Cl_2	50/18	28[a]	49[a]
3	$In(OTf)_3$ (30)	CH_2Cl_2	50/18	12[a]	50[a]
4	$In(OTf)_3$ (25)	$PhCH_3$	80/18	Trace	71[b]
5	$In(OTf)_3$ (25)	THF	50/18	0	Trace (SM)
6	$In(OTf)_3$ (25)	$PhCH_3$	100/18	0	71[b]
7	$In(OTf)_3$ (25)	$PhCH_3$	100/6	0	70[b]
8	$In(OTf)_3$ (25)	$PhCH_3$	80/6	0	70[b]
9	$In(OTf)_3$ (25)	CH_3CN	80/6	0	45[a] (complex)
11	**$In(OTf)_3$ (25)**	**$PhCH_3$**	**80/3**	**0**	**71[b], 41[c]**
12[e]	$In(OTf)_3$ (25)	$PhCH_3$	80/3	0	74[b],41[c]
13	$In(OTf)_3$ (10)	$PhCH_3$	80/3	0	47[b]

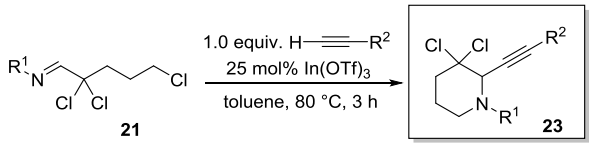
14	$In(OTf)_3$ (50)	$PhCH_3$	80/3	0	68[b]
15	$In(OTf)_3$ (25)	$PhCH_3$	80/0.5	0	46[a, d]
16[e]	$In(OTf)_3$ (25)	$PhCH_3$	100/0.5	0	52[a, d]
17[e]	$In(OTf)_3$ (25)	$PhCH_3$	100/1	0	45[a, d]
18	$InCl_3$ (25)	$PhCH_3$	80/3	0	47[a] (28% SM)
19	$Cu(OTf)_2$ (25)	$PhCH_3$	80/3	0	Trace (SM)
20	CuBr (25)	$PhCH_3$	80/3	0	SM
21	CuOAc (25)	$PhCH_3$	80/3	0	Trace (SM)
22	$Sc(OTf)_3$ (25)	$PhCH_3$	80/3	0	SM
23	AgOTf (25)	$PhCH_3$	80/3	0	24[b]
24	AgOTf (25)	$PhCH_3$	80/18	0	55[b]
25	AgOTf (25)	Hexane	80/4	0	15[a] (32% SM)
26	LiOTf (25)	$PhCH_3$	80/3	0	SM
27	$Mg(OTf)_2$ (25)	$PhCH_3$	80/3	0	SM
28	$ZnCl_2$ (25)	$PhCH_3$	80/3	0	SM
29	$Zn(OTf)_2$ (25)	$PhCH_3$	80/3	0	Trace (SM)
30	$Al(OTf)_3$ (25)	$PhCH_3$	70/18	0	SM

All reactions are carried out on 0.5 mmol scale with **21a** (1.0 equivalent), phenylacetylene (1.0 equivalent) in an, under air, sealed microwave vial. [a] Calculated from the ^1H NMR spectrum with TMB (= 1,3,5-trimethoxybenzene) as internal standard. [b] Yield after acid-base extraction. [c] Yield after column chromatography on SiO_2. [d] Reaction under microwave heating with maximal input of 300 W. [e] 2 equivalents of phenylacetylene used.

2.3.2 Scope

The scope of this reaction was evaluated by varying the amine and alkyne substituent (Table 2-3).

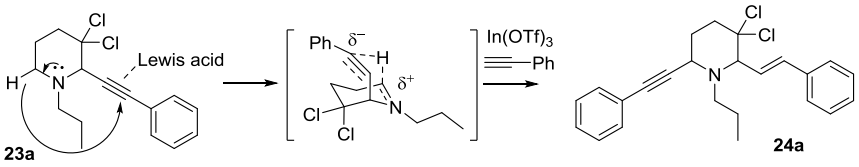
Table 2-3 Variation of the alkyne and amine substituent.



Entry	R^1	R^2	Yield **23** (%)
1 - **23a**	*n*-Pr	Ph	70 (41)
2 - **23b**	*n*-Pr	4-Et-Ph	72 (42)
3 - **23c**	*n*-Pr	4-Cl-Ph	68 (37)
4 - **23d**	*n*-Pr	2-Me-Ph	73 (42)
5 - **23e**	*n*-Pr	3-MeO-Ph	74 (42)
6 - **23f**	*n*-Pr	Cy	60 (36)
7 - **23g**	*n*-Pr	*n*-Bu	61 (30)
8 – **23h**	Allyl	Ph	70 (47)
9 – **23i**	^{i}Pr	Ph	88 (41)
10 - **23j**	*n*-Pr	TMS	92 (46)
11 – **23k**	PMB	Ph	81 (30)

All reactions were carried out on 0.5 mmol scale. Crude yield (isolated yield).

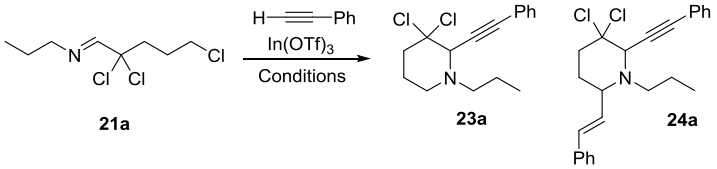
Electron rich and electron poor aromatic acetylenes are well tolerated in this reaction (Entries 1-5). Also, aliphatic acetylenes can be used and are coupled efficiently (Entries 6, 7). The application of TMS-acetylene generates a TMS-protected terminal propargylamine **23j** (Entry 10), which could be isolated by omitting the aqueous workup, and direct purification via column chromatography gave product **23j**. Deprotected analogue of **23j** can also be formed in a Cu(I) catalyzed reaction of α,α,δ-trichloroaldimine **21a** with calcium carbide (see Chapter 4). The amine substituent can be varied and other substituents like allyl and ^{i}Pr groups can be used (Entries 8 and 9). When the protecting group *para*-methoxybenzyl is used as a substituent (Entry 11), the reaction works well, which is interesting for the generation of *N*-unsubstituted 2-alkynyl-3,3-dichloropiperidines. In some cases, a side product was observed in trace amounts and for the synthesis of **23a** the product was identified as (*E*)-3,3-dichloro-6-(phenylethynyl)-1-propyl-2-styrylpiperidine (**24a**). This product probably orginates from a second addition of phenylacetylene to [1,5]-hydride shifted **23a** in a cross-dehydrogenative coupling with internal oxidant (Scheme 2-19).



Scheme 2-19 Formation of side product **24a** via [1,5]-hydride shift in **23a**.

A similar cross-dehydrogenative coupling reaction used propargylamines and acetylenes to generate 1,6-enyne structures, catalyzed by Zn(II), as discussed in §1.5.1.[28] The reported yields for this transformation were only low to moderate. However, we envisioned that it might be possible to further optimize the reaction conditions for the synthesis of 1,6-enynes **24** (Table 2-4). A few reaction conditions were evaluated; using two equivalents of phenylacetylene and 50 mol% $In(OTf)_3$, product **24a** was present in 17% yield (Entry 1). Using four equivalents of phenylacetylene the yield of **24a** increased to 25% (Entry 2). Using a stoichiometric amount of $In(OTf)_3$ caused only a small increase in the yield of **24a** (Entry 3). Changing the solvent to DCM and lowering the catalyst loading gave a lower yield (Entry 4), while using DCE at higher temperatures in combination with two equivalents of the base di-isopropylethylamine and a stoichiometric amount of $In(OTf)_3$ gave a yield of 30% **24a** (Entry 5). Similar reactions conditions with three equivalents of di-isopropylethylamine, however, did not lead to a detectable yield (Entry 6). Since the reaction conditions for the synthesis of **23a** are already peculiar due to restricted choice of catalyst and solvent, not much can be changed for the optimization of **24a**. Since the presence of α,α-chlorine atoms limits the use of metal catalysts other than In(III)-salts,[4, 29] there is no room for further optimization, and product **24a** was obtained in a maximum yield of 30%.

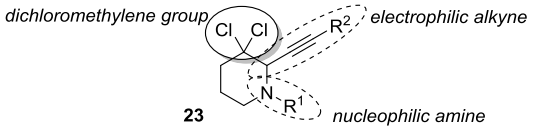
Table 2-4 Screening for reaction conditions for the generation of 1,6-enyne **24a**



Entry	Catalyst (mol%)	Solvent	T (°C)/ t (h)	Yield **23a** (%)	Yield **24a** (%)
1	$In(OTf)_3$ (50)	Toluene	80/4	53	17
2[a]	$In(OTf)_3$ (50)	Toluene	80/4	54	25
3	$In(OTf)_3$ (100)	Toluene	80/4	54	19
4	$In(OTf)_3$ (25)	DCM	50/48	61	13
5[b]	$In(OTf)_3$ (100)	DCE	80/18	54	30
6[c]	$In(OTf)_3$ (100)	DCE	90/18	77	ND

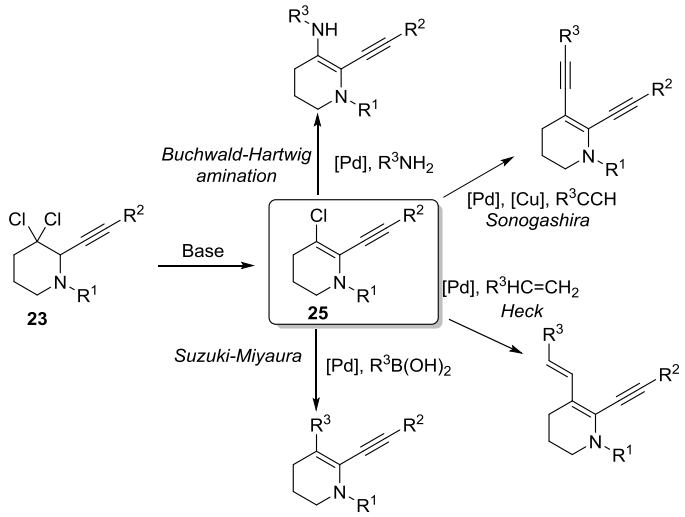
All reactions are carried out on 0.5 mmol scale with **21a** (1.0 equivalent), phenylacetylene (2.0 equivalents), solvent (2 mL) in an, under air, sealed microwave vial. Yields were calculated from the ^{1}H NMR spectrum with TMB as internal standard. [a] 4 equivalents of phenylacetylene used. [b] 2 equivalents of DIPEA added. [c] 3 equivalents of DIPEA added.

2.4 Cross-coupling reactions on *N*-alkyl-2-alkynyl-3,3-dichloropiperidines



Scheme 2-20 Functional groups in molecules **23**.

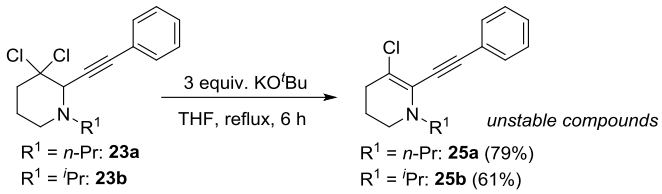
Molecules **23** possess several functional groups to further derivatize the molecule (Scheme 2-20). Next to the reactivity of the alkynyl and amine function, which was already discussed in §1.4,[30] the dichloromethylene group might be an interesting group for further derivatization. Earlier derivatization reactions of the dichloromethylene group include, among others, (regioselective) elimination of one the chlorine atoms,[5, 31] double chlorine elimination for the formation of an alkynyl group,[31c] transformation into a carbonyl moiety,[32] reduction to give a monochloromethylene or methylene group.[26] Also coupling reactions are described such as the coupling of a dichloromethylene group with an aldehyde,[33] and atom transfer radical cyclizations.[34] We reasoned that it might be interesting to eliminate one of the chlorine atoms, generating a vinyl chloride species, and use this vinyl chloride species in Pd-catalyzed cross coupling reactions (Scheme 2-21). Pd-catalyzed cross-coupling reactions have gained interest in the last few decades. This is underlined by the 2010 Nobel Prize that was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for what the Nobel committee named "great art in a test tube". Although this field has been studied extensively in the past decades, challenging substrates, such as vinyl chlorides, remain a topic of interest.



Scheme 2-21 Functionalization strategy for *N*-alkyl-2-alkynyl-3,3-dichloropiperidines **23**.

In the first place, the elimination of **23** towards vinyl chloride **25** was investigated (Scheme 2-22). Elimination with KO^{t}Bu in THF was regioselective and gave only product **25**. Products **25** were, however, unstable and could not be purified by column chromatography since complete degradation occurred. Degradation of freshly made **25** happens quickly, and within 24 hours complete degradation occurs, even in the absence of light and storage under inert atmosphere. No clear degradation products were observed but the enamine/vinyl chloride nature of molecules **25** might cause degradation in the form of hydrolysis and polymerization.

The identity of the product was nevertheless established by means of NMR of the crude product.

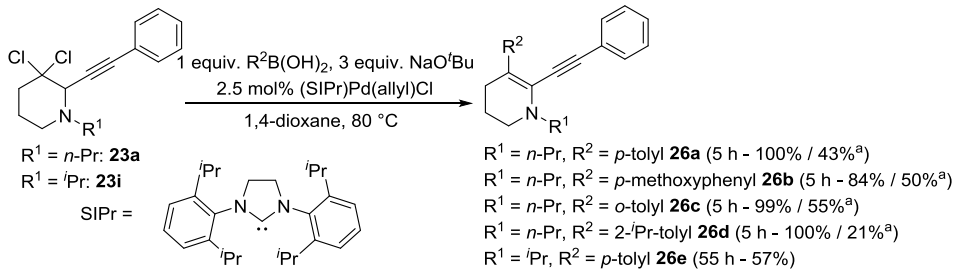


Scheme 2-22 Regioselective elimination yielding unstable vinyl chloride **25**.

To overcome the stability problems associated with molecules **25**, a strategy where molecules **25** are formed and reacted *in situ* was elaborated. Thus, in our search for Pd-catalyzed cross coupling reactions using sterically hindered bases such as KO^{t}Bu or NaO^{t}Bu, we stumbled upon a series of reports by Nolan *et al.* that would use NaO^{t}Bu, Pd(NHC) complexes in ethereal solvents to couple aryl chlorides and various coupling partners,[35] conditions that should be matching with those for elimination of our substrate **23**. The advantage of using Pd(NHC) systems is that NHC ligands are stronger σ-donating ligands than most phosphine ligands. This implies that the Pd-NHC bond is stronger and thus more stable towards degradation. As a bonus, NHC's are not prone to oxidation unlike most phosphine ligands, and are thus easy to handle.[35a]

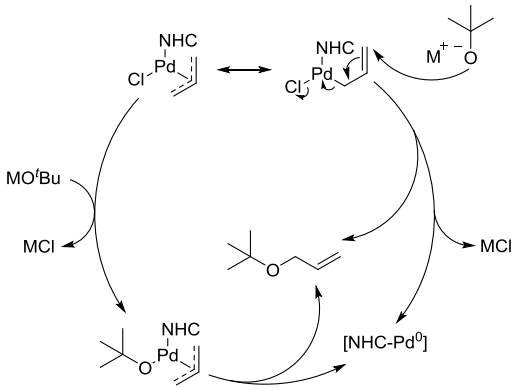
2.4.1 Suzuki-Miyaura cross-coupling reactions

For Suzuki-Miyaura cross coupling, similar reactions conditions (with one equivalent of sterically hindered base extra), indeed led, after some optimization, to products **26** (Scheme 2-23). Crude yields are high, and no column chromatography was necessary as the crude materials were pure enough for characterization. When products **26** were purified via column chromatography, huge losses of product were observed. This is probably due to the enamine-structure present in molecules **26**, which could be hydrolyzed on silica. According to the ^{1}H-NMR spectrum, product **26d** was not pure, and column chromatography was necessary to further purify this component. Product **26e** was made from the more sterically hindered **23i** and required longer reaction times. Increasing the reaction temperature, using more equivalents of coupling partner or base or catalyst did not help to overcome this problem as the stability of the intermediate elimination product **25** remained problematic and thus the sterical hindrance of the amine substituent can be seen as a limit of this reaction. Although crude product **26e** was not pure enough, column chromatography could not improve the purity of this compound.



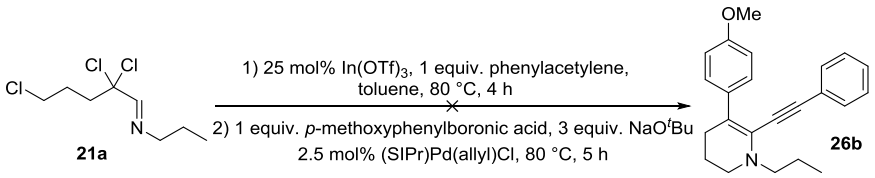
Scheme 2-23 One pot elimination and Suzuki cross-coupling on *N*-alkyl-2-alkynyl-3,3-dichloropiperidines **23**. Reactions on 0.7 mmol scale. Yields are crude yields. [a] Isolated yield after column chromatography.

Different amounts of Pd catalyst were evaluated and 2.5 mol% was the best, with higher or lower catalyst loadings leading to lower yields due to formation of Pd-black or too slow cross-coupling rates. Three equivalents of sodium *tert*-butoxide were used; one equivalent is required for the elimination reaction, one equivalent is consumed in the cross coupling reaction, and one extra equivalent is needed for ring closure of trace amounts of propargylamine **22a** and for the generation of the active Pd^0 species (Scheme 2-24).[36]



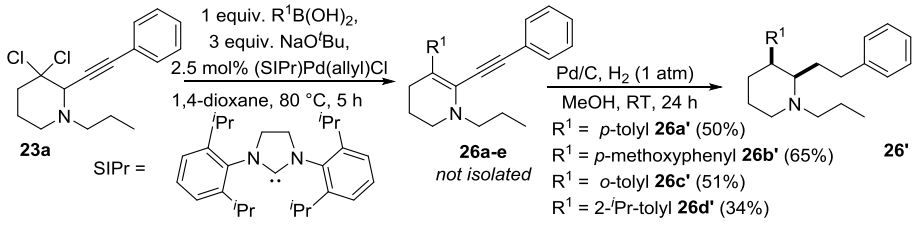
Scheme 2-24 Activation pathways for (NHC)Pd(allyl)Cl complexes.

In the spirit of green, one-pot reactions, the alkynylation and subsequent elimination/cross-coupling reaction were evaluated in one pot, but this did not result in the formation of **26b** (Scheme 2-25). The presence of $In(OTf)_3$ probably blocks the cross-coupling reaction.



Scheme 2-25 One pot alkynylation, elimination, cross-coupling: no formation of **26b**.

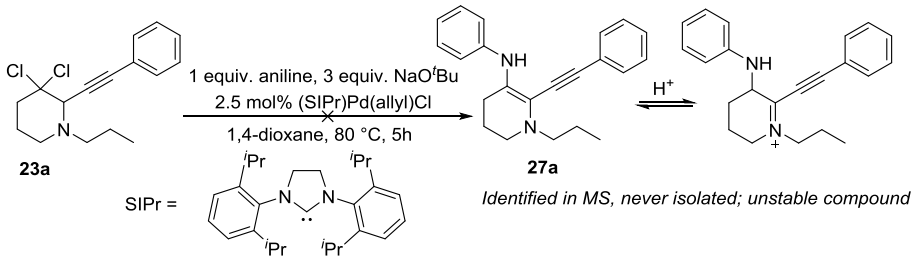
Since isolated yields of cross-coupled tetrahydropiperidines **26** were generally low due to the unstable nature of the molecule, we considered a follow-up reaction that would generate more stable compounds (Scheme 2-26). Simple hydrogenation of the unsaturations would overcome the stability problems. Therefore, the crude reaction mixtures of **26** were evaporated and redissolved in methanol with the addition of Pd on carbon and hydrogenated using a balloon with hydrogen at room temperature leading to complete conversion within 24 hours. Column chromatography of the products **26'** resulted in higher isolated yields than those obtained for **26**.



Scheme 2-26 Hydrogenation of structures **26** gives stable *N*-alkyl-2,3-disubstituted piperidines **26'**.

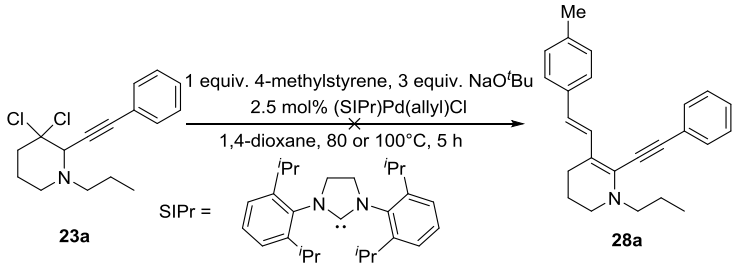
2.4.2 Heck and Buchwald-Hartwig cross-coupling reactions

The Buchwald-Hartwig amination[37] on substrate **23a** was evaluated using aniline as coupling partner (Scheme 2-27). The crude NMR spectrum contained a lot of impurities, so that column chromatography was necessary. However, due to the absence of a conjugated aryl group in position 3 of structure **27a**, the stability of the enamine structure is lower, generating more tautomeric iminium, which is prone to hydrolysis/degradation. Neither column chromatography nor purification by acid/base extraction yielded any product **27a**. Although the crude reaction mixture contained the product **27a**, as was seen by mass spectrometry, the product could not be characterized due to the unstable nature of the molecule.



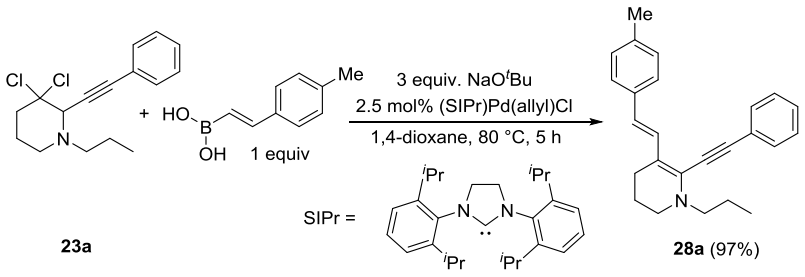
Scheme 2-27 Buchwald-Hartwig amination on substrate **23a** did not yield a stable product.

The Heck coupling on substrate **23a** does not seem possible under the given reaction conditions, and not even a trace amount of product **28a** was observed (Scheme 2-28). It is well known that Heck reactions usually require higher reaction temperatures than Suzuki or Buchwald-Hartwig cross couplings.[38] Even at 100 °C no trace of product **28a** was observed. When the reaction was carried out at 100 °C after five hours also no elimination product **24a** was observed, since this probably degrades quickly under the given reaction conditions.



Scheme 2-28 Heck reaction on substrate **23a** is not possible.

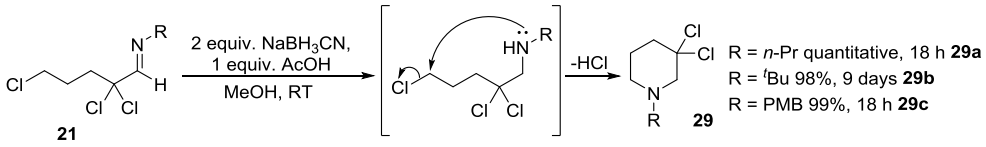
Heck cross-couplings usually require high reaction temperatures, which are not compatible with the instability of the intermediate elimination product **25**. Since Suzuki cross-couplings do give products **26**, the formation of styryl compound **28** could also be accomplished with styrylboronic acids. Indeed, when *trans*-2-(4-methylphenyl)vinylboronic acid was used as coupling partner, product **28a** was formed with a crude yield of 97% (Scheme 2-29). The crude spectra showed some impurities, and similar impurities were observed after purification with flash chromatography, for which the yield dropped to 29%. Impurities probably arise from the instable nature of product **28a**, which has a very bright yellow color, owing to the extended π-system.



Scheme 2-29 Suzuki cross-coupling gives Heck product **28a**.

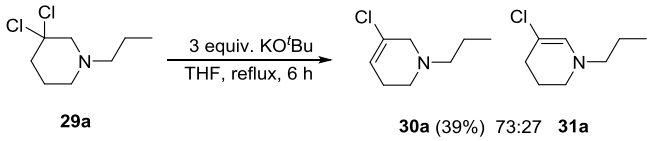
2.5 Cross-coupling reactions on non-alkynylated 3,3-dichloropiperidines

In order to evaluate the general applicability of the developed cross coupling strategy, the cross-coupling on other dichloromethylene groups, not bearing an α-alkynyl function, was investigated. The substrates for this study were easily prepared via a previously reported procedure,[39] using sodium cyanoborohydride in methanol/acetic acid, for the reduction of α,α,δ-trichloroaldimines **21**. Depending on the sterical hindrance of the amine substituent, the *in situ* ring closure needs 18 hours to 9 days for complete conversion (Scheme 2-30).



Scheme 2-30 Synthesis of *N*-alkyl-3,3-dichloropiperidines **29** from α,α,δ-trichloroaldimines **21**.

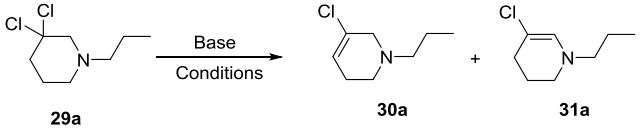
In previous work, the elimination of 3,3-dichloropiperidines **29** yields regioisomeric mixtures of **30** and **31** (Scheme 2-31).[40] The main product is vinyl chloride **30a**, since the sterically hindered base tends to deprotonate the least sterically hindered proton on position 4 of the piperidine ring.



Scheme 2-31 Previously reported method generates regioisomeric mixture of piperidines **30a** and **31a**.

The regioselectivity is reversed relative to the elimination of 2-alkynyl-3,3-dichloropiperidines **23**. Two factors play an important role in this regioselectivity. Firstly, the presence of the 2-alkynyl group lowers the acidity of the proton in position 2 of the piperidine ring and secondly, the formation of a double bond in conjugation with the triple bond of the alkynyl group results in a more stable endproduct. Both factors favor the formation of the enamine structure of products **26**, while both factors are not present in piperidines **29**. In order to obtain **30a** with full control of regioselectivity, the transformation **29a** to **30a** was optimized by varying the reaction conditions and base. Results are summarized in Table 2-5.

Table 2-5 Optimization of reaction conditions for the formation of vinyl chloride **30a** or enamine **31a**.

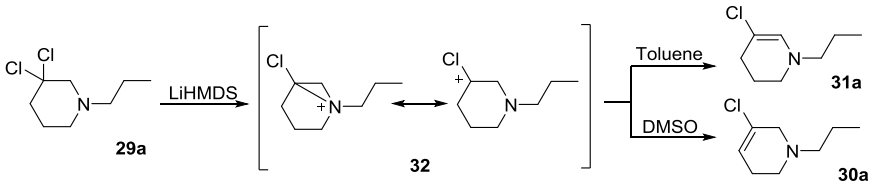


29a **30a** **31a**

Entry	Base (equiv.)	Solvent (mL)	T (°C)/ t (h)	Yield **30a** (%)	Yield **31a** (%)	Yield **29a** (%)
1	KO^{t}Bu (3)	THF (1)	70/17	19	4	11
2	NaO^{t}Bu (3)	THF (1)	70/17	4	0.1	52
3	KO^{t}Am (3)	THF (1) + $PhCH_3$ (1)	70/17	41	16	ND
4	DBU (3)	THF (1)	70/17	ND	ND	62
5	Cs_2CO_3 (3)	THF (1)	70/17	ND	ND	62
6	Proton sponge[a] (3)	THF (1)	70/17	ND	ND	46
7	KO^{t}Am (3)	$PhCH_3$ (3)	70/17	32	2	17
8	KO^{t}Bu (3)	$PhCH_3$ (2)	80/6	ND	ND	50
9	NaO^{t}Bu (3)	$PhCH_3$ (2)	80/6	ND	ND	31
10	*n*-BuLi (3)	$PhCH_3$ (1) + *n*-hexane (1)	RT/4	ND	5	ND
11	NaH (2)	$PhCH_3$ (2)	70/24	ND	ND	27
12	LDA (1.2)	THF (2)	100/17	ND	ND	72
13	BTPP[b] (1.1)	$PhCH_3$ (2)	60/20	ND	ND	90
14	LiHMDS (1.1)	$PhCH_3$ (2.5)	RT/70	ND	18	78
15	LiHMDS (1.1)	$PhCH_3$ (2.5)	60/20	ND	25	51
16	LiHMDS (2)	$PhCH_3$ (2)	100/4	ND	35	ND
17	**LiHMDS (6)**	**$PhCH_3$ (4)**	**100/2**	**ND**	**41**	**ND**
18	KHMDS (2)	$PhCH_3$ (2)	100/4	7	12	ND
19	**LiHMDS (2)**	**DMSO (2)**	**100/2.5**	**37**	**ND**	**ND**

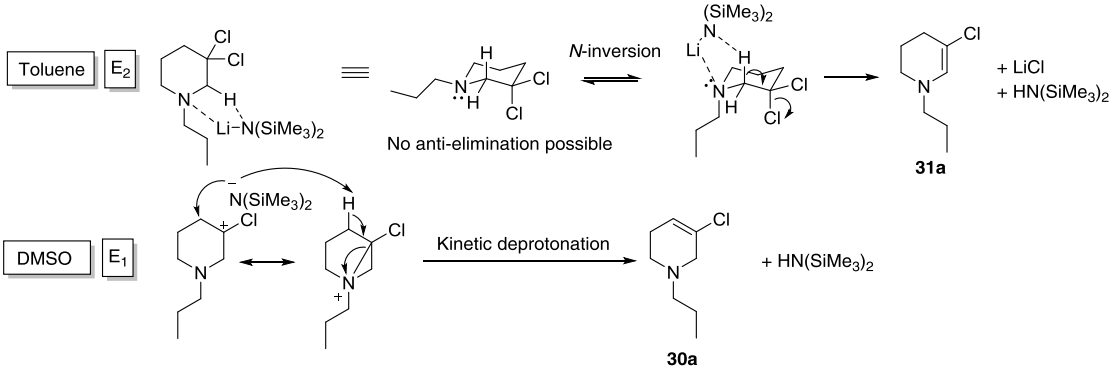
All reactions were performed at 0.5 mmol scale in a sealed vial under argon. Yields were calculated from the ^{1}H NMR spectrum with 1,4-diacetylbenzene (DAB) as internal standard. [a] *N, N, N', N'*-tetramethyl-1,8-naphthalenediamine. [b] Phosphazene base P_1-*t*-Bu-tris(tetramethylene).

Typical sterically hindered bases such as KO^{t}Bu, NaO^{t}Bu and even KO^{t}Am (Entries 1-3) yielded mostly vinyl chloride **30a** but also non-negligible amounts of enamine **31a**, next to degradation products. Weaker bases such as DBU, Cs_2CO_3 and Proton sponge did not give any elimination at all (Entries 4-6). Changing the solvent from THF to toluene gave a better vinyl chloride/enamine ratio **9a**/**10a** for KO^{t}Am (Entry 7), but in toluene no products **30a** or **31a** were observed when KO^{t}Bu or NaO^{t}Bu were used (Entries 8-9). Using stronger bases such as *n*-BuLi, NaH, LDA or BTPP did not give satisfactory results either (Entries 10-13). However, when LiHMDS is used, only vinyl chloride **30a** is formed, even at room temperature (Entry 14). Full conversion is obtained by altering the amount of LiHMDS, reaction time and temperature (Entries 15, 16) until an optimum is realized (Entry 17). KHMDS on the other hand, yields a mixture of both regioisomers again (Entry 18). In order to obtain higher yields, we reasoned that a more polar solvent should stabilize the transition-state more, leading to an enhanced reaction. Changing the solvent from toluene to DMSO led, to our surprise, to complete regioselectivity inversion and only regioisomer **31a** was observed (Entry 19). Because KHMDS did not give solely product **30a** and changing the solvent changes the regioselectivity, we reasoned that the elimination is probably not going via a straightforward E_1-type elimination mechanism and that the interaction with the lithium cation is important. Calculations suggest that the presence of the nitrogen atom in the molecule helps elimination by creation of bicyclic aziridinium ion **32** via an S_N2-type mechanism thereby stabilizing E_1 intermediate carbocations (Scheme 2-32).



Scheme 2-32 The presence of nitrogen helps elimination of one of the chlorine atoms.

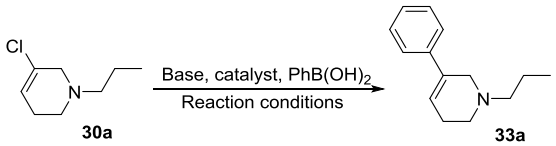
In the case of toluene, LiHMDS is not solvated and the presence of Li^+ is important. Interaction of Li^+ with nitrogen probably anchors the base so that the proton next to nitrogen is removed in the elimination reaction and product **31a** is obtained (Scheme 2-33 – top). In the case of DMSO, Li^+ is solvated and thus the base is stronger and will react faster. Meanwhile, the carbocation generated via E_1 elimination is more stabilized in a more polar solvent. Kinetic deprotonation occurs on the most accessible position leading to vinyl chloride **30a** (Scheme 2-33 – bottom).



Scheme 2-33 Solvent-dependent elimination.

With vinyl chloride **30a** in hand, the optimized reaction conditions (*vide supra* for **23**) were tested for Suzuki cross-coupling on vinyl chloride **30a** (Table 2-6, Entry 1). Although these reaction conditions gave product **33a** in a decent 68% yield, there was still a relevant amount of starting material present. Using higher reaction temperature resulted in a lower yield of **33a**; probably due to faster formation of palladium black (Entry 2). Using more or less catalyst gave no improvement and more coupling partner resulted in lower yield of **33a**, due to homocoupling of the coupling partner (Entries 3-5). Using other coupling partners such as the pinacol ester or potassium phenyl trifluoroborate did not result in an improved yield of **33a** (Entries 6-7). Since none of these adaptations had a positive effect on the yield of **33a**, common reaction conditions such as a Pd or Ni source in combination with the popular PPh_3 ligand were tried, but no coupling product was observed in these cases (Entries 8-10). Using other Pd precatalysts such as IPrPEPPSI and IPrPd(Cinnamyl)Cl (Entries 11, 12) did not give higher yields. Microwave experiments at higher temperatures faced the same problem and gave no full conversion (Entries 13, 14). Changing from Pd(NHC) catalysts to Pd sources in combination with well-known electron-rich phosphine ligands,[41] allows the reaction to be run at 50 °C, albeit in low yields (Entries 15, 16). By lowering the temperature we hoped to avoid the formation of Pd black, and have a more efficient catalytic system. Eventually, when combining 5 mol% of palladium acetate and 10 mol% of XPhos with two equivalents of sodium *tert*-butoxide in dioxane 68% of product **33a** was observed with some starting material left, and we figured that this was a good starting point to vary base and solvent to obtain an optimum in reaction conditions (Entry 17).

Table 2-6 Optimization of reaction conditions for Suzuki cross coupling of **31a**.



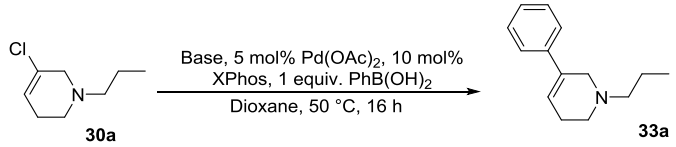
Entry	Catalyst (mol%)	Base (equiv.)	Coupling partner (equiv.)	T (°C)/t (h)	SM **30a**/ Product **33a** (%)
1	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	80/5	36/68
2	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	100/5	53/50
3	IPrPd(Allyl)Cl (5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	80/5	46/57
4	IPrPd(Allyl)Cl (1)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	80/16	63/12
5	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (2)	80/5	87/3
6	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	Pinacol ester (1.3)	80/5	47/44
7	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	$PhBF_3K$ (1.3)	80/5	45/22
8	$PdCl_2$ (2.5), PPh_3 (5)	NaO^{t}Bu (3)	$PhB(OH)_2$ (1.1)	80/5	90/0
9	$Pd(ClPPh_3)_2$ (2.5)	NaO^{t}Bu (3)	$PhB(OH)_2$ (1.1)	80/5	85/0
10	$Ni(ClPPh_3)_2$ (2.5)	NaO^{t}Bu (3)	$PhB(OH)_2$ (1.1)	80/5	92/0
11	IPrPEPPSI (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	80/5	51/37
12	IPrPd(Cinnamyl)Cl (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	80/5	54/30

13[a]	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	100/30' MW	33/41
14[b]	IPrPd(Allyl)Cl (2.5)	NaO^{t}Bu (2)	$PhB(OH)_2$ (1.3)	110/10' MW	29/41
15	$Pd(OAc)_2$ (5) + Davephos (10)	Cs_2CO_3 (2)	$PhB(OH)_2$ (1.1)	50/16	76/31
16	$Pd(OAc)_2$ (5) + SPhos (10)	CsF (2)	$PhB(OH)_2$ (1.3)	80/5	38/51
17	**$Pd(OAc)_2$ (5) + XPhos (10)**	NaO^{t}Bu (2)	**$PhB(OH)_2$ (1)**	**50/16**	**15/68**

Unless otherwise mentioned, all reactions were performed at 0.3 mmol scale in 1,4-dioxane (2 mL) in a sealed vial under argon. Yields were calculated from the ^{1}H NMR spectrum with 1,4-diacetylbenzene (DAB) as internal standard. [a] 1 mL 1,4-dioxane. [b] neat. [c] THF/H_2O 9:1 (2 mL).

With the best catalytic system in hands so far, we decided to vary the base (Table 2-7). The use of tetrabutyl ammonium fluoride did not result in a detectable yield for **33a** (Entry 2). Potassium fluoride in combination with the ligand 18-crown-6 resulted in low yield of **33a** (Entry 3) and a similar yield was observed when sodium carbonate and 15-crown-5 were used (Entry 4). Inorganic bases such as potassium phosphate, sodium carbonate and cesium carbonate, can be used, but yields are always lower than when NaO^{t}Bu was used (Entries 5-7).

Table 2-7 Screening of different bases for Suzuki cross-coupling of **30a**.



30a **33a**

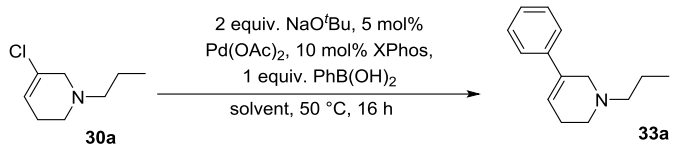
Entry	Catalyst (mol%)	Base (equiv.)	T(°C)/t (h)	SM **30a** (%)	Product **33a** (%)
1	**$Pd(OAc)_2$ (5) + Xphos (10)**	**NaO^{t}Bu (2)**	**50/16**	**15**	**68**
2	$Pd(OAc)_2$ (2,5) + Xphos (5)	TBAF (2)	50/16	69	0
3	$Pd(OAc)_2$ (5) + Xphos (10)	KF (2), 18-C-6 (2)	50/16	55	19
4	$Pd(OAc)_2$ (5) + Xphos (10)	Na_2CO_3 (2) , 15-C-5 (2)	50/16	69	16
5	$Pd(OAc)_2$ (5) + Xphos (10)	K_3PO_4 (2)	50/16	40	47
6	$Pd(OAc)_2$ (5) + Xphos (10)	Na_2CO_3 (2)	50/16	43	40
7	$Pd(OAc)_2$ (5) + Xphos (10)	Cs_2CO_3 (2)	50/16	26	59

All reactions were performed at 0.3 mmol scale in 1,4-dioxane (2 mL) in a sealed vial under argon. Yields were calculated from the ^{1}H NMR spectrum with 1,4-diacetylbenzene (DAB) as internal standard.

Different solvents like dioxane, toluene and THF give a similar result (Table 2-8– Entries 1-3) for the cross-coupling of **30a**. In 2-Me-THF the reaction did not yield any product **33a** (Entry

4) and an optimum was obtained when methanol was used (Entry 5), while acetonitrile gave a rather low yield of **33a** (Entry 6).

Table 2-8 Solvent optimization or Suzuki cross-coupling of **30a**.



Entry	Catalyst (mol%)	Solvent (mL)	T (°C)/ t (h)	SM **30a** (%)	Product **33a** (%)
1	$Pd(OAc)_2$ (5) + Xphos (10)	Dioxane (2)	50/16	15	68
2	$Pd(OAc)_2$ (5) + Xphos (10)	Toluene (2)	50/16	4	68
3	$Pd(OAc)_2$ (5) + Xphos (10)	THF (2)	50/16	15	67
4	$Pd(OAc)_2$ (5) + Xphos (10)	2-Me-THF (2)	50/16	71	0
5	**$Pd(OAc)_2$ (5) + Xphos (10)**	**MeOH (2)**	**50/16**	**0**	**95**
6	$Pd(OAc)_2$ (5) + Xphos (10)	MeCN (2)	50/16	51	14

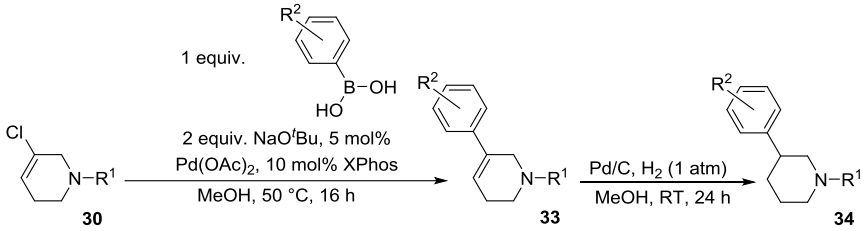
All reactions were performed at 0.3 mmol scale in 1,4-dioxane (2 mL) in a sealed vial under argon. Yields were calculated from the ^{1}H NMR spectrum with 1,4-diacetylbenzene (DAB) as internal standard.

With these optimized reaction conditions in hand, the coupling of other boronic acids was examined (Table 2-9). The coupling product **33a** of vinyl chloride **30a** with phenylboronic acid is obtained in an excellent yield of 94% (Entry 1). Other weak electron-donating groups such as 4-Me (Entry 2) and even the very sterically hindered 2-*i*-Pr (Entry 3) are well tolerated and products are obtained in excellent yields. A stronger electron-donating group such as 4-OMe (Entry 4) is also tolerated well. Phenylboronic acids with moderate electron-withdrawing groups such as 3-BnO and 3-OH (Entries 5 and 6) are tolerated well, but strong electron-withdrawing groups such as 3-CF_3, 4-CF_3 and 4-CN are difficult to couple and can only be obtained in moderate yields (Entries 7-9), while in the case of 4-NO_2 only traces of the coupling product **33j** can be seen (Entry 10). In addition, also styrylboronic acid can be used as a coupling partner although only 25% of the coupling product **33k** is obtained after column chromatography (Entry 11). The coupling of **30a** with isobutylboronic acid, which can serve as an example of alkyl boronic acids, is not possible under the giving reaction conditions (Entry 12). In view of the scope of the reaction we also examined other substituents on the nitrogen atom. To our surprise a sterically hindered group, such as *tert*-butyl on the substrate works even better, and gives 98% isolated yield of **33m** after column chromatography (Entry 13). Another interesting example is the vinyl chloride bearing a PMB (*para*-methoxybenzyl) group, as this can serve as a protective group, and product **33n** is obtained in 85% yield (Entry 14).

In a next step, the synthetic value of the double bond remaining in 3-aryl-1,2,3,6-tetrahydropyridines **33** was examined. As the reaction mixture contains palladium and the solvent is methanol, we reasoned these are typical conditions for hydrogenation. Hence, for some entries in Table 2-9, a one pot cross-coupling and hydrogenation procedure was tried. The cross-coupling was finished after 16 hours at 50 °C and then the reaction mixtures were

cooled to room temperature and the microwave vial was brought under H_2 atmosphere with a balloon. The reaction mixtures were further stirred at room temperature for 24-48 hours. In the particular case of **34f**, the pharmaceutically important drug (±)-Preclamol[42] (3-(3-hydroxyphenyl)-*N*-propylpiperidine, 3-PPP) can be synthesized in a one-pot fashion. The *S*-(-)-enantiomer acts as a selective dopamine autoreceptor agonist. It might also be possible to synthesize this in an enantioenriched way via an asymmetric hydrogenation as described by Verendel *et al.*[43]

Table 2-9 Scope for the Suzuki cross-coupling of **30**.

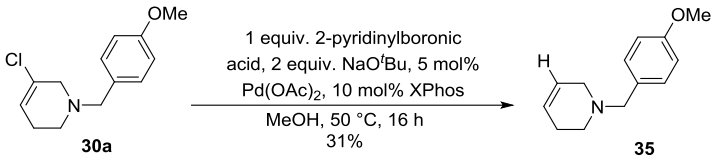


Entry	R^1	R^2	Yield **33** (%)	Yield **34** (%)
1	*n*-Pr	H, **33a**	94	89
2	*n*-Pr	4-Me, **33b**	82	-
3	*n*-Pr	2-*i*Pr, **33c**	90	-
4	*n*-Pr	4-MeO, **33d**	57	-
5	*n*-Pr	3-BnO, **33e**	71	-
6	*n*-Pr	3-OH, **33f**	75	69
7	*n*-Pr	3-CF_3, **33g**	50	-
8	*n*-Pr	4-CF_3, **33h**	37	-
9	*n*-Pr	4-CN, **33i**	31	-
10	*n*-Pr	4-NO_2, **33j**	trace	-
11	*n*-Pr	styryl, **33k**	25	-
12	*n*-Pr	isobutylboronic acid, **33l**	0	-
13	^{t}Bu	H, **33m**	98	72
14	PMB	H, **33n**	85	91

Yields after column chromatography. The yield of **34** is calculated from **30**.

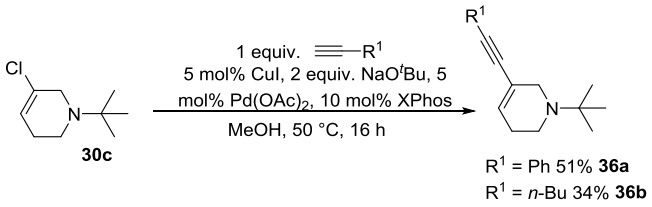
When using heteroarylboronic acids such as 2-pyridinylboronic acid, no coupling product was observed (Scheme 2-34). Oxidative addition into the C-Cl bond does occur, however. This is proven by the isolation of the hydro-dechlorinated product 1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (**35**) in 31%. It is well known that heteroarylboronic acids easily protodeboronate[41] in the presence of base and polar protic solvents such as methanol. Usually this problem is solved by using superstochiometric amounts of heteroarylboronic acid or by

changing to potassium heteroaryltrifluoroborates or *N*-methyliminodiacetic (MIDA) boronates, as they slowly hydrolyze and expose the heteroarylboronic acid *in situ.*[44] However, since not even a trace of coupling product was observed, no further attempts were made to couple heteroarylboronic acids.



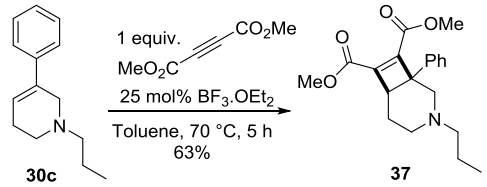
Scheme 2-34 The use of 2-pyridinylboronic acid leads to the isolation of hydro-dehalogenated compound **35**.

Aside from Suzuki-Miyaura cross couplings, the possibility was examined that these reactions conditions are viable for other cross coupling reactions (Scheme 2-35). CuI-catalyzed Sonogashira cross-coupling of phenylacetylene and vinyl chloride **30c** gives 51% isolated yield of **36a** after column chromatography. Also, alkylacetylenes, such as 1-hexyne, can be coupled, albeit giving a moderate 34% yield of **36b**. Other popular cross coupling reactions are less viable for different reasons. Buchwald-Hartwig cross-coupling reactions give unstable enamine products, which cannot be purified by column chromatography. Heck reactions on the other hand require higher temperatures, which is not feasible due to faster formation of Pd black and no cross couplings product is obtained. Earlier on though, we proved that Heck products can be obtained via a Suzuki-Miyaura cross coupling with styrylboronic acids (Scheme 2-29).



Scheme 2-35 Sonogashira cross-coupling on vinyl chloride **30c**.

The double bond in products **33** can also be used in a Lewis acid catalyzed [2+2] cycloaddition reaction with dimethylacetylene dicarboxylate (DMAD), giving rise to azabicyclic molecules **37** in a diastereoselective fashion (Scheme 2-36).

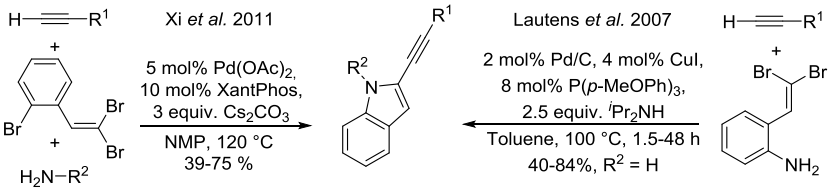


Scheme 2-36 [2+2] Cycloaddition of 1,2,3,6-tetrahydropyridine **31c** with DMAD.

2.6 Application of the dichloromethylene group in AHA coupling reactions?

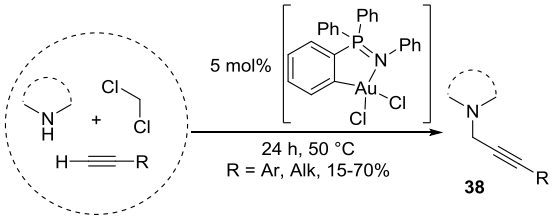
2.6.1 AHA couplings until present

The AHA coupling, or the coupling of an amine, a geminal dihaloalkane and an alkyne, is a particular A³-derived reaction where the aldehyde component is replaced by a geminal dihaloalkane. Due to the relatively stable nature of the C-Cl bond, the activation of C-Cl bonds is of utmost importance in environmental chemistry, as chlorinated compounds are often categorized as harmful. Although activation of dichloromethane and related halogenated compounds are well documented, alternative reactions are always wanted. Although some reports[45] also make use of amines, alkynes and dihalogenated compounds, the reaction mechanism is more a sequence of Pd-catalyzed Buchwald-Hartwig amination and Sonogashira cross-coupling, and these are thus not regarded as AHA couplings (Scheme 2-37).



Scheme 2-37 AHA coupling-like reactions are in fact a sequence of Buchwald-Hartwig and Sonogashira cross coupling reactions.

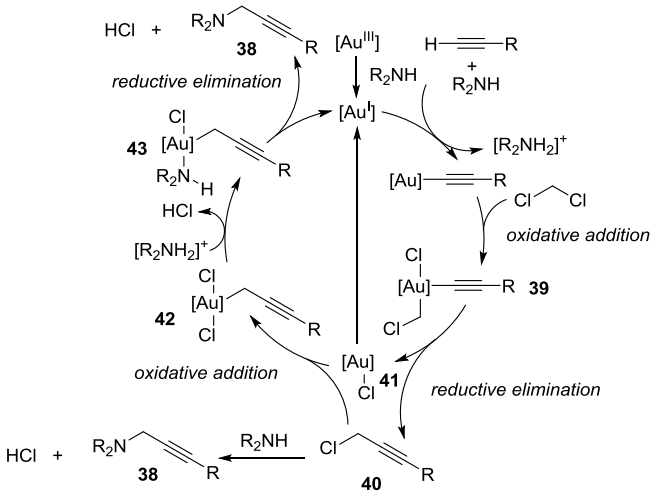
The reaction was firstly reported as a side reaction in gold-catalyzed hydroamination reactions by Urriolabeitia *et al.* in 2010 (Scheme 2-38).[46] Secondary amines, in combination with aliphatic or aromatic alkynes and dichloromethane give propargylamines **38**. The nature of the amine is important; some amines give products **38** (*i.e.* dimethylamine, dibutylamine, dihexylamine, dioctylamine, piperidine), others do not lead to products **38** (*i.e.* diphenylamine, dicyclohexylamine, diispropylamine, *N*-methyl-*N*-benzylamine).



Scheme 2-38 First reported AHA coupling.

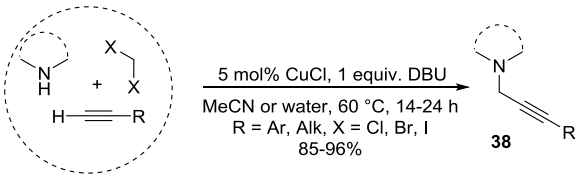
The basicity of the amine seems to play a role; the more basic the amine, the better the reaction works. Dibromomethane can also be used instead of dichloromethane and reactions are overall faster when dibromomethane is used. It is quite remarkable that dichloromethane can act as a coupling partner, because it is known that dichloromethane benefits from a sort of 'permanent anomeric effect'; there is always one lone-pair of chlorine anti-periplanar to the other C-Cl bond, which leads to stabilization of that C-Cl bond.[47] Mechanism-wise, the authors proposed that the reaction is catalyzed by gold(I) nanoparticles, generated *in situ* by reduction of gold by the amine, associated with a change in color of the solution from yellow to deep red (Scheme 2-39). As with an A³ coupling, a Au(I)-acetylide is easily formed, followed by oxidative addition of dichloromethane through activation of one of the C-Cl

bonds, generating Au(III) species **39**. Subsequent reductive elimination generates propargylchloride **40** that can react with secondary amines to generate target compound **38**, and gold species **41**, that can close the catalytic cycle generating new Au(I)-acetylide or undergo oxidative addition with propargylchloride **40** to generate Au(III)-species **42**. Reaction of **42** with quaternary ammonium salts would generate Au(III) species **43**, which upon reductive elimination gives target compound **38**.



Scheme 2-39 Proposed reaction mechanism for the synthesis of propargylamines **38** by AHA coupling.

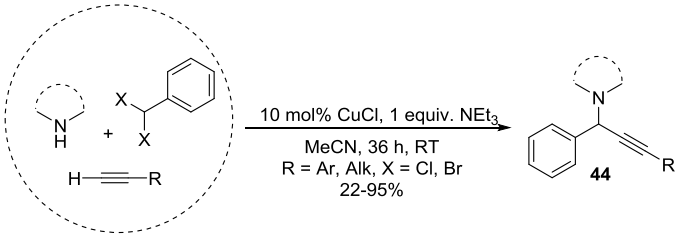
In the same year, Yu and Zhang reported a similar base-promoted AHA coupling, catalyzed by CuCl (Scheme 2-40).[48] The scope of the reaction was similar to that reported by Urriolabeitia, although yields are generally higher. Also, no coupling product **38** could be formed from primary amines or aromatic secondary amines. Upon addition of aldehyde, it was seen that AHA coupling occurs easier than A^3 coupling. The proposed reaction mechanism is similar to that proposed by Urriolabeitia (Scheme 37).



Scheme 2-40 Cu(I)-catalyzed AHA coupling.

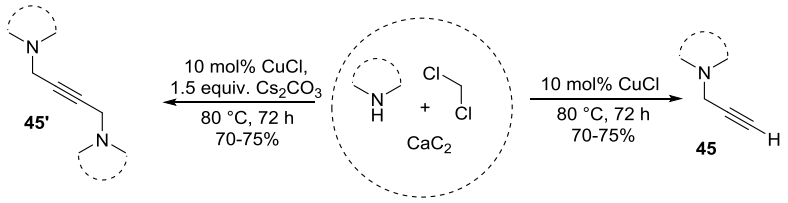
AHA couplings can not only be catalyzed by Cu(I) or Au(I), but also other transition metal catalysts, such as In(III) oxide in combination with DABCO. During the optimization process, it was seen that La(III) oxide, Zn(II) oxide, Cu(II) oxide, Ni(II) oxide and Fe(III) chloride all possess some catalytical activity.[49] Other examples consist of $CoBr_2$,[50] $FeCl_3$,[51] $Ni(Py)_4Cl_2$/Bipyridine catalytic system,[52] AgOAc,[53] and even catalyst-free AHA coupling are reported.[54] Also heterogeneous catalysts such as silica nanosphere supported iron,[55] or nano Au/CeO_2[56] can be used. Regarding the scope of dihaloalkanes, dichloromethane, dibromomethane and diiodomethane are the only dihaloalkanes that can be used for this coupling, since other systems such as chloroform or 1,2-dichloroethane are not reactive in AHA couplings. One exception is the use of benzal halides in AHA couplings (Scheme 2-41).[57] By using benzal halides, the AHA coupling can be performed at room temperature,

generating propargylamines **44** with one stereocenter. Lower reaction temperatures can be used because of enhanced reactivity of benzal halides compared to dihalomethane.



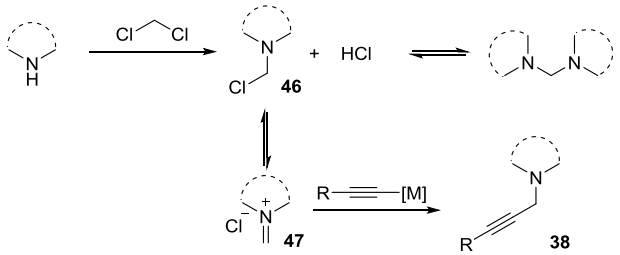
Scheme 2-41 AHA coupling using benzal halides.

One report deserves special attention, and will be discussed later in §4.2.3.3 *in extenso*, since it uses calcium carbide as an alternative terminal alkyne source in AHA couplings (Scheme 2-42).[58] Depending on whether or not a base (cesium carbonate) is added, terminal propargylamines **45** or internal propargylamines **45'** can be obtained.



Scheme 2-42 AHA coupling using calcium carbide.

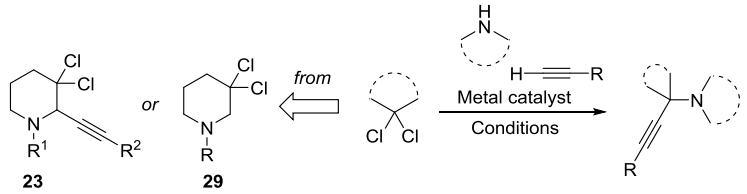
Mechanism-wise, most reports are in accordance with the reaction mechanism proposed by Urriolabeitia (Scheme 2-39). However, a few reports[53-54, 59] mention the possibility of an alternative reaction mechanism in which firstly activation or simple nucleophilic substitution of the C-Cl bond by the secondary amine occurs (Scheme 2-43). This leads to the formation of α-chloroamine **46** that, upon elimination of hydrochloric acid forms iminium **47**, which can be alkynylated *in situ* by metal acetylides to form propargylamines **38**.



Scheme 2-43 Alternative reaction mechanism for AHA couplings.

2.6.2 Scope expansion

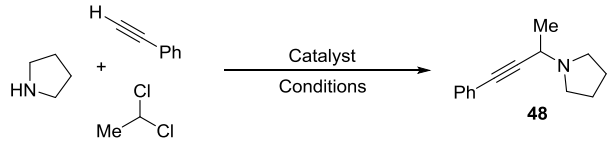
Ultimately, we would like to use previously synthesized compounds bearing dichloromethylene groups such as dichloropiperidines **23** as dihaloalkane coupling partners in AHA coupling with (secondary) amines and terminal alkynes in order to further expand the synthetic utility of the dichloromethylene group in molecules **23** or **29** (Scheme 2-44).



Scheme 2-44 Using previously synthesized compounds in AHA couplings.

We realized quickly that direct functionalization of **23** or **29** in AHA coupling is not yet possible, and given the very limited scope of dihaloalkanes in AHA couplings, this may not be surprising. Therefore we turned our attention towards expanding the scope of dihaloalkanes in the AHA coupling. We reasoned that adding two extra substituents as in **23** or **29** would lead to too much sterical hindrance, making oxidative addition over the C-Cl bond too difficult. Therefore, we started evaluating reaction conditions for the AHA coupling of 1,1-dichloroethane, which possesses an extra methyl group in comparison to dichloromethylene. Results are summarized in Table 2-10. Different catalysts including Cu(I), In(III), Fe(III), Al(III) and Pd(II) catalysts were screened, but none of them yielded any product **48**, as observed in ^{1}H NMR spectrum. Product **48** could be easily obtained from an A^3 coupling with acetaldehyde. Only in two cases (Entry 4 and 10) a trace amount of product **48** was obtained when using a Zn(II) catalyst, but the reaction could not be further improved.

Table 2-10 Screening for reaction conditions for the AHA coupling of 1,1-dichloroethane.



Entry	Catalyst (mol%)	Base (equiv.)	Solvent (mL)	T (°C) / t (h)	Yield **48** (%)
1	CuCl (10)	TEA (1)	MeCN (2)	60/24	/
2	CuCl (10)	TEA (1)	Toluene (2)	100/0.5[a]	/
3	$In(OTf)_3$ (20)	TEA (1)	Toluene (1)	55/16	/
4	$Zn(OTf)_2$ (20)	TEA (1)	Toluene (1)	55/16	trace
5	$FeCl_3$ (20)	TEA (1)	Toluene (1)	55/16	/
6	$Zn(OTf)_2$ (20)	DBU (2)	Toluene (1)	100/17	/
7	$Zn(OTf)_2$ (20)	K_2CO_3 (2)	Toluene (1)	100/17	/
8	$ZnBr_2$ (20)	DBU (2)	Toluene (1)	100/17	/
9	$Zn(OTf)_2$ (20)	DBU (2)	Dioxane (1)	100/17	/
10	$Zn(OTf)_2$ (20)	/	Toluene (1)	125/17	trace
11	Ag(OTf) (50)	/	Toluene (1)	125/17	/
12	$Zn(OTf)_2$ (20) + $AlCl_3$ (50)	/	Toluene (1)	125/17	/

13	$Zn(OTf)_2$ + PEPPSI-SIPr (20)	/	Toluene (1)	125/17	/

All reactions were carried out on 0.5 mmol scale, with 0.5 mmol 1,1-dichloroethane, 0.6 mmol pyrrolidine and 0.6 mmol phenylacetylene. [a] Reaction carried out under microwave heating.

Since the optimization of new methodology and expansion of the scope of dihaloalkanes in AHA couplings is not the main topic of this thesis, no further efforts towards AHA couplings were made.

2.7 Conclusion

In this chapter, we expanded the scope of polyhalogenated aldimines that can be used in alkynylation reactions. $In(OTf)_3$, a catalyst which showed excellent properties in earlier alkynylation reactions on polyhalogenated aldimines, proved to be the best catalyst for alkynylation reactions on α-chloroaldimines, although yields were only poor due to intrinsic hydrolytic instability of α-chloroaldimines. For α,α,δ-trichloroaldimines, $In(OTf)_3$ also proved to be the best catalyst and an extra ring closing reaction led to interesting *N*-alkyl-2-alkynyl-3,3-dichloropiperidines.

In a second part of this chapter we searched for further derivatization of previously synthesized dichloromethylene containing piperidines. The dichloromethylene group can be regioselectivily eliminated in case of *N*-alkyl-2-alkynyl-3,3-dichloropiperidines and arylated in a Suzuki-Miyaura cross-coupling. Due to the instable nature of the *in situ* formed elimination product, and instability of target molecules, Heck and Buchwald-Hartwig couplings could not be achieved. In order to widen the scope of this new cross-coupling, non-alkynylated *N*-alkyl-3,3-dichloropiperidines were synthesized and used in a similar coupling. However, regioselectivity problems arose due to the lack of the alkynyl function in the 2-position. Regioselective elimination could eventually be achieved by using LiHMDS and depending on the choice of solvent either of two regioisomers can be obtained. 5-Chloro-1,2,3,6-tetrahydropyridines could be used under similar conditions in Suzuki-Miyaura cross-couplings and the derivatization of the double bond in 4-aryl-1,2,3,6-tetrahydropyridines was demonstrated in a [2+2] cycloaddition reaction.

Lastly, we made some efforts to expand the scope of dihaloalkanes in AHA coupling reactions in order to use this reaction to further derivatize the dichloromethylene group, which is omnipresent in synthesized compounds in this chapter.

2.8 Experimental

2.8.1 Instrumentation

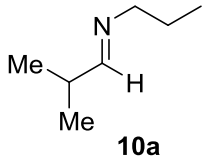
Solvents used in purification (Heptanes, Acetone and EtOAc) were distilled prior to use. All reagents were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa-Aesar, Fluorochem and J&K). Products were purified on an automated column chromatography device Biotage Isolera™ using Grace ResolvTM (12 g) columns. ^{1}H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Bruker Avance III HD spectrometer with $CDCl_3$ as solvent and TMS as the internal standard. Chemical shifts are given in parts per million (ppm), *J*-values are given in Hertz (Hz), and the number of protons for each signal are also indicated. For high resolution mass spectrometric analysis (HRMS), samples were dissolved in methanol or acetonitrile and diluted to a concentration of approximately 10^{-5} M

and measured on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions [M+H]+ are quoted.

2.8.2 Alkynylation on α-chloroaldimine systems

Synthesis of starting material 2-chloro-2-methyl-*N*-propylpropan-1-imine (**11a**).

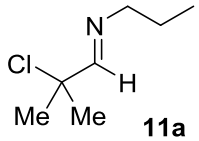
In a 100 mL round bottom flask equipped with a magnetic stirring bar were placed isobutyraldehyde (8.65 g, 120 mmol), $MgSO_4$ (7.22 g, 60 mmol), and DCM (50 mL). The solution was stirred and *n*-propylamine (7.09 g, 120 mmol) was added under stirring. The flask was equipped with a reflux condenser and a $CaCl_2$ drying tube and the reaction mixture was stirred at reflux for 2 h. Afterwards, the reaction mixture was filtered and the solvent was evaporated yielding 9.37 g (69%) of 2-methyl-*N*-propylpropan-1-imine (**10a**).



10a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 5.1 Hz, 1H, **H**C=N), 3.31 (t, *J* = 6.9 Hz, 2H, C**H**$_2$CH$_2$CH$_3$), 2.52 – 2.31 (m, 1H, C**H**(CH$_3$)$_2$), 1.71 – 1.50 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 1.07 (d, *J* = 6.9 Hz, 6H, CH(C**H**$_3$)$_2$), 0.87 (t, *J* = 7.4 Hz, 3H, CH$_2$CH$_2$C**H**$_3$).

The ^{1}H NMR spectrum was clean, and thus the imine was directly used in the next step. To a solution of 2-methyl-*N*-propylpropan-1-imine (**10a**) (9.37 g, 82 mmol) in cyclohexane (150 mL) was added *N*-chlorosuccinimide (11.35 g, 85 mmol) and the reaction mixture was refluxed at 90 °C for 3 h. Afterwards, the succinimide was filtered off and the flask was rinsed with cyclohexane (50 mL). The reaction mixture was then concentrated *in vacuo* and purified by distillation to yield 8.32 g (68% - 47% overall) of 2-chloro-2-methyl-*N*-propylpropan-1-imine (**11a**). Colorless oil, boiling point = 110 °C.



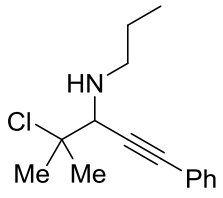
11a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (t, *J* = 1.3 Hz, 1H, **H**C=N), 3.40 (td, *J* = 6.9, 1.3 Hz, 2H, C**H**$_2$CH$_2$CH$_3$), 1.70 (s, 6H, CCl(C**H**$_3$)$_2$), 1.67 – 1.56 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 0.89 (t, *J* = 7.4 Hz, 3H, CH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.9 (**C**=N), 68.1 (**C**Cl), 62.0 (**C**H$_2$CH$_2$CH$_3$), 29.4 (CH(**C**H$_3$)$_2$), 23.6 (CH$_2$**C**H$_2$CH$_3$), 11.6 (CH$_2$CH$_2$**C**H$_3$).

Synthesis of propargylamines **12a**, **14**, **15** and aziridine **13a**.

In a 10 mL microwave vial were weighed 2-chloro-2-methyl-*N*-propylpropan-1-imine (**11a**) (74 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), In(OTf)$_3$ (70 mg, 0.125 mmol) and DCM (1.5 mL). The reaction mixture was heated and stirred at 70 °C for 24 h. Afterwards, the reaction mixture was diluted with DCM (10 mL), washed with 0.5 N NaOH solution (15 mL) and reextracted with DCM (10 mL). The organic phases were dried over $MgSO_4.3H_2O$, filtered, and the solvent was evaporated *in vacuo*. Column chromatography with heptanes/acetone on an automated chromatography instrument yielded different products.

4-chloro-4-methyl-1-phenyl-*N*-propylpent-1-yn-3-amine (**12a**)

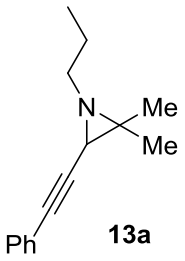


12a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H, C**H**$_{arom., ortho}$), 7.33 – 7.28 (m, 3H, C**H**$_{arom., meta and para}$), 3.59 (s, 1H, HNC**H**C≡C), 2.96 (ddd, *J* = 11.4, 7.9, 6.6 Hz, 1H, NC**H**(H)CH$_2$CH$_3$), 2.65 (ddd, *J* = 11.4, 7.9, 6.2 Hz, 1H, NCH(**H**)CH$_2$CH$_3$), 1.75 (s, 6H, ClC(C**H**$_3$)$_2$), 1.67 – 1.49 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 0.97 (t, *J* = 7.4 Hz, 3H, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7 (**C**H$_{arom., ortho}$), 128.3 (**C**H$_{arom., meta}$), 128.2 (**C**H$_{arom., para}$), 123.0 (**C**H$_{arom., ipso}$), 87.8 (HNCH**C**≡C), 85.3 (HNCHC≡**C**), 72.6 (Cl**C**(CH$_3$)CH$_3$), 61.7 (HN**C**HC≡C), 50.2

(N**C**$H_2CH_2CH_3$), 30.1 (ClC(**C**H_3)CH_3), 29.4 (ClC(CH_3)**C**H_3), 22.9 (NCH_2**C**H_2CH_3), 11.8 (NCH_2CH_2**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{15}H_{20}ClN+H]^+$: 250.1357; found 250.1346. 26.5 mg (21%), light yellow oil, R_f = 0.72 (Hept/Acetone 4/1).

55/45 mixture of invertomers of 2,2-dimethyl-3-(phenylethynyl)-1-propylaziridine (**13a**)

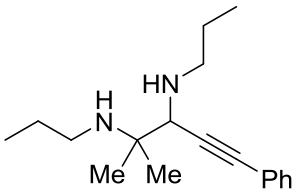


13a

Major invertomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H, C**H**$_{arom., ortho}$), 7.33 – 7.24 (m, 3H, C**H**$_{arom., meta and para}$), 2.60 – 2.48 (m, 1H, NC**H**(H)CH_2CH_3), 2.39 (ddd, *J* = 11.8, 8.7, 6.4 Hz, 1H, NCH(**H**)CH_2CH_3), 1.92 (s, 1H, NC**H**C≡C), 1.75 – 1.53 (m, 2H, NCH_2C**H**$_2CH_3$), 1.34 (s, 3H, NC(C**H**$_3$)CH_3), 1.30 (s, 3H, NC(CH_3)C**H**$_3$), 0.97 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.8 (**C**H$_{Arom., ortho}$), 128.1 (**C**H$_{Arom., meta}$), 127.8 (**C**H$_{Arom., para}$), 123.4 (**C**H$_{Arom., ipso}$), 88.1 (CHC≡**C**), 81.6 (CH**C**≡C), 55.0 (N**C**$H_2CH_2CH_3$), 42.8 (**C**(CH_3)$_2$), 40.0 (N**C**HC≡C), 23.9 (NC(CH_3)**C**H_3), 23.6 (NCH_2**C**H_2CH_3), 16.9 (NC(**C**H_3)CH_3), 12.0 (NCH_2CH_2**C**H_3).

Minor invertomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H, C**H**$_{arom., ortho}$), 7.33 – 7.24 (m, 3H, C**H**$_{arom., meta and para}$), 2.60 – 2.48 (m, 2H, , NC**H**$_2$$CH_2CH_3$), 2.53 (s, 1H, NC**H**C≡C), 1.75 – 1.53 (m, 2H, NC**H**C≡C), 1.30 (s, 3H, NC(C**H**$_3$)CH_3), 1.26 (s, 3H, NC(CH_3)C**H**$_3$), 0.97 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7 (**C**H$_{Arom., ortho}$), 128.3 (**C**H$_{Arom., meta}$), 128.1 (**C**H$_{Arom., para}$), 123.2 (**C**H$_{Arom., ipso}$), 85.2 (CHC≡**C**), 84.9 (CH**C**≡C), 48.9 (N**C**$H_2CH_2CH_3$), 41.9 (**C**(CH_3)$_2$), 36.7 (N**C**HC≡C), 27.1 (NC(CH_3)**C**H_3), 23.5 (NCH_2**C**H_2CH_3), 14.2 (NC(**C**H_3)CH_3), 12.0 (NCH_2CH_2**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{15}H_{19}N+H]^+$: 214.1590; found 214.1593. 18.2 mg (17%), light yellow oil, R_f = 0.51 (Hept/Acetone 4/1).

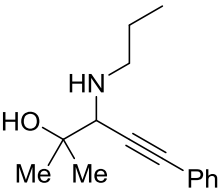
2-methyl-5-phenyl-*N*^{2},*N*^{3}-dipropylpent-4-yne-2,3-diamine (**14**)



14

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H, C**H**$_{arom., ortho}$), 7.33 – 7.27 (m, 3H, C**H**$_{arom., meta and para}$), 3.43 (s, 1H, NHC**H**C≡C), 2.95 (ddd, *J* = 11.4, 7.7, 6.4 Hz, 1H, CHNHC**H**(H)CH_2CH_3), 2.56 (ddd, *J* = 11.4, 7.7, 6.4 Hz, 1H, CHNHCH(**H**)CH_2CH_3), 2.54 (dt, *J* = 10.4, 7.2 Hz, 1H, CNHC**H**(H)CH_2CH_3), 2.45 (dt, *J* = 10.4, 7.2 Hz, 1H, CHN**H**C**H**$_2CH_2CH_3$ and CN**H**C**H**$_2CH_2CH_3$), 1.63 – 1.42 (m, 6H, CHNC**H**(H)CH_2CH_3), 1.22 (s, 3H, NHC(C**H**$_3$)CH_3), 1.18 (s, 3H, NHC(CH_3)C**H**$_3$), 0.95 (t, *J* = 7.3 Hz, 3H, CHNHCH$_2$$CH_2$C**H**$_3$), 0.94 (t, *J* = 7.3 Hz, 3H, CNHCH$_2$$CH_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.6 (**C**H$_{Arom., ortho}$), 128.2 (**C**H$_{Arom., meta}$), 127.8 (**C**H$_{Arom., para}$), 123.6 (**C**H$_{Arom., ipso}$), 90.3 (CHC≡**C**), 84.3 (CH**C**≡C), 58.5 (**C**HNHCH$_2$$CH_2CH_3$), 55.9 (**C**C$H_3$($CH_3$)), 50.7 (CHNH**C**H$_2$$CH_2CH_3$), 43.9 (CNH**C**H$_2$$CH_2CH_3$), 24.1 (C**C**$H_3$($CH_3$)), 24.1 (CNHCH$_2$**C**H$_2$$CH_3$), 23.2 (CHNHCH$_2$**C**H$_2$$CH_3$), 22.8 (C$CH_3$(**C**$H_3$)), 12.0 (CNHCH$_2$$CH_2$**C**H$_3$), 11.8 (CHNHCH$_2$$CH_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{18}H_{28}N_2+H]^+$: 273.2325; found 273.2345. 14.0 mg (10%), yellow oil, R_f = 0.80 (Hept/Acetone 4/1).

2-methyl-5-phenyl-3-(propylamino)pent-4-yn-2-ol (**15**)

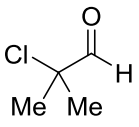


15

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.32 – 7.28 (m, 3H), 4.31 (s, 1H), 2.63 (dt, *J* = 10.7, 7.0 Hz, 1H), 2.49 (dt, *J* = 10.7, 7.0 Hz, 2H), 1.57 – 1.44 (m, 3H), 1.25 (s, 3H), 1.22 (s, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.3, 128.2, 122.9, 88.3, 85.6, 68.3, 55.9, 43.8, 24.0, 23.3, 22.7, 11.8. **HRMS** (ESI) m/z calculated for $[C_{15}H_{21}NO+H]^+$: 232.1696; found 232.1689. 3.5 mg (3%), yellow oil,

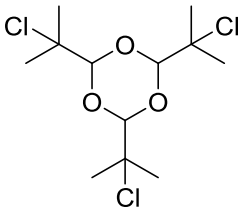
R_f = 0.75 (Hept/Acetone 4/1).

Synthesis of 2-chloro-2-methylpropanal (**16**)



16

To isobutyraldehyde (1.442 g, 20 mmol) was added sulfuryl chloride (2.83 g, 21 mmol) dropwise, at 0 °C. Then, the reaction mixture was allowed to warm to room temperature and after 2 h the reaction was finished according to TLC. The resulting mixture was poured into water (50 mL) and the phases were separated. The aqueous phase was extracted with DCM (3 x 50 mL). The combined organic fractions were washed with brine (50 mL) and dried over $MgSO_4.3H_2O$, before concentration *in vacuo*. The reaction mixture was purified via distillation leading to 1.14 g (54%) of 2-chloro-2-methylpropanal (**16**). Boiling point = 90 °C, colorless liquid. NMR-data are in accordance with the literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.43 (s, 1 H, C**H**O), 1.64 (s, 6H, C(C**H**$_3$)$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.9 (**C**HO), 69.3 (**C**Cl), 25.9 (C(**C**H$_3$)$_2$).

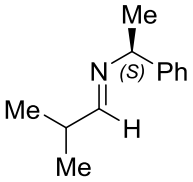


16'

After two years storage in the fridge, the sample has completely transformed (trimerized) to 2,4,6-tris(2-chloropropan-2-yl)-1,3,5-trioxane (**16'**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.88 (s, 1 H, OC**H**O), 1.57 (s, 6H, C(C**H**$_3$)$_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 102.9 (O**C**HO), 67.0 (**C**Cl), 26.6 (C(**C**H$_3$)$_2$). **HRMS** (ESI) m/z calculated for $[C_{12}H_{21}O_3Cl_3+Na]^+$: 341.0449; found 341.0463.

Synthesis of (*S*)-2-chloro-2-methyl-*N*-(1-phenylethyl)propan-1-imine (**11b**)

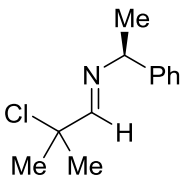
In an oven-dried 100 mL round bottom flask were placed isobutyraldehyde (3.97 g, 55 mmol), 5 g 4 Å molecular sieves (activated) and DCM (50 mL). The solution was stirred and cooled to 0 °C, then (*S*)-(-)-α-methylbenzylamine (6.06 g, 50 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. Afterwards, the molecular sieves were filtered over a path of Celite and the solvent was evaporated *in vacuo* to give 8.75 g (99%) of (*S*)-2-methyl-*N*-(1-phenylethyl)propan-1-imine (**10b**), which was pure enough to use as such in a next step.



10b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 5.3 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.25 – 7.18 (m, 1H), 4.25 (q, *J* = 6.7 Hz, 1H), 2.53 – 2.41 (m, 1H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.4, 145.3, 128.3, 126.6, 126.5, 69.3, 34.0, 24.7, 19.5, 19.4.

To a solution of (*S*)-2-methyl-*N*-(1-phenylethyl)propan-1-imine (**10b**) (8.76 g, 50 mmol) in cyclohexane (150 mL) was added *N*-chlorosuccinimide (6.68 g, 50 mmol) and the reaction mixture was refluxed at 80 °C for 3 h. The reaction mixture was cooled in an ice-bath and then the succinimide was filtered off and the flask was rinsed with cyclohexane (50 mL). The organic phase was concentrated *in vacuo* and 10.02 g (96%) of (*S*)-2-chloro-2-methyl-*N*-(1-phenylethyl)propan-1-imine (**11b**) was obtained.

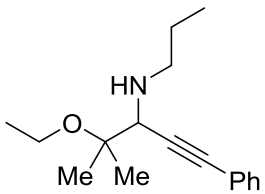


11b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.35 – 7.28 (m, 4H), 7.26 – 7.20 (m, 1H), 4.39 (q, *J* = 6.7 Hz, 1H), 1.73 (s, 3H), 1.70 (s, 3H), 1.46 (d, *J* = 6.7 Hz, 3H).

4-Ethoxy-4-methyl-1-phenyl-*N*-propylpent-1-yn-3-amine (**17**)

In a 10 mL Schlenk tube was introduced $In(OTf)_3$ (281 mg, 0.5 mmol), 4 Å molecular sieves (600 mg). These two powders were heated at 180 °C for 2 h under vacuum at the Schlenk line. After cooling and filling with argon, a solution of phenylacetylene (204 mg, 2 mmol) and (*E*)-2-chloro-2-methyl-*N*-propylpropan-1-imine (**11a**) (295 mg, 2 mmol) in chloroform (5 mL) was added and the resulting mixture was stirred for 24 h at 65 °C. Afterwards, the reaction mixture was diluted with DCM (10 mL), washed with 0.5 N NaOH solution (15 mL) and reextracted with DCM (10 mL). The organic phases were dried over $MgSO_4.3H_2O$, filtered, and the solvent was evaporated *in vacuo*. Column chromatography with heptanes/acetone on an automated chromatography instrument yielded different products. Next to propargylamine **12a** and aziridine **13a** also the following product was identified.

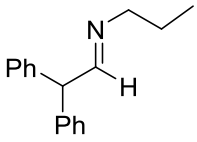


17

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 2H), 7.33 – 7.23 (m, 3H), 3.61 (s, 1H), 3.56 – 3.37 (m, 2H), 2.94 (dt, *J* = 11.4, 7.2 Hz, 1H), 2.61 (dt, *J* = 11.4, 7.2 Hz, 1H), 2.00 (br s, 1H), 1.63 – 1.51 (m, 2H), 1.36 (d, *J* = 5.5 Hz, 6H), 1.18 (t, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.2, 127.8, 123.6, 89.4, 84.3, 77.2, 59.2, 57.1, 50.5, 23.4, 22.9, 21.7, 16.1, 11.8. **HRMS** (ESI) m/z calculated for $[C_{17}H_{25}NO+H]^+$: 260.2009; found 260.2008. 40.6 mg (8%), yellow oil, R_f = 0.60 (Hept/Acetone 4/1).

Synthesis of 2-chloro-2,2-diphenyl-*N*-propylethan-1-imine (**11c**)

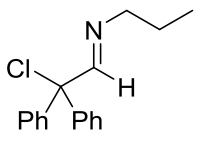
In an oven-dried 80 mL microwave vessel were placed 2,2-phenylacetaldehyde (1.962 g, 10 mmol), 1 g 4 Å molecular sieves (activated) and DCM (10 mL). The solution was stirred and cooled to 0 °C, then *n*-propylamine (709 mg, 12 mmol) was added. The reaction mixture was stirred at RT for 18 h. Afterwards, the molecular sieves were filtered over a path of Celite and the solvent was evaporated *in vacuo* to give 2.36 g (99%) of 2,2-diphenyl-*N*-propylethan-1-imine (**10c**), which was pure enough according to MS, although ^{1}H NMR shows a mixture of at least 4 different isomers, as can easily be seen from ^{13}C NMR.



10c

^{1}H NMR Too complex. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.8, 164.6, 161.2, 143.9, 142.7, 139.6, 137.6, 134.7, 132.4, 130.5, 130.0, 129.0, 128.7, 128.3, 128.3, 128.2, 127.5, 127.1, 126.3, 125.2, 124.1, 111.9, 60.2, 43.5, 39.9, 24.7, 24.5, 23.8, 22.8, 11.7, 11.3, 11.2, 10.9.

To a solution of 2,2-diphenyl-*N*-propylethan-1-imine (**10c**) (2.36 g, 10 mmol) in cyclohexane (50 mL) was added *N*-chlorosuccinimide (1.34 g, 10 mmol) and the reaction mixture was refluxed at 80 °C for 3 h. The reaction mixture was cooled in an ice-bath and then the succinimide was filtered off and the flask was rinsed with cyclohexane (50 mL). The organic phase was concentrated *in vacuo* and 1.81 g (67%) 2-chloro-2,2-diphenyl-*N*-propylethan-1-imine (**11c**) was obtained. The yield was corrected for the presence of cyclohexane and aldehyde.

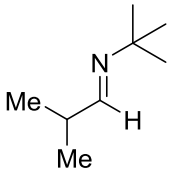


11c

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, *J* = 1.0 Hz, 1H), 7.41 – 7.28 (m, 10H), 3.53 (td, *J* = 6.9, 1.0 Hz, 2H), 1.73 – 1.61 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.2, 141.3, 128.9, 128.9, 128.6, 128.3, 128.3, 128.2, 128.0, 77.5, 62.5, 23.7, 11.8.

Synthesis of *N*-(*tert*-butyl)-2-chloro-2-methylpropan-1-imine (**11d**)

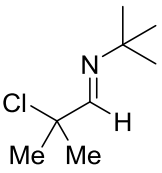
In an oven-dried 250 mL round bottom flask were placed isobutyraldehyde (7.21 g, 100 mmol), 10 g 4 Å molecular sieves (activated) and DCM (100 mL). The solution was stirred and cooled to 0 °C, then *tert*-butylamine (8.05 g, 110 mmol) was added. The reaction mixture was stirred at reflux for 1 h. Afterwards, the molecular sieves were filtered over a path of Celite and the solvent was evaporated *in vacuo* to give 7.53 g (59%) of *N*-(*tert*-butyl)-2-methylpropan-1-imine (**10d**), which was pure enough to use as such in the next step.



10d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.0 Hz, 1H), 2.47 – 2.30 (m, 1H), 1.16 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 56.0, 34.5, 29.7, 19.7.

To a solution of *N*-(*tert*-butyl)-2-methylpropan-1-imine (**10d**) (7.53 g, 59.2 mmol) in cyclohexane (150 mL) was added *N*-chlorosuccinimide (7.90 g, 19.2 mmol) and the reaction mixture was refluxed at 80 °C for 3 h. The reaction mixture was cooled in an ice-bath and then the succinimide was filtered off and the flask was rinsed with cyclohexane (50 mL). The organic phase was concentrated *in vacuo* and 3.74 g (39%) *N*-(*tert*-butyl)-2-chloro-2-methylpropan-1-imine (**11d**) was obtained.



11d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 1.68 (s, 6H), 1.18 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0, 69.1, 56.5, 29.4. **HRMS** (ESI) m/z calculated for $[C_8H_{16}NCl+H]^+$: 162.1044; found 162.1044.

2.8.3 Alkynylation on α,α,δ-trichloroaldimine systems

α,α,δ-Trichloroaldimines **21** were synthesized via two ways. A first method (A), makes use of molecular sieves (4 Å) as desiccant, and is used for non-sterically hindered amines. A second method (B) makes use of $TiCl_4$ and is used for more sterically hindered amines (*p*-methoxybenzylamine, *tert*-butylamine). Imines were not further purified and are generally pure enough to be used as such. 2,2,5-Trichloropentanal was synthesized according to a known procedure.[26]

Method A:

In a three-necked round bottom flask were introduced 4 Å molecular sieves (2 g - 66.6 g/mol, activated over weekend at 180 °C under vacuum), 2,2,5-trichloropentanal (5.68 g, 30 mmol) and toluene (30 mL). Then, non-sterically hindered amine (36.0 mmol) was added at 0 °C via a dropping funnel. The reaction mixture was heated during 2 h at 60 °C. Afterwards the reaction mixture was filtered over a glass filter and the filter was rinsed with EtOAc. The resulting solution was washed with 0.5 N NaOH solution (50 mL), extracted with DCM (3 x 50 mL) and dried over $MgSO_4$. The reaction mixture was filtered and concentrated *in vacuo* to yield the α,α,δ-trichloroaldimines **21** as orange oils.

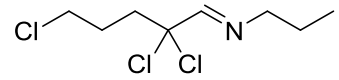
Method B:

In a three-necked round bottom flask were introduced 2,2,5-trichloropentanal (5.68 g, 30 mmol) and Et_2O (30 mL). The flask was cooled with an ice-bath and $TiCl_4$ (1.89 mL, 17.14

mmol) in dry pentane (6 mL) was added dropwise via a dropping funnel. Then, sterically hindered amine (30 mmol) and triethylamine (6.07 g, 60 mmol) in Et_2O (30 mL) was added dropwise via a dropping funnel. The ice bath was removed and the reaction mixture was stirred for 3 h at room temperature. Afterwards, the reaction mixture was filtered over a layer of K_2CO_3 on Celite and washed with Et_2O (100 mL). The organic phase was washed with 0.5 N NaOH (50 mL) and extracted with Et_2O (2 x 50 mL), the organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain a yellow oil of sterically hindered α,α,δ-trichloroaldimines **21**.

2,2,5-trichloro-*N*-propylpentan-1-imine (**21a**)

Synthesized according to method A with 2,2,5-trichloropentanal (5.68 g, 30 mmol) and *n*-propylamine (2.13 g, 36 mmol).

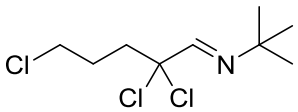


21a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (s, 1H), 3.63 (t, J = 6.4 Hz, 2H), 3.47 (t, J = 6.7 Hz, 2H), 2.62 – 2.54 (m, 2H), 2.25 – 2.15 (m, 2H), 1.72 – 1.60 (m, 2H), 0.92 (t, J = 7.4 Hz, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.6, 88.3, 61.3, 44.2, 41.1, 28.4, 23.4, 11.6. **HRMS** (ESI) m/z calculated for $[C_8H_{14}NCl_3+H]^+$: 230.0265; found 230.0259. Yellow oil, 6.45 g (95%)

N-(tert-butyl)-2,2,5-trichloropentan-1-imine (**21b**)

Synthesized according to method B with 2,2,5-trichloropentanal (5.68 g, 30 mmol) and *tert*-butylamine (2.63 g, 36 mmol).

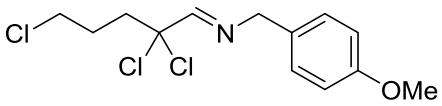


21b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (s, 1H, **H**C=N), 3.63 (t, J = 6.5 Hz, 2H, C**H**$_2$Cl$_2$), 2.63 – 2.55 (m, 2H, ClC**H**$_2$), 2.23 – 2.12 (m, 2H, CH$_2$C**H**$_2$CH$_2$), 1.21 (s, 9H, C(C**H**$_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.4 (**C**=N), 89.4 (**C**Cl$_2$), 57.2 (Cl**C**H$_2$), 44.3 (**C**(CH$_3$)$_3$), 40.9 (CH$_2$**C**H$_2$CH$_2$), 29.1 (C(**C**H$_3$)$_3$), 28.6. **HRMS** (ESI) m/z calculated for $[C_9H_{16}NCl_3+H]^+$: 244.0421; found 244.0433. Yellow oil, 6.31 g (86%).

2,2,5-trichloro-*N*-(4-methoxybenzyl)pentan-1-imine (**21c**)

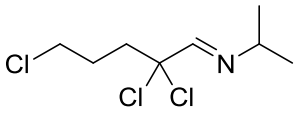
Synthesized according to method B with 2,2,5-trichloropentanal (5.68 g, 30 mmol) and (4-methoxyphenyl)methanamine (4.12 g, 30 mmol).



21c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (s, 1H), 7.16 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.65 (s, 2H), 3.80 (s, 3H), 3.61 (t, J = 6.4 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.27 – 2.12 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.3, 159.0, 129.6, 129.2, 114.1, 88.4, 62.3, 6.3, 44.2, 40.9, 28.4. Yellow oil, 5.59 g (63%).

2,2,5-trichloro-*N*-isopropylpentan-1-imine (**21d**)

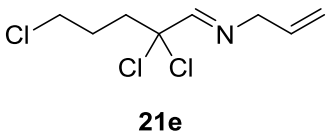


21d

Synthesized according to method A with 2,2,5-trichloropentanal (1.895 g, 10 mmol) and isopropylamine (686 mg, 12 mmol). NMR spectra are in accordance with previously published spectra.[26] Yellow oil, 1.16 g (51%).

N-allyl-2,2,5-trichloropentan-1-imine (**21e**)

Synthesized according to method A with 2,2,5-trichloropentanal (947 mg, 5 mmol) and allylamine (343 mg, 6 mmol).



21e

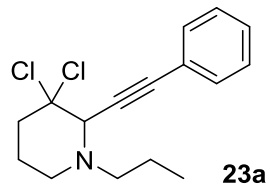
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 6.03 – 5.90 (m, 1H), 5.23 – 5.18 (m, 1H) 5.18 – 5.11 (m, 1H), 4.15 (d, *J* = 4.7 Hz, 2H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.64 – 2.55 (m, 2H), 2.32 – 2.12 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.7, 134.2, 117.1, 88.2, 61.2, 44.1, 41.0, 28.4. Yellow oil, 1.09 g (95%).

General procedure for the synthesis of 2-alkynyl-3,3-dichloropiperidines **23**

In an oven dried 10 mL microwave vial, *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (0.5 mmol), phenylacetylene (1.0 mmol) and $In(OTf)_3$ (0.125 mmol) were added successively and the vial was quickly sealed under air. Subsequently, toluene (2 mL) was added and the reaction mixture was placed in a preheated oil bath at 80 °C and allowed to reflux for 18 h. Afterwards, the reaction mixture was cooled down, diluted with CH_2Cl_2 (10 mL), washed with 0.5 N NaOH solution (15 mL) and extracted with CH_2Cl_2 (10 mL). The organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo* to obtain the corresponding products **17a-k** as yellow oils. Usually, products were clean, but short, manual column chromatography with Heptanes/EtOAc was always performed.

3,3-Dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

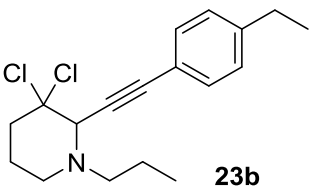


23a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.46 (m, 2H), 7.33-7.31 (m, 3H), 4.20 (s, 1H), 2.65-2.47 (m, 5H), 2.37-2.33 (m, 1H), 2.05-1.97 (m, 1H), 1.66-1.62 (m, 1H), 1.57-1.50 (m, 2H), 0.95 (t, 3H, *J* = 7.2 Hz, N-$CH_2CH_2CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 131.8, 128.4, 128.3, 122.5, 89.2, 88.9, 82.2, 65.7, 46.9, 40.4, 23.4, 20.1, 11.7. **HRMS** (ESI) m/z calculated for $[C_{16}H_{19}Cl_2N+H]^+$: 296.0967; found 296.0982. Light yellow oil, 104 mg (70%) before and 61 mg (41%) after column chromatography. R_f = 0.38 (Heptanes/EtOAc 20/1).

3,3-Dichloro-2-((4-ethylphenyl)ethynyl)-1-propylpiperidine (**23b**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), 1-ethyl-4-ethynylbenzene (65 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

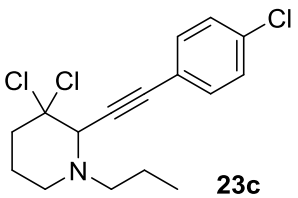


23b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.19 (s, 1H), 2.69 – 2.59 (m, 4H), 2.58 – 2.45 (m, 3H), 2.34 (d, *J* = 13.9 Hz, 1H), 2.08 – 1.94 (m, 1H), 1.68 – 1.58 (m, 1H), 1.58 – 1.46 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 145.0, 131.9, 128.1, 127.9, 119.7, 89.3, 89.2, 81.4, 65.7, 57.3, 47.0, 40.4, 28.8, 23.4, 20.1, 15.4, 11.8. **HRMS** (ESI) m/z calculated for $[C_{18}H_{23}Cl_2N+H]^+$: 324.1280; found 324.1298. Yellow oil, 117 mg (72%) before and 68 mg (42%) after column chromatography. R_f = 0.39 (Heptanes/EtOAc 20/1).

3,3-Dichloro-2-((4-chlorophenyl)ethynyl)-1-propylpiperidine (**23c**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), 1-chloro-4-ethynylbenzene (59 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

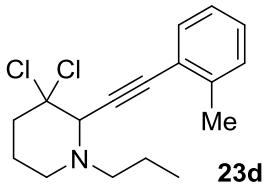


23c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 4.18 (d, *J* = 1.2 Hz, 1H), 2.66 – 2.58 (m, 2H), 2.58 – 2.43 (m, 3H), 2.41 – 2.30 (m, 1H), 2.08 – 1.94 (m, 1H), 1.70 – 1.59 (m, 1H), 1.59 – 1.46 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.6, 133.1, 128.7, 121.1, 89.1, 87.9, 83.4, 65.8, 57.3, 47.0, 40.5, 23.4, 20.1, 11.7. **HRMS** (ESI) m/z calculated for $[C_{16}H_{18}Cl_3N+H]^+$: 330.0578; found 330.0584. Yellow oil, 98 mg (68%) before and 53 mg (37%) after column chromatography. R_f = 0.40 (Heptanes/EtOAc 20/1).

3,3-Dichloro-1-propyl-2-(*o*-tolylethynyl)piperidine (**23d**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), 1-ethynyl-2-methylbenzene (58 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

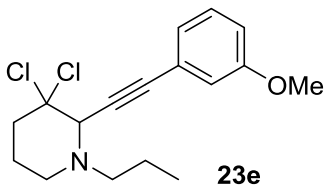


23d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.17 – 7.11 (m, 1H), 4.25 (s, 1H), 2.72 – 2.48 (m, 5H), 2.46 (s, 3H), 2.41 – 2.30 (m, 1H), 2.09 – 1.95 (m, 1H), 1.70 – 1.60 (m, 1H), 1.60 – 1.47 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 140.4, 132.3, 129.5, 128.5, 125.5, 122.5, 89.3, 87.9, 86.0, 65.8, 57.3, 47.1, 40.5, 23.4, 21.1, 20.1, 11.7. **HRMS** (ESI) m/z calculated for $[C_{17}H_{21}Cl_2N+H]^+$: 310.1124; found 310.1135. Yellow oil, 113 mg (73%) before and 65 mg (42%) after column chromatography. R_f = 0.40 (Heptanes/EtOAc 20/1).

3,3-Dichloro-2-((3-methoxyphenyl)ethynyl)-1-propylpiperidine (**23e**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), 3-Ethynylanisole (66 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

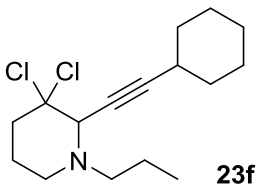


23e

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.19 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.00 – 6.97 (m, 1H), 6.89 (ddd, *J* = 8.4, 2.6, 0.7 Hz, 1H), 4.20 (s, 1H), 3.81 (s, 3H), 2.71 – 2.45 (m, 5H), 2.39 – 2.31 (m, 1H), 2.10 – 1.94 (m, 1H), 1.68 – 1.59 (m, 1H), 1.59 – 1.46 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.4, 129.4, 124.5, 123.6, 116.9, 114.9, 89.2, 88.9, 82.1, 65.7, 57.3, 55.3, 55.3, 47.0, 40.4, 23.4, 20.1, 11.7. **HRMS** (ESI) m/z calculated for $[C_{17}H_{21}Cl_2NO+H]^+$: 326.1073; found 326.1089. Yellow oil, 121 mg (74%) before and 69 mg (42%) after column chromatography. R_f = 0.49 (Heptanes/EtOAc 20/1).

3,3-Dichloro-2-(cyclohexylethynyl)-1-propylpiperidine (**23f**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), cyclohexylacetylene (54 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

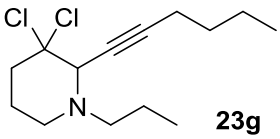


23f

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.96 (s, 1H), 2.62 – 2.36 (m, 6H), 2.31 – 2.23 (m, 1H), 2.04 – 1.88 (m, 1H), 1.83 – 1.65 (m, 4H), 1.64 – 1.55 (m, 1H), 1.55 – 1.30 (m, 8H), 0.92 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 93.7, 89.8, 72.4, 65.0, 57.1, 46.8, 40.2, 32.7, 28.8, 26.0, 24.5, 23.4, 20.0, 11.8. **HRMS** (ESI) m/z calculated for $[C_{16}H_{25}Cl_2N+H]^+$: 302.1437; found 302.1446. Yellow oil, 91.2 mg (60%) before and 54.1 mg (36%) after column chromatography. R_f = 0.46 (Heptanes/EtOAc 20/1).

3,3-Dichloro-2-(hex-1-yn-1-yl)-1-propylpiperidine (**23g**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), Hex-1-yne (41 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

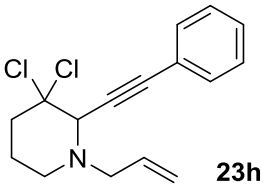


23g

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 1H), 2.57 – 2.49 (m, 2H), 2.49 – 2.38 (m, 3H), 2.33-2.23 (m, 3H), 2.02 – 1.88 (m, 1H), 1.63-1.57 (m, 1H), 1.56-1.39 (m, 6H), 0.92 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 89.7, 89.5, 72.3, 65.0, 57.1, 46.9, 40.2, 30.9, 23.3, 21.9, 19.9, 18.3, 13.5, 11.7. **HRMS** (ESI) m/z calculated for $[C_{14}H_{23}Cl_2N+H]^+$: 276.1280; found 276.1280. Yellow oil, 60.6% crude yield. Yellow oil, 83.2 mg (60%) before and 40.7 mg (30%) after column chromatography. R_f = 0.61 (Heptanes/EtOAc 20/1).

1-Allyl-3,3-dichloro-2-(phenylethynyl)piperidine (**23h**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)prop-2-en-1-amine (**21e**) (114 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

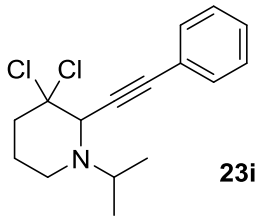


23h

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 – 7.46 (m, 2H, C**H**$_{arom.,ortho}$), 7.37 – 7.28 (m, 3H, C**H**$_{arom.,meta\ and\ para}$), 5.87 (dddd, J = 17.3, 10.1, 7.3, 5.6 Hz, 1H, H(H)C=C**H**), 5.32 (d, J = 17.0 Hz, 1H, **H**(H)C=CH), 5.21 (d, J = 10.2 Hz, 1H, H(**H**)C=CH), 4.22 (s, 1H, NC**H**CCl_2), 3.29 – 3.17 (m, 2H, NC**H**$_2$CH=CH_2), 2.72 – 2.58 (m, 2H, NC**H**$_2$$CH_2CH_2$), 2.58 – 2.46 (m, 1H, NCH_2CH_2C**H**(H)), 2.41 – 2.31 (m, 1H, NCH_2CH_2CH(**H**)), 2.08 – 1.94 (m, 1H, NCH_2C**H**(H)CH_2), 1.73 – 1.60 (m, 1H, NCH_2CH(**H**)CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 134.2 (H_2C=**C**H), 131.8 (**C**H$_{arom.,\ ortho}$) 128.5 (**C**H$_{arom.,\ para}$), 128.3 (**C**H$_{arom.,\ meta}$), 122.4 (**C**H$_{arom.,\ ipso}$), 118.7 (H_2**C**=CH), 89.2 (**C**≡CAr), 89.0 (C≡**C**Ar), 81.9 (**C**Cl_2), 65.4 (N**C**HCl_2), 58.6 (N**C**H_2CH=CH_2), 46.9 (N**C**$H_2$$CH_2CH_2$), 40.4 ($NCH_2CH_2$**C**$H_2$), 23.3 ($NCH_2$**C**$H_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{16}H_{17}Cl_2N+H]^+$: 294.0811 found 294.0826. Yellow oil, 103 mg (70%) before and 69.2 mg (47%) after column chromatography. R_f = 0.63 (Heptanes/EtOAc 20/1).

3,3-Dichloro-1-isopropyl-2-(phenylethynyl)piperidine (**23i**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-2-amine (**21d**) (115 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

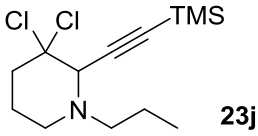


23i

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.34 (m, 2H), 7.24 – 7.20 (m, 3H), 4.19 (s, 1H), 2.90 (septet, J = 6.4 Hz, 1H), 2.71 - 2.58 (m, 2H), 2.51 - 2.42 (m, 1H), 2.27 – 2.21 (m, 1H), 1.90 – 1.78 (m, 1H), 1.60 – 1.52 (m, 1H), 1.17 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 130.7, 127.4, 127.3, 121.8, 88.8, 87.9, 83.2, 63.1, 52.3, 41.8, 39.9, 22.8, 19.6, 18.5. **HRMS** (ESI) m/z calculated for $[C_{16}H_{20}Cl_2N+H]^+$: 296.0967; found 296.0974. Yellow oil, 130 mg (88%) before and 61 mg (41%) after column chromatography. R_f = 0.51 (Heptanes/EtOAc 20/1).

3,3-Dichloro-1-propyl-2-((trimethylsilyl)ethynyl)piperidine (**23j**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), trimethylsilylacetylene (49 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL). No aqueous workup was performed, but the product was directly purified via column chromatography.

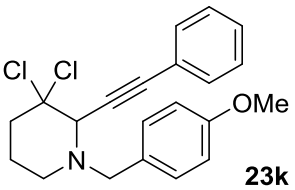


23j

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.96 (s, 1H, NC**H**Cl_2), 2.63 – 2.49 (m, 2H, NC**H**$_2$$CH_2CH_2$), 2.49 – 2.38 (m, 3H, NC**H**$_2$$CH_2CH_3$ and NCH_2CH_2C**H**(H)), 2.28 (d, J = 13.8 Hz, 1H, NCH_2CH_2CH(**H**)), 2.04 – 1.89 (m, 1H, NCH_2C**H**(H)CH_2), 1.66 – 1.54 (m, 1H, NCH_2CH(**H**)CH_2), 1.54 – 1.40 (m, 2H, NCH_2C**H**$_2$$CH_3$), 0.93 (t, J = 7.4 Hz, 3H, NCH_2CH_2C**H**$_3$), 0.20 (s, 9H, Si(C**H**$_3$)$_3$).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 98.0 (**C**≡CSi$(CH_3)_3$), 94.0 (C≡**C**Si$(CH_3)_3$), 88.9 (**C**Cl_2), 65.7 (**C**HC≡CSi$(CH_3)_3$), 57.1 (N**C**$H_2CH_2CH_3$), 46.7 (N**C**$H_2CH_2CH_2$), 40.2 (NCH_2CH_2**C**H_2), 23.3 (NCH_2**C**H_2CH_2), 20.0 (NCH_2**C**H_2CH_3), 11.7 (NCH_2CH_2**C**H_3), 0.02 (C≡CSi(**C**H_3)$_3$). **HRMS** (ESI) m/z calculated for $[C_{13}H_{23}Cl_2NSi+H]^+$: 292.1050; found 292.1049. Yellow oil, 134.0 mg (92%) before and 67.0 mg (46%) after column chromatography. R_f = 0.75 (Heptanes/EtOAc 1/1).

3,3-Dichloro-1-(4-methoxybenzyl)-2-(phenylethynyl)piperidine (**23k**)

The general procedure was used with 1-(4-methoxyphenyl)-*N*-(2,2,5-trichloropentylidene)methanamine (**21c**) (154 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).

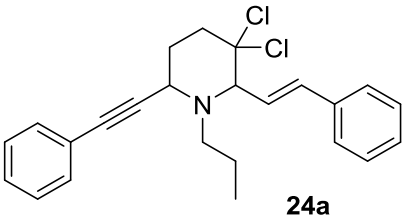


23k

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.46 (m, 2H, C**H**$_{arom.}$), 7.39 – 7.29 (m, 5H, C**H**$_{arom.}$), 6.87 (d, J = 8.6 Hz, 2H, C**H**$_{arom., PMB}$), 4.07 (s, 1H, NC**H**C≡C), 3.80 (s, 3H, OC**H**$_3$), 3.76 -3.61 (m, 2H, NC**H**$_2$PMB), 2.81 – 2.59 (m, 2H, NC**H**$_2$$CH_2CH_2$), 2.59 – 2.48 (m, 1H, NCH_2CH_2C**H**(H)), 2.35 (d, J = 13.9 Hz, 1H, NCH_2CH_2CH(**H**)), 2.11 – 1.96 (m, 1H, NCH_2C**H**(H)CH_2), 1.70 – 1.58 (m, 1H, NCH_2CH(**H**)CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.0 (**C**H$_{PMB,para}$), 131.9 (**C**H$_{arom., ortho}$), 130.1 (**C**H$_{PMB,ortho}$), 129.5 (**C**H$_{PMB,ipso}$), 128.5 (**C**H$_{arom.,}$ para), 128.3 (**C**H$_{arom.,meta}$), 122.6 (**C**H$_{arom.,}$ ipso), 113.8 (**C**H$_{PMB,meta}$), 89.3 (NCHC≡**C**), 89.2 (**C**Cl_2), 82.2 (NCH**C**≡C), 65.2 (N**C**HC≡C), 59.2 (N**C**H_2PMB), 55.2 (O**C**H_3), 46.6 (N**C**$H_2CH_2CH_2$), 40.5 (NCH_2CH_2**C**H_2), 23.4 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{21}H_{21}Cl_2NO+H]^+$: 374.1073; found 374.1060. Yellow oil, 151.7 mg (81%) before and 56.9 mg (30%) after column chromatography. R_f = 0.61 (Heptanes/EtOAc 9/1).

3,3-Dichloro-6-(phenylethynyl)-1-propyl-2-styrylpiperidine (**24a**)

The general procedure was used with *N*-(2,2,5-trichloropentylidene)propan-1-amine (**21a**) (108 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), and $In(OTf)_3$ (70.0 mg, 0.125 mmol) were reacted in toluene (2 mL).



24a

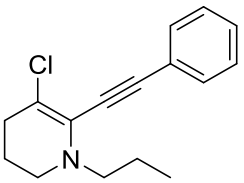
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 4H, C**H**$_{arom.}$), 7.40 – 7.30 (m, 5H, C**H**$_{arom.}$), 7.29 – 7.26 (m, 1H, C**H**$_{arom.}$), 6.69 (d, *J* = 16.0 Hz, 1H, NCHCH=C**H**), 6.21 (dd, *J* = 16.0, 8.8 Hz, 1H, NCHC**H**=CH), 4.14 (dd, *J* = 3.7, 3.0 Hz, 1H, NC**H**C≡C), 3.65 (d, *J* = 8.8 Hz, 1H, NC**H**CH=CH), 2.81 – 2.67 (m, 2H, NCHC**H**(H) and NC**H**(H)CH_2CH_3), 2.61 (dt, *J* = 14.1, 3.2 Hz, 1H, NCHCH(**H**)), 2.52 (ddd, *J* = 13.0, 8.0, 5.3 Hz, 1H, NCH(**H**)CH_2CH_3), 2.40 – 2.30 (m, 1H, $NCHCH_2C$**H**(H)), 1.90 (ddd, *J* = 13.5, 6.6, 3.1 Hz, 1H, $NCHCH_2CH$(**H**)), 1.52 – 1.39 (m, 2H, NCH_2C**H**$_2CH_3$), 0.89 (t, *J* = 7.3 Hz, 3H, NCH_2CH_2C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.6 (**C**H$_{arom.}$), 136.4 (C=**C**Ar), 131.9 (**C**H$_{arom.}$), 128.6 (**C**H$_{arom.}$), 128.4 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 127.9 (**C**H$_{arom.}$), 126.7 (**C**=CAr), 126.4 (**C**H$_{arom.}$), 122.9 (**C**H$_{arom.}$), 92.0 (**C**Cl_2), 87.1 (C≡**C**Ar), 85.8 (**C**≡CAr), 72.5 (N**C**HCH=CH), 54.0 (N**C**$H_2CH_2CH_3$), 49.3 (N**C**HCH_2CH_2), 42.2 ($NCHCH_2$**C**H_2), 28.6 (NCH**C**H_2CH_2), 21.0 (NCH_2**C**H_2CH_3), 11.8 (NCH_2CH_2**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{24}H_{25}Cl_2N+H]^+$: 398.1437; found 398.1441. Yellow oil, 1.3 mg (1%) after column chromatography. R_f = 0.56 (Heptanes/EtOAc 9/1).

2.8.4 Cross-coupling reactions on *N*-alkyl-2-alkynyl-3,3-dichloropiperidines 23

Elimination of **23** leading to **25**

In a 10 mL microwave vessel were placed 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (100 mg, 0.338 mmol) and THF (2.5 mL), the mixture was stirred and cooled to 0 °C. Then, KO^{t}Bu (114 mg, 1.013 mmol) was added portion wise, and the vial was quickly sealed. The reaction mixture was heated and stirred for 3 h at 80 °C. After cooling down to room temperature, the resulting mixture was quenched with water (4 mL). The reaction mixture was extracted with Et_2O (4, 4, 3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. No purification can be done due to the unstable nature of the compound.

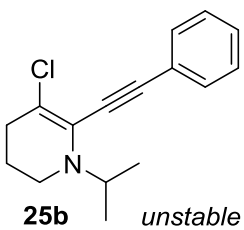
5-Chloro-6-(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**25a**)



25a *unstable compound*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 – 7.42 (m, 2H), 7.35 – 7.28 (m, 3H), 3.21 – 3.13 (m, 2H), 3.04 – 2.98 (m, 2H), 2.43 (t, *J* = 6.5 Hz, 2H), 1.92 – 1.83 (m, 2H), 1.62 – 1.48 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). Due to the unstable nature of the compound, no ^{13}C NMR and HRMS data could be obtained. 69 mg (79%), light brown oil, which becomes black after 24 h at room temperature or by storage under inert atmosphere in the fridge.

5-Chloro-1-isopropyl-6-(phenylethynyl)-1,2,3,4-tetrahydropyridine (**25b**)



25b *unstable compound*

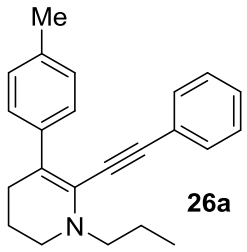
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H, C**H**$_{Arom., ortho}$), 7.34 – 7.29 (m, 3H, C**H**$_{Arom., meta and para}$), 4.24 (septet, *J* = 6.7 Hz, 1H, C**H**$(CH_3)_2$), 2.99 – 2.91 (m, 2H, NC**H**$_2$), 2.45 (t, *J* = 6.5 Hz, 2H, NCH_2CH_2C**H**$_2$), 1.90 – 1.80 (m, 2H, NCH_2C**H**$_2CH_2$), 1.12 (d, *J* = 6.7 Hz, 6H, $CH(C$**H**$_3)_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.5 (**C**H$_{arom., ortho}$), 128.4 (**C**H$_{arom., para}$),

128.3 (**C**H$_{arom., meta}$), 127.5 (N**C**=C), 123.0 (**C**H$_{arom., ipso}$), 113.7 (**C**Cl), 95.2 (C≡**C**Ar), 83.1 (**C**≡CAr), 50.8 (**C**H(CH$_3$)$_2$), 39.5 (N**C**H$_2$), 31.5 (NCH$_2$CH$_2$**C**H$_2$), 22.8 (NCH$_2$**C**H$_2$CH$_2$), 19.8 (CH(**C**H$_3$)$_2$). Scale reaction: 0.287 mmol. 51 mg product (69%), lightbrown oil, which becomes black after 24 h at room temperature or by storage under inert atmosphere in the fridge.

Suzuki-Miyaura cross-coupling of **23**

In an oven dried 10 mL microwave vial were introduced inside the glove box allylchloro[1,3-bis(2,6-di-iso-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *p*-tolylboronic acid (0.095 g, 0.700 mmol) and sodium *tert*-butoxide (0.202 g, 2.1 mmol). Subsequently, outside the glove box, 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol), dissolved in 1,4-dioxane (3 mL) was added and the reaction mixture was placed in a preheated oil bath at 80 °C and stirred for 5 h. Afterwards, the reaction mixture was cooled down, and filtered over a layer of Celite and the filter was rinsed with EtOAc (50 mL). The solvent was concentrated *in vacuo* to obtain the corresponding products **26a-e** as dark brown oils, NMR spectra of crude compounds **26a-e** show decent purity. Upon purification via column chromatography, the product is obtained as a yellow oil and the yield drops dramatically.

6-(Phenylethynyl)-1-propyl-5-(*p*-tolyl)-1,2,3,4-tetrahydropyridine (**26a**)

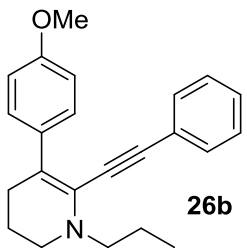


26a

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.19 (m, 5H), 7.09 (d, *J* = 7.9 Hz, 2H), 3.31 – 3.25 (m, 2H), 3.15 – 3.10 (m, 2H), 2.47 (t, *J* = 6.4 Hz, 2H), 2.32 (s, 3H), 1.97 – 1.88 (m, 2H), 1.67 – 1.54 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.9, 135.0, 131.0, 128.4, 128.2, 128.2, 127.7, 126.0, 123.7, 118.9, 92.0, 86.7, 54.8, 47.6, 28.6, 22.2, 21.4, 21.2, 11.6. **HRMS** (ESI) m/z calculated for $[C_{23}H_{25}N+H]^+$: 316.2060; found 316.2063. Light yellow oil, 220.3 mg (100%) 6-(phenylethynyl)-1-propyl-5-(*p*-tolyl)-1,2,3,4-tetrahydropyridine (**26a**) before and 95.3 mg (43%) after column chromatography. R_f = 0.59 (Heptanes/Acetone 9/1).

5-(*p*-Methoxyphenyl)-6-(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**26b**)

The general procedure was used with allylchloro[1,3-bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *p*-methoxyphenylboronic acid (106 mg, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).



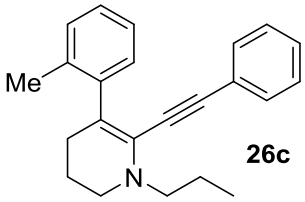
26b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.9 Hz, 2H, (C**H**)$_2$COCH$_3$), 7.23 (s, 5H, C≡C**Ar**), 6.84 (d, *J* = 8.8 Hz, 2H, (C**H**)$_2$(CH)$_2$COCH$_3$), 3.79 (s, 3H, OC**H**$_3$), 3.33 – 3.21 (m, 2H, NC**H**$_2$CH$_2$CH$_3$), 3.20 – 3.08 (m, 2H, NC**H**$_2$CH$_2$CH$_2$), 2.48 (t, *J* = 6.4 Hz, 2H, NCH$_2$CH$_2$C**H**$_2$), 2.01 – 1.85 (m, 2H, NCH$_2$C**H**$_2$CH$_2$), 1.68 – 1.56 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 0.95 (t, *J* = 7.4 Hz, 3H, NCH$_2$CH$_2$C**H**$_3$).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.5 (**C**OCH$_3$), 135.3 (NC=C**Ar**$_{ipso}$), 131.0 (C≡C**Ar**), 129.6 ((**C**H)$_2$COCH$_3$), 128.2 (C≡C**Ar**), 127.7 (C≡C**Ar**$_{para}$), 125.8 (N**C**=CAr), 123.6 (C≡C**Ar**$_{ipso}$), 118.9 (NC=**C**Ar), 112.9 ((**C**H)$_2$(CH)$_2$COCH$_3$), 91.8 (C≡**C**Ar), 86.7 (**C**≡CAr), 55.3 (O**C**H$_3$), 54.8 (N**C**H$_2$CH$_2$CH$_3$), 47.5 (N**C**H$_2$CH$_2$CH$_2$), 28.7 (NCH$_2$CH$_2$**C**H$_2$), 22.1 (NCH$_2$**C**H$_2$CH$_2$), 21.3 (NCH$_2$**C**H$_2$CH$_3$), 11.6 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{23}H_{25}NO+H]^+$: 332.2009; found 322.2001. Light yellow oil, 195 mg (84%) 5-(*p*-methoxyphenyl)-6-

(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**26b**) before and 117 mg (50%) after column chromatography. R_f = 0.41 (Heptanes/Acetone 9/1).

6-(Phenylethynyl)-1-propyl-5-(*o*-tolyl)-1,2,3,4-tetrahydropyridine (**26c**)

The general procedure was used with allylchloro[1,3-bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *o*-tolylboronic acid (0.095 g, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).

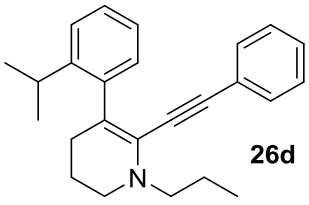


26c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 – 7.12 (m, 7H), 6.99 – 6.93 (m, 2H), 3.25 (q, *J* = 7.0 Hz, 2H), 3.19 – 3.10 (m, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 2.32 (s, 3H), 2.00 – 1.92 (m, 2H), 1.69 – 1.54 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 143.0, 136.9, 130.9, 130.1, 129.6, 128.0, 127.6, 127.0, 126.3, 125.3, 123.5, 120.5, 92.5, 85.7, 54.9, 47.4, 29.2, 22.2, 21.0, 19.6, 11.6. **HRMS** (ESI) m/z calculated for $[C_{23}H_{25}N+H]^+$: 316.2060; found 316.2079. Light yellow oil, 218 mg (99%) 6-(phenylethynyl)-1-propyl-5-(*o*-tolyl)-1,2,3,4-tetrahydropyridine (**26c**) before and 121 mg (55%) after column chromatography. R_f = 0.64 (Heptanes/Acetone 9/1).

5-(2-Isopropylphenyl)-6-(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**26d**)

The general procedure was used with allylchloro[1,3-bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), (2-isopropylphenyl)boronic acid (115 mg, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).

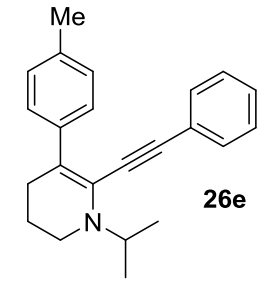


26d

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.21 (m, 2H), 7.17 – 7.07 (m, 5H), 6.94 – 6.88 (m, 2H), 3.27 – 3.21 (m, 2H), 3.16 (dd, *J* = 12.4, 6.5 Hz, 2H), 2.40 – 2.24 (m, 2H), 2.00 – 1.91 (m, 2H), 1.69 – 1.55 (m, 2H), 1.22 (d, *J* = 3.3 Hz, 3H), 1.20 (d, *J* = 3.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.8, 142.1, 130.9, 130.4, 128.0, 127.5, 127.1, 126.8, 125.3, 125.1, 123.6, 120.9, 93.3, 86.1, 55.0, 47.4, 30.4, 30.0, 24.7, 24.3, 22.2, 20.9, 11.6. **HRMS** (ESI) m/z calculated for $[C_{25}H_{29}N+H]^+$: 344.2373; found 344.2380. Light yellow oil, 240 mg (100%) 5-(2-isopropylphenyl)-6-(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**26d**) before and 50 mg (21%) after column chromatography. R_f = 0.68 (Heptanes/Acetone 9/1).

1-Isopropyl-6-(phenylethynyl)-5-(*p*-tolyl)-1,2,3,4-tetrahydropyridine (**26e**)

The general procedure was used with allylchloro[1,3-bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *p*-tolylboronic acid (0.095 g, 0.700 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-1-isopropyl-2-(phenylethynyl)piperidine (**23i**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).



26e

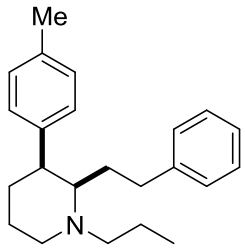
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 2H), 7.26 – 7.17 (m, 5H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.43 (septet, *J* = 6.7 Hz, 1H), 3.11 – 2.98 (m, 2H), 2.49 (t, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 1.96 – 1.85 (m, 2H), 1.17 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.2, 135.0, 131.0, 128.6, 128.3, 128.1, 127.7, 125.9, 123.7, 120.0, 92.3, 86.5, 49.9, 39.8, 29.0, 22.7, 21.1, 19.9. **HRMS** (ESI) m/z calculated for $[C_{23}H_{25}N+H]^+$: 316.2060; found 316.2073. Light yellow oil, 127 mg (57%) 1-isopropyl-6-(phenylethynyl)-5-(*p*-tolyl)-1,2,3,4-

tetrahydropyridine (**26e**) before column chromatography. R_f = 0.43 (Heptanes/Acetone 95/5).

Suzuki-Miyaura cross-coupling of **23** followed by *in situ* hydrogenation

In an oven dried 10 mL microwave vial were introduced inside the glove box allylchloro[1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *p*-tolylboronic aicd (0.095 g, 0.700 mmol) and sodium *tert*-butoxide (0.202 g, 2.100 mmol). Subsequently outside the glove box, 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol), dissolved in 1,4-dioxane (3 mL) was added and the reaction mixture was placed in a preheated oil bath at 80 °C and stirred for 5 h. Afterwards, the reaction mixture was cooled down, and filtered over a layer of Celite and the filter was rinsed with EtOAc (50 mL). The solvent was evaporated *in vacuo* and the product was redissolved in MeOH (4 mL), Pd/C (74.5 mg, 0.7 mmol) was added and the reaction mixture was stirred under H_2 atmosphere (balloon) for 24 h at room temperature. Afterwards, the reaction mixture was filtered over a layer of Celite and the filter was rinsed with EtOAc (50 mL). The solvent was evaporated *in vacuo* and the crude product was purified via column chromatography on an automated system using a Grace 12g Silica column and Heptanes/EtOAc.

2-Phenethyl-1-propyl-3-(*p*-tolyl)piperidine (**26a'**)

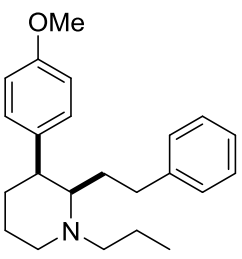


26a'

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 – 7.13 (m, 2H, C**H**$_{arom.}$), 7.13 – 7.05 (m, 5H, C**H**$_{arom.}$), 6.89 (d, *J* = 7.7 Hz, 2H, C**H**$_{arom.}$), 3.14 (dt, *J* = 12.2, 3.7 Hz, 1H, NCHC**H**), 2.89 (q, *J* = 4.8 Hz, 1H, NC**H**CH), 2.65 – 2.47 (m, 4H, NC**H**$_2$CH$_2$CH$_2$ and NC**H**$_2$CH$_2$CH$_3$), 2.32 (s, 3H, ArC**H**$_3$), 2.33 – 2.25 (m, 1H, NCHCH$_2$C**H**(H)Ar), 1.99 – 1.79 (m, 2H, NCHCH$_2$CH(**H**)Ar and NCH$_2$C**H**(H)CH$_2$), 1.79 – 1.62 (m, 3H, NCHCH(**H**)CH$_2$Ar and NCH$_2$CH(**H**)CH$_2$ and NCH$_2$CH$_2$C**H**(H)), 1.62 – 1.42 (m, 3H, NCH$_2$C**H**$_2$CH$_2$ and NCH$_2$CH$_2$CH(**H**)), 1.41 – 1.30 (m, 1H, NCHC**H**(H)CH$_2$Ar), 0.91 (t, *J* = 7.3 Hz, 3H, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.1 (**C**H$_{arom., ipso}$), 141.1 (**C**H$_{tol., ipso}$), 135.3 (**C**H$_{tol., para}$), 128.9 (**C**H$_{tol., meta}$), 128.4 (**C**H$_{arom., ortho}$), 128.1 (**C**H$_{arom., meta}$), 127.8 (**C**H$_{tol., ortho}$), 125.5 (**C**H$_{arom., para}$), 63.5 (N**C**HCHAr), 56.5 (N**C**H$_2$CH$_2$CH$_3$), 46.0 (N**C**H$_2$CH$_2$CH$_2$), 42.5 (NCH**C**HAr), 35.1 (NCHCH$_2$**C**H$_2$Ar), 25.4 (NCH**C**H$_2$CH$_2$Ar), 24.3 (NCH$_2$**C**H$_2$CH$_2$), 23.7 (NCH$_2$CH$_2$**C**H$_2$), 21.6 (NCH$_2$**C**H$_2$CH$_3$), 21.1 (Ar**C**H$_3$), 12.1 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{23}H_{31}N+H]^+$: 322.2529; found 322.2535. Light yellow oil, 114.8 mg (51%) of 2-phenethyl-1-propyl-3-(*p*-tolyl)piperidine (**26a'**) after column chromatography. R_f = 0.10 (Heptanes/EtOAc 1/1).

3-(4-Methoxyphenyl)-2-phenethyl-1-propylpiperidine (**26b'**)

The general procedure was used with allylchloro[1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *p*-methoxyhenylboronic acid (106 mg, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).



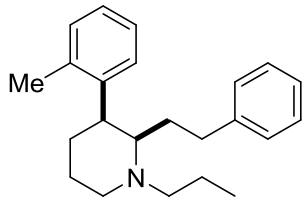
26b'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.15 (m, 4H), 7.15 – 7.09 (m, 1H), 6.92 – 6.84 (m, 4H), 3.80 (s, 3H), 3.60 – 3.47 (m, 1H), 3.20 (q, *J* = 4.4 Hz, 1H), 2.92 (d, *J* = 12.2 Hz, 1H), 2.74 – 2.51 (m, 3H), 2.20 – 1.97 (m, 2H), 1.97 – 1.78 (m, 3H), 1.78 – 1.65 (m, 3H), 1.63 – 1.53 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.4, 141.5, 133.8, 128.8, 128.4, 128.4, 128.3, 128.2, 126.0, 114.0, 63.2, 56.2, 55.3,

46.4, 41.6, 35.0, 24.9, 23.0, 22.9, 19.5, 11.7. **HRMS** (ESI) m/z calculated for $[C_{23}H_{31}NO+H]^+$: 338.2478; found 338.2488. Light yellow oil, 153.6 mg (65%) 3-(4-methoxyphenyl)-2-phenethyl-1-propylpiperidine (**26b'**) after column chromatography. R_f = 0.09 (Heptanes/EtOAc 2/1).

2-Phenethyl-1-propyl-3-(*o*-tolyl)piperidine (**26c'**)

The general procedure was used with allylchloro[1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), *o*-tolylboronic aicd (0.095 g, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).

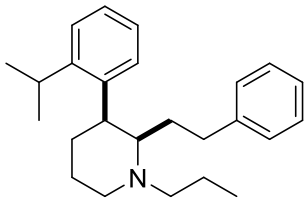


26c'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 – 7.06 (m, 7H), 6.86 (d, *J* = 7.0 Hz, 2H), 3.36 (dt, *J* = 12.4, 3.4 Hz, 1H), 2.93 (dd, *J* = 9.3, 4.8 Hz, 1H), 2.63 (dd, *J* = 8.7, 2.8 Hz, 2H), 2.59 – 2.51 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 3H), 2.28 – 2.17 (m, 1H), 2.01 (qd, *J* = 12.3, 3.8 Hz, 1H), 1.88 – 1.70 (m, 3H), 1.70 – 1.56 (m, 2H), 1.54 – 1.38 (m, 3H), 0.90 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 142.7, 141.7, 136.2, 130.4, 128.3, 128.1, 127.1, 126.0, 125.9, 125.5, 59.5, 56.3, 46.5, 39.7, 34.9, 25.3, 24.8, 24.0, 21.4, 19.1, 12.0. **HRMS** (ESI) m/z calculated for $[C_{23}H_{31}N+H]^+$: 322.2529; found 322.2535. Light yellow oil, 114.8 mg (51%) of 2-phenethyl-1-propyl-3-(*o*-tolyl)piperidine (**26c'**) after column chromatography. R_f = 0.10 (Heptanes/EtOAc 1/1).

3-(2-Isopropylphenyl)-2-phenethyl-1-propylpiperidine (**26d'**)

The general procedure was used with allylchloro[1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), (2-isopropylphenyl)boronic acid (115 mg, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).

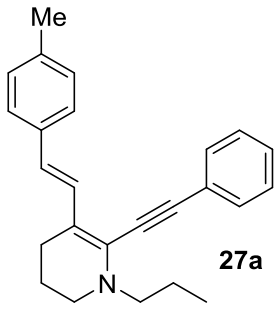


26d'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.12 (m, 7H), 6.89 – 6.82 (m, 2H), 3.46 (d, *J* = 12.3 Hz, 1H), 3.38 – 3.23 (m, 1H), 2.89 (q, *J* = 4.4 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.60 – 2.49 (m, 3H), 2.29 – 2.17 (m, 1H), 2.00 (qd, *J* = 12.4, 3.8 Hz, 1H), 1.85 – 1.59 (m, 5H), 1.56 – 1.39 (m, 3H), 1.24 (dd, *J* = 6.9, 5.1 Hz, 4H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.92 (q, *J* = 7.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.3, 142.9, 139.9, 128.4, 128.2, 126.9, 126.5, 125.7, 125.6, 125.6, 115.2, 61.3, 56.5, 46.6, 39.4, 35.6, 27.7, 25.5, 25.0, 24.9, 24.6, 24.0, 22.7, 21.4, 12.2. **HRMS** (ESI) m/z calculated for $[C_{25}H_{35}N+H]^+$: 350.2842; found 350.2861. Light yellow oil, 82.1 mg (34%) 3-(2-isopropylphenyl)-2-phenethyl-1-propylpiperidine (**26d'**) after column chromatography. R_f = 0.29 (Heptanes/EtOAc 2/1).

(*E*)-5-(4-Methylstyryl)-6-(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**27a**)

The general procedure was used with allylchloro[1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene]palladium(II) (10.0 mg, 0.018 mmol), 2-Cumylboronic acid (115 mg, 0.7 mmol), sodium *tert*-butoxide (0.202 g, 2.1 mmol), 3,3-dichloro-2-(phenylethynyl)-1-propylpiperidine (**23a**) (207 mg, 0.7 mmol) in 1,4-dioxane (3 mL).



27a

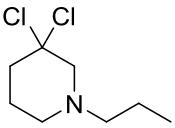
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, J = 15.9 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.38 – 7.28 (m, 5H), 7.07 (d, J = 8.0 Hz, 2H), 6.21 (d, J = 15.9 Hz, 1H), 3.41 – 3.29 (m, 2H), 3.23 – 3.09 (m, 2H), 2.40 (t, J = 6.5 Hz, 2H), 2.31 (s, 3H), 2.00 – 1.85 (m, 2H), 1.67 – 1.56 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 136.8, 135.1, 131.1, 129.5, 129.3, 129.3, 128.5, 128.4, 125.3, 123.3, 120.2, 115.3, 97.1, 84.1, 55.1, 47.6, 22.8, 21.7, 21.2, 11.5. **HRMS** (ESI) m/z calculated for $[C_{25}H_{28}N+H]^+$: 342.2216; found 342.2213. Bright yellow oil, 233 mg (97%) (*E*)-5-(4-methylstyryl)-6-(phenylethynyl)-1-propyl-1,2,3,4-tetrahydropyridine (**27a**) before and 69 mg (29%) after column chromatography. R_f = 0.60 (Heptanes/Acetone 9/1).

2.8.5 Cross-coupling reactions on non-alkynylated 3,3-dichloropiperidines

Synthesis of 3,3-dichloropiperidines **29** from α,α,δ-trichloroaldimines **21**

In a round bottom flask filled with 2,2,5-trichloro-*N*-propylpentan-1-imine (**21a**) (6.92 g, 30 mmol), MeOH (100 mL) was added, quickly followed by sodium cyanoborohydride (3.77 g, 60 mmol) and acetic acid (1,802 g, 30 mmol). The mixture was stirred at room temperature for 18 h. Afterwards the reaction mixture was poured in 0.5 N NaOH solution (100 mL) and the reaction mixture was extracted with DCM (2 x 100 mL). The organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to obtain 3,3-dichloro-1-propylpiperidine (**29a**) as a crude yellow oil (5.71 g, 97%).

3,3-Dichloro-1-propylpiperidine (**29a**)

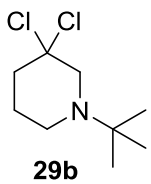


29a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.90 (s, 2H, NC**H**$_2$CCl_2), 2.45 (br s, 2H, NC**H**$_2$CH_2CH_2), 2.41 – 2.36 (m, 2H, NC**H**$_2$CH_2CH_3), 2.33 – 2.22 (m, 2H, NCH_2CH_2C**H**$_2$), 1.83 (dt, J = 11.4, 5.6 Hz, 2H, NCH_2C**H**$_2$CH_2), 1.59 – 1.45 (m, 2H, NCH_2C**H**$_2$CH_3), 0.91 (t, J = 7.4 Hz, 3H, NCH_2CH_2C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 87.5 (**C**Cl_2), 68.2 (NCH_2**C**Cl_2), 59.5 (N**C**H_2CH_2CH_3), 52.8 (NC**H**$_2$CH_2CH_2), 44.5 (NCH_2CH_2**C**H_2), 23.7 (NCH_2**C**H_2CH_2), 19.8 (NCH_2**C**H_2CH_3), 11.7 (NCH_2CH_2**C**H_3). **HRMS** (ESI) m/z calculated for $[C_8H_{14}NCl_2+H]^+$: 196.0654; found 196.0653. R_f = 0.49 (Heptane/EtOAc 9/1).

1-(*tert*-Butyl)-3,3-dichloropiperidine (**29b**)

In a round bottom flask filled with *N*-(tert-butyl)-2,2,5-trichloropentan-1-imine (**21b**) (1.223 g, 5 mmol), MeOH (10 mL) was added, quickly followed by sodium cyanoborohydride (628 mg, 10 mmol) and acetic acid (300 mg, 5 mmol). The mixture was stirred at room temperature for 9 days. Afterwards the reaction mixture was poured in 0.5 N NaOH solution (10 mL) and the reaction mixture was extracted with DCM (2 x 10 mL). The organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to obtain 1-(*tert*-butyl)-3,3-dichloropiperidine (**29b**) as a crude yellow oil (1.344 g, 98%).

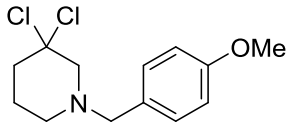


29b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.00 (s, 2H), 2.61 – 2.52 (m, 2H), 2.35 – 2.16 (m, 2H), 1.84 – 1.71 (m, 2H), 1.09 (d, J = 14.8 Hz, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 89.0, 62.8, 53.8, 45.3, 45.0, 26.4, 24.6. **HRMS** (ESI) m/z calculated for $[C_9H_{17}NCl_2+H]^+$: 210.0811; found 210.0807. R_f = 0.71 (Heptane/EtOAc 9/1).

3,3-Dichloro-1-(4-methoxybenzyl)piperidine (**29c**)

In a round bottom flask filled with 2,2,5-trichloro-*N*-(4-methoxybenzyl)pentan-1-imine (**21c**) (1.543 g, 5 mmol), MeOH (10 mL) was added, quickly followed by sodium cyanoborohydride (628 mg, 10 mmol) and acetic acid (300 mg, 5 mmol). The mixture was stirred at room temperature for 18 h. Afterwards the reaction mixture was poured in 0.5 N NaOH solution (10 mL) and the reaction mixture was extracted with DCM (2 x 10 mL). The organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to obtain 3,3-dichloro-1-(4-methoxybenzyl)piperidine (**29c**) as a crude yellow oil (1.344 g, 98%).



29c

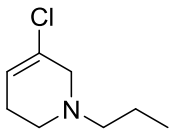
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.55 (s, 2H), 2.86 (s, 2H), 2.46 (s, 2H), 2.33 – 2.19 (m, 2H), 1.83 (dt, J = 11.1, 5.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.9, 129.9, 129.4, 113.7, 87.6, 67.8, 61.2, 55.2, 52.2, 44.5, 23.7. **HRMS** (ESI) m/z calculated for $[C_{13}H_{17}NOCl_2+H]^+$: 274.0760; found 274.0754. R_f = 0.50 (Heptane/EtOAc 9/1).

Stereoselective elimination of 3,3-dichloropiperidines **29**

In an oven dried 10 mL microwave vessel 3,3-dichloro-1-propylpiperidine (**29a**) (98 mg, 0.5 mmol) was dissolved in dry DMSO (1 mL) and the vessel was capped while an argon balloon was pierced through the septum. Then, lithium bis(trimethylsilyl)amide (167 mg, 1 mmol), dissolved in the DMSO, was added at 0 °C. The argon balloon was removed and the mixture was stirred for the indicated time at the indicated temperature. Afterwards, the reaction mixture was poured in 10 mL of 0.5 N NaOH and extracted with Et_2O (2 x 15 mL). The ethereal fractions were washed with brine (15 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*.

5-Chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**)

The general procedure was used with lithium bis(trimethylsilyl)amide (167 mg, 1 mmol), 3,3-dichloro-1-propylpiperidine (**29a**) (98 mg, 0.5 mmol) in DMSO (2 mL) at 100 °C for 2.5 h.

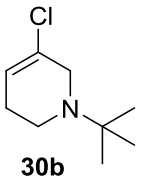


30a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.97 – 5.69 (m, 1H, **H**C=CCl), 3.09 (q, J = 2.0 Hz, 2H, NC**H**$_2$Cl$_2$), 2.55 (t, J = 5.7 Hz, 2H, NC**H**$_2$CH$_2$CH), 2.44 – 2.36 (m, 2H, NC**H**$_2$CH$_2$CH$_3$), 2.28 – 2.18 (m, 2H, NCH$_2$C**H**$_2$CH), 1.60 – 1.48 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 0.92 (t, J = 7.4 Hz, 3H, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 128.9 (HC=**C**Cl), 122.5 (H**C**=CCl), 59.5 (N**C**H$_2$CH$_2$CH$_3$), 57.6 (N**C**H$_2$CCl$_2$), 48.9 (N**C**H$_2$CH$_2$CH), 26.3 (NCH$_2$**C**H$_2$CH), 20.3 (NCH$_2$**C**H$_2$CH$_3$), 11.9 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_8H_{14}NCl+H]^+$: 160.0888; found 160.0893. Brown oil, 29.9 mg (37%) crude yield of 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) which was pure enough to use as such in the next step.

1-(*tert*-Butyl)-5-chloro-1,2,3,6-tetrahydropyridine (**30b**)

In a two-necked round bottom flask filled with 1-(*tert*-butyl)-3,3-dichloropiperidine (**29b**) (2.07 g, 9.87 mmol) in toluene (60 mL), potassium *tert*-amylate (3.74 g, 29.6 mmol) was added, and the reaction mixture was heated for 6 h at 100 °C. Afterwards the reaction mixture was poured in 0.5 N NaOH solution (60 mL) and the reaction mixture was extracted with DCM (2 x 60 mL). The reaction mixture was concentrated *in vacuo* and purified via column chromatography to yield 645 mg (38%) of 1-(*tert*-butyl)-5-chloro-1,2,3,6-tetrahydropyridine (**30b**) as a yellow oil.

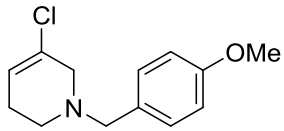


30b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.91 – 5.77 (m, 1H), 3.25 – 3.21 (m, 2H), 2.60 (t, J = 5.5 Hz, 2H), 2.23 – 2.16 (m, 2H), 1.11 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 130.0, 122.7, 54.0, 51.4, 42.2, 27.8, 25.8. **HRMS** (ESI) m/z calculated for $[C_9H_{16}NCl+H]^+$: 174.1044; found 174.1052. R_f = 0.32 (Heptane/EtOAc 9/1).

5-Chloro-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (**30c**)

In a two-necked round bottom flask filled with 3,3-dichloro-1-(4-methoxybenzyl)piperidine (**29c**) (2.74 g, 10 mmol) in toluene (60 mL), potassium *tert*-amylate (3.79 g, 30 mmol) was added, and the reaction mixture was heated for 2.5 h at 100 °C. Afterwards the reaction mixture was poured in 0.5 N NaOH solution (60 mL) and the reaction mixture was extracted with DCM (2 x 60 mL). The reaction mixture was concentrated *in vacuo* and purified via column chromatography to yield 1.59 g (67%) of 5-chloro-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (**30c**) as a yellow oil.



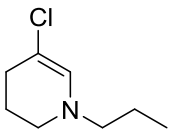
30c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.86 – 5.81 (m, 1H), 3.80 (s, 3H), 3.55 (s, 2H), 3.10 – 3.05 (m, 2H), 2.56 (t, J = 5.7 Hz, 2H), 2.24 – 2.17 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.9, 130.2, 129.8, 128.9, 122.5, 113.8, 61.1, 57.3, 55.3, 48.3, 26.3. **HRMS** (ESI) m/z calculated for $[C_{13}H_{16}NOCl+H]^+$: 238.0993; found 238.1008. R_f = 0.26 (Heptane/EtOAc 9/1).

5-Chloro-1-propyl-1,2,3,4-tetrahydropyridine (**31a**)

In an oven dried 10 mL microwave vessel 3,3-dichloro-1-propylpiperidine (**29a**) (98 mg, 0.5 mmol) was dissolved in dry toluene (1 mL) and the vessel was capped while an argon balloon was pierced through the septum. Then, lithium bis(trimethylsilyl)amide (167 mg, 1 mmol), dissolved in the indicated solvent, was added at 0 °C. The argon balloon was removed and the mixture was stirred for the indicated time at the indicated temperature. Afterwards, the reaction mixture was poured in 10 mL of 0.5 N NaOH and extracted with EtOAc (2 x 15 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. Under optimized reaction conditions, the spectra showed decent purity.

The general procedure was used with lithium bis(trimethylsilyl)amide (167 mg, 1 mmol), 3,3-dichloro-1-propylpiperidine (**29a**) (98 mg, 0.5 mmol) in toluene (2 mL) at 100 °C for 2.5 h.



31a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.07 (t, J = 1.4 Hz, 1H), 2.87 – 2.81 (m, 2H), 2.77 – 2.70 (m, 2H), 2.27 (t, J = 6.3 Hz, 2H), 1.95 – 1.87 (m, 2H), 1.54 – 1.42 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H). Brown oil, 33 mg (41%) crude yield of 5-chloro-1-propyl-1,2,3,4-tetrahydropyridine (**31a**), which cannot be purified by column chromatography.

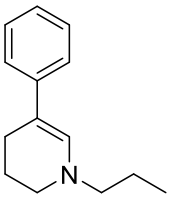
Suzuki-Miyaura cross-coupling on *N*-alkyl-5-chloro-1,2,3,6-tetrahydropyridines **30**

In an oven dried 10 mL microwave vessel were introduced $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^tBu (57.7 mg, 0.6 mmol) and phenylboronic acid (36.6 mg, 0.3 mmol). Then, under argon, a solution of 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol) in MeOH (2 mL) was added. The reaction mixture was then heated at 50 °C for 16 h. Afterwards, the reaction mixture was filtered over a layer of Celite and rinsed with EtOAc. Then, the product was concentrated *in vacuo* and purified via column

chromatography on an automated system using a Grace 12g Silica column and Heptanes/EtOAc.

5-Phenyl-1-propyl-1,2,3,6-tetrahydropyridine (**33a**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

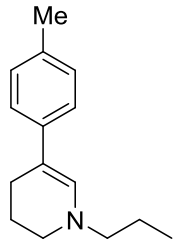


33a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 7.27 (m, 4H), 7.25 - 7.19 (m, 1H), 6.13 - 6.07 (m, 1H), 3.33 (dd, 2H, *J* = 4.5, 2.6 Hz), 2.60 (t, 2H, *J* = 5.8 Hz), 2.51 - 2.44 (m, 2H), 2.39 - 2.32 (m, 2H), 1.68 - 1.56 (m, 2H), 0.95 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.4, 135.5, 128.3, 126.9, 125.0, 122.6, 60.7, 54.9, 49.6, 26.5, 20.4, 12.0. **HRMS** (ESI) m/z calculated for $[C_{14}H_{19}N+H]^+$: 202.1590; found 202.1593. Yellow oil, 56.6 mg (94%) of 5-phenyl-1-propyl-1,2,3,6-tetrahydropyridine (**33a**) after column chromatography. R_f = 0.27 (Heptane/EtOAc 1/1).

5-(4-Methylphenyl)-1-propyl-1,2,3,6-tetrahydropyridine (**33b**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), *p*-tolylboronic acid (40.8 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

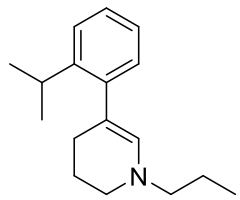


33b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, 2H, *J* = 8.0 Hz), 7.11(d, 2H, *J* = 8.0 Hz), 6.09 - 6.04 (m, 1H), 3.31 (dd, 2H, *J* = 4.5, 2.5 Hz), 2.60 (t, 2H, *J* = 5.8 Hz), 2.51 - 2.44 (m, 2H), 2.39 - 2.31 (m, 2H), 2.33 (s, 3H), 1.67 - 1.56 (m, 2H), 0.94 (t, 3H, *J* = 7.5 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 137.6, 136.6, 135.4, 129.0, 124.9, 121.8, 60.7, 54.9, 49.7, 26.5, 21.1, 20.4, 12.1. **HRMS** (ESI) m/z calculated for $[C_{15}H_{21}N+H]^+$: 216.1747; found 216.1750. Yellow oil, 53.0 mg (82%) of 5-(4-methylphenyl)-1-propyl-1,2,3,6-tetrahydropyridine (**33b**) after column chromatography. R_f = 0.14 (Heptane/EtOAc 1/1).

5-[2-(Propan-2-yl)phenyl]-1-propyl-1,2,3,6-tetrahydropyridine (**33c**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), (2-isopropylphenyl)boronic acid (49.2 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

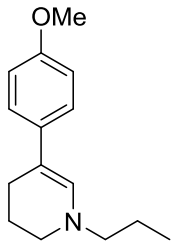


33c

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 - 7.20 (m, 2H, C**H**$_{arom.}$), 7.14 - 7.06 (m, 2H, C**H**$_{arom.}$), 5.61 - 5.56 (m, 1H, **H**C=CAr), 3.18 (septet, 1H, *J* = 6.9 Hz, C**H**$(CH_3)_2$), 3.06 (dd, 2H, *J* = 4.6, 2.5 Hz, NC**H**$_2$C$_{quat.}$), 2.64 (t, 2H, *J* = 5.8 Hz, NC**H**$_2$CH$_2$CH), 2.46 - 2.39 (m, 2H, NC**H**$_2$CH$_2$CH$_3$), 2.36 - 2.29 (m, 2H, NCH$_2$C**H**$_2$CH), 1.63 - 1.52 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 1.20 (d, 6H, *J* = 6.9 Hz, CH(C**H**$_3)_2$), 0.92 (t, 3H, *J* = 7.4 Hz, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 146.8 (**C** CH$(CH_3)_2$), 140.5 (**C**$_{quat.}$CCH$(CH_3)_2$), 137.3 (HC=**C**$_{quat.}$), 129.0 (**C**H$_{arom.}$), 127.4 (**C**H$_{arom.}$), 125.4 (**C**H$_{arom.}$), 125.3 (**C**H$_{arom.}$), 123.4 (H**C**=C$_{quat.}$), 60.7 (N**C**H$_2$CH$_2$CH$_3$), 57.7 (N**C**H$_2$C$_{quat.}$), 50.0 (N**C**H$_2$CH$_2$CH), 29.6 (N**C**H$(CH_3)_2$), 26.1 (NCH$_2$**C**H$_2$CH), 24.7 (NCH(**C**H$_3)_2$), 20.2 (NCH$_2$**C**H$_2$CH$_3$), 12.1 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{17}H_{25}N+H]^+$: 244.2060; found 244.2070. Yellow oil, 66.0 mg (90%) of 5-[2-(propan-2-yl)phenyl]-1-propyl-1,2,3,6-tetrahydropyridine (**33c**) after column chromatography. R_f = 0.29 (Heptane/EtOAc 1/1).

5-(4-Methoxyphenyl)-1-propyl-1,2,3,6-tetrahydropyridine (**33d**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), (4-methoxyphenyl)boronic acid (45.6 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

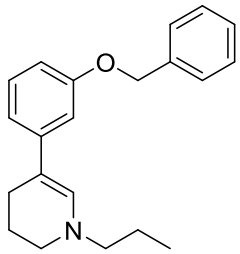


33d

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, 2H, *J* = 8.9Hz), 6.84 (d, 2H, *J* = 8.9 Hz), 6.03 - 5.98 (m, 1H), 3.79 (s, 3H), 3.30 (dd, 2H, *J* = 4.4, 2.5 Hz), 2.59 (t, 2H, *J* = 5.8 Hz), 2.50 - 2.44 (m, 2H), 2.38 - 2.31 (m, 2H), 1.67 - 1.56 (m, 2H), 0.94 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.7, 134.9, 133.1, 126.1, 121.0, 113.7, 60.7, 55.3, 55.0, 49.7, 26.5, 20.4, 12.1. **HRMS** (ESI) m/z calculated for $[C_{15}H_{21}NO+H]^+$: 232.1696; found 232.1702. Yellow oil, 39.6 mg (57%) 5-(4-methoxyphenyl)-1-propyl-1,2,3,6-tetrahydropyridine (**33d**) after column chromatography. R_f = 0.09 (Heptane/EtOAc 1/1).

5-[3-(Benzyloxy)phenyl]-1-propyl-1,2,3,6-tetrahydropyridine (**33e**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), (3-(benzyloxy)phenyl)boronic acid (68.4 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

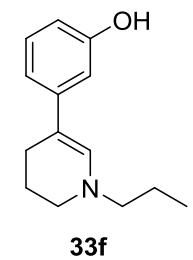


33e

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 - 7.40 (m, 2H), 7.40 - 7.34 (m, 2H), 7.34 - 7.28 (m, 1H), 7.25 - 7.18 (m, 1H), 6.99 - 6.93 (m, 2H), 6.88 - 6.81 (m, 1H), 6.14 - 6.06 (m, 1H), 3.30 (dd, 2H, *J* = 4.4, 2.5 Hz), 2.59 (t, 2H, *J* = 5.8 Hz), 2.50 - 2.43 (m, 2H), 2.39 - 2.31 (m, 2H), 1.67 - 1.55 (m, 2H), 0.94 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.9, 141.9, 137.1, 135.3, 129.2, 128.6, 127.9, 127.5, 122.9, 117.9, 113.1, 112.1, 77.4, 77.0, 76.7, 70.0, 60.6, 54.8, 49.6, 26.5, 20.3, 12.0. **HRMS** (ESI) m/z calculated for $[C_{21}H_{25}NO+H]^+$: 308.2009; found 308.2010. Light yellow oil, 65.6 mg (71%) 5-[3-(benzyloxy)phenyl]-1-propyl-1,2,3,6-tetrahydropyridine (**33e**) after column chromatography. R_f = 0.23 (Heptane/EtOAc 1/1).

3-(1-Propyl-1,2,5,6-tetrahydropyridin-3-yl)phenol (**33f**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), 3-Hydroxyphenylboronic acid (41.4 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

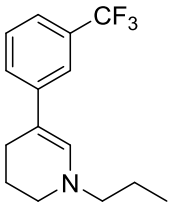


33f

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (br s, 1H), 7.13 (t, 1H, *J* = 7.7 Hz), 6.75 – 6.73 (m, 1H), 6.73 – 6.70 (m, 2H), 5.89 – 5.82 (m, 1H), 3.40 – 3.34 (m, 2H), 2.69 (t, 2H, *J* = 5.8 Hz), 2.57 - 2.48 (m, 2H), 2.38 - 2.29 (m, 2H), 1.73 - 1.61 (m, 2H), 0.94 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 157.2, 141.9, 135.4, 129.5, 123.1, 116.9, 115.5, 113.4, 60.8, 54.6, 49.9, 25.6, 19.4, 12.0. **HRMS** (ESI) m/z calculated for $[C_{14}H_{19}NO+H]^+$: 218.1539 found 218.1552. Light brown oil, 48.6 mg (75%) 3-(1-propyl-1,2,5,6-tetrahydropyridin-3-yl)phenol (**33f**) after column chromatography, yield corrected for traces of EtOAc left. R_f = 0.21 (Heptane/EtOAc 1/1).

1-Propyl-5-(3-(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridine (**33g**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), (3-(trifluoromethyl)phenyl)boronic acid (57.0 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

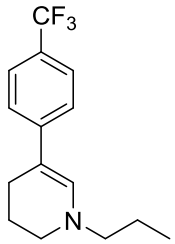


33g

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (br s, 1H, C**H**$_{arom.}$), 7.53 - 7.46 (m, 2H, C**H**$_{arom.}$), 7.44 - 7.38 (m, 2H, C**H**$_{arom.}$), 6.21 - 6.15 (m, 1H, **H**C=C$_{quat.}$), 3.34 (dd, 2H, *J* = 4.5, 2.6 Hz, NC**H**$_2$C$_{quat.}$), 2.63 (t, 2H, *J* = 5.8 Hz, NC**H**$_2$CH$_2$CH), 2.53 - 2.47 (m, 2H, NC**H**$_2$CH$_2$CH$_3$), 2.42 - 2.35 (m, 2H, NCH$_2$C**H**$_2$CH), 1.68 - 1.57 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 0.95 (t, 3H, *J* = 7.4 Hz, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 141.1 (HC=**C**$_{quat.}$), 134.5 (HC=C**C**$_{quat.}$), 130.7 (q, *J* = 32.0 Hz, **C**CF$_3$), 128.8 (HC=CC$_{quat.}$**C**HCH), 128.3 (q, *J* = 1.2 Hz, (HC=CC$_{quat.}$CH**C**H), 124.4 (H**C**=C), 124.3 (q, *J* = 272.3 Hz, **C**F$_3$), 123.6 (q, *J* = 3.9 Hz, CH**C**HCCF$_3$), 121.8 (q, *J* = 3.9 Hz, C$_{quat.}$**C**HCCF$_3$), 60.5 (N**C**H$_2$CH$_2$CH$_3$), 54.6 (N**C**H$_2$CH$_{quat.}$), 49.4 (N**C**H$_2$CH$_2$CH), 26.5 (NCH$_2$**C**H$_2$CH), 20.3 (NCH$_2$**C**H$_2$CH$_3$), 12.0 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{15}H_{18}F_3N+H]^+$: 270.1464; found 270.1460. Yellow oil, 40.4 mg (50%) 1-propyl-5-(3-(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridine (**33g**) after column chromatography. R_f = 0.23 (Heptane/EtOAc 1/1).

1-Propyl-5-(4-(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridine (**33h**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), (4-trifluoromethyl)phenylboronic acid (57.0 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

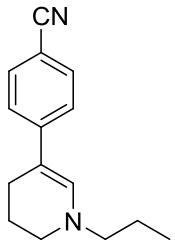


33h

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, 2H, *J* = 8.2 Hz), 7.43 (d, 2H, *J* = 8.2 Hz), 6.23 - 6.18 (m, 1H), 3.33 (dd, 2H, *J* = 4.5, 2.6 Hz), 2.62 (t, 2H, *J* = 5.8 Hz), 2.52 - 2.46 (m, 2H), 2.42 - 2.35 (m, 2H), 1.68 - 1.57 (m, 2H), 0.95 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 143.8 (q, *J* = 1.3 Hz), 134.6, 129.0 (q, *J* = 32.4 Hz), 125.3 (q, *J* = 3.8 Hz), 125.2, 124.9, 124.3 (q, *J* = 271.7 Hz), 60.6, 54.6, 49.4, 26.6, 20.3, 12.0. **HRMS** (ESI) m/z calculated for $[C_{15}H_{18}F_3N+H]^+$: 270.1464; found 270.1465. Yellow oil, 30.0 mg (37%) 1-propyl-5-(4-(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridine (**33h**) after column chromatography. R_f = 0.20 (Heptanes/EtOAc 1/1).

5-[4-(Cyano)phenyl]-1-propyl-1,2,3,6-tetrahydropyridine (**33i**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), (4-cyanophenyl)boronic acid (44.1 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

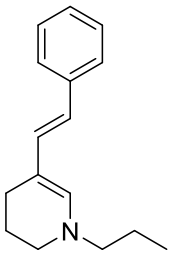


33i

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, 2H, *J* = 8.3 Hz), 7.42 (d, 2H, *J* = 8.3 Hz), 7.44 - 7.38 (m, 2H), 6.29 - 6.22 (m, 1H), 3.35 - 3.31 (m, 2H), 2.63 (t, 2H, *J* = 5.7 Hz), 2.53 - 2.47 (m, 2H), 2.44 - 2.37 (m, 2H), 1.68 - 1.55 (m, 2H), 0.95 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.6, 134.2, 132.2, 126.1, 125.5, 119.0, 110.4, 77.4, 77.0, 76.7, 60.4, 54.2, 49.2, 26.6, 20.2, 12.0. **HRMS** (ESI) m/z calculated for $[C_{15}H_{18}N_2+H]^+$: 227.1543; found 227.1545. Yellow oil, 21.2 mg (31%) 5-[4-(cyano)phenyl]-1-propyl-1,2,3,6-tetrahydropyridine (**33i**) after column chromatography. R_f = 0.08 (EtOAc).

(*E*)-1-Propyl-5-styryl-1,2,3,6-tetrahydropyridine (**33k**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), 2-Phenylvinylboronic acid (44.0 mg, 0.3 mmol) and 5-chloro-1-propyl-1,2,3,6-tetrahydropyridine (**30a**) (47.9 mg, 0.3 mmol).

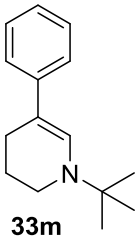


33k

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 – 7.36 (m, 2H), 7.33 – 7.26 (m, 2H), 7.22 – 7.16 (m, 1H), 6.73 (d, 1H, *J* = 16.4 Hz), 6.36 (d, 1H, *J* = 16.4 Hz), 5.95 – 5.87 (m, 1H), 3.26 – 3.21 (m, 2H), 2.58 (t, 2H, *J* = 5.8 Hz), 2.51 - 2.45 (m, 2H), 2.38 - 2.31 (m, 2H), 1.68 - 1.58 (m, 2H), 0.96 (t, 3H, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 137.7, 134.4, 129.9, 128.6, 128.0, 127.1, 126.2, 124.8, 60.6, 52.5, 49.9, 26.8, 20.3, 12.0. **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}N+H]^+$: 228.1747; found 228.1744. Yellow oil, 26.9 mg (25%) (*E*)-1-propyl-5-styryl-1,2,3,6-tetrahydropyridine (**33k**) after column chromatography, EtOAc remains visible in the spectrum, yield is corrected therefor. R_f = 0.21 (EtOAc).

1-(*tert*-Butyl)-5-phenyl-1,2,3,6-tetrahydropyridine (**33m**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and 1-(*tert*-butyl)-5-chloro-1,2,3,6-tetrahydropyridine (**30b**) (52.1 mg, 0.3 mmol).

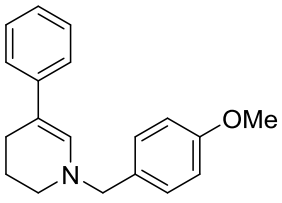


33m

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.26 (m, 4H), 7.26 – 7.19 (m, 1H), 6.12 - 6.07 (m, 1H), 3.49 (dd, 2H, *J* = 4.5, 2.4 Hz), 2.69 (t, 2H, *J* = 5.6 Hz), 2.38 - 2.30 (m, 2H), 1.18 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.9, 136.6, 128.3, 126.9, 125.3, 122.9, 54.0, 47.9, 42.7, 27.8, 25.9. **HRMS** (ESI) m/z calculated for $[C_{15}H_{21}N+H]^+$: 216.1747; found 216.1761. Light yellow oil, 63.5 mg (98%) 1-(*tert*-butyl)-5-phenyl-1,2,3,6-tetrahydropyridine (**33m**) after column chromatography. R_f = 0.12 (Heptanes/EtOAc 9/1).

1-(4-Methoxybenzyl)-5-phenyl-1,2,3,6-tetrahydropyridine (**33n**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and 5-chloro-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (**30c**) (71.3 mg, 0.3 mmol).

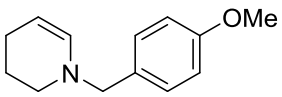


33n

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.24 (m, 6H), 7.23 – 7.18 (m, 1H), 6.87 (m, 2H), 6.15 - 6.05 (m, 1H), 3.80 (s, 3H), 3.63 (s, 2H), 3.34 (dd, 2H, *J* = 4.4, 2.4 Hz), 2.60 (t, 2H, *J* = 5.7 Hz), 2.37 - 2.29 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.8, 140.3, 135.5, 130.4, 130.3, 128.3, 127.0, 125.0, 122.6, 113.7, 62.2, 55.3, 54.6, 49.1, 26.4. **HRMS** (ESI) m/z calculated for $[C_{19}H_{21}NO+H]^+$: 280.1696 found 280.1704. White solid, melting point = 64°C, 71.1 mg (85%) 1-(*tert*-butyl)-5-phenyl-1,2,3,6-tetrahydropyridine (**33n**) after column chromatography. R_f = 0.56 (Heptanes/EtOAc 1/1).

1-(4-Methoxybenzyl)-1,2,3,6-tetrahydropyridine (**34**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), 2-pyridinylboronic acid (36.9 mg, 0.3 mmol), and 5-chloro-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (**30c**) (71.3 mg, 0.3 mmol).



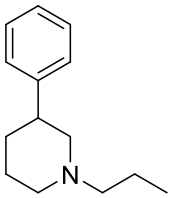
34

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.78 – 5.70 (m, 1H), 5.69 – 5.60 (m, 1H), 3.79 (s, 3H), 3.52 (s, 2H), 2.98 – 2.90 (m, 2H), 2.54 (t, 2H, J = 5.7 Hz), 2.19 - 2.11 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.7, 130.4, 130.4, 125.4, 125.3, 113.6, 62.3, 55.3, 52.7, 49.5, 26.2. **HRMS** (ESI) m/z calculated for $[C_{13}H_{17}NO]$+H: 204.1383 found 204.1383. Light yellow oil, 18.7 mg (31%) 1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine (**34**) after column chromatography. R_f = 0.13 (Heptanes/EtOAc 1/1).

Suzuki-Miyaura cross-coupling of **30** followed by *in situ* hydrogenation

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and 1-propyl-5-chloro-1,2,3,6-tetrahydropyridine (**30a**) (52.1 mg, 0.3 mmol). After 16 h at 50 °C, a balloon filled with H_2 was pierced through the septum and the reaction mixture was stirred for another 48 h at room temperature.

1-Propyl-3-phenylpiperidine (**35a**)

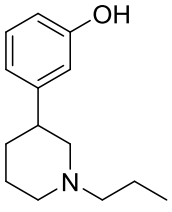


35a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.16 (m, 5H), 3.06 – 2.95 (m, 2H), 2.81 (tt, J = 11.7, 3.6 Hz, 1H), 2.35 – 2.29 (m, 2H), 1.95 – 1.88 (m, 1H), 1.79 – 1.71 (m, 2H), 1.57 – 1.51 (m, 2H), 1.48 – 1.39 (m, 1H), 1.30 – 1.23 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.9, 128.4, 127.2, 126.3, 61.4, 61.2, 54.0, 43.0, 31.7, 25.8, 20.1, 12.1. **HRMS** (ESI) m/z calculated for $[C_{14}H_{21}N+H]^+$: 204.1747; found 204.1748. Light yellow oil, 54.3 mg (89%) 1-propyl-3-phenylpiperidine (**35a**) after column chromatography. R_f = 0.07 (Heptanes/EtOAc 4/1).

(±)-Preclamol (**35f**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), 3-hydroxyphenylboronic acid (36.6 mg, 0.3 mmol), and 5-chloro-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine and (71.0 mg, 0.3 mmol). After 16 h at 50 °C, Pd/C (96 mg, 0.9 mmol) was added and the reaction mixture was heated at 50 °C under 50 psi of H_2.

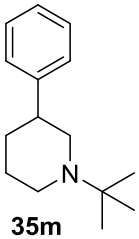


35f

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 – 7.29 (br s, 1H), 7.22 – 7.15 (m, 1H), 6.76 – 6.70 (m, 3H), 3.21 (d, J = 11.5 Hz, 1H), 3.10 (d, J = 11.2 Hz, 1H), 2.91 (tt, J = 11.9, 3.4 Hz, 1H), 2.42 (td, J = 10.7, 6.0 Hz, 1H), 2.32 (td, J = 10.8, 5.2 Hz, 1H), 2.11 – 1.87 (m, 3H), 1.86 – 1.71 (m, 2H), 1.66 – 1.43 (m, 3H), 0.85 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 157.3, 145.3, 130.0, 117.0, 115.1, 114.5, 61.2 (overlapping peak), 53.9, 42.8, 30.2, 25.2, 18.9, 12.0. **HRMS (ESI)** m/z calculated for $[C_{14}H_{21}NO+H]^+$: 220.1696; found 220.1697. Colorless oil,45.2 mg (69%) of (±)-Preclamol (**35f**) after column chromatography. R_f = 0.09 (EtOAc).

1-(*tert*-Butyl)-3-phenylpiperidine (**35m**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and 1-(*tert*-butyl)-5-chloro-1,2,3,6-tetrahydropyridine (**30c**) (52.1 mg, 0.3 mmol). After 16 h at 50 °C, a balloon filled with H_2 was pierced through the septum and the reaction mixture was stirred for another 48 h at room temperature.

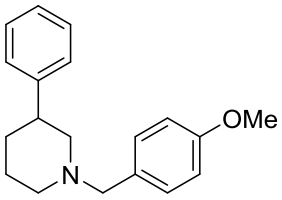


35m

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 – 7.27 (m, 2H), 7.26 – 7.197 (m, 3H), 3.19 - 3.09 (m, 2H), 2.81 (ddd, *J* = 12.2, 7.0, 3.4 Hz, 1H), 2.14 – 2.06 (m, 2H), 1.95 – 1.88 (m, 1H), 1.86 – 1.79 (m, 1H), 1.78 – 1.65 (m, 1H), 1.51 – 1.39 (m, 1H), 1.10 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.9, 128.4, 127.3, 126.5, 53.9, 46.3, 43.3, 31.5, 29.7, 26.0, 25.9. **HRMS** (ESI) m/z calculated for $[C_{15}H_{23}N+H]^+$: 218.1903; found 218.1900. Light yellow oil, 47.2 mg (72%) 1-(*tert*-butyl)-3-phenylpiperidine (**35m**) after column chromatography. R_f = 0.07 (Heptanes/EtOAc 1/1).

1-(4-Methoxybenzyl)-3-phenylpiperidine (**35n**)

The general procedure was used with $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (0.030 mg, 0.03 mmol), NaO^{t}Bu (57.7 mg, 0.6 mmol), phenylboronic acid (36.6 mg, 0.3 mmol), and 5-chloro-1-(4-methoxybenzyl)-1,2,3,6-tetrahydropyridine and (71.0 mg, 0.3 mmol). After 16 h at 50 °C, a balloon filled with H_2 was pierced through the septum and the reaction mixture was stirred for another 48 h at room temperature.

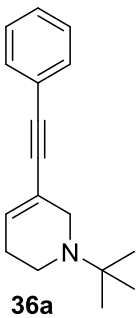


35n

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.14 (m, 6H), 6.86 – 6.80 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 3.47 (s, 2H), 3.01 – 2.94 (m, 1H), 2.94 – 2.87 (m, 1H), 2.82 (tt, 1H, *J* = 11.6, 3.6 Hz), 2.04 – 1.86 (m, 3H), 1.78 – 1.62 (m, 2H), 1.43 (ddd, 1H, *J* =24.5, 12.2, 5.0 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 158.7, 144.9, 130.3 (overlapping peak), 128.3, 127.3, 126.2, 113.6, 62.9, 60.9, 55.2, 53.6, 42.9, 31.7, 25.8. **HRMS (ESI)** m/z calculated for $[C_{19}H_{23}NO+H]^+$: 282.1852 found 282.1857. Yellow solid, melting point = 59°C, 77.2 mg (91%) 1-(4-methoxybenzyl)-3-phenylpiperidine (**35n**) after column chromatography. R_f = 0.41 (Heptanes/EtOAc 1/1).

1-(*tert*-Butyl)-5-(phenylethynyl)-1,2,3,6-tetrahydropyridine (**36a**)

In a 10 mL microwave vessel were introduced $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (14.30 mg, 0.030 mmol), CuI (2.86 mg, 0.015 mmol) and NaO^{t}Bu (57.7 mg, 0.600 mmol). The vessel was capped and then under argon, a solution of 1-(*tert*-butyl)-5-chloro-1,2,3,6-tetrahydropyridine (52.1 mg, 0.3 mmol) and phenylacetylene (30.6 mg, 0.300 mmol) in MeOH (2 mL) was added. The reaction mixture was then heated and stirred for overnight / 16 h at 70 °C. Afterwards, the reaction mixture was filtered over a layer of Celite and rinsed with EtOAc, the solvent was evaporated *in vacuo* and the crude reaction mixture was purified via column chromatography.



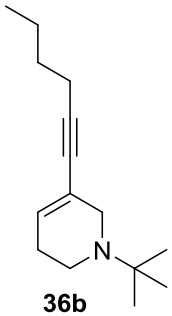
36a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 – 7.39 (m, 2H), 7.32 – 7.24 (m, 3H), 6.26 – 6.18 (m, 1H), 3.27 (dd, 2H, *J* = 4.8, 2.6 Hz), 2.63 (t, 2H, *J* = 5.6 Hz), 2.32 - 2.24 (m, 2H), 1.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 132.9, 131.5, 128.2, 127.9, 123.5, 120.7, 89.0, 87.8, 54.0, 49.0, 42.2, 27.9, 25.8. **HRMS** (ESI) m/z calculated for $[C_{17}H_{21}N+H]^+$: 240.1747; found 240.1762. Black oil, 36.4 mg (51%) 1-(*tert*-butyl)-5-(phenylethynyl)-1,2,3,6-tetrahydropyridine (**36a**) after column chromatography. R_f = 0.26 (Heptanes/EtOAc 1/1).

1-(*tert*-Butyl)-5-(hex-1-yn-1-yl)-1,2,3,6-tetrahydropyridine (**36b**)

In a 10 ml microwave vessel were introduced $Pd(OAc)_2$ (3.37 mg, 0.015 mmol), XPhos (14.30 mg, 0.030 mmol), CuI (2.86 mg, 0.015 mmol) and NaO^{t}Bu (57.7 mg, 0.600 mmol).

The vessel was capped and then under argon, a solution of 1-(*tert*-butyl)-5-chloro-1,2,3,6-tetrahydropyridine (52.1 mg, 0.3 mmol) and 1-hexyne (37.0 mg, 0.450 mmol) in MeOH (2 mL) was added. The reaction mixture was then heated and stirred for overnight / 16 h at 50 °C. Afterwards the reaction mixture was filtered over a layer of Celite and rinsed with EtOAc, the solvent was evaporated *in vacuo* and the crude reaction mixture was purified via column chromatography.

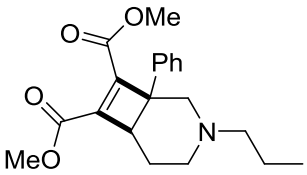


36b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.06 – 5.98 (m, 1H), 3.16 – 3.11 (m, 2H), 2.58 (t, 2H, J = 5.6 Hz), 2.28 (t, 2H, J = 7.0 Hz), 2.24 – 2.16 (m, 2H), 1.55 – 1.45 (m, 2H), 1.45 – 1.35 (m, 2H), 1.11 (s, 9H), 0.91 t, 3H, J = 7.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 130.8, 121.0, 88.5, 80.1, 54.0, 49.3, 42.3, 31.0, 27.6, 25.8, 22.0, 19.0, 13.6. **HRMS** (ESI) m/z calculated for $[C_{15}H_{25}N+H]^+$: 220.2060; found 220.2055. Black oil, 22.5 mg (34%) 1-(*tert*-butyl)-5-(hex-1-yn-1-yl)-1,2,3,6-tetrahydropyridine (**36b**) after column chromatography. R_f = 0.23 (Heptanes/EtOAc 1/1).

Dimethyl 1-phenyl-3-propyl-3-azabicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate (**37**)

In a 10 mL microwave vial were introduced 5-phenyl-1-propyl-1,2,3,6-tetrahydropyridine (50.3 mg, 0.25 mmol), dimethyl acetylenedicarboxylate (35.5 mg, 0.25 mmol), toluene (2 mL), and $BF_3.OEt_2$ (8.9 mg, 0.063 mmol). The vial was capped under air and the reaction was heated and stirred at 70 °C for 5 h. Afterwards the reaction mixture was poured into 0.5 N NaOH (10 mL) and extracted with EtOAc (2 x 10 mL). The organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo* and the crude product was purified via column chromatography.



37

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.40 (m, 2H, C**H**$_{arom.,ortho}$), 7.37 – 7.31 (m, 2H, C**H**$_{arom.,meta}$), 7.31 – 7.24 (m, 1H, C**H**$_{arom.,para}$), 5.35 (d, 1H, J = 0.8 Hz, NC**H**(H)C$_{quat.}$), 4.90 (br s, 1H, NCH(**H**)C$_{quat.}$), 3.96 (d, 1H, J = 4.5 Hz, NCH_2CH_2C**H**), 3.94 (s, 3H, CO_2C**H**$_3$), 3.65 (s, 3H, CO_2C**H**$_3$), 3.21 (td, 1H, J = 12.7, 3.6 Hz, NC**H**(H)CH(H)CH), 3.07 – 3.01 (m, 2H, NC**H**$_2CH_2CH_3$), 3.01 - 2.93 (m, 1H, NCH(**H**)CH(H)CH), 1.74 – 1.51 (m, 4H, NCH_2C**H**$_2CH$ and NCH_2C**H**$_2CH_3$), 0.87 (t, 3H, J = 7.4 Hz, NCH_2CH_2C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 167.7 (**C**O_2CH_3), 166.7 (**C**O_2CH_3), 152.2 (**C**H$_{arom.,\ quat.}$), 150.1 (**C**H$_{arom.,quat.}$), 141.5 (**C**H$_{arom.,quat.}$), 128.3 (**C**H$_{arom.,\ meta}$), 127.4 (**C**H$_{arom.,\ para}$), 126.9 (**C**H$_{arom.,ortho}$), 115.3 (N**C**$H_2C_{quat.}$), 94.1 (NCH_2**C**$_{quat.}$), 54.6 (N**C**$H_2CH_2CH_3$), 52.7 (O**C**H_3), 51.1 (O**C**H_3), 42.4 (N**C**H_2CH_2CH), 35.5 (NCH_2CH_2**C**H), 23.4 (NCH_2**C**H_2CH), 21.6 (NCH_2**C**H_2CH_3), 11.0 (NCH_2CH_2**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{20}H_{25}NO_4+H]^+$: 344.1856; found 344.1852. Light yellow oil, 54.3 mg (63%) dimethyl 1-phenyl-3-propyl-3-azabicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate (**37**) after column chromatography. R_f = 0.76 (Heptanes/EtOAc 1/1).

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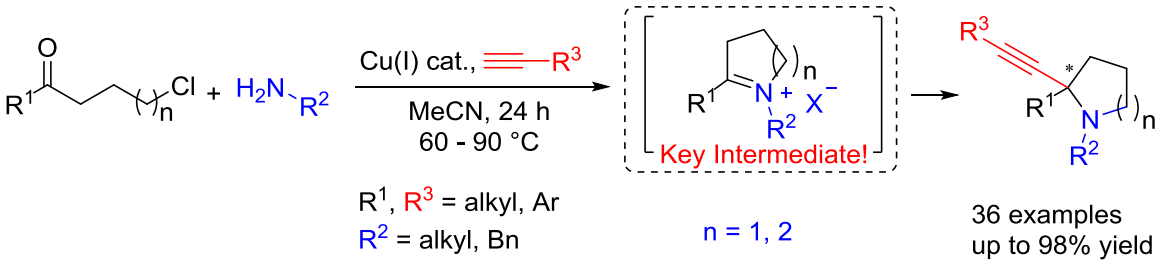
3 Coupling of ω-halogenated ketones, amines and alkynes in a KA² coupling

In this chapter the addition of alkynes to more challenging ketimines instead of aldimines, was investigated. Our efforts focused on the one-pot coupling of ketones, amines and alkynes in what is formally known as a KA² coupling. A new coupling approach was derived by using ω-chloroketones, primary amines and alkynes in a Cu(I)-catalyzed one-pot procedure resulting in the formation of α-quaternary carbons in 2-alkynyl-substituted *N*-heterocycles. The key step in this reaction is the *in situ* generation of a cyclic ketiminium species, which has enhanced reactivity for alkynylation compared to acyclic ketiminium species.



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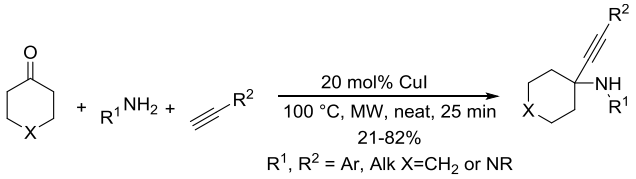
3.1 Introduction

As discussed in §1.3.7.2 ketimines are more challenging substrates for alkynylation than aldimines. Although the first report on A³ coupling dates from 1998,[1] it took until 2010 before the first report on the replacement of the aldehyde component by a ketone component was published. Challenges in A³ couplings are scarce, but the replacement of an aldehyde by a ketone, is still considered difficult. To better understand where the difficulties lie, an overview of KA² coupling methods until present will be given.

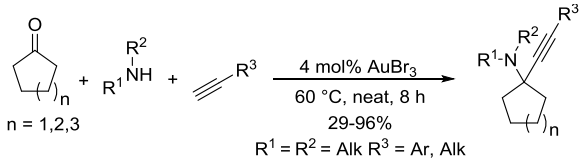
3.2 KA² coupling: literature

The one-pot A³ coupling where aldehydes are replaced by ketones was named the KA² coupling, and was firstly described by Van der Eycken *et al.* in 2010.[2] With CuI as a catalyst and under microwave irradiation, aryl/alkyl alkynes, primary benzylic amines and cyclohexanone derivatives were coupled efficiently (Scheme 3-1). With the exception of acetone, no acyclic ketones could be used due to their lower reactivity compared to cyclohexanone. The difference in reactivity can be explained by the release in ring strain that an exocyclic imine bond possesses upon alkynylation in imines derived from cyclic ketones.



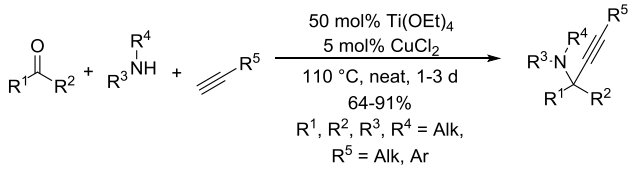
Scheme 3-1 First KA² coupling on cyclic ketones with primary amines.

In 2011, Chan *et al.* proved that secondary amines can also be coupled using a $AuBr_3$ catalyst (Scheme 3-2).[3] Next to cyclic ketones, a few acyclic aliphatic ketones could also be coupled, but aromatic ketones gave no KA² reaction product.



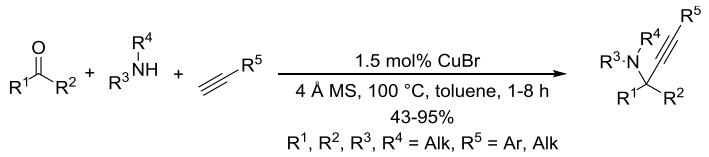
Scheme 3-2 Au(III)-catalyzed KA² coupling on cyclic ketones.

Later, in 2012, Larsen *et al.* established a dual catalytic system using 50 mol% of $Ti(OEt)_4$ and 5 mol% of $CuCl_2$ (Scheme 3-3).[4] Ti(IV)-based additives are often used for the synthesis of ketimines, as these are often difficult to synthesize, generating TiO_2 as side product.[5] Via this system, acyclic aliphatic ketones could be coupled with primary/secondary amines and alkynes. Aromatic ketones, however, remained unreactive. Longer reaction times (1-3 days) are a drawback for this reaction.



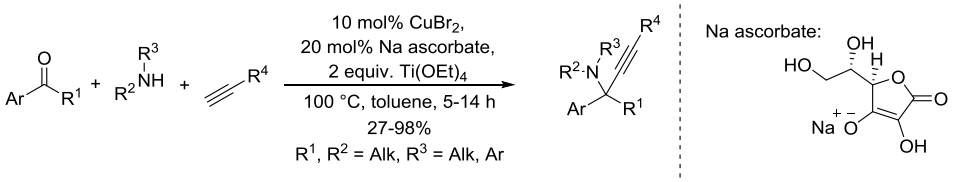
Scheme 3-3 Ti(IV)- and Cu(II)-catalyzed KA² coupling of acyclic aliphatic ketones.

In an attempt to expand the scope of the KA² coupling, Ma *et al.* found a new system consisting of CuBr and 4 Å molecular sieves for the synthesis of propargyl amines from acyclic and aromatic ketones (Scheme 3-4).[6] However, the scope is limited to the use of secondary amines. Molecular sieves are added in this case to promote the formation of ketimines. Interestingly, a low catalyst loading of 1.5 mol% could be used, together with shorter reaction times than compared to the reaction conditions reported by Larsen *et al.*



Scheme 3-4 KA² coupling of secondary amines, acyclic aliphatic ketones and alkynes.

In 2016, Ma *et al.* published new reaction conditions consisting of a $CuBr_2$/sodium ascorbate and $Ti(OEt)_4$ catalytic system and used this combination for the coupling of a broad scope of aromatic ketones (Scheme 3-5).[7] Again, primary amines cannot be used in this coupling. The role of sodium ascorbate in this reaction was not identified, and without the addition of sodium ascorbate the reaction is still possible, but the yield is lower. The actual oxidation state of the catalyst was found to be Cu(I), with sodium ascorbate acting as the reducing agent. The exact reaction mechanism remains unidentified. Although sodium L-ascorbate is a chiral molecule, the authors did not mention the possibility for enantioselective KA² coupling or investigated the enantiomeric excess after reaction.



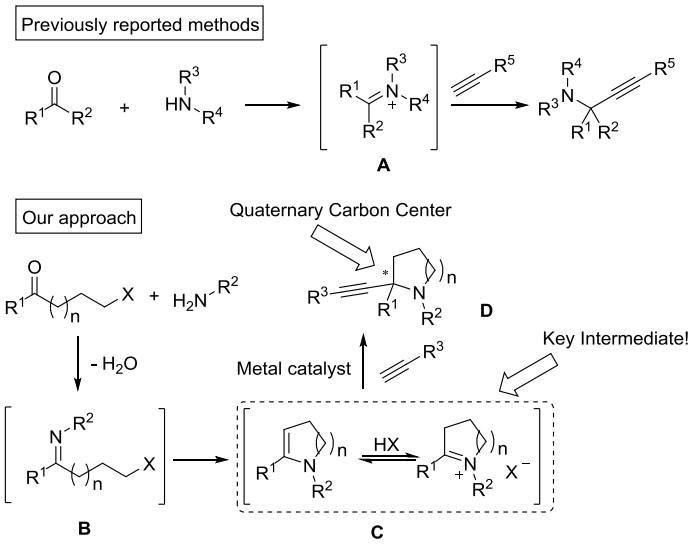
Scheme 3-5 KA² coupling of aromatic ketones.

From these reported methods, it can be concluded that Cu(I) and Cu(II) salts are the preferred catalysts for the KA² coupling. Not surprisingly, efforts were made to synthesize Cu-based heterogeneous catalysts, as these catalysts are easy to recover and can be used multiple times. Some examples of such catalysts, used for simple KA² couplings of cyclic ketones and secondary amines are, for example, Cu_2O on TiO_2 nanoparticles,[8] Cu_2O on nano-ZnO particles,[9] a Cu_2O on nano-$CuFe_2O_4$ system which is magnetically recoverable,[10] a Cu(II) hydromagnesite nanomaterial,[11] which was also used in the first decarboxylative KA² coupling, a polystyrene-supported *N*-phenylpiperazine Cu(II) complex,[12] and CuI supported on Amberlyst A-21.[13]

3.3 New approach towards 2-alkynyl *N*-heterocycles

Clearly, primary amines in combination with acyclic (aromatic) ketones remain a challenging combination for alkynylation as KA² couplings generally work better with secondary amines, generating *in situ* ketiminium species **A**. Since we would like to expand the scope by using primary amines and to make an entry towards possibly biologically interesting alkynyl-substituted *N*-heterocycles **D**, it was reasoned that adding a ω-halo atom to the ketone might result in a cyclic ketiminium species **C** by substitution of the ω-halo atom by the *in situ*

generated imine **B** (Scheme 3-6). This is supported by previous work[14] from our group that shows that ω-chlorinated aldimines upon standing become solid due to the formation of similar iminium chlorides.



Scheme 3-6 New approach for alkynylation on ketiminium substrates.

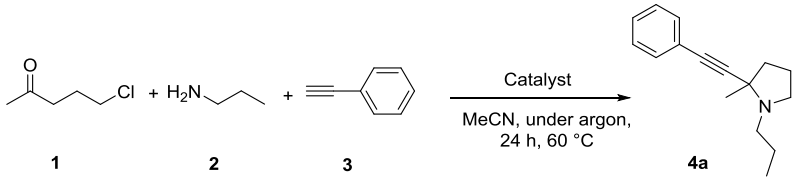
The 2-alkynyl *N*-heterocycles **D** have been synthesized previously via an intramolecular hydroamination of aminoalkyl acetylenes followed by alkynylation.[15] However, these approaches require the prior synthesis of the aminoalkynes, involving a two-step synthesis from either alkynyl alcohols or from alkynoic acids. In this chapter, we describe a straightforward entry to 2-alkynyl-substituted *N*-heterocycles, starting from commercially available starting materials via a one-pot, three-component synthesis.

3.4 Optimization of the reaction conditions for KA² coupling

As a starting point for the optimization of the reaction under investigation commercially available 5-chloropentan-2-one (**1**), *n*-propylamine (**2**) and phenylacetylene (**3**) were reacted in the presence of various metal catalysts in acetonitrile to give 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**) (Table 3-1). An excess of 3.5 equivalents of *n*-propylamine was used, as *n*-propylamine also acts as a base to trap the equivalent of HCl that is formed and because of its volatility. A small excess of 1.2 equivalents of phenylacetylene was used because in all cases traces of the Glaser homocoupling product were observed. Classical A³ catalysts such as Zn, Fe, Al, Ni and Sc salts were not able to catalyze this transformation (Entries 1-7). Remarkably, even $In(OTf)_3$, which worked well for chlorinated imines, was not able to catalyze this reaction.[14, 16] $AuPPh_3Cl$ (Entry 8) and AgOTf (Entry 9) gave low yields of **4a** and 46% of 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine. CuCl (77%, Entry 11) gave a lower yield than $CuCl_2$ (87%, Entry 12), while when the counter anion was changed to triflate (83%, Entries 18 and 19) no improvement of the yield was observed. Changing to Cu_2O (87%, Entry 13) was equally good, while CuO showed less catalytic activity (50%, Entry 16). When the catalyst loading was lowered to 5 mol%, only 65% yield of 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**) was obtained (Entry 14), while by increasing the catalyst loading to 20 mol% the yield became nearly quantitative (Entry 15). The coupling reaction proved also feasible with magnetically recoverable $CuFe_2O_4$, albeit in lower yield (42%, Entry 23), and is comparable to CuO (50%, Entry 16). This yield could probably be improved if Cu_2O is impregnated on the $CuFe_2O_4$ nanoparticles as reported previously.[10] When copper

phenylacetylide was added in 20 mol% instead of a copper catalyst, the isolated yield of **4a** was slightly lower (80%, Entry 24). Copper phenylacetylide is the reacting species in this reaction, and addition to the *in situ* formed iminium ion generates Cu^+ which could start a new catalytic circle thereby avoiding waste generated from the catalyst anion. The slightly lower yield can be explained by the polymeric structure of copper phenyl acetylide that is hard to break up.[17] An advantage of using copper phenylacetylide or any copper arylacetylide is that it can be recovered easily after basic workup of the reaction, since it is only slightly soluble in the extraction solvent or the basic aqueous phase. This could be very important for large scale applications, where recovery of catalyst is a strong advantage. For the evaluation of different alkynes as coupling partners, copper phenyl acetylide cannot be used since different alkynes will then be built into the molecule.

Table 3-1 Screening of catalysts for the KA² coupling of 5-chloropentan-2-one, phenylacetylene and *n*-propylamine.

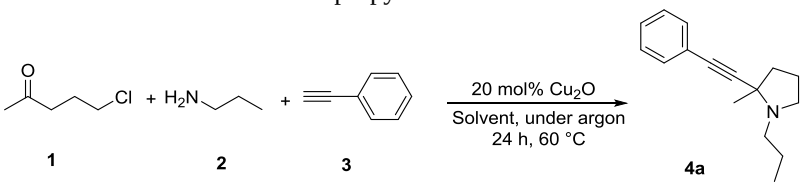


Entry	Catalyst (mol%)	Yield of **4a** (%)	Entry	Catalyst (mol%)	Yield of **4a**
1	$Sc(OTf)_3$ (20)	0	13	Cu_2O (10)	87
2	$Zn(OTf)_2$ (20)	0	14	Cu_2O (5)	65
3	$In(OTf)_3$ (20)	0	**15**	**Cu_2O (20)**	**99**
4	$FeBr_3$ (20)	0	16	CuO (20)	50
5	$FeCl_2$ (20)	0	17	$Cu(OH)_2$ (20)	87
6	$Al(OTf)_3$ (20)	0	18	CuOTf (20)	83
7	$Ni(OTf)_2$ (20)	0	19	$Cu(OTf)_2$ (20)	83
8	$AuPPh_3Cl$ (20)	18	20	Cu^0 (20)	15
9	AgOTf (20)	46	21	$Cu(OAc)_2$ (20)	85
10	CuI (20)	82	22	$CuSO_4$ (20)	84
11	CuCl (20)	77	23	$CuFe_2O_4$ (20)	42
12	$CuCl_2$ (20)	87	24	Copper phenylacetylide (20)	80

All reactions were carried out with 1 mmol 5-chloropentan-2-one (**1**), 1.2 mmol phenylacetylene (**3**), 3.5 mmol *n*-propylamine (**2**) and 2 mL acetonitrile for 24 h at 60 °C. Yields were calculated from the ^{1}H NMR spectrum with 1,3,5-trimethoxybenzene as internal standard.

The reaction was then further optimized with regard to the solvent. Solvents such as EtOAc, THF, 2-MeTHF, TBME, DMSO, DMF, DCM, EtOH, toluene, and dioxane were also well tolerated, giving yields ranging from 56 to 99% (Table 3-2). Water as a solvent still gave a yield of 12% (Entry 11), most likely because of a disfavored ketone-iminium equilibrium, as water is a byproduct of the reaction. This observation allows the use of non-dried solvents. Interestingly, the reaction can also be conducted neat (Entry 14), although a small decrease in yield is observed in this case. The use of a basic 'solvent' such as triethylamine, leads also to complete conversion of the reagents (Entry 15). Due to the classification of triethylamine as 'hazardous' in the CHEM21 solvent selection guide, this solvent was not considered for the scope investigation.[18] As a result, different solvents can be used, and acetonitrile as the best solvent, will be used for the investigation of the scope.

Table 3-2 Screening of solvents for the KA² coupling of 5-chloropentan-2-one, phenylacetylene and *n*-propylamine



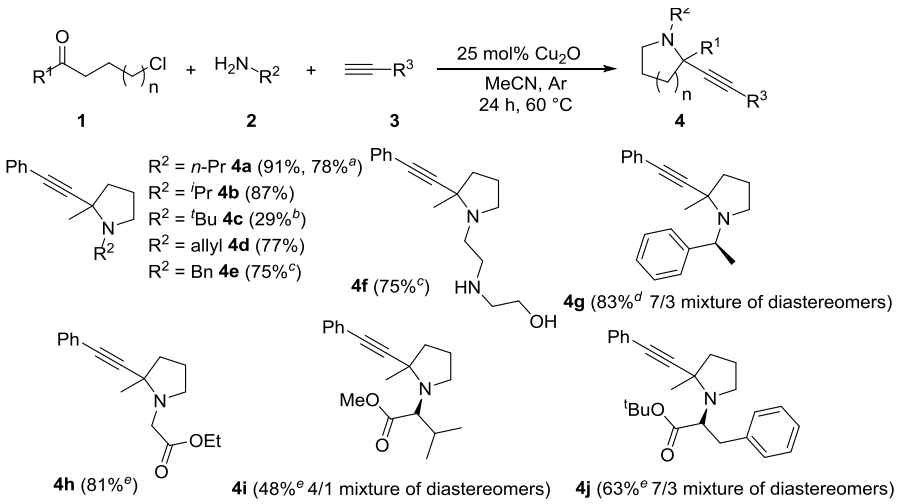
Entry	Solvent	Yield **4a** (%)	Entry	Solvent	Yield **4a** (%)
1	MeCN	99	9	Dioxane	83
2	EtOAc	64	10	EtOH	74
3	THF	99	11	H_2O	12
4	MTBE	96	12	MeTHF	62
5	DMSO	56	13	MeOH	57
6	DMF	63	14	Neat	93
7	DCM	78	15	NEt_3	99
8	Toluene	81			

All reactions were carried out with 0.20 mmol Cu_2O, 1 mmol 5-chloropentan-2-one, 1.2 mmol phenylacetylene, 3.5 mmol *n*-propylamine and 2 mL solvent for 24 hours at 60 °C. Yields were calculated from the ^{1}H NMR spectrum with 1,3,5-trimethoxybenzene as internal standard.

Finally, the optimized reaction conditions for the formation of 2-methyl-2-(phenylethynyl)pyrrolidine (**4**) were established as follows: 1 equivalent of 5-chloropentan-2-one, 3.5 equivalents of *n*-propylamine, 1.2 equivalents of phenylacetylene, and 20 mol% of Cu_2O in acetonitrile for 24 h at 60 °C.

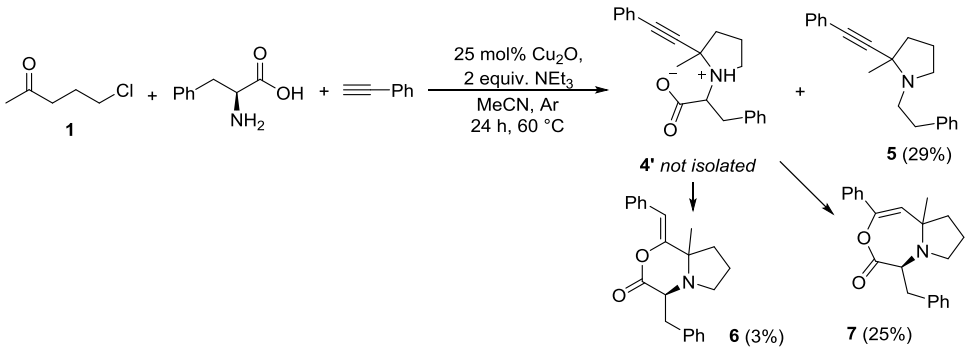
3.5 Scope investigation for the newly developed KA² coupling

To investigate the scope of the reaction, first the primary amine component was varied (Scheme 3-7). With *n*-propylamine (**2**), an isolated yield of 91% was obtained for the product **4a**, while the more sterically hindered isopropylamine was also tolerated and gave a yield of 87%. The reaction of 5-chloropentan-2-one with *tert*-butylamine did not yield any reaction product **4c** at 60 °C. By raising the temperature to 90 °C, product **4c** was isolated in 29% yield. This lower yield can be explained by the difficult formation of the ketimine and subsequent difficult ring-closing reaction[14] as a result of sterical hindrance and by the low boiling point of ^{t}BuNH$_2$ (46 °C). Amines, with readily removable protecting groups such as allylamine or benzylamine, furnished yields of 77% and 75%, respectively. Molecule **4f** shows that the primary amine reacts exclusively, even in the presence of a secondary amine and hydroxy function in a reasonable 75% yield. Although secondary amines are more nucleophilic and hence react faster with the ketone, no alkynylation of this ketimine occurs. Under the given reaction conditions this ketimine can thus undergo hydrolysis, leading back to starting material. (*S*)-Methylbenzylamine afforded a 7/3 mixture of diastereomers in 83% yield. It is known that α-amino esters are also good coupling partners in KA² couplings.[19] Therefore, glycine ethyl ester was used as amine component, and the product **4h** was obtained in 42% yield. By using the more stable glycine ethyl ester hydrochloride in the presence of 2 equivalents of triethylamine, the yield increased to 81%. Other α-aminoesters, derived from natural α-amino acids such as L-valine methyl ester hydrochloride and L-phenylalanine ^{t}Bu ester hydrochloride, gave under the same reaction conditions (2 equivalents of NEt_3) 48% of a 4/1 diastereomeric mixture and a 63% yield of a 7/3 diastereomeric mixture, respectively.



Scheme 3-7 Evaluation of different amine substituents for the KA² coupling. Unless otherwise stated, 3.5 equivalents of amine were used. [a]10 mmol scale. [b] 90 °C. [c] 2 equivalents of amine were used. [d] 1 equivalent of amine was used; 1 equivalent of NEt_3 was added. [e] 1 equivalent of aminoester.HCl was used, and 2 equivalents of NEt_3 were added.

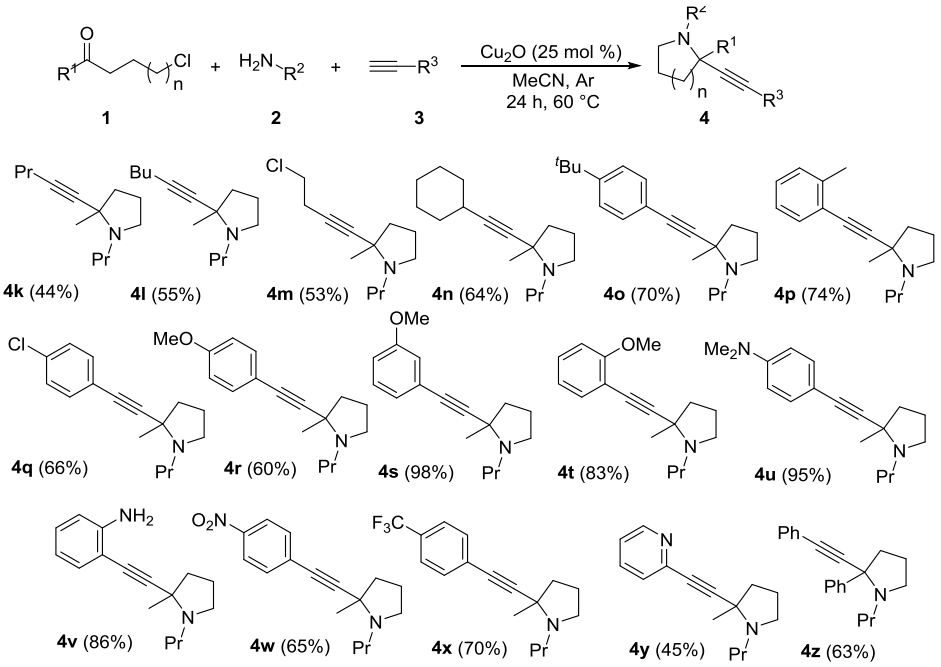
After amino esters were tested, we also investigated the use of amino acids (Scheme 3-8). We reasoned that the presence of an acid would not be problematic for the reaction, as long as the acid is neutralized with a base (as is the case for the formation of hydrochloric acid from ring closure – therefore 2 equivalents of triethylamine were added and a similar outcome was obtained when 3 equivalents of triethylamine were used). Indeed, reaction occurred when L-phenylalanine is used. Unfortunately, a mixture of different compounds was obtained after reaction. Component **5** originates from decarboxylation of the intended product or any of the intermediates. Components **6** and **7** are formed from the intended product **4'** via intramolecular attack of the carbonyl moiety on the alkyne moiety in a 6-*exo*-*dig* or a 7-*endo*-*dig* cyclization.



Scheme 3-8 KA² coupling with amino acids results in the formation of a variety of reaction products.

Next, different alkynes were evaluated (Scheme 3-9). In general, alkyl-substituted alkynes reacted well in this conversion, resulting in yields of 40-64%. 1-Pentyne as a coupling partner resulted in a low yield of 44%, probably due to its low boiling point (40 °C). When 1-hexyne with a boiling point of 71-72 °C was used, the yield increased to 55%. When 4-chlorobut-1-yne was used, product **4m** was isolated in 53% yield. Trace amounts of 2-(but-3-en-1-yn-1-yl)-2-methyl-1-propylpyrrolidine and 4-(2-methyl-1-propylpyrrolidin-2-yl)-*N*-propylbut-3-yn-1-amine were observed, resulting from the conjugated elimination of HCl and the substitution

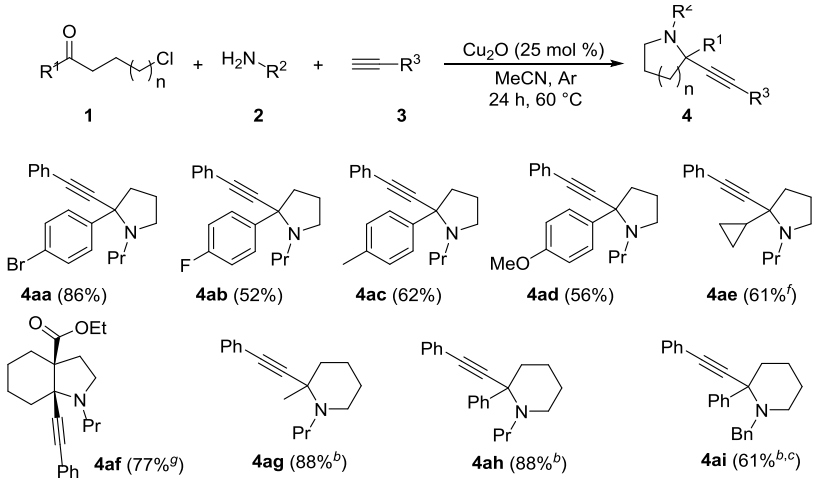
of chlorine by *n*-propylamine in 2-(4-chlorobut-1-yn-1-yl)-2-methyl-1-propylpyrrolidine (**4m**). The use of cyclohexylacetylene results in the formation of product **4n** in 64%. Next, a range of aromatic alkynes were evaluated. Electron-donating substituents (4-*t*-Bu, 2-Me, 2-MeO, 4-MeO) were tolerated well, resulting in yields of 60-98%. 4-Ethynyl-*N*,*N*-dimethylaniline leads to a very high yield of 95%. The reaction of **1** with 2-ethynylaniline also led to the expected alkynylpyrrolidine **4v** in 86% yield. Under these reaction conditions, no additional intramolecular hydroamination, leading to a 2-indolopyrrolidine as previously reported under comparable conditions, was observed.[20] Next to electron-donating groups, electron-withdrawing groups, according to Hammett constants,[21] like 3-MeO, 4-chloro, 4-trifluoromethyl and 4-nitro gave reasonable yields of 98, 66, 70 and 65% respectively. In a special case, the heteroarylalkyne 2-ethynylpyridine could also be coupled, albeit resulting in a moderate yield of 45%.



Scheme 3-9 Evaluation of different aliphatic and aromatic alkynes in the KA² coupling. Unless otherwise stated, 3.5 equivalents of amine were used.

Next, different ketones were screened (Scheme 3-10). As stated above, aromatic ketones are difficult coupling partners in KA² reactions. Under our conditions, the commercially available 4-chlorobutyrophenone could be easily coupled with *n*-propylamine and phenylacetylene leading to 2-phenyl-2-(phenylethynyl)-1-propylpyrrolidine (**4z**) in 63% yield. In addition, substituted 4-chlorobutyrophenones could be coupled, and the corresponding pyrrolidines were isolated in 52-86% yield. In general, the yields are lower than for the aliphatic ketones, probably because of increased steric hindrance in aromatic ketiminium intermediates. When 1,7-dichloroheptan-4-one was used, solely pyrrolidine **4ae**, which contains a cyclopropyl ring, was obtained in toluene. Besides the commercially available ketones tested above, a wide variety of chloroketones can be accessed by a plethora of literature methods.[22] For example, bicyclic product **4af**, containing an ester moiety, was prepared from ethyl 1-(2-chloroethyl)-2-oxocyclohexanecarboxylate. Lastly, the formation of other nitrogen heterocycles was evaluated. To our delight, the formation of piperidine **4ag** from the commercially available 6-chlorohexan-2-one was possible in 88% yield. The formation of **4ah** from 5-chloro-1-phenylpentan-1-one did not work at 60 °C and required a higher temperature of 90 °C, leading

to a comparable yield of 88%. In addition, product **4ai**, which contains a Bn group, was obtained at elevated temperature (90 °C) in 61% yield. Unfortunately, the reaction of 4-chlorobutan-2-one or 7-chloroheptan-2-one with phenylacetylene and Cu_2O under the developed conditions did not lead to any formation of the corresponding 2-alkynylazetidines and –azepanes and only starting materials were isolated.



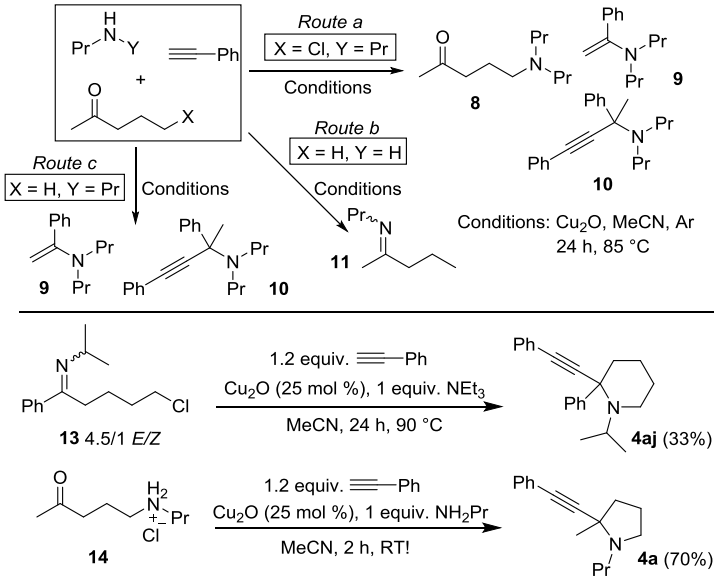
Scheme 3-10 Evaluation of different ω-chloroketones in the KA² coupling. Unless otherwise stated, 3.5 equivalents of amine were used. [b] 90 °C. [c] 2 equivalents of amine were used. [d] 1 equivalent of amine was used; 1 equivalent of NEt_3 was added. [e] 1 equivalent of aminoester.HCl was used, and 2 equivalents of NEt_3 were added. [f] Prepared from 1,7-dichloroheptan-4-one in toluene. [g] Prepared from ethyl 1-(2-chloroethyl)-2-oxocyclohexanecarboxylate.

In order to show the robustness of the developed method and to prove that the reaction could be scaled up, a gram-scale experiment was conducted. On a 10 mmol scale, the product **4a** could be isolated in 78% yield.

3.6 Reaction mechanism: control experiments

To gain insight into the reaction mechanism, as proposed in Scheme 3-6, a series of control experiments was set up. First, the reaction of 5-chloropentan-2-one with dipropylamine and phenylacetylene was evaluated. At 85 °C, a complex mixture of substitution product 5-(dipropylamino)pentan-2-one (**8**), the hydroamination product *N*-(1-phenylvinyl)-*N*-propylpropan-1-amine (**9**), and the subsequent alkynylation product 2,4-diphenyl-*N*,*N*-dipropylbut-3-yn-2-amine (**10**) could be distinguished in the ^{1}H NMR spectrum of the reaction mixture (Scheme 3-11, route a). When non-chlorinated 2-pentanone was reacted with *n*-propylamine and phenylacetylene, besides some imine **11**, no alkynylated product was formed (Scheme 3-11, route b), underlining the importance of the ω-chloroatom. When dipropylamine was used instead of *n*-propylamine in combination with non-chlorinated ketone, hydroamination of phenylacetylene, followed by alkynylation of the intermediate formed iminium occurred, as described by Larsen *et al.*[23] However, no incorporation of the ketone component was seen. This proves that both the primary amine and the presence of the ω-chlorine atom on the ketone are necessary for the coupling reaction. Next, ω-chloroimine **13** was synthesized[24] and reacted with phenylacetylene at 90 °C in the presence of 25 mol% Cu_2O and 1 equivalent of NEt_3. The corresponding 2-alkynylpiperidine **4aj** was isolated in 33% yield, proving that the proposed reaction mechanism in Scheme 6 is plausible. Alkynylation reactions of enamines have been reported to proceed via the corresponding iminium compounds, thus supporting the proposed reaction mechanism.[25] Preliminary alkylation of the primary amine by the alkyl chloride moiety of **1**, followed by intramolecular

iminium formation is more plausible, since 5-aminopentan-2-one **14** (as its ammonium salt), which was prepared independently, furnished upon reaction with phenylacetylene, 1 equivalent of propylamine and 25 mol% Cu_2O the alkynylpyrrolidine **4a** in 70% yield already at room temperature after 2 h.



Scheme 3-11 Control experiments.

3.7 Conclusion

In conclusion, a new, mild Cu(I)-catalyzed synthesis of 2-alkynylpyrrolidines and –piperidines bearing a quaternary α-carbon center was reported.[26] Different primary aliphatic amines can be used in combination with ω-chlorinated ketones. A broad range of functional groups (Cl, MeO, CF_3, NO_2, NH_2, NMe_2) is well tolerated on the alkyne moiety. Different substituted aromatic ketones, which traditionally are difficult reaction partners, could be coupled. Moreover, this synthesis uses simple, cheap, and commercially available starting materials. The key step is the *in situ* generation of a cyclic ketiminium species, which has an enhanced reactivity toward alkynylation in comparison to acyclic ketiminium species.

3.8 Experimental

3.8.1 Instrumentation

All reactions were carried out under argon in oven dried 10 mL microwave vials. Solvents used in purification (Heptanes and EtOAc) were distilled prior to use. All ketones, amines and acetylenes were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa-Aesar, Fluorochem and J&K). Products were purified on an automated column chromatography device Biotage IsoleraTM using Grace ResolvTM (12 g) columns. ^1H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Bruker Avance III HD spectrometer using $CDCl_3$ as solvent and TMS as the internal standard. Assignments were determined using 2D (HSQC, HMBC and DEPT) spectra. Chemical shifts are given in parts per million (ppm), *J*-values are given in Hertz (Hz), and number of protons for each signal are also indicated. For high resolution mass spectrometric analysis (HRMS), samples were dissolved in CH_3OH and diluted to a concentration of approximately 10^{-5} mol/L and measured on a microTOF

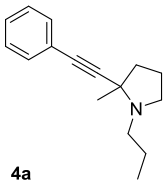
spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions $[M+H]^+$ are quoted.

3.8.2 Procedures and characterization data for scope examples 4

In an oven-dried 10 mL microwave vial were added Cu_2O (36 mg, 0.25 mmol), ketone (1 mmol), alkyne (1.2 mmol) and amine (3.5 mmol). Then, acetonitrile (2 mL) was added and the microwave vial was capped and flushed with argon for 5 minutes using a balloon. Then, the reaction mixture was placed in a preheated oil-bath at 60 °C and stirred for 24 h. Afterwards, the reaction mixture was poured in 0.5 N NaOH solution (10 mL) and extracted with DCM (10, 10, 5 mL). The organic phases were combined and dried over $MgSO_4$, filtered (copper phenyl acetylides can be separated here) and concentrated *in vacuo*. Then, the product was purified via column chromatography on a 12 g Grace column with Heptanes/EtOAc.

2-Methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



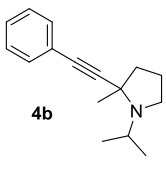
4a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 - 7.28 (m, 2H, $CH_{arom., ortho}$), 7.24 - 7.15 (m, 3H, $CH_{arom., meta and para}$), 3.13 - 3.04 (m, 1H, NC(**H**)HCH_2CH_2), 2.58 (m, 1H, NC(**H**)HCH_2CH_3), 2.43 - 2.34 (m, 1H, NC(H)**H**CH_2CH_2), 2.25 (ddd, 1H, *J* = 11.8, 9.5, 4.9 Hz, NC(H)**H**CH_2CH_3), 2.14 - 2.03 (m, 1H, NCH_2CH_2C(H)**H**), 1.86 - 1.66 (m, 3H, $NCH_2C\mathbf{H}_2C$(**H**)H), 1.56 - 1.38 (m, 2H, $NCH_2C\mathbf{H_2}CH_3$), 1.36 (s, 3H, $C\mathbf{H_3}C_{quat}$), 0.86 (t, 3H, *J* = 7.4 Hz, $NCH_2CH_2C\mathbf{H_3}$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.8 ($\mathbf{C}_{arom., ortho}$), 128.3 ($\mathbf{C}_{arom., meta}$), 127.8 ($\mathbf{C}_{arom., para}$), 123.8 ($\mathbf{C}_{arom., quat}$), 91.2 (C≡**C**Ph), 84.6 (**C**≡CPh), 60.5 ($CH_3\mathbf{C}_{quat}$), 52.4 ($N\mathbf{C}H_2CH_2CH_3$), 51.6 ($N\mathbf{C}H_2CH_2CH_2$), 40.7 ($NCH_2CH_2\mathbf{C}H_2$), 25.8 ($C\mathbf{C}H_3$), 22.6 ($NCH_2\mathbf{C}H_2CH_3$), 20.6 ($NCH_2\mathbf{C}H_2CH_2$), 12.4 ($NCH_2CH_2\mathbf{C}H_3$).
HRMS (ESI) m/z calculated for $[C_{16}H_{21}N+H]^+$: 228.1747; found 228.1755. Yellow oil, 207.6 mg (91%) isolated yield of 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**) after column chromatography. R_f = 0.25 in Hept/EtOAc 9/1.

Large scale procedure: Cu_2O (358 mg, 2.5 mmol), 5-chloropentan-2-one (1.206 g, 10 mmol), phenylacetylene (1.226 g, 12 mmol) and *n*-propylamine (2.069 g, 35 mmol) were weighed and acetonitrile (20 mL) was added in a round bottomed flask and the flask was equipped with a reflux condensor. The reaction mixture was heated at 60 °C for 24 hours. Then, the reaction mixture was poured in 0.5 N NaOH solution (100 mL) and extracted with DCM (100, 100, 50 mL). The organic phases were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Then, the product was purified via column chromatography on a 40 g Grace column with Heptanes/EtOAc, yielding a yellow oil, 1.781 g (78%) of 2-methyl-2-(phenylethynyl)-1-propylpyrrolidine (**4a**).

1-Isopropyl-2-methyl-2-(phenylethynyl)pyrrolidine (**4b**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and isopropylamine (207 mg, 3.5 mmol).



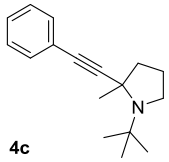
4b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.34 (m, 2H, $CH_{arom., ortho}$), 7.31 – 7.22 (m, 3H, $CH_{arom., meta and para}$), 3.15 (septet, *J* = 6.5 Hz, 1H, NC**H**), 3.01 (td, *J* = 8.6, 3.6 Hz, 1H, NC(H)**H**), 2.82 (dd, *J* = 16.1, 8.1 Hz, 1H, NC(**H**)H), 2.21 – 2.12 (m, 1H, NCH_2CH_2C(H)**H**), 1.95 – 1.68 (m, 3H, $NCH_2C\mathbf{H}_2C$(**H**)H), 1.49 (s, 3H, $C_{quat}C\mathbf{H}_3$), 1.21 and 1.16 (d, *J* = 6.6 Hz, 2 x 3H, $NCH(C\mathbf{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.4 (**C**$_{arom., ortho}$), 128.2 (**C**$_{arom., meta}$), 127.6 (**C**$_{arom., para}$), 123.9 (**C**$_{arom., quat}$), 93.9 (C≡**C**Ph), 83.5 (**C**≡CPh), 58.6 (**C**$_{quat}$ CH_3), 48.4 (N**C**HCH_3CH_3), 46.8 (N**C**$H_2CH_2CH_2$), 42.3 (NCH_2CH_2**C**H_2), 27.7 (C**C**H_3), 24.2 ($NCH(CH_3)$**C**H_3), 21.0 (NCH_2**C**H_2CH_2), 19.8 ($NCH($**C**$H_3)CH_3$).
HRMS (ESI) m/z calculated for $[C_{16}H_{21}N+H]^+$: 228.1747; found 228.1743. Yellow oil, 198.8 mg (87%) isolated yield of 1-isopropyl-2-methyl-2-(phenylethynyl)pyrrolidine (**4b**) after column chromatography. R_f = 0.64 in 1/1 Hept/EtOAc.

1-(*Tert*-butyl)-2-methyl-2-(phenylethynyl)pyrrolidine (**4c**)

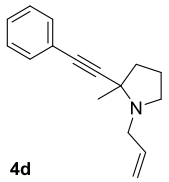
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *tert*-butylamine (256 mg, 3.5 mmol). Reaction temperature: 85 °C.


4c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.33 (m, 2H, C**H**$_{arom., ortho}$), 7.31 – 7.18 (m, 3H, C**H**$_{arom., meta and para}$), 3.14 – 2.96 (m, 2H, NC**H$_2$**), 2.18 (dt, *J* = 12.1, 7.3 Hz, 1H, NCH_2CH_2C**H**(H)), 2.03 – 1.89 (m, 1H $NCH_2CH_2CH($**H**$)$), 1.86 – 1.67 (m, 2H, NCH_2C**H**$_2CH_2$), 1.57 (s, 3H, C$_{quat}$C**H$_3$**), 1.32 (s, 9H, NC(C**H$_3$**)$_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.1 (**C**$_{arom., ortho}$), 128.2 (**C**$_{arom., meta}$), 127.5 (**C**$_{arom., para}$), 124.2 (**C**$_{arom., quat}$), 96.5 (C≡**C**Ph), 83.4 (**C**≡CPh), 56.9 (**C**$_{quat}CH_3$), 54.3 (N**C**$(CH_{3)3)}$, 47.6 (N**C**$H_2CH_2CH_2$), 45.3 (NCH_2CH_2**C**H_2), 31.9 (C$_{quat}$**C**H_3), 28.9 (NC(**C**$H_3)_3$), 21.9 (NCH_2**C**H_2CH_2).
HRMS (ESI) m/z calculated for $[C_{17}H_{23}N+H]^+$: 242.1903; found 242.1898. Yellow oil, 69.7 mg (29%) isolated yield of 1-(*tert*-butyl)-2-methyl-2-(phenylethynyl)pyrrolidine (**4c**) after column chromatography. R_f = 0.47 in 1/1 Hept/EtOAc.

1-Allyl-2-methyl-(phenylethynyl)pyrrolidine (**4d**)

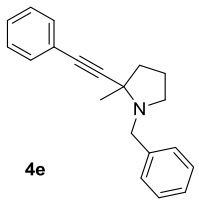
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and allylamine (200 mg, 3.5 mmol).


4d

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.39 (m, 2H, C**H**$_{arom., ortho}$), 7.35 – 7.22 (m, 3H, C**H**$_{arom., meta and para}$), 6.03 - 5.86 (m, 1H, CH_2=C**H**), 5.23 (d, *J* = 17.0 Hz, 1H, C**H**(H)=CH), 5.09 (d, *J* = 10.1 Hz, 1H, C(**H**)H=CH), 3.44 (dd, *J* = 13.2, 5.3 Hz, 1H, NC(**H**)HCH=CH_2), 3.17 – 3.06 (m, 1H, NC(**H**)HCH_2CH_2), 2.95 (dd, *J* = 13.2, 7.7 Hz, 1H, NC(H)**H**CH=CH_2), 2.56 - 2.41 (m, 1H, NC(H)**H**CH_2CH_2), 2.26 – 2.12 (m, 1H, NCH_2CH_2C(H)**H**), 1.93 – 1.73 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.46 (s, 3H, C$_{quat}$C**H**$_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.0 (NCH_2**C**H=CH_2), 131.7 (**C**$_{arom., ortho}$), 128.2 (**C**$_{arom., meta}$), 127.8 (**C**$_{arom., para}$), 123.5 (**C**$_{arom., quat}$), 116.5 (NCH_2CH=**C**H_2), 90.7 (C≡**C**Ph), 84.8 (**C**≡CPh), 60.1 (**C**$_{quat}CH_3$), 53.5 (N**C**H_2CH=CH_2), 51.7 (N**C**$H_2CH_2CH_2$), 40.6 (NCH_2CH_2**C**H_2), 25.8 (C**C**H_3), 20.4 (NCH_2**C**H_2CH_2).
HRMS (ESI) m/z calculated for $[C_{16}H_{19}N+H]^+$: 226.1590; found 226.1595. Yellow oil, 172.5 mg (77%) isolated yield of 1-allyl-2-methyl-(phenylethynyl)pyrrolidine (**4d**) after column chromatography. R_f = 0.65 in 1/1 Hept/EtOAc.

1-Benzyl-2-methyl-2-(phenylethynyl)pyrrolidine (**4e**)

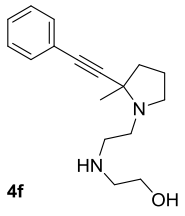
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and benzylamine (214 mg, 2 mmol).



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 – 7.41 (m, 2H, C**H**$_{arom., ortho}$), 7.39 - 7.33 (m , 2H, NCH_2C**H**$_{arom., ortho}$), 7.32 – 7.26 (m, 5H, C**H**$_{arom., meta}$ and NCH_2C**H**$_{arom., meta and para}$), 7.25 – 7.19 (m, 1H, C**H**$_{arom., para}$), 4.00 and 3.38 (d, *J* = 13.1 Hz, 2 x 1H, NC**H**$_2$Ph), 2.91 (td, *J* = 9.1, 3.1 Hz, 1H, NC(H)**H**CH_2CH_2), 2.48 (dd, *J* = 16.5, 8.9 Hz, 1H, NC(**H**)HCH_2CH_2), 2.28 – 2.15 (m, 1H, NCH_2CH_2C(H)**H**), 1.95 – 1.82 (m, 2H, NCH_2CH_2C(**H**)H and NCH_2C(H)**H**CH_2), 1.94 – 1.80 (m, 1H, NCH_2C(**H**)HCH_2), 1.52 (s, 3H, $C_{quat}C$**H$_3$**).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.3 (NCH_2**C**$_{arom., quat}$), 131.7 (**C**$_{arom., ortho}$), 128.8 (NCH_2**C**$_{arom., ortho}$), 128.2 (NCH_2**C**$_{arom., meta}$), 128.2 (**C**$_{arom., meta}$), 127.7 (NCH_2**C**$_{arom., para}$), 126.7 (**C**$_{arom., para}$), 123.6 (**C**$_{arom., quat}$), 91.0 (C≡**C**Ph), 84.7 (**C**≡CPh), , 60.2 (**C**$_{quat}CH_3$), 54.7 (N**C**H_2Ph), 51.7 (N**C**$H_2CH_2CH_2$), 40.6 (NCH_2CH_2**C**H_2), 26.1 (C_{quat}**C**H_3), 20.5 (NCH_2**C**H_2CH_2).
HRMS (ESI) m/z calculated for $[C_{20}H_{21}N+H]^+$: 276.1747; found 276.1755. Yellow oil, 207.4 mg (75%) isolated yield of 1-benzyl-2-methyl-2-(phenylethynyl)pyrrolidine (**4e**) after column chromatography. R_f = 0.47 in 9/1 Hept/EtOAc. Compound is known in literature.[15]

2-((2-(2-Methyl-2-(phenylethynyl)pyrrolidin-1-yl)ethyl)amino)ethan-1-ol (**4f**)

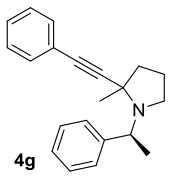
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and 2-((aminoethyl)amino)ethanol (208 mg, 2 mmol).



^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.36 (m, 2H, C**H**$_{arom., ortho}$), 7.33 – 7.19 (m, 3H, C**H**$_{arom., meta and para}$), 3.65 (t, *J* = 5.2 Hz, 2H, C**H**$_2$OH), 3.19 – 3.08 (m, 1H, NC(H)**H**CH_2CH_2), 3.00 - 2.87 (m, 1H, NC(H)**H**CH_2NH), 2.89 – 2.62 (m, 6H, NCH_2C**H**$_2$N**H**C**H**$_2CH_2O$**H**), 2.56 – 2.43 (m, 2H, NC(**H**)HCH_2CH_2 and NC(**H**)HCH_2NH), 2.24 – 2.12 (m, 1H, NCH_2CH_2C(H)**H**), 1.97 – 1.74 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.43 (s, 3H, C**H$_3$**C_{quat}).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.7 (**C**H$_{arom., ortho}$), 128.2 (**C**H$_{arom., meta}$), 127.8 (**C**H$_{arom., para}$), 123.4 (**C**H$_{arom., quat}$), 90.7 (**C**≡CCH), 84.5 (C≡**C**CH), 60.9 (**C**H_2OH), 60.4 (CH_3**C**$_{quat}$), 51.4 (N**C**$H_2CH_2CH_2$), 51.2 (**C**H_2CH_2OH), 49.8 (N**C**H_2CH_2NH), 47.8 (NCH_2**C**H_2NH), 40.4 (NCH_2CH_2**C**H_2), 25.8 (**C**H_3C_{quat}), 20.7 (NCH_2**C**H_2CH_2).
HRMS (ESI) m/z calculated for $[C_{17}H_{24}N_2O+H]^+$: 273.1961; found 273.1959. Yellow oil, 205.0 mg (75%) isolated yield of 2-((2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)ethyl)amino)ethan-1-ol (**4f**) after column chromatography with gradient of 100% Heptane to 100% DCM to 20% 7N NH_3 in MeOH. R_f = 0.41 in 9/1 DCM/(7N NH_3 in MeOH).

2-Methyl-1-((*S*)-1-phenylethyl)-2-(phenylethynyl)pyrrolidine (**4g**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol), (*S*)-methylbenzylamine (121 mg, 1 mmol) and triethylamine (101 mg, 1 mmol).



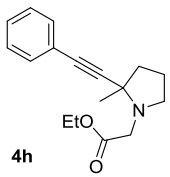
^{1}H NMR (400 MHz, $CDCl_3$) Major isomer δ = 7.49 – 7.38 (m, 4H, C≡CCC**H**$_{arom., ortho}$ and NCHCC**H**$_{arom., ortho}$), 7.34 – 7.24 (m, 5H, C≡CPhC**H**$_{arom., meta and para}$ and NCHPhC**H**$_{arom., meta}$), 7.23 – 7.16 (m, 1H, NCHPhC**H**$_{arom., para}$), 4.01 (q, *J* = 6.7 Hz, 1H, NC**H**), 3.13 (td, *J* = 8.4, 2.9 Hz, 1H, NC(H)**H**CH_2CH_2), 2.82 (dd, *J* = 16.2, 8.5 Hz, 1H, NC(**H**)HCH_2CH_2), 2.20 – 2.10 (m, 1H, NCH_2CH_2C(H)**H**), 1.93 – 1.73 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.48 (d, *J* = 6.8 Hz, 3H, NCHC**H$_3$**), 1.00 (s, 3H, C**H$_3$**C_{quat}).
Minor isomer δ = 7.42 – 7.34 (m, 4H, C≡CCC**H**$_{arom., ortho}$ and NCHPhC**H**$_{arom., ortho}$), 7.32 – 7.22 (m, 5H, C≡CPhC**H**$_{arom., meta and para}$ and NCHPhC**H**$_{arom., meta}$), 7.22 – 7.15 (m, 1H,

NCHPhC**H**$_{arom.,\ para}$), 3.86 (q, *J* = 6.7 Hz, 1H, NC**H**), 2.76 (td, *J* = 9.0, 4.0 Hz, 1H, NC(H)**H**CH$_2$CH$_2$), 2.46 (dd, *J* = 16.8, 8.9 Hz, 1H, NC(**H**)HCH$_2$CH$_2$), 2.23 (ddd, *J* = 12.8, 8.8, 5.1 Hz, 1H, NCH$_2$CH$_2$C(H)**H**), 1.96 (ddd, *J* = 12.3, 9.7, 7.4 Hz, 1H, NCH$_2$CH$_2$C(**H**)H), 1.83 – 1.57 (m, 2H, NCH$_2$C**H**$_2$CH$_2$), 1.65 (s, 3H, C**H**$_3$C$_{quat}$), 1.49 (d, *J* = 6.7 Hz, 3H, NCHC**H**$_3$).

^{13}C NMR (100 MHz, CDCl$_3$) Major isomer δ = 147.0 (NCH**C**CH$_{arom.,\ ortho}$), 131.6 (C≡CC**C**H$_{arom.,\ ortho}$), 128.2 (C≡CCCH**C**H$_{arom.,\ meta}$), 128.0 (NCHCCH**C**H$_{arom.,\ meta}$), 127.7 (C≡CCCHCH**C**H$_{arom.,\ para}$), 127.6 (NCHC**C**H$_{arom.,\ ortho}$), 126.6 (NCHCCHCH**C**H$_{arom.,\ para}$), 123.8 (C≡C**C**CH), 92.7 (**C**≡CCCH), 84.6 (C≡**C**CCH), 60.1 (CH$_3$**C**$_{quat}$), 58.4 (N**C**H), 49.3 (N**C**H$_2$CH$_2$CH$_2$), 42.2 (NCH$_2$CH$_2$**C**H$_2$), 28.0 (**C**H$_3$C$_{quat}$), 21.6 (NCH**C**H$_3$), 20.4 (NCH$_2$**C**H$_2$CH$_2$).
Minor isomer δ = 146.5 (NCH**C**CH$_{arom.,\ ortho}$), 131.7 (C≡CC**C**H$_{arom.,\ ortho}$), 128.2 (C≡CCCH**C**H$_{arom.,\ meta}$), 128.1 (NCHCCH**C**H$_{arom.,\ meta}$), 127.6 (C≡CCCHCH**C**H$_{arom.,\ para}$), 127.5 (NCHC**C**H$_{arom.,\ ortho}$), 126.5 (NCHCCHCH**C**H$_{arom.,\ para}$), 123.8 (C≡C**C**$_{arom.,\ quat}$), 92.1 (**C**≡CCCH), 84.3 (C≡**C**CCH), 61.5 (N**C**H), 59.0 (CH$_3$**C**$_{quat}$), 52.6 (N**C**H$_2$CH$_2$CH$_2$), 43.5 (NCH$_2$CH$_2$**C**H$_2$), 29.8 (**C**H$_3$C$_{quat}$), 24.1 (NCH**C**H$_3$), 21.2 (NCH$_2$**C**H$_2$CH$_2$).
HRMS (ESI) m/z calculated for [C$_{21}$H$_{23}$N+H]$^+$: 290.1903; found 290.1907. 7/3 mixture of diastereomers. Yellow oil, 240.0 mg, 83% isolated yield of 2-methyl-1-((*S*)-1-phenylethyl)-2-(phenylethynyl)pyrrolidine (**4g**) after column chromatography. R_f (major isomer) = 0.16, R_f (minor isomer) = 0.25 in 9/1 Hept/EtOAc. Major compound reported in literature.[15a]

Ethyl 2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)acetate (**4h**)

The general procedure was used with Cu$_2$O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol), glycine ethyl ester hydrochloride (140 mg, 1 mmol) and triethylamine (202 mg, 2 mmol).



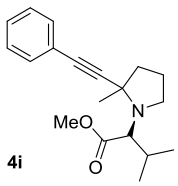
4h

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.45 – 7.36 (m, 2H, C**H**$_{arom.,\ ortho}$), 7.33 – 7.23 (m, 3H, C**H**$_{arom.,\ meta\ and\ para}$), 4.28 - 4.12 (m, 2H, CH$_3$C**H**$_2$O), 3.60 (d, *J* = 16.6 Hz, 1H, NC(H)**H**C=O), 3.44 – 3.34 (m, 1H, NC(H)**H**CH$_2$CH$_2$), 3.17 (d, *J* = 16.6 Hz, 1H, NC(**H**)HC=O), 2.62 – 2.47 (m, 1H, NC(**H**)HCH$_2$CH$_2$), 2.23 – 2.08 (m, 1H, NCH$_2$CH$_2$C(H)**H**), 2.00 – 1.79 (m, 3H, NCH$_2$C**H**$_2$C(**H**)H), 1.47 (s, 3H, C**H**$_3$C$_{quat}$), 1.27 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$O).

^{13}C NMR (100 MHz, CDCl$_3$) δ = 171.6 (**C**=O), 131.7 (**C**H$_{arom.,\ ortho}$), 128.2 (**C**H$_{arom.,\ meta}$), 127.9 (**C**H$_{arom.,\ para}$), 123.2 (C≡C**C**CH), 89.9 (**C**≡CCCH), 85.0 (C≡**C**CCH), 60.6 (CH$_3$**C**$_{quat}$ and CH$_3$**C**H$_2$O), 52.6 (N**C**H$_2$C=O), 52.5 (N**C**H$_2$CH$_2$CH$_2$), 40.0 (NCH$_2$CH$_2$**C**H$_2$), 25.6 (**C**H$_3$C$_{quat}$), 20.7 (NCH$_2$**C**H$_2$CH$_2$), 14.2 (**C**H$_3$CH$_2$O).
HRMS (ESI) m/z calculated for [C$_{17}$H$_{21}$NO$_2$+H]$^+$: 272.1645; found 272.1648. Yellow oil, 218.7 mg (81%) isolated yield of ethyl 2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)acetate (**4h**) after column chromatography. R_f = 0.59 in 1/1 Hept/EtOAc.

Methyl (2*R*)-3-methyl-2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)butanoate (**4i**)

The general procedure was used with Cu$_2$O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol), l-valine methyl ester hydrochloride (168 mg, 1 mmol) and triethylamine (202 mg, 2 mmol).



4i

^{1}H NMR (400 MHz, CDCl$_3$) Major isomer δ = 7.42 – 7.35 (m, 2H, C**H**$_{arom.,\ ortho}$), 7.29 – 7.22 (m, 3H, C**H**$_{arom.,\ meta\ and\ para}$), 3.41 (s, 3H, OC**H**$_3$), 3.40 – 3.32 (m, 1H, NC(H)**H**CH$_2$), 3.08 (d, *J* = 10.5 Hz, 1H, NC**H**), 3.06 – 2.99 (m, 1H, NC(**H**)HCH$_2$), 2.16 – 2.07 (m, 1H, NCH$_2$CH$_2$C(H)**H**), 2.02 – 1.94 (m, 1H,

C**H**$(CH_3)_2$), 1.93 – 1.82 (m, 1H, $NCH_2C(H)\mathbf{H}CH_2$), 1.81 – 1.69 (m, 2H, $NCH_2C(\mathbf{H})HC(\mathbf{H})H$), 1.45 (s, 3H, $C_{quat}C\mathbf{H}_3$), 0.96 and 0.86 (d, *J* = 6.6 Hz, 2 x 3H, $CH(C\mathbf{H}_3)_2$).

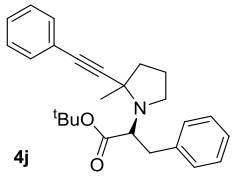
Minor isomer δ = 7.42 – 7.36 (m, 2H, $C\mathbf{H}_{arom.,\ ortho}$), 7.31 – 7.24 (m, 3H, $C\mathbf{H}_{arom.,\ meta\ and\ para}$), 3.67 (s, 3H, $OC\mathbf{H}_3$), 3.43 (d, *J* = 9.1 Hz, 1H, NC**H**), 3.23 – 3.14 (m, 1H, $NC(H)\mathbf{H}CH_2$), 3.01 (m, 1H, $NC(\mathbf{H})HCH_2$), 2.26 – 2.17 (m, 1H, $NCH_2CH_2C(H)\mathbf{H}$), 2.13 – 2.06 (m, 1H, C**H**$(CH_3)_2$), 1.91 – 1.76 (m, 3H, $NCH_2C\mathbf{H}_2C(\mathbf{H})H$), 1.30 (s, 3H, $C_{quat}C\mathbf{H}_3$), 1.02 and 0.91 (d, *J* = 6.7 Hz,2 x 3H, $CH(C\mathbf{H}_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$) Major isomer δ = 174.0 (**C**=O), 131.7 ($\mathbf{C}H_{arom.,\ ortho}$), 128.1 ($\mathbf{C}H_{arom.,\ meta}$), 127.6 ($\mathbf{C}H_{arom.,\ para}$), 123.8 ($\mathbf{C}_{arom.,\ quat}$), 92.6 ($\mathbf{C}{\equiv}CC_{arom.,\ quat}$), 83.2 ($C{\equiv}\mathbf{C}C_{arom.,\ quat}$), 64.7 (N**C**H), 57.8 ($CH_3\mathbf{C}$), 50.6 ($O\mathbf{C}H_3$), 44.0 ($N\mathbf{C}H_2$), 41.7 ($NCH_2CH_2\mathbf{C}H_2$), 29.0 ($\mathbf{C}HCH_3CH_3$), 26.1 ($\mathbf{C}H_3C_{quat}$), 21.2 ($NCH_2\mathbf{C}H_2CH_2$), 19.9 and 19.5 ($CH(\mathbf{C}H_3)_2$).
Minor isomer δ = 175.0 (**C**=O), 131.5 ($\mathbf{C}H_{arom.,\ ortho}$), 128.2 ($\mathbf{C}H_{arom.,\ meta}$), 127.7 ($\mathbf{C}H_{arom.,\ para}$), 123.7 ($\mathbf{C}_{arom.,\ quat}$), 94.1 ($\mathbf{C}{\equiv}CC_{arom.,\ quat}$), 82.3 ($C{\equiv}\mathbf{C}C_{arom.,\ quat}$), 65.2 (N**C**H), 59.5 ($CH_3\mathbf{C}$), 50.9 ($O\mathbf{C}H_3$), 44.8 ($N\mathbf{C}H_2$), 41.1 ($NCH_2CH_2\mathbf{C}H_2$), 28.9 ($\mathbf{C}HCH_3CH_3$), 25.2 ($\mathbf{C}H_3C_{quat}$), 22.0 ($NCH_2\mathbf{C}H_2CH_2$), 20.2 and 19.1 ($CH(\mathbf{C}H_3)_2$).

HRMS (ESI) m/z calculated for $[C_{19}H_{25}NO_2+H]^+$: 300.1958; found 300.1969. Yellow oil, 142.7 mg (48%) isolated yield of methyl (2*R*)-3-methyl-2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)butanoate (**4i**) after column chromatography. 4/1 mixture of diastereomers. R_f (major isomer) = 0.6, R_f (minor isomer) = 0.5 in 9/1 Hept/EtOAc.

<u>*Tert*-butyl (2*R*)-2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)-3-phenylpropanoate (**4j**)</u>

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol), l-phenylalanine *tert*-butyl ester hydrochloride (258 mg, 1 mmol) and triethylamine (202 mg, 2 mmol).



4j

^{1}H NMR (400 MHz, $CDCl_3$) Major isomer δ = 7.44 – 7.35 (m, 2H, C≡CCC**H**), 7.32 – 7.25 (m, 3H, C≡CCCHC**H**C**H**), 7.24 – 7.11 (m, 5H, CH_2**Ph**), 3.84 (dd, *J* = 10.9, 4.5 Hz, 1H, NC**H**), 3.33 – 3.21 (m, 2H, NCHC(H)**H** and $NC(H)\mathbf{H}CH_2CH_2$), 3.16 – 3.01 (m, 2H, NCHC(**H**)H and $NC(\mathbf{H})HCH_2CH_2$), 2.29 – 2.11 (m, 1H, $NCH_2CH_2C(H)\mathbf{H}$), 1.96 – 1.74 (m, 3H, $NCH_2C\mathbf{H}_2C(\mathbf{H})H$), 1.46 (s, 3H, $C\mathbf{H}_3C_{quat}$), 1.26 (s, 9H, $(C\mathbf{H}_3)_3C_{quat}$).

Minor isomer δ = 7.42 – 7.34 (m, 2H, C≡CCC**H**), 7.29 – 7.14 (m, 8H, Bn and C≡CCCHC**H**C**H**), 3.73 (t, *J* = 7.8 Hz, 1H, NC**H**), 3.42 – 3.31 (m, 1H, $NC(H)\mathbf{H}CH_2CH_2$), 3.23 – 3.12 (m, 1H, $NC(\mathbf{H})HCH_2CH_2$), 2.99 (d, *J* = 7.8 Hz, 2H, $NCHC\mathbf{H_2}$), 2.23 – 2.12 (m, 1H, $NCH_2CH_2C(H)\mathbf{H}$), 1.97 – 1.85 (m, 1H, $NCH_2C\mathbf{H}_2CH_2$), 1.85 – 1.68 (m, 2H, $NCH_2C\mathbf{H}_2C(\mathbf{H})H$), 1.26 (s, 3H,$C\mathbf{H}_3CC{\equiv}C$), 1.19 (s, 9H, $(C\mathbf{H}_3)_3C_{quat}$).

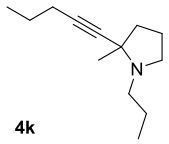
^{13}C NMR (100 MHz, $CDCl_3$) Major isomer δ = 172.6 (C=O), 138.8 ($NCHCH_2\mathbf{C}$), 131.6 (C≡CC**C**H), 129.5 ($NCHCH_2C\mathbf{C}H$), 128.3 ($NCHCH_2CCH\mathbf{C}H$), 128.1 (C≡CCCH**C**H), 127.8 (C≡CCCHCH**C**H), 126.1 ($NCHCH_2CCH\mathbf{C}H$), 123.5 (C≡C**C**CH), 93.6 (**C**≡CCCH), 83.2 (C≡**C**CCH), 80.1 ($(CH_3)_3\mathbf{C}_{quat}$), 62.2 ($N\mathbf{C}HCH_2$), 59.5 ($CH_3\mathbf{C}_{quat}$), 45.8 ($N\mathbf{C}H_2CH_2CH_2$), 41.1 ($NCH_2CH_2\mathbf{C}H_2$), 35.5 ($NCH\mathbf{C}H_2$), 27.8 ($(\mathbf{C}H_3)_3C_{quat}$), 27.2 ($\mathbf{C}H_3C_{quat}$), 21.7 ($NCH_2\mathbf{C}H_2CH_2$).

Minor isomer δ = 172.6 (C=O), 138.8 ($NCHCH_2\mathbf{C}$), 131.8 (C≡CC**C**H), 129.4 ($NCHCH_2C\mathbf{C}H$), 128.0 ($NCHCH_2CCH\mathbf{C}H$), 128.0 (C≡CCCH**C**H), 127.6 (C≡CCCHCH**C**H), 126.2 ($NCHCH_2CCH\mathbf{C}H$), 123.9 (C≡C**C**CH), 93.2 (**C**≡CCCH), 83.5 (C≡**C**CCH), 80.3 ($(CH_3)_3\mathbf{C}_{quat}$), 62.2 ($N\mathbf{C}HCH_2$), 58.4 ($CH_3\mathbf{C}_{quat}$), 46.4 ($N\mathbf{C}H_2CH_2CH_2$), 42.1 ($NCH_2CH_2\mathbf{C}H_2$), 38.9 ($NCH\mathbf{C}H_2$), 28.0 ($(\mathbf{C}H_3)_3C_{quat}$), 27.7 ($\mathbf{C}H_3C_{quat}$), 22.0 ($NCH_2\mathbf{C}H_2CH_2$).

HRMS (ESI) m/z calculated for $[C_{26}H_{31}NO_2+H]^+$: 390.2428; found 390.2446. 7/3 mixture of diastereomers. Yellow oil, 244.9 mg (63%) isolated of *tert*-butyl (2*R*)-2-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)-3-phenylpropanoate (**4j**) yield after column chromatography. R_f(major isomer) = 0.31, R_f(minor isomer) = 0.39 in 9/1 Hept/EtOAc.

2-Methyl-2-(pent-1-yn-1-yl)-1-propylpyrrolidine (**4k**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-pentyne (82 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

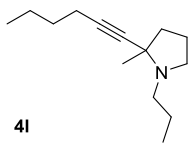


4k

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.17 – 2.97 (m, 1H, NC(H)**H**CH_2CH_2), 2.63 – 2.47 (m, 1H, NC(H)**H**CH_2CH_3), 2.42 – 2.30 (m, 1H, NC(**H**)HCH_2CH_2), 2.26 – 2.09 (m, 3H, C≡CC**H$_2$**CH_2CH_3 and NC(**H**)HCH_2CH_3), 2.05 – 1.95 (m, 1H, NCH_2CH_2C(H)**H**), 1.86 – 1.68 (m, 3H, NCH_2CH_2C(**H**)H), 1.60 – 1.37 (m, 4H, $C{\equiv}CCH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_3$), 1.31 (s, 3H, CH_3C_{quat}), 0.98 (t, *J* = 7.4 Hz, 3H, $C{\equiv}CCH_2CH_2CH_3$), 0.92 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2CH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 84.1 (C≡**C**$CH_2CH_2CH_3$), 81.3 (**C**≡$CCH_2CH_2CH_3$), 59.9 (**C**CH_3), 52.3 (N**C**$H_2CH_2CH_3$), 51.4 (N**C**$H_2CH_2CH_2$), 40.8 (NCH_2CH_2**C**H_2), 26.0 (C**C**H_3), 22.7 (C≡C**C**$H_2CH_2CH_3$), 22.5 (NCH_2**C**H_2CH_3), 20.7 ($C{\equiv}CCH_2$**C**H_2CH_3), 20.5 (NCH_2**C**H_2CH_2), 13.4 ($C{\equiv}CCH_2CH_2$**C**H_3), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{13}H_{23}N+H]^+$: 194.1903; found 194.1912. Yellow oil, 85.8 mg (44%) isolated yield of 2-methyl-2-(pent-1-yn-1-yl)-1-propylpyrrolidine (**4k**) after column chromatography. R_f = 0.51 in 1/1 Hept/EtOAc.

2-(Hex-1-yn-1-yl)-2-methyl-1-propylpyrrolidine (**4l**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-hexyne (99 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

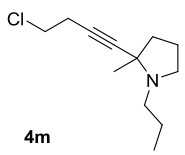


4l

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16 – 3.00 (m, 1H, NC(H)**H**CH_2CH_2), 2.53 (td, *J* = 10.8, 6.6 Hz, 1H, NC(H)**H**CH_2CH_3), 2.43 – 2.29 (m, 1H, NC(**H**)HCH_2CH_2), 2.27 – 2.12 (m, 3H, NC(**H**)HCH_2CH_3 and C≡CC**H$_2$**$CH_2CH_2CH_3$), 2.09 – 1.93 (m, 1H, NCH_2CH_2C(H)**H**), 1.88 – 1.65 (m, 3H, NCH_2CH_2C(**H**)H), 1.61 – 1.35 (m, 6H, $NCH_2CH_2CH_3$ en $C{\equiv}CCH_2CH_2CH_2CH_3$), 1.31 (s, 3H, CH_3C_{quat}), 0.92 (td, *J* = 7.1, 4.1 Hz, 6H, $NCH_2CH_2CH_3$ and $C{\equiv}CCH_2CH_2CH_2CH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 84.2 (C≡**C**$CH_2CH_2CH_2CH_3$), 81.1 (**C**≡$CCH_2CH_2CH_2CH_3$), 59.9 (**C**$_{quat}CH_3$), 52.3 (N**C**$H_2CH_2CH_3$), 51.4 (N**C**$H_2CH_2CH_2$), 40.7 (NCH_2CH_2**C**H_2), 31.4 ($C{\equiv}CCH_2$**C**$H_2CH_2CH_3$), 26.0 (C**C**H_3), 22.4 (NCH_2**C**H_2CH_3), 21.9 (C≡C**C**$H_2CH_2CH_2CH_3$), 20.5 (NCH_2**C**H_2CH_2), 18.3 ($C{\equiv}CCH_2CH_2$**C**H_2CH_3), 13.6 ($C{\equiv}CCH_2CH_2CH_2$**C**H_3), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{14}H_{25}N+H]^+$: 208.2060; found 208.2059. Yellow oil, 113.0 mg (55%) isolated yield of 2-(hex-1-yn-1-yl)-2-methyl-1-propylpyrrolidine (**4l**) after column chromatography. R_f = 0.63 in 1/1 Hept/EtOAc.

2-(4-Chlorobut-1-yn-1-yl)-2-methyl-1-propylpyrrolidine (**4m**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-chlorobut-1-yne (106 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



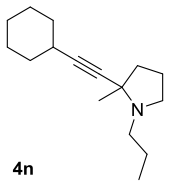
4m

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.56 (t, *J* = 7.3 Hz, 2H, ClC**H$_2$**CH_2), 3.14 – 3.03 (m, 1H, NC(H)**H**CH_2CH_2), 2.65 (t, *J* = 7.2 Hz, 2H, $ClCH_2$C**H$_2$**), 2.58 –

2.48 (m, 1H, NC(H)**H**CH_2CH_3), 2.41 – 2.30 (m, 1H, NC(**H**)HCH_2CH_2), 2.24 – 2.25 (m, 1H, NC(**H**)HCH_2CH_3), 2.06 – 1.95 (m, 1H, NCH_2CH_2C(H)**H**), 1.86 – 1.68 (m, 3H, $NCH_2C\mathbf{H_2}C$(**H**)H), 1.60 – 1.37 (m, 2H, $NCH_2C\mathbf{H_2}CH_3$), 1.31 (s, 3H, $CC\mathbf{H_3}$), 0.92 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 83.6 (**C**≡CCH_2CH_2Cl), 80.0 (C≡**C**CH_2CH_2Cl), 59.8 (**C**CH_3), 52.2 (N**C**$H_2CH_2CH_3$), 51.3 (N**C**$H_2CH_2CH_2$), 42.8 (C≡CCH_2**C**H_2Cl), 40.6 (NCH_2CH_2**C**H_2), 25.7 (C**C**H_3), 23.2 (C≡C**C**H_2CH_2Cl), 22.4 (NCH_2**C**H_2CH_3), 20.4 (NCH_2**C**H_2CH_2), 12.2 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{12}H_{20}NCl+H]^+$: 214.1357; found 214.1354. Yellow oil, 114.0 mg (53%) isolated yield of 2-(4-chlorobut-1-yn-1-yl)-2-methyl-1-propylpyrrolidine (**4m**) after column chromatography. R_f = 0.37 in 1/1 Hept/EtOAc.

2-(Cyclohexylethynyl)-2-methyl-1-propylpyrrolidine (**4n**)

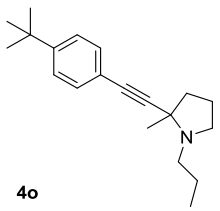
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), cyclohexylacetylene (130 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).


4n

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.14 – 3.02 (m, 1H, NC(H)**H**CH_2CH_2), 2.59 – 2.49 (m, 1H, NC(H)**H**CH_2CH_3), 2.46 – 2.30 (m, 2H, NC(**H**)HCH_2CH_2 and C≡CC**H**), 2.26 – 2.13 (m, 1H, NC(**H**)HCH_2CH_3), 2.09 – 1.93 (m, 1H, NCH_2C(H)**H**CH_2), 1.86 – 1.64 (m, 7H, NCH_2C(**H**)$HC\mathbf{H_2}$ and $CH(C(H)\mathbf{H}CH_2)_2C$(H)**H**), 1.59 – 1.38 (m, 5H, $NCH_2C\mathbf{H_2}CH_3$ and $CH(C(\mathbf{H})HC(H)\mathbf{H})_2CH_2$), 1.38 – 1.24 (m, 6H, $C_{quat}C\mathbf{H_3}$ and $CH(CH_2C(\mathbf{H})H)_2C(\mathbf{H})H$), 0.92 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 88.6 (CH**C**≡C), 81.0 (CHC≡**C**), 59.8 (C≡C**C**$_{quat}$), 52.3 (N**C**$H_2CH_2CH_3$), 51.4 (N**C**$H_2CH_2CH_2$), 40.8 (NCH_2**C**H_2CH_2), 33.3 ($CH(\mathbf{C}H_2CH_2)_2CH_2$), 33.2 ($CH(\mathbf{C}H_2CH_2)_2CH_2$), 28.9 (**C**$H(CH_2CH_2)_2CH_2$), 26.1 ($CH(CH_2\mathbf{C}H_2)_2CH_2$), 26.0 (**C**$H_3C_{quat}$), 24.7 ($CH(CH_2CH_2)_2$**C**$H_2$), 22.4 ($NCH_2$**C**$H_2CH_3$), 20.5 ($NCH_2CH_2$**C**$H_2$), 12.3 ($NCH_2CH_2$**C**$H_3$).
HRMS (ESI) m/z calculated for $[C_{16}H_{27}N+H]^+$: 234.2216; found 234.2220. Yellow oil, 148.9 mg (64%) isolated yield of 2-(cyclohexylethynyl)-2-methyl-1-propylpyrrolidine (**4n**) after column chromatography. R_f = 0.26 in 9/1 Hept/EtOAc.

2-((4-(*Tert*-butyl)phenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4o**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-*tert*-butylphenylacetylene (190 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

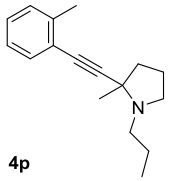

4o

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 and 7.30 (d, *J* = 7.5 Hz, 2 x 2H, C**H**$_{arom.}$), 3.15 (t, *J* = 8.6 Hz, 1H, NC(H)**H**CH_2CH_2), 2.69 -2.59 (m, 1H, NC(H)**H**CH_2CH_3), 2.51 – 2.40 (m, 1H, NC(**H**)HCH_2CH_2), 2.39 – 2.24 (m, 1H, NC(**H**)HCH_2CH_3), 2.21 – 2.09 (m, 1H, NCH_2CH_2C(H)**H**), 1.91 – 1.77 (m, 3H, $NCH_2C\mathbf{H_2}C$(**H**)H), 1.60 – 1.45 (m, 2H, $NCH_2C\mathbf{H_2}CH_3$), 1.43 (s, 3H, $CC\mathbf{H_3}$), 1.30 (s, 9H, $C(C\mathbf{H_3})_3$), 0.93 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.9 (**C**$_{arom., quat}C(CH_3)_3$), 131.4 (**C**$_{arom., meta}$), 125.2 (**C**$_{arom., ortho}$), 120.7 (**C**$_{arom., quat}$), 90.4 (**C**≡CPh), 84.5 (C≡**C**Ph), 60.4 (**C**CH_3), 52.3 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.6 (NCH_2CH_2**C**H_2), 34.7 (**C**$(CH_3)_3$), 31.2 ($C(\mathbf{C}H_3)_3$), 25.7 (C**C**H_3), 22.5 (NCH_2**C**H_2CH_3), 20.5 (NCH_2**C**H_2CH_2), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{20}H_{29}N+H]^+$: 284.2373; found 284.2382. Yellow oil, 198.7 mg (70%) isolated yield of 2-((4-(*tert*-butyl)phenyl)ethynyl)-2-methyl-1-propylpyrrolidine

(**4o**) after column chromatography. R_f = 0.66 in 1/1 Hept/EtOAc.

2-Methyl-1-propyl-2-(*o*-tolylethynyl)pyrrolidine (**4p**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 2-methylphenylacetylene (139 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

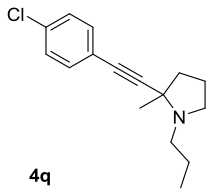


4p

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 7.5 Hz, 1H, C**H**$_{arom., ortho}$), 7.20 – 7.06 (m, 3H, C**H**$_{arom., meta and para}$), 3.22 - 3.13 (m, 1H, NC(H)**H**CH_2CH_2), 2.74 – 2.60 (m, 1H, NC(H)**H**CH_2CH_3), 2.51 – 2.38 (m, 1H, NC(**H**)HCH_2CH_2), 2.41 (s, 3H, $C_{arom}CC\mathbf{H_3}$), 2.37 – 2.28 (m, 1H, NC(**H**)HCH_2CH_3), 2.23 – 2.10 (m, 1H, NCH_2CH_2C(H)**H**), 1.93 – 1.76 (m, 3H, $NCH_2C\mathbf{H_2}C$(**H**)H), 1.63 – 1.47 (m, 2H, $NCH_2C\mathbf{H_2}CH_3$), 1.46 (s, 3H, C**H**$_3$), 0.93 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.8 (**C**$_{arom., ortho}CH_3$), 131.9 (**C**$_{arom., ortho}$), 129.3 (**C**$_{arom., meta}$ $C_{arom., ortho}CH_3$), 127.7 (**C**$_{arom., meta}$), 125.4 (**C**$_{arom., para}$), 123.5 (**C**$_{arom., quat}$), 95.2 (C≡**C**Ph), 83.3 (**C**≡CPh), 60.6 (**C**CH_3), 52.4 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.8 ($NCH_2CH_2\mathbf{C}H_2$), 25.9 (C**C**H_3), 22.5 ($NCH_2\mathbf{C}H_2CH_3$), 21.0 ($C_{arom\ ortho}CC\mathbf{H_3}$), 20.6 ($NCH_2\mathbf{C}H_2CH_2$), 12.2 ($NCH_2CH_2\mathbf{C}H_3$).
HRMS (ESI) m/z calculated for $[C_{17}H_{23}N+H]^+$: 242.1903; found 242.1900. Yellow oil, 179.3 mg (74%) isolated yield of 2-methyl-1-propyl-2-(o-tolylethynyl)pyrrolidine (**4p**) after column chromatography. R_f = 0.71 in 1/1 Hept/EtOAc.

2-((4-Chlorophenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4q**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-chlorophenylacetylene (164 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4q

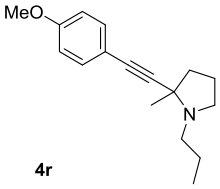
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.4 Hz, 2H, C**H**CHCCl), 7.25 (d, *J* = 8.5 Hz, 2H, CHC**H**CCl), 3.26 (td, *J* = 9.1, 3.8 Hz, 1H, NC(H)**H**CH_2CH_2), 2.78 – 2.66 (m, 1H, NC(H)**H**CH_2CH_3), 2.58 – 2.48 (m, 1H, NC(**H**)HCH_2CH_2), 2.45 – 2.33 (m, 1H, NC(**H**)HCH_2CH_3), 2.23 – 2.13 (m, 1H, NCH_2CH_2C(H)**H**), 2.01 – 1.82 (m, 3H, NCH_2CH_2C(**H**)H, $NCH_2C\mathbf{H_2}CH_3$), 1.67 – 1.54 (m, 2H, $NCH_2C\mathbf{H_2}CH_2$), 1.51 (s, 3H, $C\mathbf{H_3}C_{quat}$), 0.95 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.0 (**C**Cl), 132.9 (ClCCH**C**H), 128.5 (ClC**C**H), 121.7 (ClCCH**C**H), 91.1 (ArC≡**C**), 84.2 (Ar**C**≡C), 61.4 ($CH_3\mathbf{C}$), 52.2 (N**C**$H_2CH_2CH_3$), 51.4 (N**C**$H_2CH_2CH_2$), 40.2 ($NCH_2CH_2\mathbf{C}H_2$), 25.1 (**C**H_3C), 21.9 ($NCH_2\mathbf{C}H_2CH_3$), 20.5 ($NCH_2\mathbf{C}H_2CH_2$), 12.1 ($NCH_2CH_2\mathbf{C}H_3$).

HRMS (ESI) m/z calculated for $[C_{16}H_{20}ClN+H]^+$: 262.1357; found 262.1354. Yellow oil, 173.0 mg (66%) isolated yield of 2-((4-chlorophenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4q**) after column chromatography. R_f = 0.65 in 1/1 Hept/EtOAc.

2-((4-Methoxyphenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4r**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-methoxyphenylacetylene (159 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

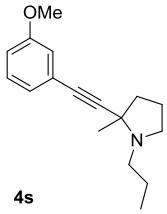


4r

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.7 Hz, 2H, C**H**$_{arom., meta}$), 6.81 (d, *J* = 8.7 Hz, 2H, C**H**$_{arom., ortho}$), 3.79 (s, 3H, OC**H$_3$**), 3.18 – 3.10 (m, 1H, NC(H)**H**CH_2CH_2), 2.71 – 2.57 (m, 1H, NC(H)**H**CH_2CH_3), 2.50 – 2.40 (m, 1H, NC(**H**)HCH_2CH_2), 2.36 – 2.26 (m, 1H, NC(**H**)HCH_2CH_3), 2.20 – 2.07 (m, 1H, NCH_2CH_2C(H)**H**), 1.92 – 1.75 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.62 – 1.45 (m, 2H, NCH_2C**H**$_2CH_3$), 1.42 (s, 3H, CC**H**$_3$), 0.94 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2 (**C**OCH_3), 133.0 (**C**$_{arom., meta}$), 115.9 (**C**$_{arom., quat}$), 113.8 (**C**$_{arom., ortho}$), 89.5 (**C**≡CPh), 84.2 (C≡**C**Ph), 60.3 (**C**CH_3), 55.3 (O**C**H_3), 52.3 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.6 (NCH_2CH_2**C**H_2), 25.8 (C**C**H_3), 22.5 (NCH_2**C**H_2CH_3), 20.5 (NCH_2**C**H_2CH_2), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{17}H_{23}NO+H]^+$: 258.1852; found 258.1864. Yellow oil, 153.9 mg (60%) isolated yield of 2-((4-methoxyphenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4r**) after column chromatography. R_f = 0.52 in 1/1 Hept/EtOAc.

2-((3-Methoxyphenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4s**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 3-methoxyphenylacetylene (159 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

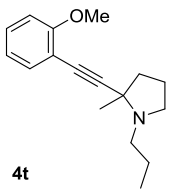


4s

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (t, *J* = 7.9 Hz, 1H, C**H**$_{arom., meta}$), 7.00 (d, *J* = 7.6 Hz, 1H, C**H**$_{arom., ortho}$), 6.93 (s, 1H, C**H**$_{arom., ortho}COCH_3$), 6.83 (dd, *J* = 8.3, 2.3 Hz, 1H, C**H**$_{arom., para}$), 3.79 (s, 3H, OC**H$_3$**), 3.20 – 3.11 (m, 1H, NC(H)**H**CH_2CH_2), 2.70 - 2.60 (m, 1H, NC(H)**H**CH_2CH_3), 2.50 – 2.42 (m, 1H, NC(**H**)HCH_2CH_2), 2.36 – 2.27 (m, 1H, NC(**H**)HCH_2CH_3), 2.22 - 2.10 (m, 1H, NCH_2CH_2C(H)**H**), 1.91 – 1.75 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.63 – 1.46 (m, 2H, NCH_2C**H$_2$**CH_3), 1.43 (s, 3H, CC**H**$_3$), 0.94 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.3 (**C**OCH_3), 129.2 (**C**$H_{arom., meta}$), 124.7 (**C**$_{arom., quat}$), 124.3 (**C**$H_{arom., ortho}$), 116.7 (**C**$H_{arom., ortho}COCH_3$), 114.2 (**C**$H_{arom., para}$), 91.0 (C≡**C**Ph), 84.4 (**C**≡CPh), 60.4 (**C**$_{quat}CH_3$), 55.3 (CO**C**H_3), 52.3 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.6 (NCH_2CH_2**C**H_2), 25.7 (C**C**H_3), 22.4 (NCH_2**C**H_2CH_3), 20.5 (NCH_2**C**H_2CH_2), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{17}H_{23}NO+H]^+$: 258.1852; found 258.1864. Yellow oil, 251.3 mg (98%) isolated yield of 2-((3-methoxyphenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4s**) after column chromatography. R_f = 0.60 in 1/1 Hept/EtOAc.

2-((2-Methoxyphenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4t**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 2-methoxyphenylacetylene (159 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



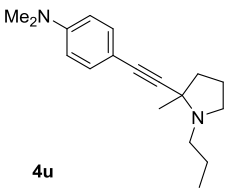
4t

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (dd, *J* = 7.5, 1.4 Hz, 1H, CH_3OCC**H**), 7.21 (td, *J* = 7.9, 1.4 Hz, 1H, CH_3OCCHC**H**), 6.85 (t, *J* = 7.5 Hz, 1H, C≡CCCHC**H**), 6.81 (d, *J* = 8.3 Hz, 1H, C≡CCC**H**CH), 3.82 (s, 3H, C**H**$_3$O), 3.21 – 3.07 (m, 1H, NC(H)**H**CH_2CH_2), 2.73 – 2.60 (m, 1H, NC(H)**H**CH_2CH_3), 2.54 – 2.45 (m, 1H, NC(**H**)HCH_2CH_2), 2.43 – 2.33 (m, 1H, NC(**H**)HCH_2CH_3), 2.24 – 2.10 (m, 1H, NCH_2CH_2C(H)**H**), 1.95 – 1.72 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.65 – 1.46 (m, 2H, NCH_2C**H$_2$**CH_3), 1.45 (s, 3H, C**H$_3$**C$_{quat}$), 0.94 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0 (CH_3O**C**), 133.4 (CH_3OC**C**H), 129.0 (CH_3OCCH**C**H), 120.3 (C≡CCCH**C**H), 113.1 (C≡**C**CCH), 110.8 (C≡CC**C**H), 95.4 (**C**≡CCCH), 80.5 (C≡**C**CCH), 60.6 (CH_3**C**$_{quat}$), 55.7 (**C**H_3O), 52.3 (N**C**$H_2CH_2CH_3$), 51.4 (N**C**$H_2CH_2CH_2$), 40.6 (NCH_2CH_2**C**H_2), 25.7 (**C**H_3C_{quat}), 22.5 (NCH_2**C**H_2CH_3), 20.6 (NCH_2**C**H_2CH_2), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{17}H_{23}NO+H]^+$: 258.1852; found 258.1859. Yellow oil, 212.8 mg (83%) isolated yield of 2-((2-methoxyphenyl)ethynyl)-2-methyl-1-propylpyrrolidine (**4t**) after column chromatography. R_f = 0.55 in 1/1 Hept/EtOAc.

<u>*N*,*N*-dimethyl-4-((2-methyl-1-propylpyrrolidin-2-yl)ethynyl)aniline (**4u**)</u>

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-ethynyl-*N*,*N*-dimethylaniline (174 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



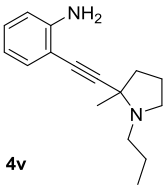
4u

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.7 Hz, 2H, C≡CCC**H**), 6.60 (d, *J* = 8.7 Hz, 2H, C≡CCCHC**H**), 3.18 – 3.07 (m, 1H, NC(H)**H**CH_2CH_2), 2.94 (s, 6H, N(C**H**$_3$)$_2$), 2.69 – 2.57 (m, 1H, NC(H)**H**CH_2CH_3), 2.51 – 2.40 (m, 1H, NC(**H**)HCH_2CH_2), 2.37 – 2.23 (m, 1H, NC(**H**)HCH_2CH_3), 2.19 – 2.07 (m, 1H, NCH_2CH_2C(H)**H**), 1.93 – 1.72 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.61 – 1.44 (m, 2H, NCH_2C**H**$_2CH_3$), 1.42 (s, 3H, C**H**$_3C_{quat}$), 0.93 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.8 (CH_3NCH_3**C**), 132.6 (C≡CC**C**H), 111.9 (C≡CCCH**C**H), 110.9 (C≡C**C**CH), 88.4 (**C**≡CCCH), 85.0 (C≡**C**CCH), 60.4 (CH_3**C**$_{quat}$), 52.3 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.7 (NCH_2CH_2**C**H_2), 40.3 (N(**C**H_3)$_2$), 25.9 (**C**H_3C_{quat}), 22.5 (NCH_2**C**H_2CH_3), 20.5 (NCH_2**C**H_2CH_2), 12.3 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{18}H_{26}N_2+H]^+$: 271.2169; found 271.2178. Yellow oil, 256.8 mg (95%) isolated yield of *N*,*N*-dimethyl-4-((2-methyl-1-propylpyrrolidin-2-yl)ethynyl)aniline (**4u**) after column chromatography. R_f = 0.63 in 1/1 Hept/EtOAc.

<u>2-((2-Methyl-1-propylpyrrolidin-2-yl)ethynyl)aniline (**4v**)</u>

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 2-ethynylaniline (141 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



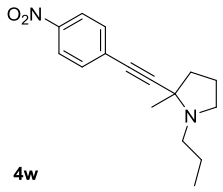
4v

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 6.7 Hz, 1H, C≡CCC**H**), 7.08 (t, *J* = 7.7 Hz, 1H, C≡CCCHC**H**), 6.73 – 6.61 (m, 2H, H_2NCC**H**C**H**), 4.14 (broad s, 2H, N**H**$_2$), 3.25 – 3.12 (m, 1H, NC(H)**H**CH_2CH_2), 2.74 – 2.60 (m, 1H, NC(H)**H**CH_2CH_3), 2.51 – 2.39 (m, 1H, NC(**H**)HCH_2CH_2), 2.35 – 2.24 (m, 1H, NC(**H**)HCH_2CH_3), 2.23 – 2.09 (m, 1H, NCH_2CH_2C(H)**H**), 1.94 – 1.77 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.63 – 1.48 (m, 2H, NCH_2C**H**$_2CH_3$), 1.46 (s, 3H, C**H**$_3C_{quat}$), 0.93 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.4 (**C**NH_2), 132.2 (C≡CC**C**H), 129.1 (C≡CCCH**C**H), 117.9 (H_2NCCH**C**H), 114.2 (H_2NC**C**H), 108.5 (C≡C**C**CH), 96.4 (**C**≡CCCH), 80.9 (C≡**C**CCH), 60.7 (CH_3**C**$_{quat}$), 52.4 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.8 (NCH_2CH_2**C**H_2), 26.0 (NCH_2**C**H_2CH_2), 22.4 (NCH_2**C**H_2CH_3), 20.5 (**C**H_3C_{quat}), 12.2 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{16}H_{22}N_2+H]^+$: 243.1856; found 243.1854. Yellow oil, 209.4 mg (86%) isolated yield of 2-((2-methyl-1-propylpyrrolidin-2-yl)ethynyl)aniline (**4v**) after column chromatography. R_f = 0.49 in 1/1 Hept/EtOAc.

2-Methyl-2-((4-nitrophenyl)ethynyl)-1-propylpyrrolidine (**4w**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-nitrophenylacetylene (177 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4w

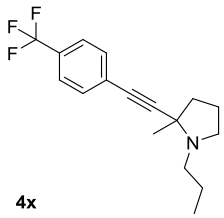
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 8.6 Hz, 2H, C**H**$_{arom., ortho}$), 7.53 (d, *J* = 8.7 Hz, 2H, C**H**$_{arom., meta}$), 3.23 – 3.13 (m, 1H, NC(H)**H**CH_2CH_2), 2.71 – 2.59 (m, 1H, NC(H)**H**CH_2CH_3), 2.49 – 2.40 (m, 1H, NC(**H**)HCH_2CH_2), 2.35 – 2.25 (m, 1H, NC(**H**)HCH_2CH_3), 2.23 – 2.12 (m, 1H, NCH_2CH_2C(H)**H**), 1.91 – 1.79 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.63 – 1.48 (m, 2H, NCH_2C**H$_2$**CH_3), 1.46 (s, 3H, $C_{quat}C$**H**$_3$), 0.95 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.8 (**C**NO_2), 132.4 (**C**$_{arom., meta}$), 130.7 (**C**$_{arom., quat}$), 123.5 (**C**$_{arom., ortho}$), 97.5 (**C**≡CPh), 83.2 (C≡**C**Ph), 60.5 (**C**CH_3), 52.2 (N**C**$H_2CH_2CH_3$), 51.4 (N**C**$H_2CH_2CH_2$), 40.4 (NCH_2CH_2**C**H_2), 25.4 (C_{quat}**C**H_3), 22.4 (NCH_2**C**H_2CH_3), 20.6 (NCH_2**C**H_2CH_2), 12.2 (NCH_2CH_2**C**H_3).

HRMS (ESI) m/z calculated for $[C_{16}H_{20}N_2O_2+H]^+$: 273.1598; found 273.1610. Red oil, 177.3 mg (65%) isolated yield of 2-methyl-2-((4-nitrophenyl)ethynyl)-1-propylpyrrolidine (**4w**) after column chromatography. R_f = 0.56 in 1/1 Hept/EtOAc.

2-Methyl-1-propyl-2-((4-(trifluoromethyl)phenyl)ethynyl)pyrrolidine (**4x**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-trifluormethylphenylacetylene (204 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4x

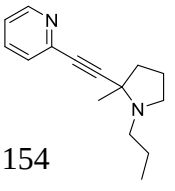
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.3 Hz, 2H, CF_3CC**H**), 7.49 (d, *J* = 8.3 Hz, 2H, C≡CCC**H**), 3.24 – 3.09 (m, 1H, NC(H)**H**CH_2CH_2), 2.71 – 2.57 (m, 1H, NC(H)**H**CH_2CH_3), 2.51 – 2.38 (m, 1H, NC(**H**)HCH_2CH_2), 2.30 (ddd, *J* = 11.7, 9.5, 4.8 Hz, 1H, NC(**H**)HCH_2CH_3), 2.22 – 2.10 (m, 1H, NCH_2CH_2C(H)**H**), 1.94 – 1.74 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.66 – 1.45 (m, 2H, NCH_2C**H$_2$**CH_3), 1.44 (s, 3H, C**H**$_3C_{quat}$), 0.94 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.9 (C≡CC**C**H or C≡C**C**CH), 129.5 (q, *J* = 32.7 Hz, CF_3**C**), 127.6 (q, *J* = 1.5 Hz, C≡CC**C**H or C≡C**C**CH), 125.1 (q, *J* = 3.8 Hz, CF_3C**C**H), 124.1 (q, *J* = 272.5 Hz, **C**F_3), 94.1 (**C**≡CCCH), 83.4 (C≡**C**CCH), 60.4 (CH_3**C**$_{quat}$), 52.3 (NC**H$_2$**CH_2CH_3), 51.5 (NC**H$_2$**CH_2CH_2), 40.5 (NCH_2CH_2**C**H_2), 25.5 (**C**H_3C_{quat}), 22.4 (NCH_2**C**H_2CH_3), 20.6 (NCH_2**C**H_2CH_2), 12.2 (NCH_2CH_2**C**H_3).

HRMS (ESI) m/z calculated for $[C_{17}H_{20}NF_3+H]^+$: 296.1621; found 296.1632. Yellow oil, 207.5 mg (70%) isolated yield of 2-methyl-1-propyl-2-((4-(trifluoromethyl)phenyl)ethynyl)pyrrolidine (**4x**) after column chromatography. R_f = 0.59 in 1/1 Hept/EtOAc.

2-((2-Methyl-1-propylpyrrolidin-2-yl)ethynyl)pyridine (**4y**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 2-ethynylpyridine (124 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4y

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (d, *J* = 4.0 Hz, 1H, NC**H**$_{arom., meta}$), 7.61 (t, *J* = 7.1 Hz, 1H, C**H**$_{arom., para}$), 7.39 (d, *J* = 7.7 Hz, 1H, C**H**$_{arom., ortho}$),

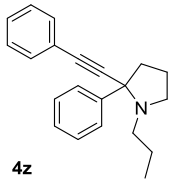
7.24 – 7.10 (m, 1H, C**H**$_{arom., meta}$), 3.22 -3.13 (m, 1H, NC(H)**H**CH_2CH_2), 2.78 – 2.60 (m, 1H, NC(H)**H**CH_2CH_3), 2.54 – 2.44 (m, 1H, NC(**H**)HCH_2CH_2), 2.43 – 2.30 (m, 1H, NC(**H**)HCH_2CH_3), 2.26 - 2.18 (m, 1H, NCH_2CH_2C(H)**H**), 2.01 – 1.68 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.67 – 1.51 (m, 2H, NCH_2C**H$_2$**CH_3), 1.47 (s, 3H, CC**H**$_3$), 0.94 (t, *J* = 7.3 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.9 (N**C**H$_{arom., meta}$), 143.7 (**C**$_{arom., quat}$), 136.0 (**C**$_{arom., para}$), 127.3 (**C**$_{arom., ortho}$), 122.4 (**C**$_{arom., meta}$), 91.6 (C≡**C**Ph), 84.3 (**C**≡CPh), 60.3 (**C**CH_3), 52.2 (N**C**$H_2CH_2CH_3$), 51.5 (N**C**$H_2CH_2CH_2$), 40.4 (NCH_2CH_2**C**H_2), 25.6 (C**C**H_3), 22.4 (NCH_2**C**H_2CH_3), 20.5 (NCH_2**C**H_2CH_2), 12.2 (NCH_2CH_2**C**H_3).

HRMS (ESI) m/z calculated for $[C_{15}H_{20}N_2+H]^+$: 229.1699; found 229.1705. Yellow oil, 101.9 mg (45%) isolated yield of 2-((2-methyl-1-propylpyrrolidin-2-yl)ethynyl)pyridine (**4y**) after column chromatography. R_f = 0.17 in 1/1 Hept/EtOAc.

2-Phenyl-2-(phenylethynyl)-1-propylpyrrolidine (**4z**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 4-chlorobutyrophenone (183 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4z

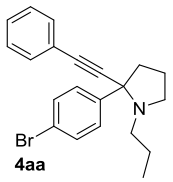
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 7.6 Hz, 2H, C**H**$_{arom.}$), 7.52 – 7.46 (m, 2H, C**H**$_{arom.}$), 7.37 – 7.21 (m, 6H, C**H**$_{arom.}$), 3.36 (td, *J* = 8.5, 4.4 Hz, 1H, NC(H)**H**CH_2CH_2), 2.64 – 2.54 (m, 1H, NC(**H**)HCH_2CH_2), 2.40 – 2.26 (m, 3H, N**C**$H_2CH_2CH_3$ and NCH_2CH_2C(H)**H**), 2.09 – 1.87 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.55 – 1.40 (m, 2H, NCH_2C**H$_2$**CH_3), 0.85 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.6 (C_{quat}**C**CH), 131.8 (**C**H$_{arom.}$), 128.2 (**C**H$_{arom.}$), 128.1 (**C**H$_{arom.}$) 127.9 (**C**H$_{arom.}$), 127.1 (**C**H$_{arom.}$), 126.8 (**C**H$_{arom.}$), 123.6 (**C**H$_{arom.}$), 88.7 (**C**≡CCH), 87.8 (C≡**C**CH), 68.9 (**C**$_{quat}$C≡CCH), 52.3 (N**C**$H_2CH_2CH_3$), 50.6 (N**C**$H_2CH_2CH_2$), 44.8 (NCH_2CH_2**C**H_2), 22.1 (NCH_2**C**H_2CH_3), 21.7 (NCH_2**C**H_2CH_2), 12.0 (NCH_2CH_2**C**H_3).

HRMS (ESI) m/z calculated for $[C_{21}H_{23}N+H]^+$: 290.1903; found 290.1896. Yellow oil, 182.5 mg (63%) isolated yield of 2-phenyl-2-(phenylethynyl)-1-propylpyrrolidine (**4z**) after column chromatography. R_f = 0.56 in 9/1 Hept/EtOAc.

2-(4-Bromophenyl)-2-(phenylethynyl)-1-propylpyrrolidine (**4aa**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 4’-bromo-4-chlorobutyrophenone (262 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4aa

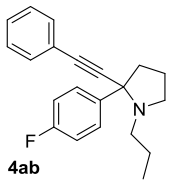
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 and 7.45 (d, *J* = 8.4 Hz,2 x 2H, C**H**$_{arom.}$), 7.52 – 7.47 (m, 2H, C**H**$_{arom.}$), 7.35 – 7.26 (m, 3H, C**H**$_{arom.}$), 3.36 (td, *J* = 8.6, 2.5 Hz, 1H, NC(H)**H**CH_2CH_2), 2.66 – 2.51 (m, 1H, NC(**H**)HCH_2CH_2), 2.40 – 2.23 (m, 3H, N**C**$H_2CH_2CH_3$ and NCH_2CH_2C(H)**H**), 2.10 - 1.87 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.54 – 1.35 (m, 2H, NCH_2C**H$_2$**CH_3), 0.85 (t, *J* = 7.3 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.0 (**C**$_{arom., quat}$), 131.8 (**C**H$_{arom.}$), 131.1 (**C**H$_{arom.}$), 128.7 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 128.0 (**C**H$_{arom.}$), 123.3 (**C**$_{arom., quat}$), 120.9 (**C**$_{arom., quat}$), 88.1 (C≡**C**CCH), 88.1 (**C**≡CCCH), 68.5 (**C**$_{quat}$C≡CCCH), 52.3 (N**C**$H_2CH_2CH_3$), 50.6 (N**C**$H_2CH_2CH_2$), 44.8 (NCH_2CH_2**C**H_2), 22.1 (NCH_2**C**H_2CH_3), 21.7 (NCH_2**C**H_2CH_2), 12.0 (NCH_2CH_2**C**H_3).

HRMS (ESI) m/z calculated for $[C_{21}H_{22}NBr+H]^+$: 368.1008; found 368.1013. Yellow oil, 316.8 mg (86%) isolated yield of 2-(4-bromophenyl)-2-(phenylethynyl)-1-propylpyrrolidine (**4aa**) after column chromatography. R_f = 0.51 in 9/1 Hept/EtOAc.

2-(4-Fluorophenyl)-2-(phenylethynyl)-1-propylpyrrolidine (**4ab**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 4-chloro-4'-fluorobutyrophenone (201 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

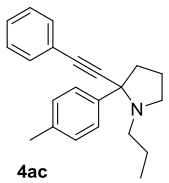


4ab

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (dd, *J* = 8.3, 5.7 Hz, 2H, NCCC**H**$_{arom.}$), 7.53 – 7.45 (m, 2H, C≡CC**H**$_{arom., ortho}$), 7.35 – 7.27 (m, 3H, C≡CC**H**$_{arom., meta and para}$), 7.01 (t, *J* = 8.6 Hz, 2H, FCC**H**$_{arom.}$), 3.40 – 3.31 (m, 1H, NC(H)**H**CH_2CH_2), 2.65 – 2.51 (m, 1H, NC(**H**)HCH_2CH_2), 2.37 – 2.25 (m, 3H, N**CH_2**CH_2CH_3 and NCH_2CH_2C(H)**H**), 2.06 – 1.90 (m, 3H, NCH_2C**H_2**C(**H**)H), 1.54 - 1.38 (m, 2H, NCH_2C**H_2**CH_3), 0.85 (t, 3H, NCH_2CH_2C**H_3**).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1 (d, *J* = 245.0 Hz, F**C**$_{arom. quat}$), 139.4 (d, *J* = 2.8 Hz, NC**C**$_{arom. quat}$), 131.8 (C≡C**C**H$_{arom., ortho}$), 128.5 (d, *J* = 7.9 Hz, FCCH**C**H$_{arom.}$), 128.3 (C≡C**C**H$_{arom., meta}$), 128.0 (**C**H$_{arom., para}$), 123.5 (**C**$_{arom. quat}$), 114.8 (d, *J* = 21.2 Hz, FC**C**H$_{arom.}$), 88.5 (**C**≡CCH), 88.0 (C≡**C**CH), 68.4 (**C**$_{quat}$C≡CCH), 52.2 (N**C**$H_2CH_2CH_3$), 50.6 (N**C**$H_2CH_2CH_2$), 44.8 (NCH_2CH_2**C**H_2), 22.1 (NCH_2**C**H_2CH_3), 21.7 (NCH_2**C**H_2CH_2), 12.0 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{21}H_{22}NF+H]^+$: 308.1809; found 308.1820. Yellow oil, 160.0 mg (52%) isolated yield of 2-(4-fluorophenyl)-2-(phenylethynyl)-1-propylpyrrolidine (**4ab**) after column chromatography. R_f = 0.59 in 9/1 Hept/EtOAc.

2-(Phenylethynyl)-1-propyl-2-(p-tolyl)pyrrolidine (**4ac**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 4-chloro-4'-methylbutyrophenone (197 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

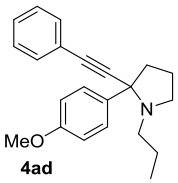


4ac

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 8.1 Hz, 2H, NCCC**H**$_{arom.}$), 7.52 – 7.46 (m, 2H, C≡CC**H**$_{arom., ortho}$), 7.35 – 7.26 (m, 3H, C≡CC**H**$_{arom., meta and para}$), 7.15 (d, *J* = 8.0 Hz, 2H, CH_3CC**H**$_{arom.}$), 3.36 (td, *J* = 8.6, 2.4 Hz, 1H, NC(H)**H**CH_2CH_2), 2.64 – 2.53 (m, 1H, NC(**H**)HCH_2CH_2), 2.44 – 2.24 (m, 6H, N**CH_2**CH_2CH_3 and NCH_2CH_2C(H)**H** and CC**H_3**), 2.08 – 1.89 (m, 3H, NCH_2C**H_2**C(**H**)H), 1.55 – 1.39 (m, 2H, NCH_2C**H_2**CH_3), 0.85 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H_3**).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.6 (C_{quat}**C**CH), 136.7 (**C**$_{quat}CH_3$), 131.8 (C≡C**C**H$_{arom., ortho}$), 128.8 (CH_3C**C**H$_{arom.}$), 128.2 (C≡CC**H**$_{arom., meta}$), 127.8 (C≡CC**H**$_{arom., para}$), 126.8 (NCC**C**H$_{arom.}$), 123.7 (C≡C**C**CH), 88.9 (**C**≡CCH), 87.6 (C≡**C**CH), 68.7 (**C**$_{quat}$C≡CCH), 52.3 (N**C**$H_2CH_2CH_3$), 50.5 (N**C**$H_2CH_2CH_2$), 44.7 (NCH_2CH_2**C**H_2), 22.1 (NCH_2**C**H_2CH_3), 21.6 (NCH_2**C**H_2CH_2), 21.0 (Ph**C**H_3), 12.0 (NCH_2CH_2**C**H_3).
HRMS (ESI) m/z calculated for $[C_{22}H_{25}N+H]^+$: 304.2060; found 304.2073. Yellow oil, 188.1 mg (62%) isolated yield of 2-(phenylethynyl)-1-propyl-2-(p-tolyl)pyrrolidine (**4ac**) after column chromatography. R_f = 0.34 in 9/1 Hept/EtOAc.

2-(4-Methoxyphenyl)-2-(phenylethynyl)-1-propylpyrrolidine (**4ad**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 4-chloro-4'-methoxybutyrophenone (213 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



4ad

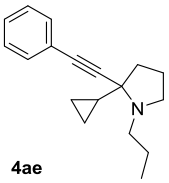
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.8 Hz, 2H, NCCC**H**$_{arom.}$), 7.52 – 7.45 (m, 2H, C≡CC**H**$_{arom., ortho}$), 7.33 – 7.22 (m, 3H, C≡CC**H**$_{arom., meta and para}$), 6.87 (d, *J* = 8.8 Hz, 2H, CH_3OCC**H**$_{arom.}$), 3.77 (s, 3H, OC**H$_3$**), 3.34 (td, *J* = 8.6, 2.5 Hz, 1H, NC(H)**H**CH_2CH_2), 2.62 – 2.52 (m, 1H, NC(**H**)HCH_2CH_2), 2.38 – 2.23 (m, 3H, NC**H$_2$**CH_2CH_3 and NCH_2CH_2C(H)**H**), 2.09 – 1.88 (m, 3H, NCH_2C**H$_2$**C(**H**)H), 1.55 – 1.37 (m, 2H, NCH_2C**H$_2$**CH_3), 0.85 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9 (**C**OCH_3), 135.7 (NC**C**$_{arom., quat}$), 131.9 (C≡C**C**H$_{arom., ortho}$), 128.3 (C≡C**C**H$_{arom., meta}$), 128.1 (NCCC**H**$_{arom.}$), 127.9 (C≡C**C**H$_{arom., para}$), 123.8 (C≡C**C**$_{arom., quat}$), 113.5 (CH_3OC**C**H$_{arom.}$), 89.0 (**C**≡CCH), 87.8 (C≡**C**CH), 68.5 (**C**$_{quat}$C≡CCH), 55.3 (O**C**H_3), 52.3 (N**C**$H_2CH_2CH_3$), 50.6 (N**C**$H_2CH_2CH_2$), 44.7 (NCH_2CH_2**C**H_2), 22.2 (NCH_2**C**H_2CH_3), 21.7 (NCH_2**C**H_2CH_2), 12.1 (NCH_2CH_2**C**H_3).

HRMS (ESI) m/z calculated for $[C_{22}H_{25}NO+H]^+$: 320.2009; found 320.2009. Yellow oil, 180.1 mg (56%) isolated yield of 2-(4-methoxyphenyl)-2-(phenylethynyl)-1-propylpyrrolidine (**4ad**) after column chromatography. R_f = 0.39 in 9/1 Hept/EtOAc.

2-Cyclopropyl-2-(phenylethynyl)-1-propylpyrrolidine (**4ae**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 1,7-dichloroheptan-4-one (183 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (118 mg, 2 mmol) in 2 mL toluene.



4ae

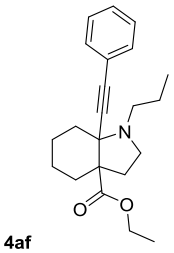
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.32 (m, 2H, C**H**$_{arom., ortho}$), 7.33 – 7.19 (m, 3H, C**H**$_{arom., meta and para}$), 3.19 (td, *J* = 8.7, 4.0 Hz, 1H, NC**H$_2$**CH_2CH_2), 2.95 – 2.84 (m, 1H, NC**H$_2$**CH_2CH_3), 2.48 (dd, J = 16.7, 9.0 Hz, 1H, NC**H$_2$**CH_2CH_2), 2.34 – 2.20 (m, 1H, NC**H$_2$**CH_2CH_3), 2.20 – 2.07 (m, 1H, NCH_2CH_2C**H$_2$**), 2.07 – 1.96 (m, 1H, NCH_2CH_2C**H$_2$**), 1.95 – 1.78 (m, 2H, NCH_2C**H$_2$**CH_2), 1.63 – 1.45 (m, 2H, NCH_2C**H$_2$**CH_3), 0.94 (t, *J* = 7.4 Hz, 3H, NCH_2CH_2C**H$_3$**), 0.90 – 0.81 (m, 1H, C**H**$(CH_2)_2$), 0.75 – 0.62 (m, 1H, CH(C**H$_2$**)$_2$), 0.58 – 0.48 (m, 1H, CH(C**H$_2$**)$_2$), 0.42 – 0.31 (m, 2H, CH(C**H$_2$**)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.9 (**C**H$_{arom., ortho}$), 128.3 (**C**H$_{arom., meta}$), 127.9 (**C**H$_{arom., para}$), 123.6 (**C**$_{arom., quat}$), 86.8 (**C**≡C), 86.7 (C≡**C**), 66.9 (N**C**$_{quat}$), 52.8 (N**C**$H_2CH_2CH_3$), 51.8 (N**C**$H_2CH_2CH_2$), 40.1 (NCH_2CH_2**C**H_2), 22.4 (NCH_2**C**H_2CH_3), 20.8 (NCH_2**C**H_2CH_2), 17.3 (**C**H$(CH_2)_2$), 12.5 (NCH_2CH_2**C**H_3), 3.0 (CH(**C**$H_2)_2$), -0.6 (CH(**C**$H_2)_2$).

HRMS (ESI) m/z calculated for $[C_{18}H_{23}N+H]^+$: 254.1903; found 254.1911. Yellow oil, 154.0 mg (61%) isolated yield of 2-cyclopropyl-2-(phenylethynyl)-1-propylpyrrolidine (**4ae**) after column chromatography. R_f = 0.28 in 9/1 Hept/EtOAc.

Ethyl 7a-(phenylethynyl)-1-propyloctahydro-3a*H*-indole-3a-carboxylate (**4af**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), ethyl 1-(2-chloroethyl)-2-oxocyclohexanecarboxylate (233 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).



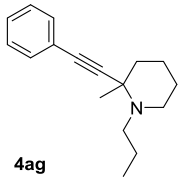
4af

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.30 (m, 2H, C**H**$_{arom., ortho}$), 7.28 – 7.19 (m, 3H, C**H**$_{arom., meta and para}$), 4.19 (q, *J* = 7.0 Hz, 2H, COOC**H$_2$**CH_3), 3.20 – 3.11 (m, 1H, NC**H$_2$**CH_2C_{quat}), 2.65 – 2.37 (m, 3H, NC**H$_2$**C**H$_2$**C_{quat} and NC**H$_2$**CH_2CH_3), 2.37 – 2.19 (m, 2H, NC**H$_2$**CH_2CH_3 and NCC**H$_2$**$CH_2CH_2CH_2$), 1.96 (d, *J* = 14.4 Hz, 1H, NCC**H$_2$**$CH_2CH_2CH_2$), 1.89 – 1.77 (m, 1H, $NCCH_2CH_2CH_2C$**H$_2$**), 1.75 – 1.56 (m, 4H, $NCCH_2C$**H$_2$**C**H$_2$**C**H$_2$** and NCH_2C**H$_2$**C_{quat}), 1.56 – 1.35 (m, 4H, $NCCH_2C$**H$_2$**C**H$_2$**CH_2 and NCH_2C**H$_2$**CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, $COOCH_2C$**H$_3$**), 0.93 (t, *J* = 7.3 Hz, 3H,

$NCH_2CH_2C\mathbf{H}_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.6 (**C**$OOCH_2CH_3$), 131.8 (**C**$H_{arom., ortho}$), 128.2 (**C**$H_{arom., meta}$), 127.7 (**C**$H_{arom., para}$), 123.8 (**C**$_{arom., quat}$), 89.8 (**C**≡CCH), 85.4 (C≡**C**CH), 63.3 (N**C**$_{quat}$), 60.3 ($COO\mathbf{C}H_2CH_3$), 55.4 (**C**$_{quat}COOCH_2CH_3$), 50.9 ($N\mathbf{C}H_2CH_2CH_3$), 47.8 ($N\mathbf{C}H_2CH_2C_{quat}$), 32.7 ($NCCH_2CH_2CH_2\mathbf{C}H_2$), 32.2 ($NCH_2\mathbf{C}H_2C_{quat}$), 29.9 ($NC\mathbf{C}H_2CH_2CH_2CH_2$), 22.4 ($NCCH_2CH_2\mathbf{C}H_2CH_2$), 21.8 ($NCH_2\mathbf{C}H_2CH_3$), 19.6 ($NCCH_2\mathbf{C}H_2CH_2CH_2$), 14.4 ($COOCH_2\mathbf{C}H_3$), 12.3 ($NCH_2CH_2\mathbf{C}H_3$).
HRMS (ESI) m/z calculated for $[C_{22}H_{29}NO_2+H]^+$: 340.2271; found 340.2276. Colorless oil, 154.0 mg (61%) isolated yield of ethyl 7a-(phenylethynyl)-1-propyloctahydro-3a*H*-indole-3a-carboxylate (**4af**) after column chromatography. R_f = 0.61 in 9/1 Hept/EtOAc.

2-Phenyl-2-(phenylethynyl)-1-propylpiperidine (**4ag**)

The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 6-chlorohexan-2-one (135 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol).

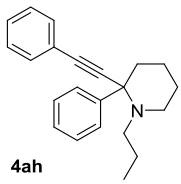

4ag

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 - 7.39 (m , 2H, C**H**$_{arom., ortho}$), 7.31 – 7.19 (m, 3H, C**H**$_{arom., meta and para}$), 2.83 – 2.77 (m, 1H, NC(H)**H**CH_2CH_2), 2.77 – 2.69 (m, 1H, NC(H)**H**CH_2CH_3), 2.39 (td, *J* = 11.8, 2.7 Hz, 1H, NC(**H**)HCH_2CH_2), 2.13 (ddd, *J* = 13.0, 9.4, 4.9 Hz, 1H, NC(**H**)HCH_2CH_3), 1.84 – 1.74 (m, 1H, $NCH_2C(H)\mathbf{H}CH_2$), 1.74 – 1.38 (m, 7H, $NCH_2C\mathbf{H}_2CH_3$ and $NCH_2C\mathbf{H}_2C(\mathbf{H})HC\mathbf{H}_2$), 1.44 (s, 3H, C**H**$_3C_{quat}$), 0.90 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.7 (**C**$H_{arom., ortho}$), 128.2 (**C**$H_{arom., meta}$), 127.6 (**C**$H_{arom., para}$), 123.8 (C≡**C**CH), 90.9 (**C**≡CCH), 85.6 (C≡**C**CH), 55.7 ($CH_3\mathbf{C}_{quat}$), 53.7 ($N\mathbf{C}H_2CH_2CH_3$), 49.1 ($NC\mathbf{H}_2CH_2CH_2$), 40.5 ($C_{quat}\mathbf{C}H_2$), 28.8 ($\mathbf{C}H_3C_{quat}$), 26.3 ($NCH_2\mathbf{C}H_2CH_2$), 22.0 ($NCH_2CH_2\mathbf{C}H_2$), 21.7 ($NCH_2\mathbf{C}H_2CH_3$), 12.1 ($NCH_2CH_2\mathbf{C}H_3$).
HRMS (ESI) m/z calculated for for $[C_{17}H_{23}N+H]^+$: 242.1903; found 242.1912. Colorless oil, 212.5 mg (88%) isolated yield of 2-phenyl-2-(phenylethynyl)-1-propylpiperidine (**4ag**) after column chromatography. R_f = 0.31 in 9/1 Heptane/EtOAc.

2-Phenyl-2-(phenylethynyl)-1-propylpiperidine (**4ah**)

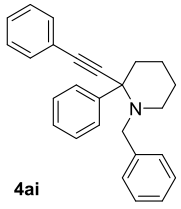
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloro-1-phenylpentan-1-one (197 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *n*-propylamine (207 mg, 3.5 mmol). Reaction time: 24 h, reaction temperature: 90 °C.


4ah

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 7.5 Hz, 2H, NCCC**H**$_{arom., ortho}$), 7.61 – 7.50 (m, 2H, C≡CC**H**$_{arom., ortho}$), 7.38 – 7.20 (m, 6H, C**H**$_{arom}$), 3.03 (d, *J* = 11.1 Hz, 1H, NC(H)**H**CH_2CH_2), 2.50 (t, *J* = 11.9 Hz, 1H, NC(**H**)HCH_2CH_2), 2.33 – 2.17 (m, 1H, NC(H)**H**CH_2CH_3), 2.05 – 1.95 (m, 1H, NC(**H**)HCH_2CH_3), 1.90 – 1.77 (m, 3H, $NCH_2CH_2C(H)\mathbf{H}C\mathbf{H}_2$), 1.77 – 1.58 (m, 3H, $NCH_2C(\mathbf{H})HC\mathbf{H}_2$), 1.50 – 1.31 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$), 0.74 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2C\mathbf{H}_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.2 (NC**C**$_{quat}$), 131.8 (**C**$H_{arom.}$), 128.3 (**C**$H_{arom.}$), 128.0 (**C**$H_{arom.}$), 127.9 (**C**$H_{arom.}$), 127.0 (**C**$H_{arom.}$), 126.8 (**C**$H_{arom.}$), 123.7 (**C**$_{quat}$(C≡CPh)), 89.5 (**C**≡CPh), 88.1 (C≡**C**Ph), 65.8 (N**C**$_{quat}$), 54.6 ($N\mathbf{C}H_2CH_2CH_3$), 48.4 ($N\mathbf{C}H_2CH_2CH_2$), 43.6 ($NCH_2CH_2CH_2\mathbf{C}H_2$), 26.1 ($NCH_2\mathbf{C}H_2CH_2$), 22.5 ($NCH_2CH_2\mathbf{C}H_2$), 20.9 ($NCH_2\mathbf{C}H_2CH_3$), 11.8 ($NCH_2CH_2\mathbf{C}H_3$).
HRMS (ESI) m/z calculated for $[C_{22}H_{25}N+H]^+$: 304.2060; found 304.2054. Colorless oil, 267.0 mg (88%) isolated yield of 2-phenyl-2-(phenylethynyl)-1-propylpiperidine (**4ah**) after column chromatography. R_f = 0.47 in 9/1 Hept/EtOAc.

1-Benzyl-2-phenyl-2-(phenylethynyl)piperidine (**4ai**)

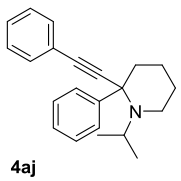
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloro-1-phenylpentan-1-one (197 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and benzylamine (107 mg, 1 mmol). Reaction time: 24 h, reaction temperature: 90 °C.


4ai

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 7.6 Hz, 2H, NCCC**H**$_{arom., ortho}$), 7.64 – 7.55 (m, 2H, C≡CCC**H**$_{arom., ortho}$), 7.40 – 7.28 (m, 7H, C**H**$_{arom.}$), 7.28 – 7.20 (m, 3H, C**H**$_{arom.}$), 7.20 – 7.11 (m, 1H, C**H**$_{arom., para}$(Bn)), 3.65 (d, *J* = 14.0 Hz, 1H, NC(H)**H**Bn), 3.07 (d, *J* = 14.0 Hz, 1H, NC(**H**)HBn), 2.82 (d, *J* = 11.7 Hz, 1H, NC(H)**H**CH_2), 2.51 (td, *J* = 11.5, 4.0 Hz, 1H, NC(**H**)HCH_2), 2.01 – 1.79 (m, 3H, $NCH_2CH_2C(H)$**H**C**H**$_2$), 1.74 – 1.52 (m, 3H, NCH_2CH_2C(**H**)HC**H**$_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.7 (NC**C**$_{quat}$), 140.1 (**C**$_{quat}$(Bn)), 131.9 (**C**H$_{arom.}$), 128.4 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 128.1 (**C**H$_{arom.}$), 128.0 (**C**H$_{arom.}$), 127.3 (**C**H$_{arom.}$), 126.7 (**C**H$_{arom.}$), 126.5 (**C**H$_{arom.}$), 123.5 (HC**C**$_{quat}$C≡C), 90.0 (Ph**C**≡C), 87.5 (PhC≡**C**), 65.6 (N**C**$_{quat}$), 56.8 (N**C**H_2Bn), 48.4 (N**C**$H_2CH_2CH_2CH_2$), 43.5 ($NCH_2CH_2CH_2C$**H**$_2$), 25.9 (NCH_2**C**$H_2CH_2CH_2$), 22.6 (NCH_2CH_2**C**H_2CH_2).
HRMS (ESI) m/z calculated for for $[C_{26}H_{25}N+H]^+$: 352.2060; found 352.2077. Colorless oil, 212.4 mg (60%) isolated yield of 1-benzyl-2-phenyl-2-(phenylethynyl)piperidine (**4ai**) after column chromatography. R_f = 0.61 in 9/1 Hept/EtOAc.

1-*Iso*propyl-2-phenyl-2-(phenylethynyl)piperidine (**4aj**)

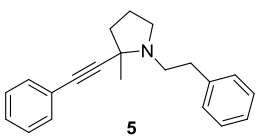
The general procedure was used with Cu_2O (36 mg, 0.25 mmol), *N*-(5-chloro-1-phenylpentylidene)propan-2-amine (238 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and triethylamine (101 mg, 1 mmol). Reaction time: 24 h, reaction temperature: 90 °C.


4aj

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 7.6 Hz, 2H, NCCC**H**$_{arom., ortho}$), 7.55 – 7.49 (m, 2H, C≡CCC**H**$_{arom., ortho}$), 7.39 – 7.28 (m, 5H, C**H**$_{arom}$), 7.27 – 7.21 (m, 1H, C**H**$_{arom.}$), 2.90 – 2.78 (m, 3H, N**H**$_2CH_2CH_2$ and N**H**$(CH_3)_2$), 1.92 – 1.72 (m, 4H, $NCH_2C(H)$**H**C(H)**H**C**H**$_2$), 1.71 – 1.52 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.06 and 0.91 (d, *J* = 6.6 Hz,2 x 3H, NCH(C**H**$_3)_2$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.1 (NC**C**$_{quat}$), 131.5 (C≡C**C**H$_{arom., ortho}$), 128.4 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 128.1 (**C**H$_{arom.}$), 128.0 (**C**H$_{arom.}$), 128.0 (**C**H$_{arom.}$), 127.9 (**C**H$_{arom.}$), 127.0 (**C**H$_{arom.}$), 127.0 (**C**H$_{arom.}$), 126.9 (**C**H$_{arom.}$), 123.9 (C≡C**C**H$_{arom., quat}$), 90.8 (**C**≡CPh), 89.5 (C≡**C**Ph), 64.7 (N**C**$_{quat}$), 49.0 (N**C**H), 45.2 ($NCH_2CH_2CH_2$**C**H_2), 41.2 (N**C**$H_2CH_2CH_2CH_2$), 26.7 (NCH_2CH_2**C**H_2), 23.0 (NCH_2**C**H_2CH_2), 22.9 (NCH(**C**$H_3)_2$), 16.0 (NCH(**C**$H_3)_2$).
HRMS (ESI) m/z calculated for for $[C_{22}H_{25}N+H]^+$: 304.2060; found 304.2054. Colorless oil, 101.3 mg (33%) isolated yield of 1-*iso*propyl-2-phenyl-2-(phenylethynyl)piperidine (**4aj**) after column chromatography. R_f = 0.45 in 9/1 Hept/EtOAc.

3.8.3 Procedure and characterization data for side products 5, 6 and 7

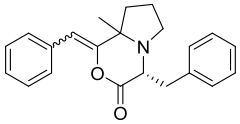
2-Methyl-1-phenethyl-2-(phenylethynyl)pyrrolidine (**5**)


5

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.34 (m, 2H, C≡CC**H**$_{arom., ortho}$), 7.31 – 7.22 (m, 7H, C**H**$_{arom.}$), 7.19 (t, *J* = 7.0 Hz, 1H, C**H**$_{arom.}$), 3.31 – 3.20 (m, 1H, NC**H**(H)CH_2CH_2), 2.98 (td, *J* = 10.9, 6.2 Hz, 1H, NC**H**(H)CH_2Ph), 2.92 – 2.75 (m, 2H, NCH_2C**H**$_2$Ph), 2.67 – 2.54 (m, 2H, NCH(**H**)CH_2Ph and NCH(**H**)CH_2CH_2), 2.23 – 2.12 (m, 1H, NCH_2CH_2C(**H**)H), 1.98 – 1.78 (m, 3H, NCH_2C**H**$_2$C(H)**H**), 1.43 (s, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.8 (CH_2**C**$_{arom.}$), 131.7 (C≡CC**C**H$_{arom., ortho}$), 128.8 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 128.2 (**C**H$_{arom.}$),

127.7 (C≡C**C**H$_{arom.,\ para}$), 126.0 (CH$_2$C**C**H$_{arom.,\ para}$), 123.5 (C≡C**C**$_{arom.}$), 90.8 (**C**≡CC$_{arom.}$), 84.6(C≡**C**C$_{arom.}$), 60.5 (N**C**$_{quat}$), 52.1 (N**C**H$_2$CH$_2$Ph), 51.5 (N**C**H$_2$CH$_2$CH$_2$), 40.6 (NCH$_2$CH$_2$**C**H$_2$), 36.0 (NCH$_2$**C**H$_2$Ph), 25.6 (**C**H$_3$), 20.6 (NCH$_2$**C**H$_2$CH$_2$). **HRMS** (ESI) m/z calculated for for [C$_{21}$H$_{23}$N+H]$^+$: 290.1903; found 290.1905. Colorless oil, 85 mg (29%) isolated yield of 2-methyl-1-phenethyl-2-(phenylethynyl)pyrrolidine (**5**) after column chromatography. R$_f$ = 0.70 in 9/1 Hept/EtOAc.

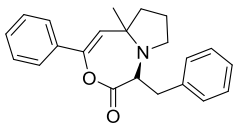
(4*R*)-4-benzyl-1-benzylidene-8a-methyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3(4*H*)-one (**6**)



6

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.70 – 7.10 (m, 10H, C**H**$_{arom.}$), 5.85 (s, 1H, C=C**H**), 3.62 (dd, *J* = 7.7, 7.7 Hz, 1H, NC**H**C=O), 3.26 – 3.19 (m, 1H, NC**H**(H) CH$_2$CH$_2$), 3.10 (dd, *J* = 13.9, 8.3 Hz, 1H, NCHC**H**(H)), 3.02 (dd, *J* = 13.9, 7.0 Hz, 1H, NCHCH(**H**)), 2.72 – 2.60 (m, 1H, NCH(**H**)CH$_2$CH$_2$), 2.24 – 2.12 (m, 1H, NCH$_2$CH$_2$C(**H**)H), 1.95 – 1.81 (m, 3H, NCH$_2$C**H**$_2$C(H)**H**), 1.49 (s, 3H, C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ = 169.1 (**C**=O), 152.3 (O**C**=C), 137.1 (CH$_2$**C**$_{arom.}$), 134.2 (**C**H$_{arom.}$), 134.1 (**C**H$_{arom.}$), 133.6 (OC**C**$_{arom.}$), 129.3 (**C**H$_{arom.}$), 129.3 (**C**H$_{arom.}$), 129.2 (**C**H$_{arom.}$), 129.2 (**C**H$_{arom.}$), 128.6 (**C**H$_{arom.}$), 128.5 (**C**H$_{arom.}$), 127.4 (**C**H$_{arom.}$), 126.8 (**C**H$_{arom.}$), 109.0 (OC=**C**), 65.4 (N**C**HCH$_2$), 62.4 (N**C**$_{quat}$), 56.7 (N**C**H$_2$CH$_2$CH$_2$), 39.3 (NCH$_2$CH$_2$**C**H$_2$), 38.0 (NCH**C**H$_2$), 28.6 (**C**H$_3$), 24.2 (NCH$_2$**C**H$_2$CH$_2$). **HRMS** (ESI) m/z calculated for for [C$_{22}$H$_{23}$NO$_2$+H]$^+$: 334.1802; found 352.1911 and 366.2063 as the hydrolysis product (calculated: [C$_{22}$H$_{25}$NO$_3$+H]$^+$: 352.1907) and methanol-transesterification product (calculated: [C$_{23}$H$_{27}$NO$_3$+H]$^+$: 366.2064). Colorless oil, 11.3 mg (3%) isolated yield of (4*R*)-4-benzyl-1-benzylidene-8a-methyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-3(4*H*)-one (**6**) after column chromatography. R$_f$ = 0.45 in 9/1 Hept/EtOAc.

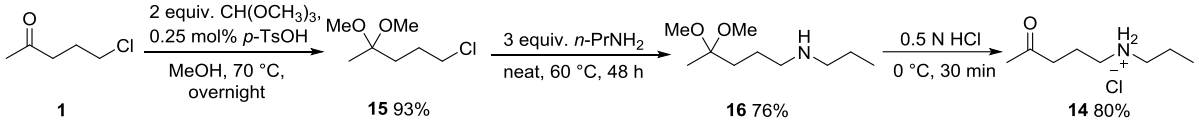
(5*R*)-5-Benzyl-9a-methyl-2-phenyl-7,8,9,9a-tetrahydropyrrolo[1,2-*d*][1,4]oxazepin-4(5*H*)-one (**7**)



7

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.57 (d, *J* = 7.5 Hz, 2H, C**H**$_{arom.}$), 7.34 – 7.18 (m, 8H, C**H**$_{arom.}$), 5.76 (s, 1H, C=C**H**), 3.75 (dd, *J* = 7.0, 7.0 Hz, 1H, NC**H**C=O), 3.23 (dd, *J* = 14.8, 6.3 Hz, 1H, NCHC**H**(H)), 3.18 – 3.10 (m, 1H, NC**H**(H)CH$_2$CH$_2$), 2.91 (dd, *J* = 14.7, 7.6 Hz, 1H, NCHCH(**H**)), 2.62 – 2.53 (m, 1H, NCH(**H**)CH$_2$CH$_2$), 2.17 – 2.03 (m, 1H, NCH$_2$CH$_2$C(**H**)H), 1.95 – 1.80 (m, 3H, NCH$_2$C**H**$_2$C(H)**H**), 1.39 (s, 3H, C**H**$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ = 169.9 (**C**=O), 153.2 (O**C**=C), 138.0 (CH$_2$**C**$_{arom.}$), 133.6 (OC**C**$_{arom.}$), 129.2 (**C**H$_{arom.}$), 129.0 (**C**H$_{arom.}$), 128.5 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 127.3 (**C**H$_{arom.}$), 126.5 (**C**H$_{arom.}$), 109.6 (OC=**C**), 65.3 (N**C**$_{quat}$), 59.9 (N**C**HCH$_2$), 49.8 (N**C**H$_2$CH$_2$CH$_2$), 39.5 (NCH$_2$CH$_2$**C**H$_2$), 34.2 (NCH**C**H$_2$), 25.2 (**C**H$_3$), 23.8 (NCH$_2$**C**H$_2$CH$_2$). **HRMS** (ESI) m/z calculated for for [C$_{22}$H$_{23}$NO$_2$+H]$^+$: 334.1802; found 352.1911 and 366.2063 as the hydrolysis product (calculated: [C$_{22}$H$_{25}$NO$_3$+H]$^+$: 352.1907) and methanol-transesterification product (calculated: [C$_{23}$H$_{27}$NO$_3$+H]$^+$: 366.2064). Colorless oil, 84.1 mg (25%)isolated yield of (5*R*)-5-benzyl-9a-methyl-2-phenyl-7,8,9,9a-tetrahydropyrrolo[1,2-*d*][1,4]oxazepin-4(5*H*)-one (**7**) after column chromatography. R$_f$ = 0.50 in 9/1 Hept/EtOAc.

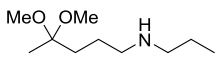
3.8.4 Procedure and characterization data for mechanistic control experiments



Product **15** was synthesized according to a known literature method, and a similar yield was obtained.[27] Then, the substitution reaction of **15** with *n*-propylamine yielded product **16** in 76%, the reaction was only complete after 48 h at 60 °C, proving the difficult substitution. The deprotection of **16** in aqueous HCl was very fast. Product **14** is stable as ammonium salt, upon basifying, the free amine decomposes, probably due to rapid intramolecular imine-enamine formation.

4,4-dimethoxy-*N*-propylpentan-1-amine (**16**)

In a microwave vessel 80 mL were introduced 1-chloro-4,4-dimethoxypentane (**15**) (5.00 g, 30 mmol) and *n*-propylamine (7.39 ml, 90 mmol) at 0 °C under argon. The reaction mixture was heated at 60 °C for 48 h, and then cooled. Afterwards, the reaction mixture was poured in 100 mL 0.5 N NaOH (neutralization of HCl salts) and extracted with Et_2O (2 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The product was not further purified, and used as such in the next step.

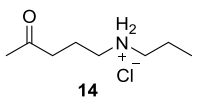

16

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.17 (s, 6H, C(OC**H**$_3$)$_2$), 2.61 (t, *J* = 7.3 Hz, 2H, NC**H**$_2$CH$_2$CH$_2$), 2.57 (t, *J* = 7.2 Hz, 2H, NC**H**$_2$CH$_2$CH$_3$), 1.67 – 1.58 (m, 2H, NCH$_2$CH$_2$C**H**$_2$), 1.57 – 1.40 (m, 4H, NCH$_2$C**H**$_2$CH$_2$ and NCH$_2$C**H**$_2$CH$_3$), 1.27 (s, 3H, C$_{quat}$C**H**$_3$), 1.24 – 1.11 (br s, 1H, N**H**), 0.92 (t, 3H, *J* = 7.4 Hz, NCH$_2$CH$_2$C**H**$_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 101.7 (**C**$_{quat}$(OCH$_3$)$_2$), 52.0 (N**C**H$_2$CH$_2$CH$_3$), 50.2 (N**C**H$_2$CH$_2$CH$_2$), 48.0 (C$_{quat}$(O**C**H$_3$)$_2$), 34.4 (NCH$_2$CH$_2$**C**H$_2$), 25.1 (NCH$_2$**C**H$_2$CH$_2$), 23.3 (NCH$_2$**C**H$_2$CH$_3$), 21.0 (**C**H$_3$C$_{quat}$(OCH$_3$)$_2$), 11.8 (NCH$_2$CH$_2$**C**H$_3$).

HRMS (ESI) m/z calculated for $[C_{10}H_{23}NO_2+H]^+$: 190.1802; found 190.1801. Orange oil, 4.31 g (76%) crude yield of 4,4-dimethoxy-*N*-propylpentan-1-amine (**16**)**.**

4-Oxo-*N*-propylpentan-1-aminium chloride (**14**)

In a round bottomed flask were introduced 4,4-dimethoxy-*N*-propylpentan-1-amine (**16**) (0.946 g, 5 mmol) in 10 mL of DCM and 8 ml of H_2O under argon and then at 0 °C 2 mL of 3 N HCl was added. Upon addition, the reaction mixture immediately changed color from orange to black after 1 equivalent of HCl was added. The reaction mixture was further stirred at 0 °C for 1 h. Then, the aqueous phase was separated and concentrated *in vacuo.* The crude product was then purified via reverse phase column chromatography on a C18 column, eluting with 0.3 N HCl/MeCN.


14

^{1}H NMR (400 MHz, D_2O) δ = 4.18 (t, *J* = 7.4 Hz, 2H, NC**H**$_2$CH$_2$CH$_2$), 3.77 (t, *J* = 7.4 Hz, 2H, NC**H**$_2$CH$_2$CH$_3$), 3.22 (t, *J* = 7.8 Hz, 2H, NCH$_2$CH$_2$C**H**$_2$), 2.44 (s, 3H, C**H**$_3$C=O), 2.21 (p, *J* = 8.0 Hz, NCH$_2$C**H**$_2$CH$_2$), 1.85 – 1.73 (m, 2H,NCH$_2$C**H**$_2$CH$_3$), 0.95 (t, 3H, *J* = 7.4 Hz, NCH$_2$CH$_2$C**H**$_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.0 (**C**=O), 60.3 (N**C**H$_2$CH$_2$CH$_2$), 52.2 (N**C**H$_2$CH$_2$CH$_3$), 40.8 (NCH$_2$CH$_2$**C**H$_2$), 20.3 (NCH$_2$**C**H$_2$CH$_3$), 18.3 (NCH$_2$**C**H$_2$CH$_2$), 17.0 (**C**H$_3$C=O), 10.7

($NCH_2CH_2\mathbf{C}H_3$). MeCN was used as reference in these spectra (2.06 ppm in ^{1}H and 1.47 ppm in ^{13}C).

HRMS (ESI) According to previous literature,[28] γ-aminoketones are unstable. The product peak was never observed, instead, the cyclic iminium, the presumable intermediate in the reaction, was obtained. m/z calculated for $[C_8H_{15}N+H]^+$: 126.1277; found 126.1286. Brown oil, 719 mg (80%) crude yield of 4-oxo-*N*-propylpentan-1-aminium chloride (**13**) after column chromatography**.** R_f = 0.55 in 0.3 M HCl.

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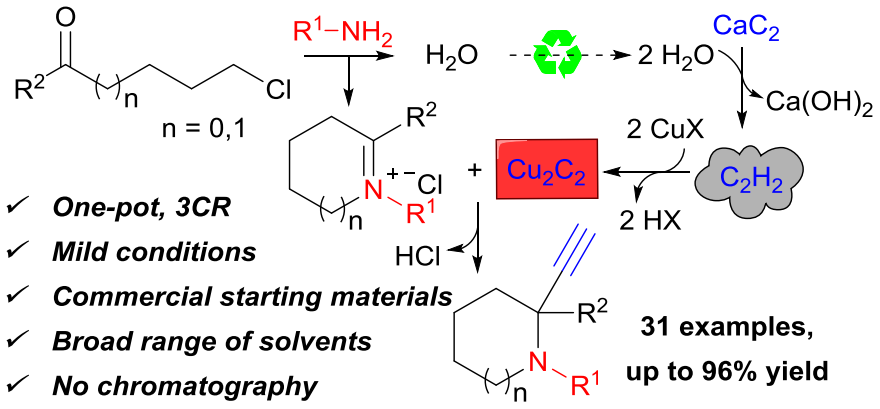
4 Calcium Carbide as alkyne source in one-pot KA² couplings

In this chapter we intend to use calcium carbide as an alternative and green acetylene source in alkynylation reactions on halogenated imines, in order to synthesize terminal propargylamines. To date, there are only a handful of reports describing the use of calcium carbide in organic synthesis reactions, other than hydrolysis. To better understand the reactivity of calcium carbide and problems associated with the use of calcium carbide, a literature overview of these reactions is included in the first part of this chapter. In the second part, different imine systems for alkynylation with calcium carbide were evaluated, and expansion towards a one-pot procedure is included. We can conclude that iminium species always needs to be formed, otherwise no alkynylation can occur. Exceptionally, the A³ coupling between an aldehyde, a primary amine and calcium carbide gave some coupling product, but conversion eventually halted around 10%. Lastly, a few test reactions regarding the use of calcium carbide in Sonogashira cross-coupling reactions on aliphatic halides were evaluated, but no coupling product was observed in this case.



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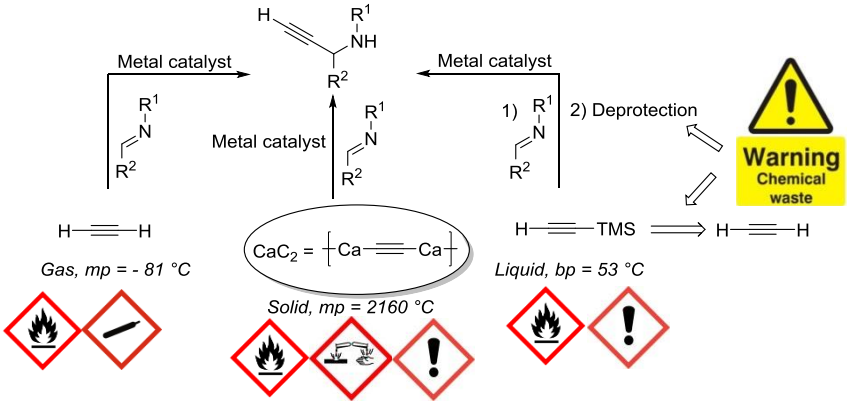
4.1 Introduction

4.1.1 Rationalization

Calcium carbide can be seen as an alternative to the use of acetylene or protected acetylene (*e.g.* TMS-acetylene) in organic synthesis (Scheme 4-1). Problems associated with acetylene are its intrinsic instability[1] that causes the molecule to be highly flammable and explosive (although this hazard is not identified as such with the GHS pictogram 'Explosive').[1-2] These properties are often exploited as acetylene is used as fuel in welding, where very high flame temperatures are needed. For industrial applications, the use of pressurized acetylene has historically been regarded as safe, since it has been used for years.[2] In an organic research laboratory, acetylene, however, is an unwanted reagent, owing to its difficult handling as a gas and dangerous properties. Often, TMS-acetylene is used instead of acetylene in, among others, alkynylation reactions.[3] Since TMS-acetylene is a liquid at room temperature, handling and storage are easy. The use of TMS-acetylene is essentially non eco-friendly, since TMS-acetylene has to be synthesized from an acetylene source and TMS-chloride, and the TMS-group has to be removed after alkynylation to generate the terminal propargylamine, generating a lot of waste in the process.



Scheme 4-1 Rationalization for the use of calcium carbide.

Handling and storage of calcium carbide or TMS-acetylene is thus much easier than using acetylene. From an economical point of view it is more interesting to use calcium carbide, since it is much cheaper than TMS-acetylene.[4]

4.1.2 Calcium carbide properties

Calcium carbide is made industrially in an electric arc furnace from a mixture of lime (CaO) and coke (C) at temperatures around 2200 °C, according to Equation 1.

$$CaO + 3\,C \xrightarrow{\Delta} CaC_2 + CO \quad (1)$$

Calcium carbide formed in this way generally has a gas/volumetric purity of around 75 – 80%, and is sold as such. Alternatively, calcium carbide can be synthesized from CaO and renewable fine biochars such as apricot shell, willow wood, bamboo, corncob and pine wood. In addition, the parameters of this process are milder; the formation of calcium carbide can be accomplished in less than 5 minutes, whereas in the classical process this takes up to 2 hours and the temperature needed for this transformation should only be 1650 °C.[5]

Calcium carbide is used, on industrial scale, for the synthesis of acetylene via simple hydrolysis, generating calcium hydroxide as byproduct (Equation 2).

$$CaC_2 + 2\,H_2O \rightarrow C_2H_2 + Ca(OH)_2 \quad (2)$$

The carbide lamp is an example of an application using this reaction. Dripping of water on calcium carbide produced acetylene, which could be set on fire, giving a bright and steady flame, which could be used for light (Figure 4-1).

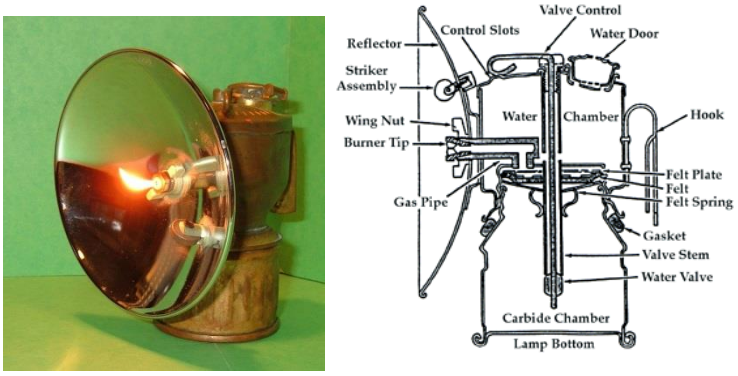


Figure 4-1 Left: Lit carbide lamp. Right: Schematic overview of the carbide lamp.

Impurities (up to 25%!) can be present, which might be problematic for catalysis applications, since these impurities can interact with the transition metal catalyst, making it inactive. From hydrolysis of calcium carbide, next to acetylene other gases such as carbon monoxide, methane, ethane and propyne are formed in small quantities, but the most important impurities are phosphides, which upon hydrolysis, form phosphine next to calcium hydroxide (Equation 3).[6]

$$Ca_3P_2 + 6\,H_2O \rightarrow 2\,PH_3 + 3\,Ca(OH)_2 \quad (3)$$

Acetylene is also generated industrially from natural gas and petroleum-based hydrocarbons. Chemical uses account for 88%, and industrial uses (primarily cutting and welding) accounts for 12% of the total consumption. China is with 95% of the total acetylene production and consumption the most important player.[7] Other commercial applications of calcium carbide, next to the generation of acetylene, are the production of the fertilizer calcium cyanamide (from calcium carbide and nitrogen) and the use as desulfurization reagent in iron/steel production. Again, China controls the global calcium carbide market with 96% of total production and consumption.[8] Exact figures for the production and consumption of calcium carbide are not known, but amounts are very high, since for the generation of calcium carbide a staggering figure of 56 Mt of CO_2 was emitted by China alone in 2013.[9]

Calcium carbide has many different forms and is in pure form a colorless material, but due to the presence of impurities it is often a grey-brown solid. Different crystal structures of calcium carbide exist and are named calcium carbide I, II, III and IV.[10] The stable form at room temperature is a distorted rock-salt structure with the C_2^{2-} units lying parallel.[11]

Due to its high polarity, calcium carbide is soluble in almost none of the classical organic solvents. In water, it very quickly hydrolyses. The higher the polarity of the solvent, the more chance of slight solubility, and reactions involving calcium carbide in solvents like DMSO, DMF and MeCN are possible (*vide infra*). Liquid ammonia is known to solute some carbides.[12] Small amounts of water present in solvents cause immediate hydrolysis, generating acetylene *in situ*.

4.2 Organic synthesis reactions using calcium carbide

Although calcium carbide is a chemical component produced on megaton scale, reactions other than the hydrolysis for the generation of acetylene are scarce. A SciFinder search for the use of calcium carbide in 'any role' in reactions, results as of March 2018 only in 117 references, with the majority being patents (often Chinese) for acetylene generation from calcium carbide. When we plot the amount of publications versus year/decade, it is clear that calcium carbide has received increased attention in the last five years (Figure 4-2).

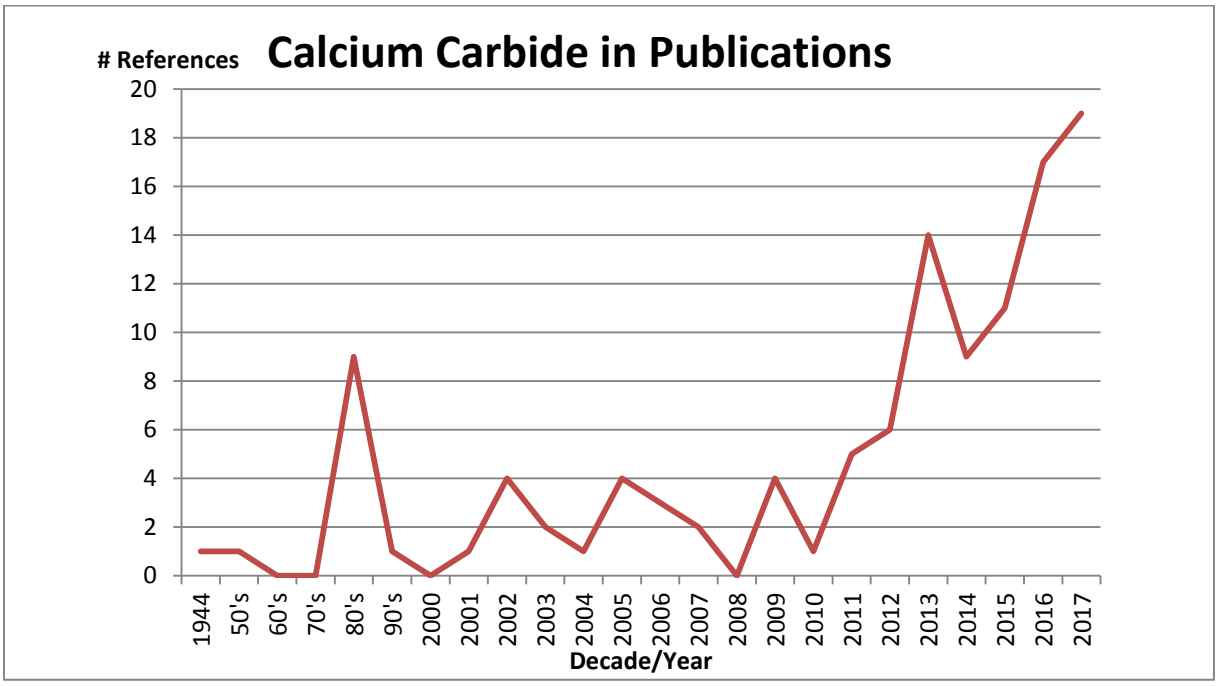
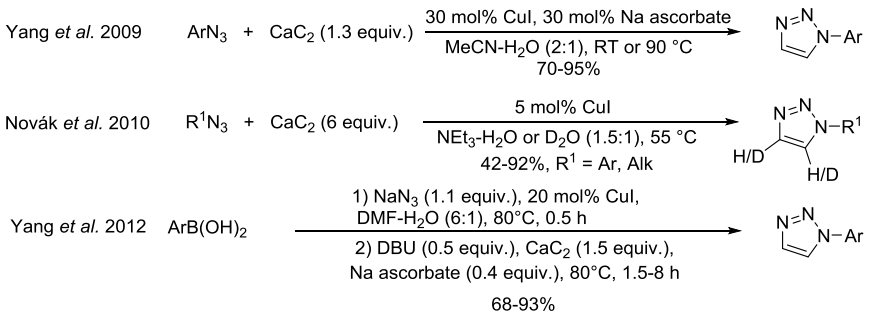


Figure 4-2 Number of scientific publications (journal articles and patents) using CaC_2 in organic synthesis.

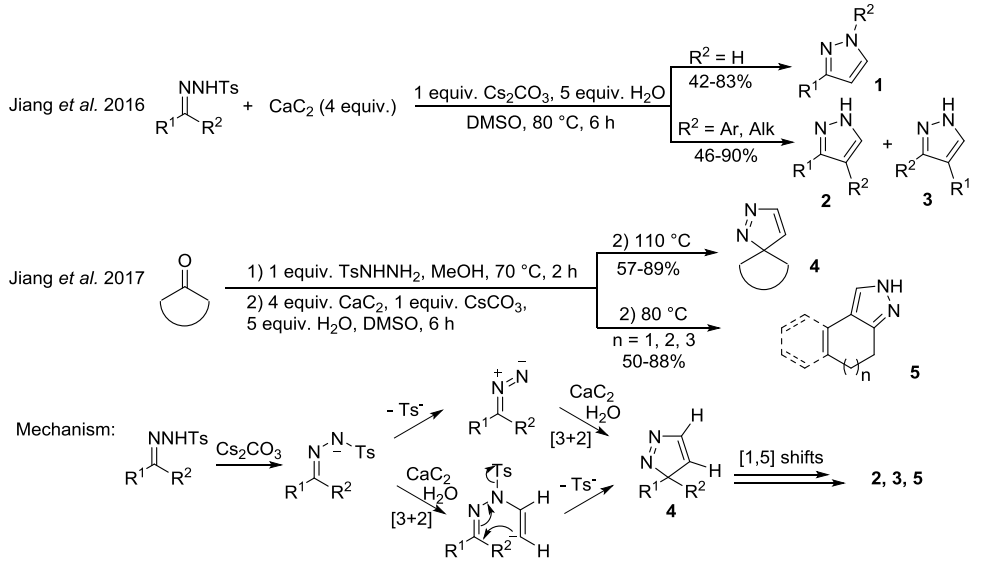
4.2.1 Calcium carbide as dipolarophile in organic synthesis reactions

Calcium carbide, or rather the hydrolysis product of calcium carbide, can be used in cycloaddition reactions as dipolarophile. The first example is the Huisgen [3+2] cycloaddition of azides and alkynes, and was firstly reported in 2009 by Yang *et al.* (Scheme 4-2).[13] The reaction conditions were slightly adapted by Novák *et al.* in 2010, and allowed the use of alkylazides next to arylazides, while also D_2O was used generating deuterated 1,2,3-triazoles.[14] In 2012, Yang *et al.* reported a similar procedure as in 2009, but starting from arylboronic acids, generating arylazides *in situ*.[15]



Scheme 4-2 Calcium carbide in [3+2] 'Huisgen' cycloadditions.

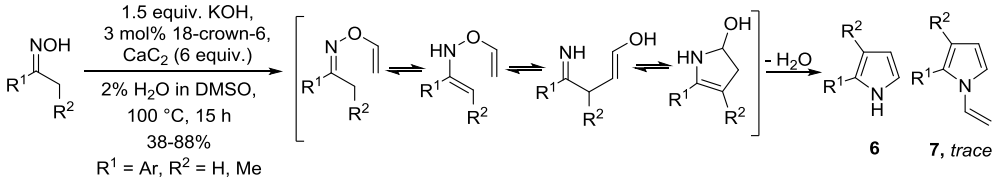
A second example consists of the [3+2] cycloaddition of tosylhydrazones and alkynes, followed by *in situ* [1,5] rearrangement of spirocyclic pyrazoles **4** and was first reported by Jiang *et al.* in 2016 (Scheme 4-3).[16] When the reaction was carried out with hydrazones derived from aldehydes, cycloaddition (either with *in situ* formed azomethine imines or diazo compounds) and elimination of the tosyl-group, is followed by a [1,5]-hydride shift, giving pyrazoles **1**. When ketone-derived hydrazones were used on the other hand, one of the two ketone side chains undergoes a [1,5]-sigmatropic rearrangement, giving a mixture of regioisomeric pyrazoles **2** and **3**. In 2017, the same group published a similar reaction, starting from cyclic ketones, that form spirocyclic pyrazoles **4** that, in some cases, underwent a [1,5]-sigmatropic rearrangement, and [1,5]-hydride shift to form fused pyrazoles **5**.[17]



Scheme 4-3 [3+2] cycloadditions of *in situ* formed azomethine imines and calcium carbide.

4.2.2 Calcium carbide as electrophile in organic synthesis reactions

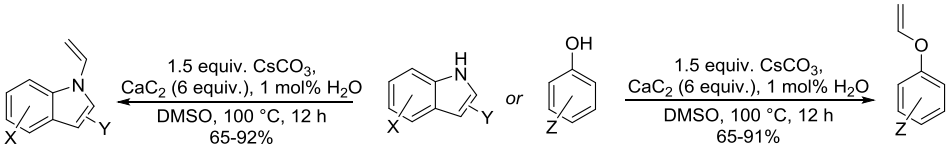
Although counterintuitive, calcium carbide, or again rather the hydrolysis product acetylene, can be used in different reactions as an electrophile. The first reported reaction was the substitution of acetylene by calcium carbide in a Trofimov reaction[18] - this is the reaction of oximes and acetylene in superbasic reaction media – and was reported by Wacharasindhu *et al.* in 2015 (Scheme 4-4).[19] Using superbasic conditions, the authors made pyrroles **6** and trace amounts of vinyl pyrroles **7** from ketoximes. The authors proposed a mechanism where the ketoxime adds to the *in situ* hydrolyzed calcium carbide, and tautomerization generates an enamine that undergoes a sigmatropic rearrangement to form an enol-imine intermediate that ultimately ring closes and upon loss of water generates the pyrrole **6**.



Scheme 4-4 Trofimov-like reaction using calcium carbide instead of acetylene.

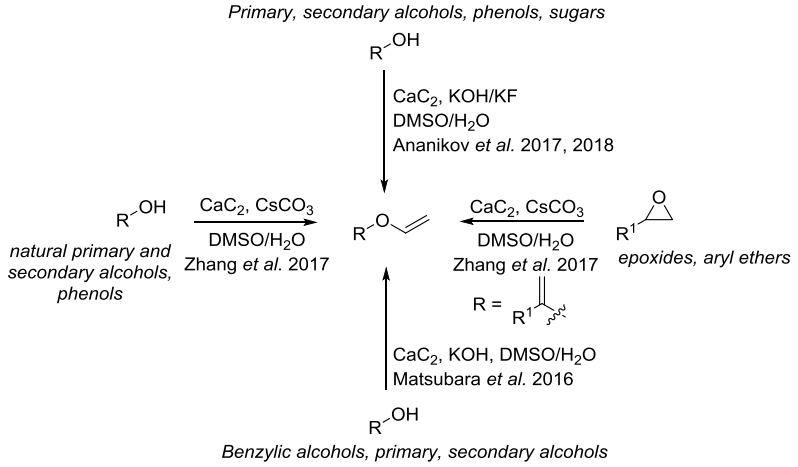
The presence of trace amounts of vinyl pyrrole **7** probably prompted the authors to investigate this vinylation reaction more, resulting in a follow up report in 2016 (Scheme 4-5).[20] In this

report, the authors described the vinylation of indoles and phenols with calcium carbide and assisted by cesium carbonate.



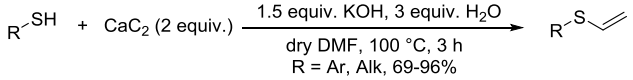
Scheme 4-5 Vinylation of indoles and phenols by calcium carbide.

Similar vinylation reactions, *i.e.* analogues of the Favorskii-Reppe reaction, were later described on benzylic alcohols using a KOH/DMSO system by Matsubara *et al.*,[21] on natural alcohols and derivatives assisted by cesium carbonate and reported by Zhang *et al.*,[22] on different alcohols (including sugars for the generation of bio-based polymers)[23] using a combination of KOH/KF in DMSO and reported by Ananikov *et al.*,[23-24] and lastly on epoxides and aryl ethers containing lignin β-O-4 linkages, assisted by cesium carbonate and resulting in cleavage of C-O bonds as reported by Zhang *et al.* (Scheme 4-6).[25]



Scheme 4-6 Vinylation of alcohols and derivatives with calcium carbide.

Another substrate that is prone to vinylation are thiols, generating vinyl thioethers (Scheme 4-7).[26]



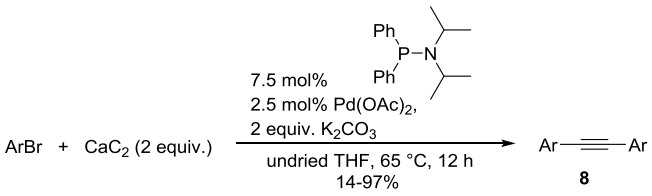
Scheme 4-7 Vinylation of thiols generates vinyl thioethers.

4.2.3 Calcium carbide as nucleophile in organic synthesis reactions

4.2.3.1 Sonogashira cross-coupling reactions

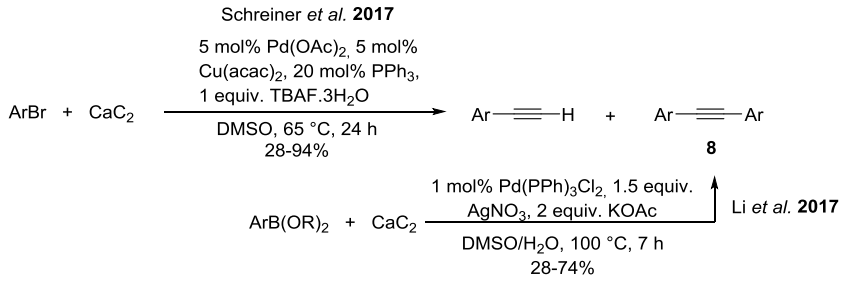
In Sonogashira cross-coupling reactions terminal alkynes are usually coupled with aryl halides under copper and palladium catalysis. Terminal alkynes can be replaced by calcium carbide, as coupling partners in Sonogashira cross-coupling reactions. However, since the product that is formed is a terminal alkyne, a second Sonogashira cross-coupling can occur, resulting in internal alkynes. Indeed, in 2006 Cheng *et al.* reported on the synthesis of

symmetric diaryl ethynes from calcium carbide and aryl bromides, under copper and amine free palladium catalysis (Scheme 4-8).[27]



Scheme 4-8 Copper-free Sonogashira cross coupling of calcium carbide and aryl bromides.

In 2011, Wacharasindhu *et al.* developed a CuI and $Pd(OAc)_2/PPh_3$ catalyzed and TEA promoted Sonogashira cross coupling of aryl iodides with calcium carbide in acetonitrile that could be done at room temperature thereby producing similar symmetrical diaryl ethynes **8**.[28] Similar reaction conditions were further exploited in the synthesis of poly(*p*-phenyleneethynylene)s (PPEs) polymeric systems.[29] In 2017, Schreiner *et al.* reported a Sonogashira cross-coupling assisted by tetrabutylammonium fluoride generating mixtures of terminal alkynes and symmetrical diaryl ethynes **8** (Scheme 4-9).[30] Depending on the amount of calcium carbide used, the reaction temperature and the slow addition via syringe pump of TBAF and water, the reaction could be tuned towards the synthesis of terminal alkyne, but always with non-negligible amounts of symmetrical diaryl ethyne **8**. The synthesis of terminal alkynes can probably be optimized via the use of flow systems, as already demonstrated for the use of acetylene gas.[31]

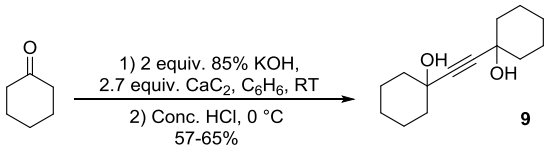


Scheme 4-9 Sonogashira cross-coupling of aryl bromides and calcium carbide gives mixtures of terminal alkynes and symmetrical diaryl ethyne **8**.

Alternatively, internal alkynes **8** can be synthesized from calcium carbide with arylboronic acids or esters, catalyzed by Pd(II) and with superstochiometric amounts of silver nitrate and potassium acetate as described by Li *et al.* in 2017.[32]

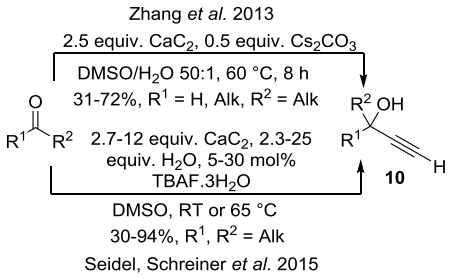
4.2.3.2 Alkynylation reactions on aldehydes/ketones

Alkynylation reactions using calcium carbide on carbonyl compounds such as aldehydes and ketones are known, and an early 1952 report already discussed the coupling of calcium carbide and cyclohexanone. As with Sonogashira cross-coupling reactions, the coupling of calcium carbide and cyclohexanone results in the formation of an acetylenic alcohol, that can undergo a second alkynylation reaction resulting in an internal alkyne: 1,1'-ethynylene-*bis*-cyclohexanol (**9**) (Scheme 4-10).[33]



Scheme 4-10 First reported reaction using calcium carbide for double alkynylation of cyclohexanone.

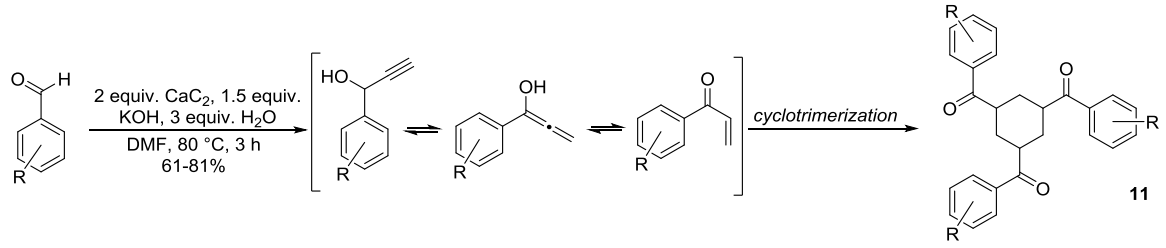
It took until 2013 before Zhang *et al.* reported the use of calcium carbide for the metal-free synthesis of terminal acetylenic alcohols **10** by single addition of calcium carbide to aldehydes and ketones (Scheme 4-11 top).[34] The substrate scope for aldehydes is limited to aldehydes that are branched in the α-position, as no product was obtained for straight-chain aldehydes and aryl aldehydes, probably due to reactivity of these aldehydes towards bases. A similar trend was seen for ketones. The fact that only single alkynylation occurred and no double alkynylation products were observed, was explained by a proposed reaction mechanism where the active nucleophile is a calcium(hydroxy) acetylide.



Scheme 4-11 Single alkynylation of aldehydes/ketones using calcium carbide.

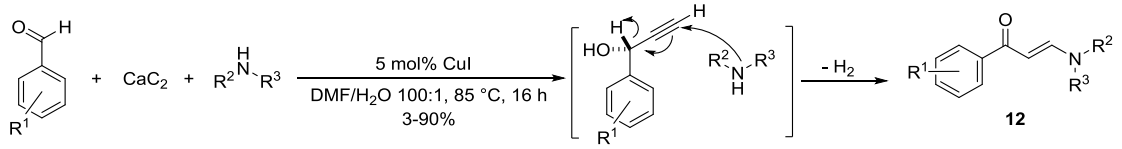
Improved yields and expanded substrate scope (also aryl- and straight chain ketones) for the alkynylation of ketones assisted by tetrabutyl ammonium fluoride was reported by Seidel, Schreiner *et al*. (Scheme 4-11 bottom).[35] Yields were generally higher than when Cs_2CO_3 was used, and a similar explanation was given for the decreased reactivity of straight chain and arylketones; a lower limit of pK_a^{DMSO} value of 26.4 was found for ketones. When the pK_a of the substrate is lower, aldol condensation is a major competitive reaction, resulting in low yields of intended products **10**.

In 2016, Yang *et al.* reported on the synthesis of 1,3,5-triaroylcyclohexanes **11** from reactions of calcium carbide with benzaldehydes (Scheme 4-12).[36] Mechanistically, this reaction is proposed to go via alkynylation of benzaldehyde to get a terminal propargyl alcohol that undergoes alkyne-allene rearrangement and tautomerization to form an enone. The enone can then undergo a cyclotrimerization with the help of a base to produce 1,3,5-triaroylcyclohexanes **11**.[37] Mechanistically, this cyclotrimerization resembles other radical cyclotrimerizations.[38]



Scheme 4-12 Alkynylation of benzaldehydes with calcium carbide forms, after cyclotrimerization, 1,3,5-triaroylcyclohexanes **11**.

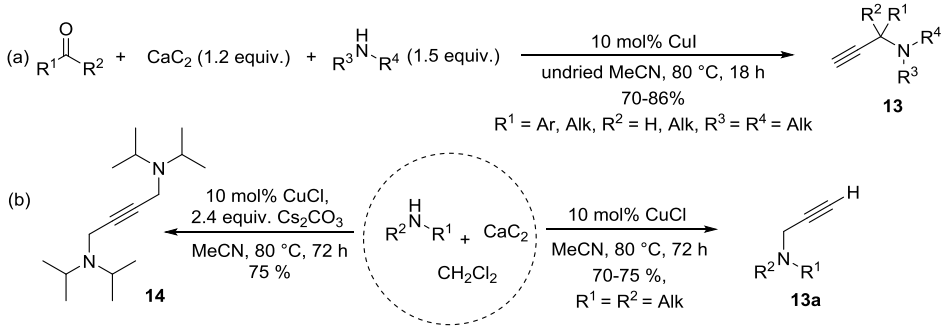
One particular example, described by Zhang *et al.* in 2013, used calcium carbide to link an electrophile (an aldehyde) and a nucleophile (an amine) (Scheme 4-13).[39] One would expect that the combination of an aldehyde, an amine and an alkyne (calcium carbide) generates propargylamines as A^3-coupling products, and under slightly different reaction conditions it will do (*vide infra*). However, when these three coupling partners are coupled under CuI catalysis in DMF, they generate enaminones **12** by sequential nucleophilic attack of the calcium (copper) carbide on the aldehyde, followed by nucleophilic attack (hydroamination) of the amine moiety on the triple bond of the *in situ* generated propargylic alcohol, which firstly tautomerizes to an allenyl enolate. The aldehyde hydride is via redox isomerization abstracted by water in this process, generating one molecule of H_2. Regarding the scope of the reaction, only aryl aldehydes can be used, since alkyl aldehydes give rise to propargylamines **13** (*vide infra*), and the bulkier the secondary amine the better the reaction goes, while in case of non-bulky amines again propargylamine **13** was formed. This last limitation could be overcome by reacting other primary or non-bulky secondary amines with the generated enaminones **12** resulting in substitution of the amine moiety.



Scheme 4-13 Three component synthesis of enaminones **12** from calcium carbide, aryl aldehydes and secondary amines.

4.2.3.3 Alkynylation reactions on iminium ions

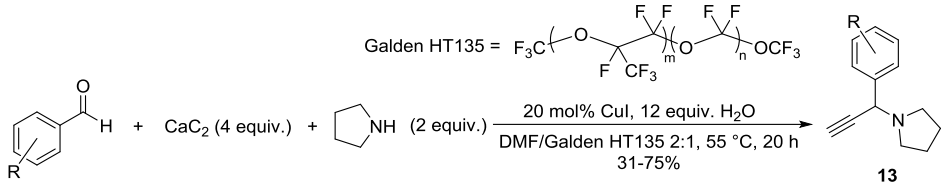
The first report discussing alkynylation with calcium carbide on iminium systems, came from Zhang and co-workers in 2012 (Scheme 4-14).[40] Upon mixing an aldehyde, an amine and calcium carbide with catalytic amounts of Cu(I)-salts in acetonitrile, propargylamines **13** are formed. Regarding the scope of the reaction, only secondary amines could be used, since primary alkyl of aryl amines did not give rise to propargylamines. Alkyl and aryl aldehydes can be used, along with a single example of a reactive ketone, cyclohexanone. Aldehydes can also be replaced by dichloromethane in an AHA coupling and depending on whether a base (cesium carbonate) was added, *mono*-propargylamines **13a** or symmetrical *bis*-propargylamines **14** could be obtained. Water, present in undried acetonitrile, again speeds up the reaction, and is thought to break up the polymeric structure of calcium carbide, rendering it more soluble.



Scheme 4-14 The use of calcium carbide in A³ and AHA coupling reactions.

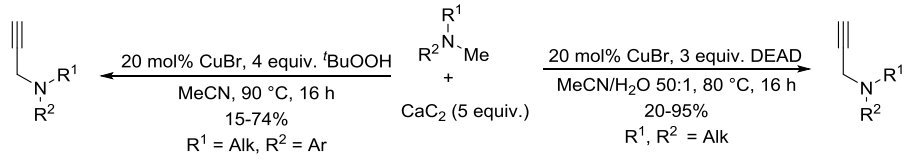
Propargylamines **13** are further exploited in Huisgen [3+2] cycloadditions with sodium azide and an aryl bromide under CuI and *N*,*N*'-dimethylethylenediamine catalysis to generate 1,2,3-triazoles or in a one-pot sequential Sonogashira cross-coupling reactions with an aryl iodide, under palladium acetate and triphenylphosphine catalysis for the generation of internal propargylamines. Interestingly, a one pot A³ coupling, and sequential AHA coupling of propargylamine **13** could lead to unsymmetrical *bis*-propargylamines.

Matsubara *et al.* reported on a different method for A³ coupling with calcium carbide, based on a quadraphasic phase-vanishing system in which acetylene gas is evolved from calcium carbide (Scheme 4-15).[41] Calcium carbide (ρ = 2.22 g cm^{-3}) is added first and lies on the bottom of the reaction tube, then Galden HT135 (ρ = 1.72 g cm^{-3}), a fluorous solvent is added, followed by a layer of water (ρ = 1.0 g cm^{-3}) and on top of that the organic solvent (THF or DMF), in which the reagents for A³, click or Sonogashira (only aryl iodides) coupling are present. Careful stirring dissolves water (the phase that vanishes) into the fluorous solvent, where it reacts with calcium carbide, resulting in formation of acetylene gas which dissolves in the organic phase, where it is used as coupling partner.



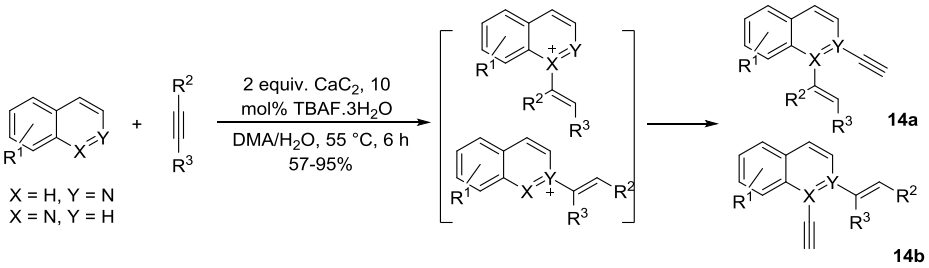
Scheme 4-15 A³ coupling with calcium carbide in a quadraphasic phase-vanishing system.

A next example, published by Zhang *et al.*, uses an external oxidant in a cross dehydrogenative coupling of calcium carbide with tertiary amines, via the *in situ* formation of an iminium species (Scheme 4-16).[42] When tertiary anilines were used, *tert*-butyl hydroperoxide is the oxidant, and no water is used, while in the case of tertiary aliphatic amines diethyl azodicarboxylate and a small amount of water are necessary for the reaction to occur.



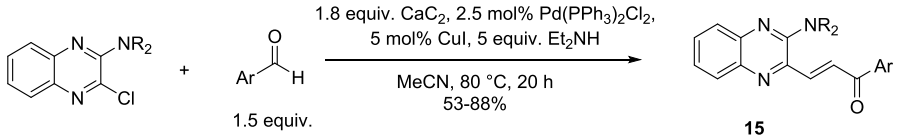
Scheme 4-16 Cross dehydrogenative coupling of calcium carbide with tertiary amines.

Samzadeh-Kermani published in 2017 the alkynylation of (iso)quinolines with calcium carbide aided by an internal alkyne under TBAF.3H_2O catalysis. Hydroamination of the (iso)quinoline with the internal alkyne produces an iminium species, which easily undergoes alkynylation with calcium carbide in the generation of dihydro(iso)quinolines **14** (Scheme 4-17).[43]



Scheme 4-17 Three-component coupling of an (iso)quinoline, internal alkyne and calcium carbide.

In 2017 Bakherad *et al*. described the use of calcium carbide in a combined Sonogashira cross-coupling/A³ coupling for the synthesis of quinoxaline chalcones **15**, showing the importance of both methods. The reaction mechanism is explained by a Sonogashira cross-coupling of the A³ product, followed by isomerization of the triple bond to form an allene and hydrolysis of the thus formed iminium species (Scheme 4-18).[44]



Scheme 4-18 Combined Sonogashira/A³ coupling with calcium carbide.

4.2.4 General conclusions for the use of calcium carbide in organic synthesis

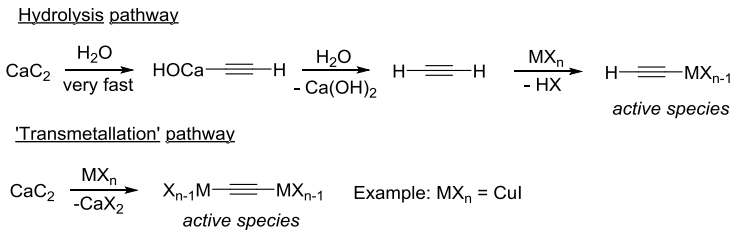
Many of the prior (§4.2.1-4.2.3) discussed reports use similar reactions conditions when applying calcium carbide in organic synthesis. Firstly, only a handful of solvents can (partly) dissolve calcium carbide. Due to the ionic nature of calcium carbide, it is obvious that this reagent will only dissolve in similar polar solvents, such as the aprotic polar solvents dimethyl sulfoxide, *N*,*N*-dimethyl formamide and acetonitrile. Water cannot be used as solvent, since it immediately reacts with calcium carbide and generates acetylene gas.

In almost all cases, small amounts of water help the reaction. Some reports argue that the presence of trace amounts water helps to break the polymeric structure of calcium carbide and that a calcium acetylide is the active species, whereas other reports claim that the presence of water causes acetylene to form, which is then further used as the active species. What the exact role of water is, is still unclear and might be different for different reactions, but it is certain that water is an important additive. Sometimes, the slow addition of water and other additives to the reaction over time via an infusion pump positively affects the reaction outcome.

For additions of calcium carbide to iminium species, the presence of Cu(I) salts is always necessary, and it is well known that in A³ coupling reactions copper acetylides are excellent nucleophiles for similar alkynylation additions to iminium species.

In the next paragraph additions of calcium carbide to previously synthesized polyhalogenated aldimines will be discussed. Some of the parameters mentioned in this paragraph, such as the addition of water or the use of copper(I) salts as catalyst, might not be compatible with the under study polyhalogenated moiety in the aldimines. Nevertheless, we investigated the alkynylation of polyhalogenated aldimines with calcium carbide.

Different modes of activation for calcium carbide can be distinguished (Scheme 4-19). A first path describes the hydrolysis of calcium carbide for the generation of acetylene, which is activated by a transition metal catalyst in a similar pathway as described in A³ couplings. A second pathway directly transmetallates calcium carbide with the transition metal catalyst resulting in another metal carbide (*e.g.* Cu_2C_2).



Scheme 4-19 Modes of activation for calcium carbide.

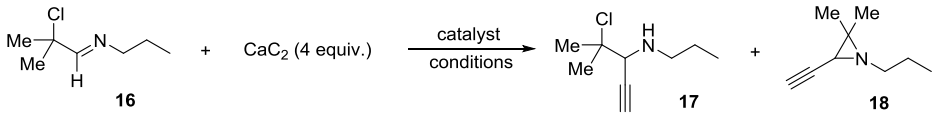
Reactions where CuI were used, typically changed color from heterogeneous grey to heterogeneous red, probably due to the formation of copper acetylide (Cu_2C_2), a heat and shock sensitive explosive in dry form. It is therefore very important never to synthesize this component in pure form, but rather to generate it catalytically *in situ*. Next to copper acetylide, other coinage metals such as silver and gold are known to form acetylides. Alkali metals (Li, Na, K, Rb, Cs, and Fr), alkaline earth metals (Be, Mg, Sr, Ba, and Ra) and lanthanides (rare earth metals) are also known to form carbides like calcium carbide. Also, group III metals such as Sc, Y and La and group 13's Al form carbides, but other group 13 metals such as Ga, In and Tl do not form carbides.[45]

4.3 Calcium carbide addition on polyhalogenated imine systems

4.3.1 Initial tries: addition to polychlorinated aldimines

At first, we investigated the addition of calcium carbide to α-chloroaldimines and the one-pot three-component A³ coupling of α-chloroaldehydes, amines and calcium carbide. The drawback of direct addition of calcium carbide to preformed α-chloroaldimine is that water will probably have to be added to the reaction mixture over time to hydrolyze calcium carbide for the generation of acetylene, while under A³ reaction conditions water is formed slowly as byproduct from the condensation of aldehyde and amine. However, from earlier alkynylation experiments on polyhalogenated aldimines (Chapter 2) we concluded that A³ reaction conditions are often not compatible, resulting in side reactions and low yields or no formation of A³ couplings product whatsoever. α-Chloroaldimine **16** was chosen as model substrate for addition of calcium carbide, thereby focusing on In(III) or Cu(I) catalysis, since these catalysts proved to be good catalysts for either alkynylation of α-chloroaldimine systems or calcium carbide additions. Different reaction conditions were screened for the synthesis of terminal propargylamine **17** or aziridine **18** (Table 4-1).

Table 4-1 Screening for reaction conditions for the addition of calcium carbide to α-chloroaldimines.



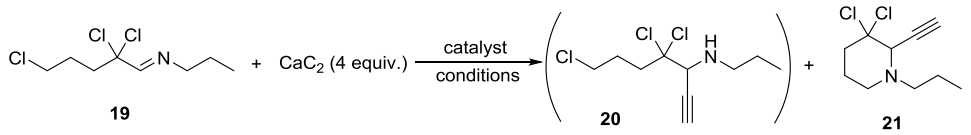
Entry	Catalyst (mol%)	H_2O (equiv.)	Solvent (mL)	T (°C) / t (h)	Outcome
1	CuI (20)	/	MeCN (2)	80/4	SM recovered
2	$In(OTf)_3$ (20)	/	MeCN (2)	80/4	SM recovered
3	$In(OTf)_3$ (20)	1	MeCN (2)	50/24	SM recovered
4[a]	CuI (20)	1	MeCN (2)	80/24	SM recovered
5[b]	/	1	DMSO (2)	80/24	Degradation
6	$In(OTf)_3$ (20) + CuI (20)	1	MeCN (2)	70/24	SM recovered
7	CuI (20)	3	$CHCl_3$ (2)	70/24	SM recovered
8	$In(OTf)_3$ (20) + CuI (20)	3	$CHCl_3$ (2)	70/24	SM recovered
9	$In(OTf)_3$ (20)	3	$CHCl_3$ (2)	70/24	SM recovered

All reactions were carried out on 0.5 mmol scale. [a] 20 mol% 18-crown-6 added. [b] 1 equivalent of KOH added.

In Entry 1 20 mol% CuI was used as a catalyst for the coupling of calcium carbide to α-chloroaldimine, but after 4 hours at 80 °C, only starting material **16** was obtained. In entry 2, $In(OTf)_3$ was used instead of CuI, with a similar result. No degradation of the starting material **16** occurred, which is remarkable since hydrolysis of the starting material was seen in case of alkynylation with phenylacetylene on this substrate. Most likely, traces of water will react faster with calcium carbide so that hydrolysis of the starting material is not a problem. In entry 3 one equivalent of water was added, but only starting material was obtained. Entry 4 uses CuI and 18-crown-6 to better dissolve the calcium carbide, but again only starting material was obtained. Entry 5 applies superbasic conditions (KOH in DMSO) but this leads to complete degradation after 24 hours at 80 °C. A combination of both $In(OTf)_3$ and CuI also results in the recovery of starting material (Entry 6). Changing to a halogenated solvent (chloroform) did not change the outcome of the reaction (Entries 7-9). Due to the inability of In to form carbides, the targeted reaction is probably not possible, and we quickly turned our attention to the use of α,α,δ-trichloroaldimines for coupling with calcium carbide, as this gave some promising result (Table 4-2). When $In(OTf)_3$ was used, the ideal catalyst for alkynylations with terminal alkynes, the obtained reaction mixture is very complex (Entries 1,2). When CuI was used in combination with 18-crown-6, 21% of product **21** was seen in NMR-screening with TMB (Entry 3). Conducting the reaction in the absence of 18-crown-6 led to 81% of product **21**, while 16% SM **19** was still present and 36% of **21** was isolated after acid-base workup of this reaction mixture (Entry 4). Using an extra equivalent of water led to an increase in yield to 49% after acid-base workup or 58% after filtration of the reaction mixture over a silica plug (Entry 5). Using more catalyst resulted in lowered yield of **21**

(Entry 6). More water and higher reaction temperature resulted in degradation of the reaction mixture, and no SM or products 18 or 19 were observed (Entry 7). Other counter ion catalyst also gave low yields of **21** (Entries 8, 9). Conducting the reaction at 60 °C with three equivalents of water (Entry 10) gave a similar yield as for 2 equivalents at 50 °C, without the presence of starting material after reaction. From Entry 7 it is clear that degradation easily occurs in this reaction and that low yields are thus inherent. The reaction was also evaluated under A³ conditions starting from 2,2,5-trichloropentanal and *n*-propylamine but no product **21** was observed.

Table 4-2 Screening for reaction conditions for the addition of calcium carbide to α,α,δ-trichloroaldimines.

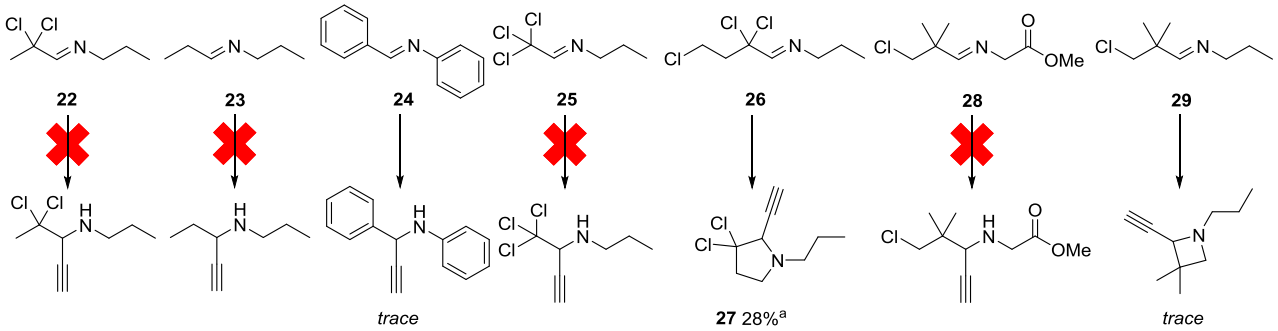


Entry	Catalyst (mol%)	H_2O (equiv.)	T (°C) / t (h)	SM **19** (%)	Product **21** (%)
1[a]	$In(OTf)_3$ (20)	2	80/18	Complex, no SM or product	
2[b]	$In(OTf)_3$ (20)	1	80/4	Complete degradation	
3[b]	CuI (20)	1	50/24	ND	21
4	CuI (20)	1	50/24	16	81, 36[c]
5	CuI (20)	2	50/24	ND	49[c], 58[d]
6	CuI (50)	2	50/24	ND	32[c]
7	CuI (20)	3	80/1.5	Complete degradation	
8	CuBr (20)	2	50/24	18	34
9	CuOTf.toluene (20)	2	50/24	15	25
10	CuI (20)	3	60/24	/	57[d]

All reactions were carried out on 0.5 mmol scale in MeCN (2 mL). Yields are NMR yields determined from the ^{1}H NMR spectrum by addition of internal standard TMB. ND: Not determined. [a] 8 equivalents of CaC_2 used. [b] 20 mol% 18-crown-6 added. [c] Yield after acid-base workup. [d] Yield after filtration over silica plug.

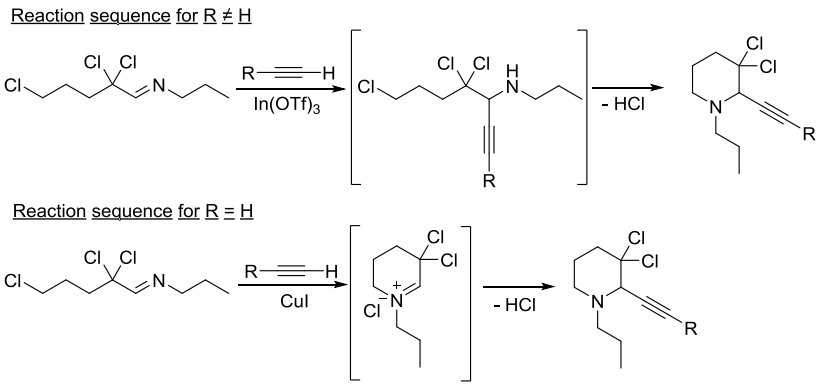
In order to understand why α,α,δ-trichloroaldimines **19** were reactive substrates and α-chloroaldimines **16** were not reactive, we investigated the substrate scope for the calcium carbide addition to other (poly)halogenated aldimines. Reaction conditions (Table 4-2, Entry 10) were used for addition to (poly)halogenated substrates (Scheme 4-20). α,α-Dichloroaldimine **22** was not reactive under the given reaction conditions, and the starting material was recovered. Non-halogenated aldimine **23** was also not reactive under the given reaction conditions, leading to recovery of the starting material. Benzaldimine **24** showed slight reactivity as a trace amount of intended product was detected via mass spectrometry, but the product could not be isolated. α,α,α-trichloroaldimine **25** was again not reactive under the given reaction conditions, and the starting material was recovered after workup. β-Chloroaldimine **28** did not give rise to the formation of propargylamine, but β-chloroaldimine

29 gave a trace amount of propargylamine reaction product, as seen in mass spectrometry, but the product could not be isolated.



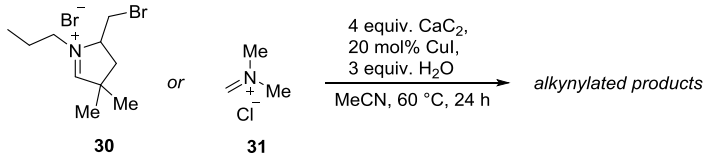
Scheme 4-20 Addition of CaC_2 (4 equivalents), water (3 equivalents) in MeCN (2 mL) to substrates (0.5 mmol) at 60 °C for 24 h, gave in some cases propargylamine moieties. [a] Yield after acid-base workup.

In chapter two, we investigated the alkynylation on α,α,δ-trichloroaldimines and we concluded that alkynylation is followed sequentially by ring closure to form *N*-alkyl-2-alkynyl-3,3-dichloropiperidines. From the results obtained in this chapter, the sequential reaction might be reversed here: an intramolecular substitution of the chloride by the imine nitrogen can create a cyclic aldiminium intermediate, which can be alkynylated by copper acetylide. This mechanism was ruled out in chapter two, since there we sometimes obtained propargylamines that were not ring closed, but might be applicable here, since here no propargylamines that are not yet ring closed were obtained (Scheme 4-21). This theory prompted us to investigate more substrates that can form iminium species.



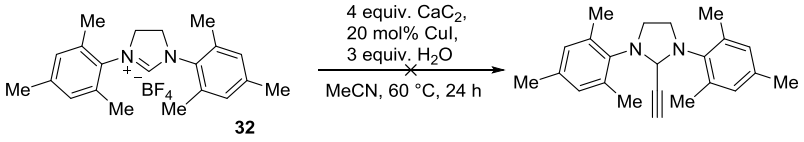
Scheme 4-21 Alkynylation – intramolecular substitution sequence might be inversed for calcium carbide additions.

Iminium ions **30**, which were synthesized according to a literature procedure,[46] and **31** (Böhme's salt, analogue of Eschenmoser's salt) were evaluated for coupling with calcium carbide, and both iminium species underwent alkynylation (Scheme 4-22). In the case of pyrrolinium bromide **30** different reaction products were obtained due to the instable nature of the starting material and reaction products. For iminium species **31** a mixture of single alkynylation and double alkynylation product was obtained. No effort was put in the isolation of the different compounds, since it was only the intention to verify that an iminium species could act as a substrate for copper catalyzed reaction with calcium carbide.



Scheme 4-22 Proving the necessity of an iminium species for coupling with calcium carbide.

Simple iminium systems might be present in substrates that one not directly thinks of as being iminiums, for example dihydroimidazolium **32** contains a *C-N* double bond and was thus used in alkynylation reaction with calcium carbide, but no reaction product was obtained (Scheme 4-23).



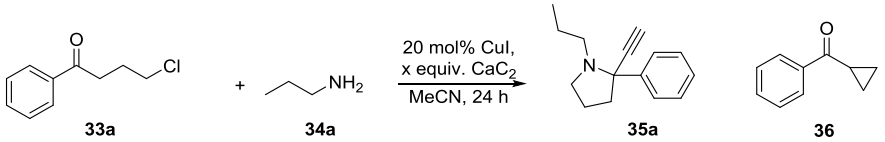
Scheme 4-23 Addition of calcium carbide to dihydroimidazole **32** did not result in the formation of propargylamine.

4.3.2 Calcium carbide in KA² couplings

With the knowledge that reactive systems should contain an iminium species, we were curious on whether we could use the optimized system under A³ conditions, starting from difficult ketone substrates. Table 4-3 gives an overview of the optimization for reaction conditions for the coupling of calcium carbide, a primary amine and an ω-chloroketone. By using the same, optimized reaction conditions as for the coupling of α,α,δ-trichloroaldimines, we found that 34% of reaction product **35a** could be isolated after acid-base workup (Entry 1). When only 1 equivalent of water was added at the beginning of the reaction and another two equivalents of water after 2 hours, it was clear that the yield increased (Entry 2). The low yields could be explained by the isolation of cyclopropyl phenyl ketone **36**, which is probably formed via deprotonation of starting material **33a** by calcium carbide or its hydrolysis product $Ca(OH)_2$, acting as a base in this case. To compare the reactivity of calcium carbide and normal terminal alkynes, one equivalent of phenylacetylene was added to the reaction mixture (Entry 3), but only reaction product **35a** was formed, since no incorporation of phenylacetylene was seen. This means that either the copper carbide species is more reactive than a copper phenylacetylide species or that the first is formed easier than the latter. Conducting the reaction at 50 °C resulted in a decreased yield in both cases where 8 equivalents of water were added either over the first eight hours (Entry 4) or at the beginning of the reaction (Entry 5), which gave the lowest yield. When 16 equivalents of water were used no intended reaction product **35a** was obtained (Entry 6). Although all calcium carbide is probably hydrolyzed in this case, a lot of cyclopropyl phenyl ketone **36** is obtained, which cannot be caused by calcium carbide but rather by $Ca(OH)_2$, the base that is formed from hydrolysis of calcium carbide. Preformation of imine by addition of calcium carbide, water and CuI after two hours results in an increased yield (Entries 7 and 8). The use of two equivalents of calcium carbide resulted in an incomplete conversion at 50 °C (Entry 9), while more equivalents of *n*-propylamine did not improve the yields dramatically (Entries 10-12). When *tert*-butylamine is used instead of *n*-propylamine, no propargylamine is formed, probably due to too high sterical demand for the *in situ* formation of cyclic iminium intermediate. When benzylamine is used instead of *n*-propylamine, a comparable 44% yield

of propargylamine was formed when using two equivalents of calcium carbide and one equivalent of water at 60 °C.

Table 4-3 Screening for reaction conditions for the addition of A³ coupling between ω-chloroketones, primary amines and calcium carbide.

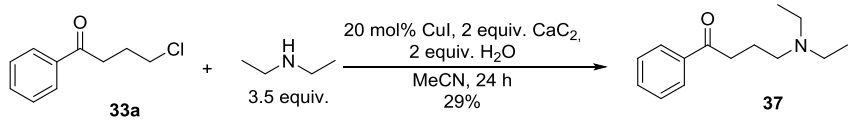


33a 34a 35a 36

Entry	CaC_2 (equiv.)	H_2O (equiv.)	T (°C) / t (h)	**35** (%)	**36** (%)	**33a** (%)
1	4	2	60/24	34[a]	ND	ND
2	4	1[b]	60/24	49[a]	36	/
3[c]	4	2	60/24	34[a]	ND	ND
4	4	8[d]	60/24	21	53	ND
5	4	8	60/24	8	27	ND
6	4	16	60/24	0	77	ND
7[e]	3	5	50/24	18	24	45
8	3	5	50/24	12	39	42
9	2	3	50/24	22	30	45
10	2	1	60/24	41	/	25
11	4	1	60/24	44	/	21
12	2	0	60/24	36	40	7

All reactions were carried out on 0.5 mmol scale in MeCN (2 mL) with 20 mol% CuI. Yields are NMR yields determined from the ^{1}H NMR spectrum by addition of internal standard TMB. ND: Not determined. [a] Yield after acid-base workup. [b] 2 equivalents of water added after 2 h. [c] 1 equivalent of phenylacetylene added. [d] 0.5 mL of 8 M water in MeCN was added over 5 h. [e] Preformation of imine, after 2 h other reagents were added.

When a secondary amine (*e.g.* diethylamine) was used instead of *n*-propylamine, no alkynylation product was observed, since no cyclic iminium species could be formed. Therefore, we can conclude that a cyclic iminium species has enhanced reactivity towards nucleophiles compared to the acyclic iminium species (Scheme 4-24). Due to an excess of diethylamine, the ω-chloro atom is substituted by diethylamine and after acid-base workup 29% of γ-aminoketone **37** was obtained.

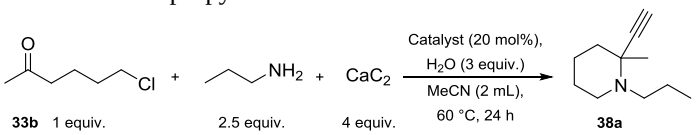


33a 37

Scheme 4-24 Using secondary amines, no alkynylation occurs.

To further discover the possibilities of this reaction, we anticipated that substrate **33a** specifically was a difficult target molecule, due to the possibility of formation of cyclopropyl ketone **36a**. Therefore, we turned our attention towards the synthesis of piperidines **38**, by using 6-chlorohexan-2-one **33b** instead of γ-chlorobutyrophenone **33a** as starting material. Immediately, it was observed that this system gives much better yields, as no cyclobutyl methyl ketone was formed, and we focused on this system to optimize the catalyst and the solvent.

Table 4-4 Evaluation of different catalysts for the three-component coupling of 6-chlorohexan-2-one, *n*-propylamine and calcium carbide



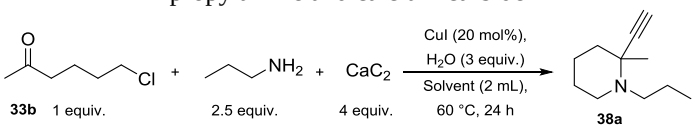
Entry	Catalyst	^{1}H NMR yield **38a** (%)
1	Cu_2O (10)	65
2	$Fe(OTf)_2$ (20)	0
3	$Fe(OTf)_3$ (20)	0
4	$Sc(OTf)_3$ (20)	0
5	$In(OTf)_3$ (20)	0
6	$Zn(OTf)_2$ (20)	0
7	NaOH (20)	0
8	$Mg(OTf)_2$ (20)	0
9	$AuPPh_3Cl$ (20)	22
10	AgOTf (20)	88
11	CuOTf (20)	90
12	CuO (20)	41
13	CuI (20)	99
14	CuOAc (20)	92

All reactions were carried out with 0.5 mmol 6-chlorohexan-2-one, 2 mmol calcium carbide, 1.25 mmol *n*-propylamine, 0.1 mmol catalyst, 1.5 mmol water and 2 mL acetonitrile for 24 hours at 60 °C. Yields were calculated from the ^{1}H NMR spectrum by addition of 1,3,5-trimethoxybenzene as internal standard.

Firstly, a number of transition-metal catalysts were screened for the formation of 2-ethynyl-2-methyl-1-propylpiperidine **38a** (Table 4-4). Cu_2O gave a decent yield of 65% (Entry 1), while other transition metals such as Fe(II), Fe(III), Sc(III), In(III), Zn(II), Na(I) or Mg(II) (Entries 2-8) were not able to catalyse this transformation. Other coinage metal salts such as $AuPPh_3Cl$ (22%) or AgOTf (88%) were able to catalyse the reaction (entries 9&10), although copper, the cheaper of the three coinage metals, would be the catalyst of choice. Cu(II) gave a lower

yield (41% - entry 12) than Cu(I) salts (90-99% - entries 11, 13 and 14) with CuI being the best (99%).

Table 4-5 Evaluation of different solvents for the three-component coupling of 6-chlorohexan-2-one, *n*-propylamine and calcium carbide

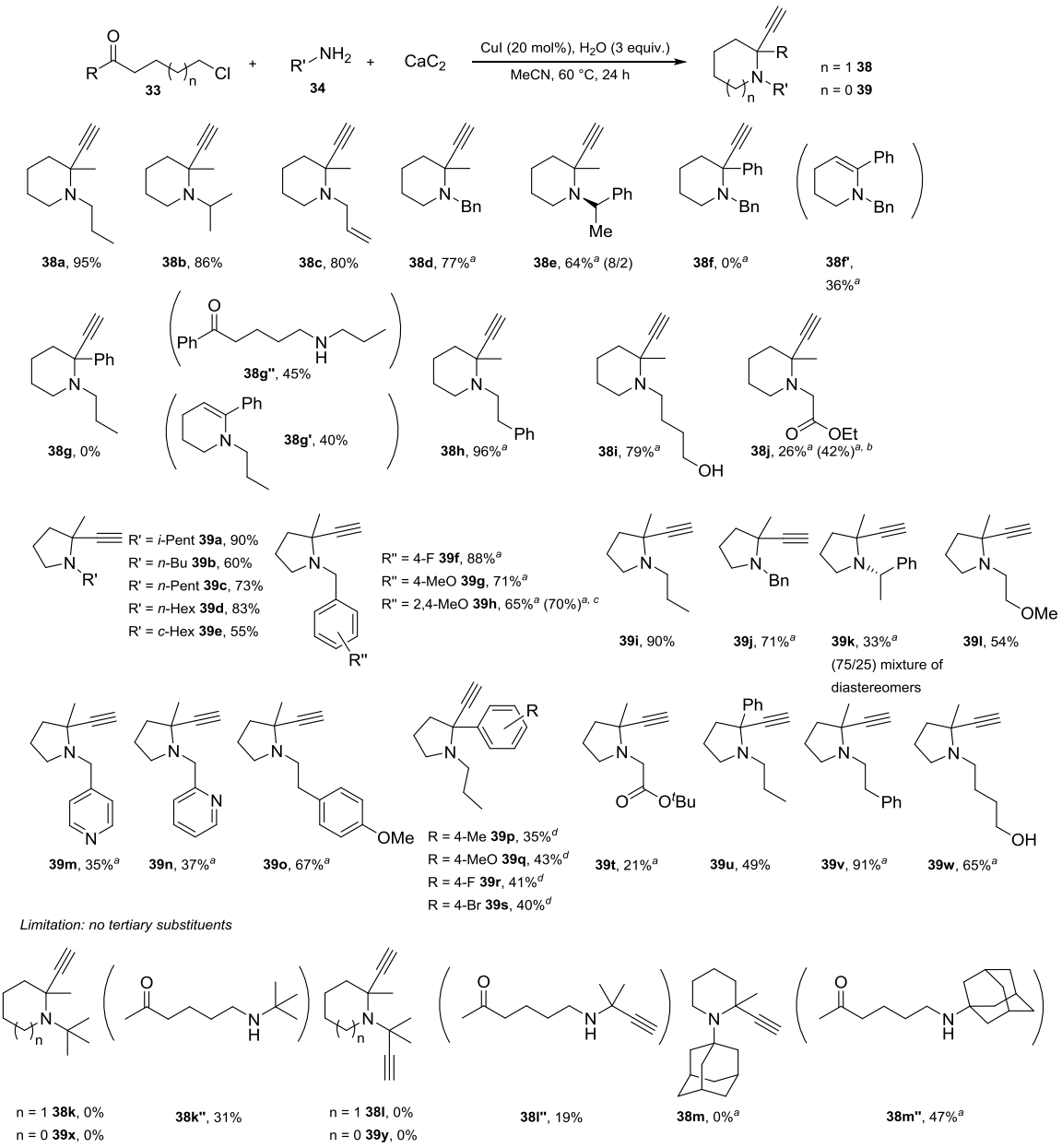


Entry	Solvent	^{1}H NMR yield **38a** (%)
1	MeCN	99
2	DMSO	36
3	DMF	72
4	MeOH	64
5	DCM	63
6	Toluene	80
7	2-Me THF	76
8	Sulfolane	51
9	Dimethyl carbonate	76

All reactions were carried out with 0.5 mmol 6-chlorohexan-2-one, 2 mmol calcium carbide, 1.25 mmol *n*-propylamine, 0.1 mmol CuI, 1.5 mmol water and 2 mL solvent for 24 hours at 60 °C. Yields were calculated from the ^{1}H NMR spectrum by addition of 1,3,5-trimethoxybenzene as internal standard.

Although a screening yield of 99% was obtained, we investigated the use of other solvents (Table 4-5), since this is also a critical parameter for the solubility of calcium carbide and greenness of the reaction.[47] To our surprise, all of the screened solvents gave the product **38a**; even less polar solvents such as DCM or toluene (entries 5&6) were still able to catalyse this transformation in good yields. Solvents considered as 'recommended' such as sulfolane or dimethyl carbonate were also able to catalyse this transformation, underlining the broad range of solvents that be used. Since calcium carbide is only slightly soluble in polar solvents, it is virtually insoluble in apolar solvents, pointing towards a different reacting species other than calcium carbide. On the other hand, the solubility of acetylene is not considered problematic, since it readily dissolves in most organic solvents,[48] and probably immediately reacts to form copper acetylide (Cu_2C_2). For safety reasons the neat reaction was not evaluated, since the presumed intermediate copper acetylide (Cu_2C_2) is highly explosive in dry form.[49] When this species is formed in a small amount *in situ* in solution, the safety risks are reduced to a minimum. The addition of water was key, and addition of one equivalent of water at the beginning of the reaction combined with addition of another two equivalents of water after two hours gave the best result. Together with the one equivalent of water that is formed from the reaction of the ketone with the amine, 4 equivalents of water are formed, which could form 2 equivalents of acetylene.

After optimization of the reaction conditions, the scope of the reaction was evaluated by using different primary amines and ω-chlorinated ketones **33** (Scheme 4-25).



Scheme 4-25 Scope of the reaction. Reaction conditions: **33** (0.5 mmol), **34** (1.25 mmol), calcium carbide (2.0 mmol), CuI (0.1 mmol), H_2O (0.5 mmol), MeCN (2 mL), 60 °C, 24 h. H_2O (1.0 mmol) added after 2 h. Reported yields are yields after acid-base workup. [a] **34** (0.5 mmol), triethylamine (0.75 mmol). [b] Reaction carried out in COware where calcium carbide and water are separated from the other reagents. [c] Reaction carried out on 5 mmol scale. [d] Components are not 100% pure, but purity could not be improved via column chromatography.

The reaction of 6-chlorohexan-2-one **33b**, *n*-propylamine **34a** and calcium carbide in acetonitrile for 24 hours at 60 °C gave product **38a** in 95% yield after simple acid-base workup, thereby avoiding the use of column chromatography. The use of more sterically hindered isopropylamine resulted in a slightly diminished yield of 86% of product **38b**. Other amine substituents such as allyl and benzyl gave yields of 80% and 77% respectively. The use of chiral (*S*)-(−)-1-phenylethylamine resulted in the formation of an 4:1 diastereomeric mixture of **38e** in 64% yield. The use of tertiary substituents on the primary amine such as

tert-butyl, dimethyl-propyne or adamantyl did not lead to intended products **38k**, **38l** or **38m** but gave δ-aminoketones **38k''**, **38l''**, **38m''** in low yields. From the previous chapter, we know that sterical hindrance around the reacting electrophilic iminium species complicates the addition of nucleophilic species. Therefore, the reaction temperature was increased to 90 °C, but even then no products **38k**, **38l** or **38m** were obtained. Using δ-chlorovalerophenone as ketone did not result in the formation of intended products **38f** or **38g** either. In the case of combination with *n*-benzylamine, cyclic enamine **38f'** was obtained, while combination with *n*-propylamine resulted in a mixture of δ-aminoketone **38g''** and cyclic enamine **38g'**. Since both cyclic enamines are formed, tautomerization to the cyclic iminium should be possible, but might be less favoured, since the enamine structure is stabilized by conjugation with the phenyl group. Again, repetition of the reaction at higher reaction temperatures (90 °C, or 130 °C in DMSO instead of acetonitrile) gave a similar outcome and no intended products **38f** or **38g** were obtained. Phenethylamine as coupling partner gave a high yield of 96% of product **38h**, while also an alcohol functionalized amine could be used to form product **38i** in 79% yield. The α-aminoester derived from glycine, gave a low yield of 26% of the intended product **38j**, while no other products were obtained after filtration over a plug of silica, to avoid aqueous workup. Since we were convinced that the problem lies in the stability of the α-aminoester under the given reaction conditions, where also $Ca(OH)_2$ is formed, we investigated the reaction in Skrydstrup's COware vessel, a two-chamber glass system.[50] When the reaction was run in the COware vessel, the isolated yield of **38j** rose to 42% (Figure 4-3). This improvement could be explained by the absence of basic Ca-salts (CaC_2 or $Ca(OH)_2$) that could cause hydrolysis of the ester function.

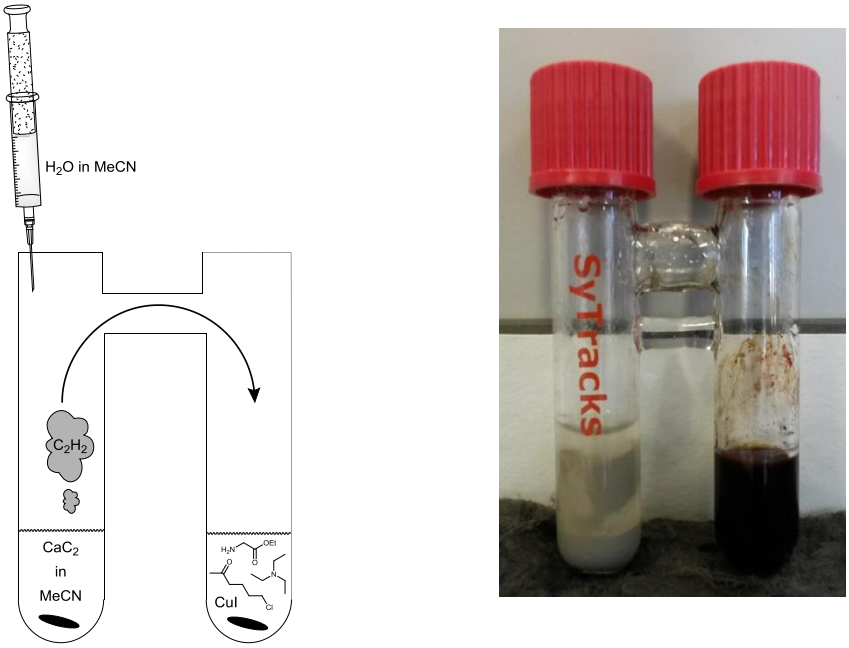
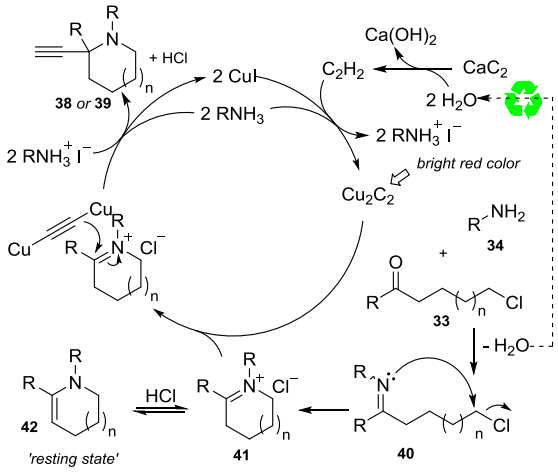


Figure 4-3 COware vessel schematic overview (left), after the reaction (right).

Next to the formation of piperidines via 6-chlorohexan-2-one as ketone equivalent, also pyrrolidines can be formed via 5-chloropentan-2-one as ketone equivalent. Product **39i** was formed in 90% yield, due to its volatility the product is isolated as its hydrochloric acid salt **39i'**. Reaction of 5-chloropentan-2-one with benzylamine gave a similar yield of 71%, while reaction with chiral (*S*)-(−)-1-phenylethylamine only gave a sluggish 31% yield, and here a diastereomeric mixture (75/25) was formed. Again, tertiary substituted amines did not give

the intended products **39x** or **39y**, and no γ-aminoketones were observed in this case, as they are not stable. When more sterically hindered γ-chlorobutyrophenone was used, product **39u** was formed in 49% yield. The reason why pyrrolidine **39u** is formed and piperidine **38g** not, might be explained by the increased ring strain of dihydropyrroles compared to tetrahydropyridines, rendering the first to be more reactive than the latter. Different substituted γ-chlorobutyrophenones could be used to obtain different pyrrolidines **39p**, **39q**, **39r** and **39s**, albeit in low yields. Examples of amines, bearing pyridinyl moieties, could also be used and gave pyrrolidines **39m** and **39n** in 35% and 37% respectively. Different substituted benzylamines could also be used to generate pyrrolidines **39f**, **39g** and **39h** in good yields. Product **39h** was also prepared on gram scale with a comparable yield, proving the scalability of this reaction. Interestingly, pyrrolidine **39t**, an intermediate of a poly ADP Ribose Polymerase (PARP) inhibitor, previously prepared in a three-step synthesis,[3a] could be prepared in one step via this synthesis, albeit in a low 21% yield. Overall, yields of pyrrolidines **39** are lower than yields of piperidines **38**, as this has to do with an occurring side reaction for 5-chloropentan-2-one; α-deprotonation, followed by substitution of the chlorine atom leads to methyl cyclopropyl ketone as side product. Only cyclopropanation occurs, since no cyclopentanone (via α-deprotonation on the methyl group instead of the methylene group) is formed in the case of 5-chloropentan-2-one. No side product is formed in the case of 6-chlorohexan-2-one.

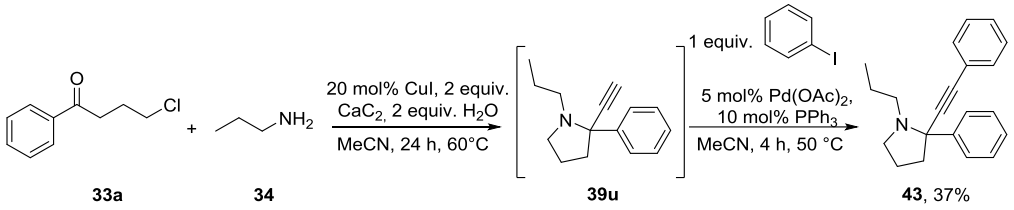


Scheme 4-26 Proposed reaction mechanism.

From a mechanistic point of view (Scheme 4-26), calcium carbide is thought to be hydrolysed to form acetylene. This assumption is underlined by the fact that the reaction can be conducted in a COware vessel, where acetylene is formed in a separate vessel. Also, many different (apolar) solvents can be used for this coupling, proving that the solubility of calcium carbide is of no importance. In a separate experiment, calcium carbide was dissolved in acetonitrile and CuI was added. After 15 minutes the reaction mixture remained grey (as the starting materials are both grey), even at 60 °C. Upon addition of water, the reaction mixture starts to become reddish, indicating the formation of copper acetylide (Cu_2C_2). A similar reddish color was observed in the actual three-component coupling, pointing towards the formation of Cu_2C_2. The ω-chlorinated ketone **33** and primary amine **34** react to form ketimine **40**, thereby releasing a molecule of water, which is directly consumed to hydrolyse calcium carbide. The role of calcium carbide in this is double; in the first place it forms the reagent acetylene, but it also acts as a drying agent, thereby promoting the formation of ketimine **40**. Ketimine **40** then undergoes an intramolecular substitution reaction to form ketiminium species **41**. The addition of Cu_2C_2 to this species and protonation leads to the

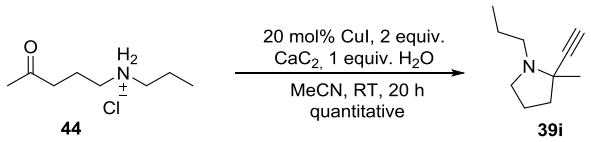
formation of terminal propargylamine **38** or **39**, and regeneration of the catalyst. Ketiminium **41** is in tautomeric equilibrium with enamine **42**, and depending on the stability of enamine **42** this tautomer can become a 'resting state' for the reaction. Especially when the R group of the ketone is an aryl group, extra stabilization by conjugation pushes the equilibrium towards enamine **42**. The only by-products of this transformation are HCl and $Ca(OH)_2$.

The terminal propargylamine *e.g.* in compound **39u** can be used in a Sonogashira cross-coupling to generate internal propargylamines, such as **43** (Scheme 4-27).



Scheme 4-27 One-pot sequential KA² coupling involving calcium carbide, followed by Sonogashira cross-coupling.

Interestingly, when the HCl salt of γ-aminoketone **44** was used as substrate, the reaction could be carried out at room temperature with full conversion in 20 hours to terminal propargylamine **39i** (Scheme 4-28).



Scheme 4-28 Using γ-aminoketone **44**, reaction product **39i** is formed at room temperature.

NMR curiosity

In a few ^{1}H-NMR spectra of compounds **38** and **39** the integration of the terminal C(sp) proton of the alkyne was not exactly in accordance with one proton (Figure 4-4). This problem was identified by measuring the relaxation times of the protons in the molecule, *i.e.* **39h** (see report on the right). From this measurement we can conclude that the relaxation time for the terminal proton is way larger (19.5 s) than for the other protons in the molecule (1.2 – 3.7 s), so that in a standard proton measurement an integration error could arise. Indeed, when the relaxation time in the standard measurement was gradually enlarged, the integration of the proton was also enlarged. When the relaxation time of the measurement is set to approximately 6 times the relaxation time of the slowest relaxating proton, no integration error arose anymore. Since this enlargement of relaxation time means increasing measurement time, not all ^{1}H NMR spectra were measured with larger relaxation time.

Brief Report
Peak 1 at 7.241 ppm
T1 = 3.667s
Peak 2 at 6.476 ppm
T1 = 3.750s
Peak 3 at 3.853 ppm
T1 = 1.441s
Peak 4 at 3.819 ppm
T1 = 2.339s
Peak 5 at 3.330 ppm
T1 = 1.448s
Peak 6 at 2.995 ppm
T1 = 1.301s
Peak 7 at 2.492 ppm
T1 = 1.171s
Peak 8 at 2.360 ppm
T1 = 19.549s
Peak 9 at 2.139 ppm
T1 = 1.529s
Peak 10 at 1.836 ppm
T1 = 1.359s
Peak 11 at 1.489 ppm
T1 = 1.238s

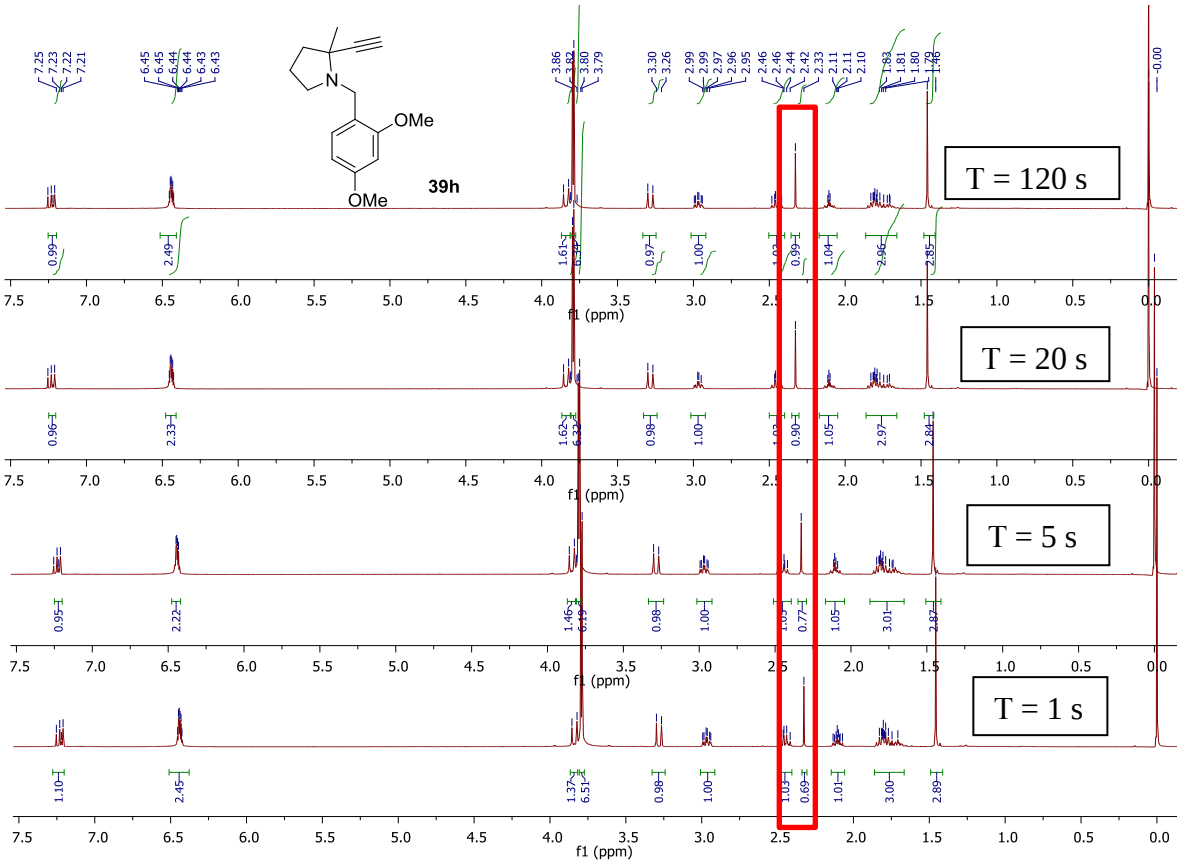
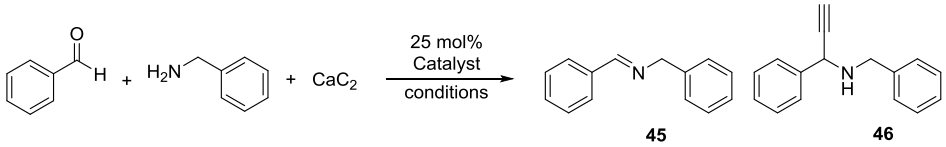


Figure 4-4 Influence of the relaxation time (T1) on the singlet at δ = 2.33 ppm (C≡C**H**) in molecule **39h**.

4.3.3 A³ coupling of calcium carbide, an aldehyde and a primary amine

In the literature only additions of calcium carbide to iminium systems are known. We wondered whether we could also use imine systems to add calcium carbide to. Since a small amount of coupling product from the reaction of *N*-benzylideneaniline **24** with calcium carbide was obtained (cf. Scheme 4-20), we thought that it might be possible to optimize the reaction conditions to obtain a higher yield of this product. We chose to start from benzaldehyde (no α-hydrogens, no chance for aldol condensations) and benzylamine as starting materials to obtain *N*-benzylidenebenzylamine **45** as imine or *N*-benzyl-1-phenylprop-2-yn-1-amine **46** as envisioned reaction product. NMR data for this component are known in literature,[51] and therefore simple NMR yields were calculated for this reaction (Table 4-6). A number of catalysts that are known to form acetylides were screened for this transformation (Entries 1-13). Not surprisingly, the coinage metals (Cu, Ag, Au) gave a trace amount of intended product **46**, with AgOAc (Entry 3) giving a detectable yield of 4%. Encouraged by this result, we evaluated a number of other Ag(I) catalysts (Entries 14-18). We can conclude that the stronger basic the counter ion is, the better the reaction works. Addition of Lewis acidic boron trifluoride to the AgOAc catalyzed reaction resulted in the similar outcome (Entry 19), while addition of *N,N,N',N'*-tetramethylethylenediamine resulted in a lowered yield, and some degradation (Entry 20). The superbasic system KOH in DMSO was not reactive and only imine **45** was obtained (Entry 21). Different other polar solvents were evaluated with HFIP and DMF being non-reactive (Entries 22, 24), DMSO giving degradation (Entry 23), MeOH giving some product (Entry 25), but less than MeCN and 1,4-dioxane giving a better yield of 7% **46** (Entry 26).

Table 4-6 Evaluation of different catalysts and solvents for coupling of benzaldehyde, benzylamine and CaC_2.



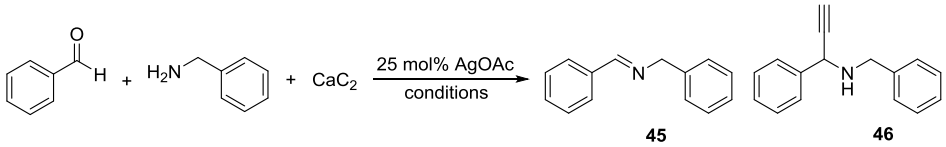
Entry	Catalyst	T (°C) / t (h)	**45** (%)	**46** (%)	Entry	Catalyst	T (°C) / t (h)	**45** (%)	**46** (%)
1	$NiCl_2$	90/24	99	-	14	$AgCO_2CF_3$	90/24	98	2
2	$MgCl_2$	90/24	99	-	15	AgOTf	90/24	99	-
3	AgOAc	90/24	96	4	16	$Ag(SbF_6)$	90/24	99	trace
4	$AlCl_3$	90/24	99	-	17	AgI	90/24	99	-
5[a]	$NaAuCl_4$	90/24	99	trace	18	$AgBF_4$	90/24	96	4
6[a]	AuCl(IPr)	90/24	99	-	19[b]	AgOAc	90/24	96	4
7	$BF_3.OEt_2$	90/24	99	-	20[c]	AgOAc	90/24	82	2
8	Cu_2O	90/24	99	trace	21[d]	/	90/24	99	-
9	$FeCl_2$	90/24	99	-	22[e]	AgOAc	90/24	99	-
10	$FeCl_3$	90/24	99	-	23[f]	AgOAc	90/24	degradation	
11	$Sc(OTf)_3$	90/24	99	-	24[g]	AgOAc	90/24	99	-
12	$CeCl_3$	90/24	99	-	25[h]	AgOAc	90/24	88	2
13	$Yb(OTf)_3$	90/24	99	-	26[i]	AgOAc	90/24	85	7

All reactions were carried out on 1 mmol scale in MeCN (2 mL) with 2 equivalents of CaC_2 and without addition of extra equivalents of water. Yields are NMR yields determined from the ^1H NMR spectrum by addition of internal standard TMB. - : not observed. [a] 2.5 mol% catalyst used. [b] 25 mol% $BF_3.OEt_2$ added. [c] 25 mol% TMEDA added. [d] 1 equivalent of KOH in DMSO used, no MeCN. [e] solvent = HFIP [f] solvent = DMSO [g] solvent = DMF [h] solvent = MeOH [i] solvent = 1,4-dioxane.

With the 'optimum' catalyst and solvent in hands, we evaluated some other reaction parameters (Table 4-7). Conducting the reaction in the microwave for 2 hours at 110 °C, gave a disappointing 2% yield of **46** (Entry 1). Addition of Cu_2O next to AgOAc did not have a beneficial impact on the reaction outcome (Entry 2). Performing the reaction at 110 °C for 24 hour, gave a similar result (Entry 3) as at 90 °C (Table 4, Entry 26). The outcome of the reaction was not dependent on the concentration of the solution, because either more concentrated (Entry 4), neat (Entry 5) or more diluted solution (Entry 6) gave a similar result. Using a superstochiometric amount (110 mol%) of AgOAc did not change the reaction outcome (Entry 7). Conducting the reaction at lower temperature (50 °C) gave a slightly lower yield, but the reaction still occurred (Entry 8). Crown ethers 18-crown-6 (Entry 9) and 15-crown-5 (Entry 10) were added to make calcium carbide more soluble, but in the case of 18-crown-6 this gave no improvement, while adding 15-crown-5 completely shuts down the reaction. Addition of benzaldehyde after one hour of mixing the other reagents (preformation

of silver acetylide) gave the best screened yield of 11% (Entry 11). Performing the reaction in an open flask, lead to 6% yield of **46** (Entry 12), proving that loss of acetylene as gaseous side-product is not an issue for this reaction.

Table 4-7 Further optimization for the coupling of benzaldehyde, benzylamine and calcium carbide.



45 46

Entry	Solvent (mL)	Additive (mol%)	T (°C) / t (h)	**45** (%)	**46** (%)
1	1,4-dioxane (2)	-	110/2 (MW)	98	2
2	1,4-dioxane (2)	Cu_2O (25)	110/24	96	4
3	1,4-dioxane (2)	-	110/24	94	6
4	1,4-dioxane (1)	-	110/24	89	7
5	-	-	90/24	96	4
6	1,4-dioxane (10)	-	110/24	84	8
7[a]	1,4-dioxane (2)	-	110/24	93	7
8	1,4-dioxane (2)	-	50/24	96	4
9	1,4-dioxane (2)	18-crown-6 (50)	50/24	95	5
10	1,4-dioxane (2)	15-crown-5 (50)	50/24	99	-
11[b]	**1,4-dioxane (2)**	**-**	**90/5**	**89**	**11**
12[c]	1,4-dioxane (2)	-	90/5	93	6

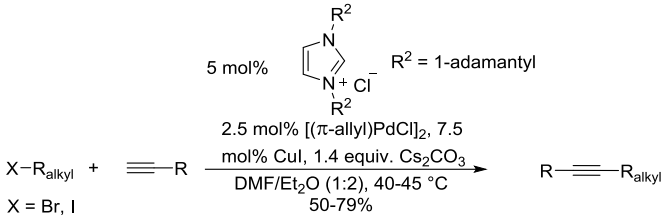
All reactions were carried out on 0.5 mmol scale in MeCN (2 mL) with 20 mol% CuI. Yields are NMR yields determined from the ^{1}H NMR spectrum by addition of internal standard TMB. ND: Not determined. [a] 110 mol% catalyst used. [b] Benzaldehyde is added only after one hour. [c] Reaction carried out in an open flask.

Although propargylamine **46** is clearly formed under different reaction conditions, the conversion always fluctuated around 5-10%. Higher reaction temperatures usually lead to faster formation of reaction products, but in this case it did not. This may be explained by inhibition of the reaction by the formation of the reaction product **46**, but no straightforward explanation can be found for this possibility.

4.3.4 Other reactions with calcium carbide

We felt that the nucleophilic properties of calcium carbide are stronger than its electrophilic or dipolarophilic properties (both probably via hydrolysis and formation of acetylene). Sonogashira cross-coupling reactions have been described already in the literature, giving mixtures of terminal and internal alkynes, where control towards the formation of terminal alkynes is difficult. Nonetheless, we were interested in these reactions since terminal alkynes are an interesting class of molecules and hydrolysis with deuterated water, could easily

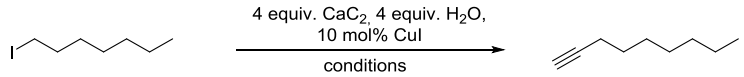
generate deuterated terminal alkynes. The Sonogashira reactions of acetylene with aryl halides have been investigated in the past; therefore we turned our attention on whether we could perform simple S_N2-like substitutions of an alkyl halide and calcium carbide. A precedent for this reaction, involving terminal alkynes and primary alkyl bromides is known in literature, and uses a Pd(NHC) and CuI catalyst for this coupling (Scheme 4-29).[52]



Scheme 4-29 Sonogashira cross-coupling with primary aliphatic halides.

Similar reaction conditions were tried for the synthesis of terminal alkynes from a primary aliphatic iodide (1-iodoheptane) and calcium carbide. An equimolar amount of water as calcium carbide was added over time with a syringe pump to generate acetylene/dissolve calcium carbide, but in all cases 1-iodoheptane was recovered without formation of the intended product (Table 4-8).

Table 4-8 Sonogashira cross-coupling on 1-iodoheptane with calcium carbide.



Entry	Solvent (mL)	Additives (mol%)	T (°C) / t (h)	Outcome
1	MeCN (2)	-	50/3	SM recovered
2	MeCN (2)	Pd(allyl)(IPr)Cl (2.5)	50/4	SM recovered
3	MeCN (2)	Pd(allyl)(IPr)Cl (2.5) + Cs_2CO_3 (100)	50/4	SM recovered
4	DMF/Et_2O (1/2)	Pd(allyl)(IPr)Cl (2.5)	45/16	SM recovered
5	DMF/Et_2O (1/2)	Pd(allyl)(IPr)Cl (2.5) + Cs_2CO_3 (100)	45/16	SM recovered

All reactions were carried out on 1 mmol scale with 20 mol% CuI, 4 equivalents of calcium carbide, and 4 equivalents of water added evenly over the indicated reaction time.

In a previous attempt where calcium carbide under copper(I) catalysis was used in KA^2 coupling in the presence of phenylacetylene, copper acetylide was found to be more reactive (or easier formed) than copper phenylacetylide. However, coupling with phenylacetylene does occur for this Sonogashira reaction and does not occur for coupling calcium carbide.

4.4 Experimental

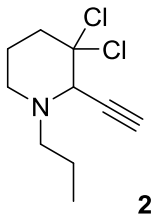
4.4.1 General

Calcium carbide was obtained from Sigma-Aldrich in granulated form (pieces) and technical quality (≥ 75% gas-volumetric). Calcium carbide is always ground in a mortar with a pestle,

until it is a fine powder and then quickly weighed. When the ground calcium carbide is left standing, it quickly hydrolyzed and changed color from grey to grey-white, thereby producing a hydrogen sulfide smell. Calcium carbide can be stored for at least two years while it is often exposed to the atmosphere, with only small loss of activity, and is thus considered 'easy to store'.

3,3-Dichloro-2-ethynyl-1-propylpiperidine (**21**)

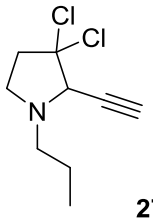
In a 10 mL microwave vessel were introduced CaC_2 (128 mg, 2 mmol), (*E*)-*N*-(2,2,5-trichloropentylidene)propan-1-amine (**19**) (115 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), MeCN (2 mL) and H_2O (18 mg, 1 mmol). The vessel was quickly capped and placed in a preheated oil bath at 50 °C for 24 h. The reaction mixture turns red after a while, probably due to the formation of copper acetylide. Afterwards, the reaction mixture was quenched by addition of 2 mL water and subjected to acid-base workup; addition of 3 M HCl solution (10 mL) and extraction of the aqueous phase with MTBE (2 x 15 mL). The aqueous phase was then basified with 5 M NaOH, forming insoluble $Ca(OH)_2$ and extracted with MTBE (3 x 15 mL). The organic phases were combined and dried over $MgSO_4.3H_2O$, and concentrated *in vacuo* to yield 53.5 mg (49%) of 3,3-dichloro-2-ethynyl-1-propylpiperidine (**21**). The product was pure, and thus no further purification was necessary.



21

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.00 (s – t like, 1H), 2.63 – 2.51 (m, 2H), 2.51 – 2.38 (m, 4H), 2.35 – 2.28 (m, 1H), 2.06 – 1.89 (m, 1H), 1.66 – 1.56 (m, 1H), 1.56 – 1.41 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 88.7, 76.7, 76.3, 65.1, 57.0, 46.7, 40.2, 23.3, 20.0, 11.7. **HRMS** (ESI) m/z calculated for $[C_{10}H_{15}NCl_2+H]^+$: 220.0654; found 220.0650. Yellow oil. R_f = 0.68 (Heptane/EtOAc 9/1).

3,3-Dichloro-2-ethynyl-1-propylpyrrolidine (**27**)

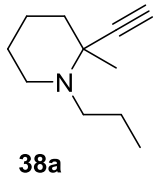


27

28.3 mg (28%) after acid-base workup. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.91 (d, *J* = 1.9 Hz, 1H, NC**H**), 3.10 – 2.98 (m, 1H, NC**H**(H)CH_2C_{quat}), 2.84 – 2.72 (m, 4H, NC**H**(H)C**H**$_2C_{quat}$ and NC**H**(H)CH_2CH_3), 2.59 – 2.51 (m, 1H,), 2.55 (d, *J* = 2.0 Hz, 1H, C≡C**H**), 1.58 – 1.48 (m, 2H, $NCH_2C\mathbf{H}_2CH_3$), 0.94 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 88.4 (**C**≡CH), 77.5 (**C**Cl_2), 76.4 (C≡**C**H), 70.5 (**C**C≡CH), 55.1 ($NCH_2CH_2CH_3$), 49.5 ($NCH_2CH_2C_{quat}$), 45.6 ($NCH_2CH_2C_{quat}$), 21.1 ($NCH_2CH_2CH_3$), 11.7 ($NCH_2CH_2CH_3$). **HRMS** (ESI) m/z calculated for $[C_9H_{13}NCl_2+H]^+$: 206.0498; found 206.0495. Yellow oil. R_f = 0.70 (Heptane/EtOAc 9/1).

2-Ethynyl-2-methyl-1-propylpiperidine (**38a**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

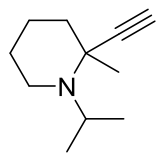


38a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.81 – 2.73 (m, 1H), 2.65 (ddd, *J* = 12.8, 9.7, 6.5 Hz, 1H), 2.29 (s, 1H), 2.28 (td, *J* = 12.0, 2.7 Hz, 1H), 2.03 (ddd, *J* = 12.8, 9.4, 4.8 Hz, 1H), 1.75 – 1.38 (m, 8H), 1.37 (s, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 84.9, 72.5, 55.2, 53.5, 48.9, 40.3, 28.9, 26.1, 21.74, 21.73, 12.0. **HRMS** (ESI) m/z calculated for $[C_{11}H_{19}N+H]^+$: 166.1590; found 166.1583. R_f = 0.38 (Hept/EtOAc 9/1). Yellow oil. 78.7 mg (95%) of 2-ethynyl-2-methyl-1-propylpiperidine (**38a**) after acid/base workup.

2-Ethynyl-1-isopropyl-2-methylpiperidine (**38b**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *i*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

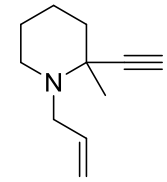


38b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.41 (septet, *J* = 6.6 Hz, 1H, C**H**$(CH_3)_2$), 2.71 – 2.64 (m, 1H, NCH(**H**)CH_2), 2.54 (td, *J* = 11.8, 2.5 Hz, 1H, NC**H**(H)CH_2), 2.29 (s, 1H, C≡C**H**), 1.67 – 1.46 (m, 5H, $NCH_2C\mathbf{H}_2CH(\mathbf{H})C\mathbf{H}_2$), 1.41 (s, 3H, $C_{quat}C\mathbf{H}_3$), 1.40 – 1.33 (m, 1H, $NCH_2CH_2C\mathbf{H}(H)CH_2$), 1.06 (d, *J* = 6.6 Hz, 3H, $CHC\mathbf{H}_3(CH_3)$), 1.02 (d, *J* = 6.7 Hz, 3H, $CHCH_3(C\mathbf{H}_3)$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 88.0 (HC≡**C**), 72.6 (H**C**≡C), 53.8 (N$\mathbf{C}_{quat.}$), 47.2 (N**C**H$(CH_3)_2$), 42.2 ($NCH_2CH_2CH_2\mathbf{C}H_2$), 40.5 ($N\mathbf{C}H_2CH_2CH_2CH_2$), 28.8 ($C_{quat.}\mathbf{C}H_3$), 26.7 ($NCH_2CH_2\mathbf{C}H_2CH_2$), 23.6 ($CHCH_3(\mathbf{C}H_3)$), 22.2 ($NCH_2\mathbf{C}H_2CH_2CH_2$), 15.9 ($CH\mathbf{C}H_3(CH_3)$). **HRMS** (ESI) m/z calculated for $[C_{11}H_{19}N+H]^+$: 166.1590; found 166.1599. Yellow oil. 70.8 mg (86%) of 2-ethynyl-1-isopropyl-2-methylpiperidine (**38b**) after acid/base workup.

1-Allyl-2-ethynyl-2-methylpiperidine (**38c**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), allylamine (71 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

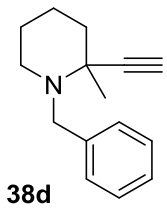


38c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.84 (dddd, *J* = 17.2, 10.1, 8.2, 4.6 Hz, 1H, H(H)C=C**H**C(H)H), 5.17 (dtd, *J* = 17.1, 2.0, 1.2 Hz, 1H, $\mathbf{H}_{trans}$(H)C=CHC(H)H), 5.08 (dtd, *J* = 10.1, 1.9, 0.8 Hz, 1H, H($\mathbf{H}_{cis}$)C=CHC(H)H), 3.47 (ddt, *J* = 14.0, 4.6, 1.9 Hz, 1H, H(H)C=CHC(**H**)H), 2.81 – 2.73 (m, 1H, NCH(**H**)CH_2), 2.65 (ddt, *J* = 14.0, 8.2, 0.8 Hz, 1H, H(H)C=CHC(H)**H**), 2.33 (s, 1H, C≡C**H**), 2.22 (td, *J* = 12.0, 2.8 Hz, 1H, NC**H**(H)CH_2), 1.73 (ddd, *J* = 5.2, 4.4, 2.3 Hz, 1H, $NCH_2CH_2CH_2C(\mathbf{H})H$), 1.64 – 1.53 (m, 4H, $NCH_2C\mathbf{H}_2CH(\mathbf{H})C(H)\mathbf{H}$), 1.52 – 1.42 (m, 1H, $NCH_2CH_2C\mathbf{H}(H)$), 1.40 (s, 3H, $C\mathbf{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 137.0 (H_2C=**C**), 116.6 ($H_2\mathbf{C}$=C), 84.3 (HC≡**C**), 73.0 (H**C**≡C), 55.1 (N$\mathbf{C}_{quat.}$), 54.6 (H_2C=C$\mathbf{C}H_2$), 48.6 (N**C**$H_2CH_2CH_2CH_2$), 40.2 ($NCH_2CH_2CH_2\mathbf{C}H_2$), 28.7 ($\mathbf{C}H_3$), 25.9 ($NCH_2CH_2\mathbf{C}H_2CH_2$), 21.7 ($NCH_2\mathbf{C}H_2CH_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{11}H_{17}N+H]^+$: 164.1434; found 164.1438. Yellow oil, 65.5 mg (80%) of 1-allyl-2-ethynyl-2-methylpiperidine (**38c**) after acid/base workup.

1-Benzyl-2-ethynyl-2-methylpiperidine (**38d**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), benzylamine (54 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).



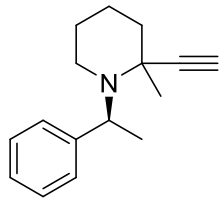
38d

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.17 (m, 5H, C$\mathbf{H}_{arom.}$), 4.04 (d, *J* = 14.0 Hz, 1H, C(**H**)HPh), 3.07 (d, *J* = 14.0 Hz, 1H, C(H)**H**Ph), 2.59 – 2.49 (m, 1H, NC**H**(H)CH_2), 2.36 (s, 1H, C≡C**H**), 2.24 (td, *J* = 12.0, 3.0 Hz, 1H, NCH(**H**)CH_2), 1.81 – 1.73 (m, 1H, $NCH_2CH_2CH_2C(\mathbf{H})H$), 1.68 – 1.48 (m, 4H, $NCH_2C\mathbf{H}_2CH(\mathbf{H})C(H)\mathbf{H}$), 1.46 (s, 3H, C$\mathbf{H}_3$), 1.43 – 1.34 (s, 1H, $NCH_2CH_2C\mathbf{H}(H)$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 140.6 (**C**$H_{arom., quat.}$), 128.6 (**C**$H_{arom., ortho}$), 128.1 (**C**$H_{arom., meta}$), 126.5 (**C**$H_{arom., para}$), 84.5 (HC≡**C**), 72.7 (H**C**≡C), 55.5 (N**C**H_2Ph), 55.0 (N$\mathbf{C}_{quat.}$), 48.7 (N**C**$H_2CH_2CH_2CH_2$), 40.3 ($NCH_2CH_2CH_2\mathbf{C}H_2$), 29.1

(**C**H_3), 26.0 (NCH_2CH_2**C**H_2CH_2), 21.9 (NCH_2**C**$H_2CH_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{15}H_{19}N+H]^+$: 214.1590; found 214.1583. Yellow oil, 81.6 mg (77%) of 1-benzyl-2-ethynyl-2-methylpiperidine (**38d**) after acid/base workup.

2-Ethynyl-2-methyl-1-((*S*)-1-phenylethyl)piperidine (**38e**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), L-1-phenylethylamine (60.6 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

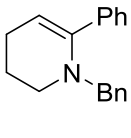


38e

Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 8.0 Hz, 2H, C**H**$_{arom.,ortho}$), 7.37 – 7.27 (m, 3H, C**H**$_{arom.,meta\ and\ para}$), 4.42 (q, *J* = 6.8 Hz, 1H, NC**H**CH_3), 2.63 (tt, *J* = 12.0, 2.7 Hz, 1H, NCH(**H**)CH_2), 2.44 – 2.37 (m, 1H, NC**H**(H)CH_2), 2.36 (s, 1H, C≡C**H**), 1.75 – 1.67 (m, 2H, NCH_2CH_2C**H**(H)C(**H**)H), 1.62 – 1.53 (m, 2H, NCH_2CH_2CH(**H**)C(H)**H**), 1.53 – 1.50 (m, 1H, $NCCH_2$**H**(H)) 1.49 (s, 3H, $C_{quat.}$C**H**$_3$), 1.48 (d, *J* = 5.8 Hz, 3H, NCHC**H**$_3$), 1.35 – 1.26 (m, 1H, $NCCH_2$H(**H**)). Minor isomer (most of the signals are overlapping with the major diastereomer, only clear signals): **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.42 (q, *J* = 6.6 Hz, 1H, NC**H**CH_3), 1.98 (s, 1H, C≡C**H**), 1.38 (d, *J* = 6.6 Hz, 3H, NCHC**H**$_3$). Major isomer: **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.8 (**C**H$_{arom.,\ quat.}$), 127.8 (**C**H$_{arom.,\ meta}$), 127.2 (**C**H$_{arom.,\ ortho}$), 126.0 (**C**H$_{arom.,\ para}$), 87.8 (HC≡**C**), 72.8 (H**C**≡C), 54.2 (N**C**HCH_3), 53.7 (N**C**$_{quat.}$), 42.3 ($NCH_2CH_2CH_2$**C**H_2), 42.0 (N**C**$H_2CH_2CH_2CH_2$), 29.4 ($C_{quat.}$**C**H_3), 26.8 (NCH_2**C**$H_2CH_2CH_2$), 22.3 (NCH_2CH_2**C**H_2CH_2), 12.8 (NCH**C**H_3). Minor isomer (only clear signals): **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 146.4 (**C**H$_{arom.,\ quat.}$), 86.8 (HC≡**C**), 72.3 (H**C**≡C). **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}N+H]^+$: 228.1747; found 228.1750. Yellow oil, 72.2 mg (64%) of 2-ethynyl-2-methyl-1-((*S*)-1-phenylethyl)piperidine (**38e**) as an 8/2 mixture of diastereomers after acid/base workup.

1-Benzyl-6-phenyl-1,2,3,4-tetrahydropyridine (**38f'**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), benzylamine (53.6 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

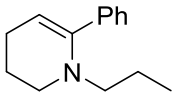


38f'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.48 (m, 2H, C**H**$_{arom.}$), 7.35 – 7.21 (m, 8H, C**H**$_{arom.}$), 5.04 (t, *J* = 3.9 Hz, 1H, NC=C**H**), 3.85 (s, 2H, C**H**$_2$Ph), 3.09 – 2.96 (m, 2H, NC**H**$_2$), 2.15 (td, *J* = 6.4, 4.0 Hz, 2H, NCH_2CH_2C**H**$_2$), 1.69 – 1.55 (m, 2H, NCH_2C**H**$_2CH_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.5 (**C**$_{arom.,quat.}$), 140.1 (**C**$_{arom.,quat.}$), 139.8 (**C**$_{arom.,quat.}$), 128.6 (**C**H$_{arom.}$), 128.55 (**C**H$_{arom.}$), 128.3 (**C**H$_{arom.}$), 128.2 (**C**H$_{arom.}$), 128.1 (**C**H$_{arom.}$), 127.9 (**C**H$_{arom.}$), 127.4 (**C**H$_{arom.}$), 127.3 (**C**H$_{arom.}$), 127.1 (**C**H$_{arom.}$), 126.7 (**C**H$_{arom.}$), 106.7 (NC=**C**H), 55.5 (N**C**H_2Ph), 47.5 (N**C**$H_2CH_2CH_2$), 24.0 (NCH_2CH_2**C**H_2), 19.3 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{18}H_{19}N+H]^+$: 250.1590; found 250.1595. Yellow oil. 44.6 mg (36%) of 1-benzyl-6-phenyl-1,2,3,4-tetrahydropyridine (**38f'**) after acid/base workup, corrected for the presence of starting material and solvent.

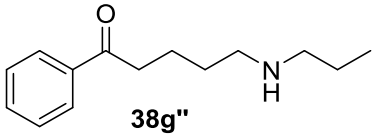
6-Phenyl-1-propyl-1,2,3,4-tetrahydropyridine (**38g'**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).



38g'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.36 (m, 2H, C**H**$_{arom.,ortho}$), 7.30 – 7.20 (m, 3H, C**H**$_{arom.,meta,\ para}$), 4.87 (t, *J* = 3.9 Hz, 1H, NC=C**H**), 3.13 – 3.09 (m, 2H, NC**H**$_2$CH$_2$CH$_2$), 2.61 – 2.58 (m, 2H, NC**H**$_2$CH$_2$CH$_3$), 2.14 (td, *J* = 6.4, 4.0 Hz, 2H, NCH$_2$CH$_2$C**H**$_2$), 1.75 – 1.69 (m, 2H, NCH$_2$C**H**$_2$CH$_2$), 1.53 – 1.42 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 0.75 (t, *J* = 7.4 Hz, 3H, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.9 (N**C**$_{quat}$), 140.5 (NC**C**$_{quat}$), 128.1 (**C**H$_{arom.,ortho}$), 127.4 (**C**H$_{arom.,meta}$), 127.1 (**C**H$_{arom.,para}$), 105.1 (NC=**C**H), 53.8 (NCH$_2$CH$_2$**C**H$_3$), 47.8 (N**C**H$_2$CH$_2$CH$_2$), 24.0 (NCH$_2$CH$_2$**C**H$_2$), 21.7 (NCH$_2$**C**H$_2$CH$_3$), 20.2 (NCH$_2$**C**H$_2$CH$_2$), 11.4 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{14}H_{19}N+H]^+$: 202.1590; found 202.1587. Yellow oil. 40.0 mg (40%) of 6-phenyl-1-propyl-1,2,3,4-tetrahydropyridine (**38g'**) after acid/base workup.

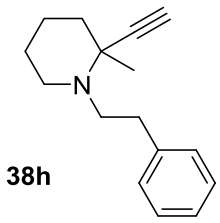


38g''

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.91 (m, 2H, C**H**$_{arom.,ortho}$), 7.56 – 7.50 (m, 1H, C**H**$_{arom.,para}$), 7.48 – 7.41 (m, 2H, C**H**$_{arom.,meta}$), 2.98 (t, *J* = 7.3 Hz, 2H, C=OC**H**$_2$), 2.67 – 2.61 (m, 2H, NC**H**$_2$CH$_2$CH$_2$), 2.59 – 2.63 (m, 2H, NC**H**$_2$CH$_2$CH$_3$), 1.83 – 1.75 (m, 2H, C=OCH$_2$C**H**$_2$), 1.62 – 1.53 (m, 2H, NCH$_2$C**H**$_2$CH$_2$), 1.53 – 1.42 (m, 2H, NCH$_2$C**H**$_2$CH$_3$), 0.91 (t, *J* = 7.4 Hz, 3H, NCH$_2$CH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 200.2 (**C**=O), 137.1 (C=O**C**$_{quat}$), 132.9 (**C**H$_{arom.,para}$), 128.6 (**C**H$_{arom.,meta}$), 127.9 (**C**H$_{arom.,ortho}$), 51.9 (NCH$_2$CH$_2$**C**H$_3$), 49.7 (N**C**H$_2$CH$_2$CH$_2$), 38.4 (C=O**C**H$_2$), 29.8 (NCH$_2$**C**H$_2$CH$_2$), 23.2 (NCH$_2$**C**H$_2$CH$_3$), 22.1 (NCH$_2$CH$_2$**C**H$_2$), 11.8 (NCH$_2$CH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{14}H_{21}NO+H]^+$: 220.1696; found 220.1691. Yellow oil. 49.8 mg (45%) of 1-phenyl-5-(propylamino)pentan-1-one (**38g''**) after acid/base workup.

2-Ethynyl-2-methyl-1-phenethylpiperidine (**38h**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), phenethylamine (60.6 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

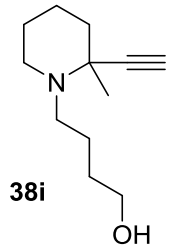


38h

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.23 (m, 2H, C**H**$_{arom.,meta}$), 7.22 – 7.13 (m, 3H, C**H**$_{arom.,ortho,\ para}$), 2.96 (ddd, *J* = 12.6, 10.6, 6.0 Hz, 1H, NC**H**(H)CH(H)Ph), 2.90 – 2.78 (m, 2H, NCH(H)C**H**(H)Ph and NC**H**(H)CH$_2$CH$_2$CH$_2$), 2.68 (ddd, *J* = 13.0, 10.2, 5.9 Hz, 1H, NCH(H)CH(**H**)Ph), 2.41 (td, *J* = 11.8, 2.7 Hz, 1H, NCH(**H**)CH$_2$CH$_2$CH$_2$), 2.33 (ddd, *J* = 12.7, 10.2, 5.1 Hz, 1H, NCH(**H**)CH(H)Ph), 2.26 (s, 1H, C≡C**H**), 1.74 – 1.42 (m, 6H, NCH$_2$C**H**$_2$C**H**$_2$C**H**$_2$), 1.34 (s, 3H, C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 140.9 (**C**$_{arom.,quat.}$), 128.8 (**C**H$_{arom.,ortho}$), 128.2 (**C**H$_{arom.,meta}$), 125.9 (**C**H$_{arom.,para}$), 84.7 (**C**≡CH), 72.7 (C≡**C**H), 55.1 (**C**C≡CH), 53.7 (N**C**H$_2$CH$_2$Ph), 49.1 (N**C**H$_2$CH$_2$CH$_2$CH$_2$), 40.2 (NCH$_2$CH$_2$CH$_2$**C**H$_2$), 35.5 (NCH$_2$**C**H$_2$Ph), 28.7 (**C**H$_3$), 26.1 (NCH$_2$**C**H$_2$CH$_2$CH$_2$), 21.7 (NCH$_2$CH$_2$**C**H$_2$CH$_2$). **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}N+H]^+$: 228.1747; found 228.1754. Yellow oil. 108.7 mg (96%) of 2-ethynyl-2-methyl-1-phenethylpiperidine (**38h**) after acid/base workup.

4-(2-Ethynyl-2-methylpiperidin-1-yl)butan-1-ol (**38i**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 4-aminobutanol (45 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

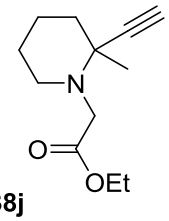


38i

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.68 (br s, 1H, O**H**), 3.64 (ddd, *J* = 10.8, 5.3, 3.8 Hz, 1H, C(**H**)HOH), 3.48 (ddd, *J* = 11.1, 8.9, 2.9 Hz, 1H, C(H)**H**OH), 2.90 – 2.81 (m, 1H, NC**H**(H)$CH_2)_3C_{quat}$), 2.74 (ddd, *J* = 13.2, 9.9, 4.3 Hz, 1H, NC(H)**H**$(CH_2)_3$OH), 2.34 (s, 1H, C≡C**H**), 2.31 (td, *J* = 11.9, 2.8 Hz, 1H, NCH(**H**)$CH_2)_3C_{quat}$), 2.17 (dt, *J* = 13.3, 4.4 Hz, 1H, NC(**H**)H$(CH_2)_3$OH), 1.81 – 1.68 (m, 3H, HOCH$_2$CH(**H**)C**H(**H)CH_2NCH$_2$CH$_2$CH$_2$CH(**H**)C_{quat}), 1.65 – 1.50 (m, 7H, HOCH$_2$C**H**(H)CH**(H)**CH_2NCH$_2$C**H**$_2$C**H**$_2$C**H**(H)C_{quat}), 1.43 (s, 3H, C**H**$_3$).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 83.8 (HC≡**C**), 73.3 (H**C**≡C), 62.9 (**C**H$_2$OH), 55.5 (**C**$_{quat.}$), 51.2 (N**C**H$_2$$(CH_2)_3$OH), 48.3 (N**C**H$_2$$(CH_2)_3C_{quat.}$), 39.8 (N$(CH_2)_3$**C**H$_2C_{quat.}$), 32.2 (NCH$_2$**C**H$_2$$(CH_2)_2$OH), 28.2 (**C**H$_3$), 26.4 (N$(CH_2)_2$**C**H$_2CH_2$OH), 25.4 (NCH$_2$**C**H$_2$$(CH_2)_2C_{quat.}$), 21.5 (N$(CH_2)_2$**C**H$_2CH_2C_{quat.}$). **HRMS** (ESI) m/z calculated for $[C_{12}H_{21}NO+H]^+$: 196.1696; found 196.1699. Yellow oil, 77.5 mg (79%) of 4-(2-ethynyl-2-methylpiperidin-1-yl)butan-1-ol (**38i**) after acid/base workup.

Ethyl 2-(2-ethynyl-2-methylpiperidin-1-yl)acetate (**38j**)

The reaction was carried out with CaC_2 (256 mg, 4 mmol), CuI (19.05 mg, 0.1 mmol) and MeCN (2 mL) in reactor tube one, and 6-chlorohexan-2-one (67 mg, 0.5 mmol), glycine ethyl ester hydrochloride (69.8 mg, 0.5 mmol), triethylamine (126 mg, 1.25 mmol) and MeCN (2 mL) in reactor tube two. Then, H_2O (180 mg, 10 mmol) in MeCN (0.5 mL) was added with an infusion pump over two hours.

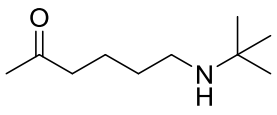


38j

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.17 (qd, *J* = 7.1, 1.8 Hz, 2H, OC**H**$_2$CH$_3$), 3.55 (d, *J* = 16.6 Hz, 1H, C=OC**H**(H)), 2.91 (d, *J* = 16.6 Hz, 1H, C=OCH(**H**)), 2.79 (m, 1H, NC**H**(H)CH$_2$CH$_2$CH$_2$), 2.45 (dd, *J* = 10.1, 5.9 Hz, 1H, NCH(**H**)CH$_2$CH$_2$CH$_2$), 2.33 (s, 1H, C≡C**H**), 1.75 – 1.54 (m, 6H, NCH$_2$C**H**$_2$C**H**$_2$C**H**$_2$), 1.38 (s, 3H, C_{quat}C**H**$_3$), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 171.8 (**C**=O), 83.7 (**C**≡CH), 73.2 (C≡**C**H), 60.5 (O**C**H$_2$CH$_3$), 55.2 (N**C**$_{quat}$), 54.3 (C=O**C**H$_2$), 50.8 (N**C**H$_2$CH$_2$CH$_2$CH$_2$), 39.6 (NCH$_2$CH$_2$CH$_2$**C**H$_2$), 28.6 (C_{quat}**C**H$_3$), 25.8 (NCH$_2$CH$_2$**C**H$_2$CH$_2$), 21.6 (NCH$_2$**C**H$_2$CH$_2$CH$_2$), 14.2 (OCH$_2$**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{12}H_{19}NO_2+H]^+$: 210.1489; found 210.1484. Yellow oil. 44.0 mg (42%) of ethyl 2-(2-ethynyl-2-methylpiperidin-1-yl)acetate (**38j**) after acid/base workup.

6-(*tert*-Butylamino)hexan-2-one (**38k''**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *tert*-butylamine (91 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

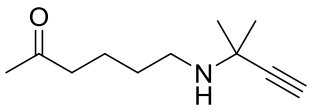


38k"

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.58 – 2.51 (t, *J* = 7.2 Hz, 2H, C**H**$_2$N), 2.44 (t, *J* = 7.4 Hz, 2H, C=OC**H**$_2$), 2.13 (s, 3H, C=OC**H**$_3$), 1.67 – 1.56 (m, 2H, C=OCH$_2$C**H**$_2$), 1.49 – 1.40 (m, *J* = 8.2, 7.0 Hz, 2H, NCH$_2$C**H**$_2$), 1.09 (s, 9H, C(C**H**$_3)_3$). The N-H proton can not be distinguished. **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 208.8 (**C**=O), 50.2 (**C**$(CH_3)_3$), 43.6 (C=O**C**H$_2$), 42.3 (N **C**H$_2$), 30.7 (NCH$_2$**C**H$_2$), 29.9 (**C**H$_3$C=O), 29.1 (C(**C**H$_3)_3$), 21.8 (C=OCH$_2$**C**H$_2$). **HRMS** (ESI) m/z calculated for $[C_{10}H_{21}NO+H]^+$: 172.1696; found 172.1701. Yellow oil. 26.7 mg (31%) of 6-(*tert*-butylamino)hexan-2-one (**38k''**) after acid/base workup, corrected for the presence of starting material and solvent.

6-((2-Methylbut-3-yn-2-yl)amino)hexan-2-one (**38l''**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 2-methylbut-3-yn-2-amine (104 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

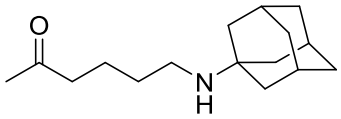


38l"

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.70 (t, *J* = 7.2 Hz, 2H, C**H**$_2$N), 2.46 (t, *J* = 7.4 Hz, 2H, C=OC**H**$_2$), 2.25 (s, 1H, C≡C**H**), 2.14 (s, 3H, C=OC**H**$_3$), 1.71 – 1.58 (m, 2H, C=OCH$_2$C**H**$_2$), 1.53 – 1.43 (m, 2H, NCH$_2$C**H**$_2$), 1.35 (s, 6H, C(C**H**$_3$)$_2$). The N-H proton can not be distinguished. **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 208.8 (**C**=O), 89.1 (**C**≡CH), 69.5 (C≡**C**H), 49.7 (**C**$_{quat}$(CH$_3$)$_2$), 43.9 (N**C**H$_2$), 43.5 (C=O**C**H$_2$), 30.1 (NCH$_2$**C**H$_2$), 29.9 (C$_{quat}$(**C**H$_3$)$_2$), 29.6 (**C**H$_3$C=O), 21.6 (C=OCH$_2$**C**H$_2$). **HRMS** (ESI) m/z calculated for $[C_{11}H_{19}NO+H]^+$: 182.1539; found 182.1532. Yellow oil. 17.2 mg (19%) of 6-((2-methylbut-3-yn-2-yl)amino)hexan-2-one (**38l''**) after acid/base workup.

6-((Adamantan-1-yl)amino)hexan-2-one (**38m''**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 6-chlorohexan-2-one (67 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), amantadine (76 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

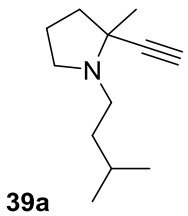


38m"

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.57 (m, *J* = 7.4 Hz, 2H, C**H**$_2$N), 2.44 (t, *J* = 7.4 Hz, 2H, C=OC**H**$_2$), 2.13 (s, 3H, C=OC**H**$_3$), 2.06 (br s, 3H, C**H**$_{adamantyl}$), 1.70 – 1.57 (m, 14H, C**H**$_{2,adamantyl}$ C=OCH$_2$C**H**$_2$), 1.48 – 1.39 (m, 2H, NCH$_2$C**H**$_2$). The N-H proton can not be distinguished. **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 208.9 (**C**=O), 50.3 (**C**$_{quat.,adamantyl}$), 43.6 (C=O**C**H$_2$), 42.9 (C$_{quat.,adamantyl}$**C**H$_2$), 40.1 (N**C**H$_2$), 36.8 (C$_{quat.,adamantyl}$CH$_2$CH**C**H$_2$), 30.8 (NCH$_2$**C**H$_2$), 29.9 (**C**H$_3$C=O), 29.7 (C$_{quat.,adamantyl}$CH$_2$**C**H), 21.8 (C=OCH$_2$**C**H$_2$). **HRMS** (ESI) m/z calculated for $[C_{16}H_{27}NO+H]^+$: 250.2165; found 250.2161. Yellow oil. 58.0 mg (47%) of 6-((adamantan-1-yl)amino)hexan-2-one (**38m''**) after acid/base workup, corrected for the presence of starting material and solvent.

2-Ethynyl-1-isopentyl-2-methylpyrrolidine (**39a**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), isoamylamine (109 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

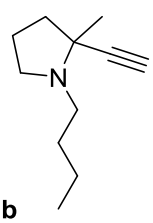


39a

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16 – 3.06 (m, 1H), 2.71 – 2.59 (m, 1H), 2.40 – 2.29 (m, 1H), 2.29 – 2.19 (m, 1H), 2.26 (s, 1H), 2.15 – 2.01 (m, 1H), 1.88 – 1.70 (m, 3H), 1.63 (septet, *J* = 6.6 Hz, 1H), 1.42 – 1.34 (m, 2H), 1.36 (s, 3H), 0.91 (d, *J* = 6.6, 3H), 0.90 (d, *J* = 6.6, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 85.3, 71.7, 59.8, 51.2, 48.1, 40.5, 38.2, 26.6, 25.6, 23.0, 22.5, 20.3. **HRMS** (ESI) m/z calculated for $[C_{12}H_{21}N+H]^+$: 180.1747; found 180.1755. Yellow oil. 80.0 mg (90%) of 2-ethynyl-1-isopentyl-2-methylpyrrolidine (**39a**) after acid/base workup.

1-Butyl-2-ethynyl-2-methylpyrrolidine (**39b**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-butylamine (91 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

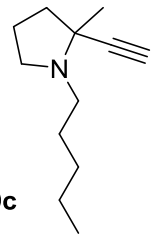


39b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16 – 3.08 (m, 1H), 2.66 – 2.56 (m, 1H), 2.42 – 2.30 (m, 1H), 2.30 – 2.19 (m, 1H), 2.26 (s, 1H), 2.12 – 2.01 (m, 1H), 1.87 – 1.72 (m, 3H), 1.53 – 1.30 (m, 4H), 1.36 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 85.2, 71.7, 59.9, 51.2, 49.8, 40.5, 31.3, 25.6, 20.9, 20.3, 14.0. **HRMS** (ESI) m/z calculated for $[C_{11}H_{19}N+H]^+$: 166.1590; found 166.1600. Yellow oil. 49 mg (60%) of 1-butyl-2-ethynyl-2-methylpyrrolidine (**39b**) after acid/base workup.

2-Ethynyl-2-methyl-1-pentylpyrrolidine (**39c**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-pentylamine (109 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

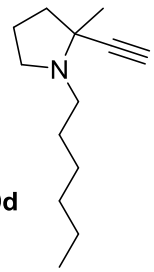


39c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16 – 3.09 (m, 1H), 2.60 (ddd, *J* = 11.8, 9.7, 6.7 Hz, 1H), 2.40 – 2.32 (m, 1H), 2.28 – 2.18 (m, 1H), 2.25 (s, 1H), 2.12 – 2.01 (m, 1H), 1.87 – 1.71 (m, 3H), 1.56 – 1.44 (m, 2H), 1.36 (s, 3H), 1.34 – 1.27 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 85.3, 71.7, 59.8, 51.2, 50.1, 40.5, 30.0, 28.9, 25.7, 22.6, 20.3, 14.1. **HRMS** (ESI) m/z calculated for $[C_{12}H_{21}N+H]^+$: 180.1747; found 180.1750. Yellow oil. 65 mg (73%) of 2-ethynyl-2-methyl-1-pentylpyrrolidine (**39c**) after acid/base workup.

2-Ethynyl-1-hexyl-2-methylpyrrolidine (**39d**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-hexylamine (126 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

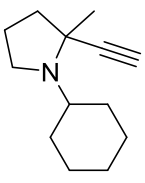


39d

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.16 – 3.07 (m, 1H), 2.60 (ddd, *J* = 11.8, 9.7, 6.7 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.29 – 2.17 (m, 1H), 2,25 (s, 1H), 2.13 – 2.01 (m, 1H), 1.88 – 1.70 (m, 3H), 1.54 – 1.44 (m, 2H), 1.36 (s, 3H), 1.33 – 1.28 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 85.3, 71.7, 59.8, 51.3, 50.1, 40.5, 31.9, 29.2, 27.5, 25.7, 22.7, 20.3, 14.1. **HRMS** (ESI) m/z calculated for $[C_{13}H_{23}N+H]^+$: 194.1903; found 194.1900. Yellow oil. 80 mg (83%) of 2-ethynyl-1-hexyl-2-methylpyrrolidine (**39d**) after acid/base workup.

1-Cyclohexyl-2-ethynyl-2-methylpyrrolidine (**39e**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-hexylamine (49.6 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).



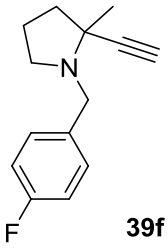
39e

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.05 – 2.93 (m, 1H), 2.84 – 2.74 (m, 1H), 2.71 – 2.59 (m, 1H), 2.25 (s, 1H), 2.21 – 2.12 (m, 1H), 2.12 – 2.02 (m, 1H), 1.85 – 1.69 (m, 6H), 1.65 – 1.56 (m, 1H), 1.41 (s, 3H), 1.36 – 1.20 (m, 4H),

1.17 – 1.04 (m, 1H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 88.5, 70.7, 57.9, 57.2, 47.3, 42.2, 34.4, 30.4, 28.0, 26.2, 26.1, 26.0, 21.0. **HRMS** (ESI) m/z calculated for $[C_{13}H_{21}N+H]^+$: 192.1747; found 192.1744. Yellow oil. 53 mg (55%) of 1-cyclohexyl-2-ethynyl-2-methylpyrrolidine (**39e**) after acid/base workup.

2-Ethynyl-1-(4-fluorobenzyl)-2-methylpyrrolidine (**39f**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *p*-fluorobenzylamine (63 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

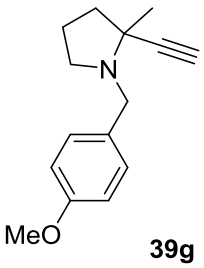


39f

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.27 (m, 2H), 7.02 – 6.93 (m, 2H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.26 (d, *J* = 13.2 Hz, 1H), 2.84 (td, *J* = 9.1, 3.2 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.34 (s, 1H), 2.18 – 2.08 (m, 1H), 1.88 – 1.76 (m, 2H), 1.76 – 1.65 (m, 1H), 1.43 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.2 (d, *J* = 244.2 Hz), 135.8 (d, *J* = 2.9 Hz), 130.1 (d, *J* = 7.9 Hz), 114.9 (d, *J* = 21.2 Hz), 85.1, 71.9, 59.5, 53.7, 51.4, 40.5, 26.0, 20.3. **HRMS** (ESI) m/z calculated for $[C_{14}H_{16}NF+H]^+$: 218.1340; found 218.1347. Yellow oil. 95 mg (88%) of 2-ethynyl-1-(4-fluorobenzyl)-2-methylpyrrolidine (**39f**) after acid/base workup.

2-Ethynyl-1-(4-methoxybenzyl)-2-methylpyrrolidine (**39g**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 4-methoxybenzylamine (69 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

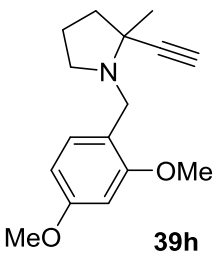


39g

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.83 (d, *J* = 12.9 Hz, 1H), 3.79 (s, 3H), 3.23 (d, *J* = 12.9 Hz, 1H), 2.85 (td, *J* = 9.1, 3.2 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.34 (s, 1H), 2.12 (td, *J* = 11.1, 7.2 Hz, 1H), 1.86 – 1.64 (m, 3H), 1.43 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.5, 132.2, 129.8, 113.6, 85.2, 71.8, 59.5, 55.3, 53.8, 51.4, 40.6, 26.0, 20.3. **HRMS** (ESI) m/z calculated for $[C_{15}H_{19}NO+H]^+$: 230.1539; found 230.1530. Yellow oil. 81 mg (71%) of 2-ethynyl-1-(4-methoxybenzyl)-2-methylpyrrolidine (**39g**) after acid/base workup.

1-(2,4-Dimethoxybenzyl)-2-ethynyl-2-methylpyrrolidine (**39h**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 2,4-dimethoxybenzylamine (84 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

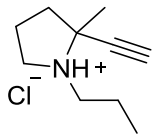


39h

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.20 (m, 1H), 6.46 – 6.42 (m, 2H), 3.84 (d, *J* = 13.4 Hz, 1H), 3.79 (d, *J* = 3.4 Hz, 6H), 3.28 (d, *J* = 13.4 Hz, 1H), 2.97 (td, *J* = 9.1, 3.2 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.33 (s, 1H), 2.15 – 2.06 (m, 1H), 1.86 – 1.67 (m, 3H), 1.46 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 158.7, 130.7, 120.8, 103.9, 98.6, 85.5, 71.6, 59.8, 55.4, 55.4, 51.7, 48.0, 40.5, 25.9, 20.4. **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}NO_2+H]^+$: 260.1645; found 260.1642. Yellow oil. 84 mg (65%) of 1-(2,4-dimethoxybenzyl)-2-ethynyl-2-methylpyrrolidine (**39h**) after acid/base workup. Low integration for the C≡C**H** proton is caused by a very high relaxation time (T_1 = 19.69 s) for this proton, when the relaxation time for the proton measurement was increased, the integration became more correct.

2-Ethynyl-2-methyl-1-propylpyrrolidine hydrochloride (**39i'**)

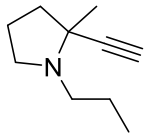
The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).



39i'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.48 (br s, 1H, N**H**$^+$), 3.98 – 3.80 (m, 1H,), 3.16 (tdd, *J* = 12.0, 4.2, 2.7 Hz, 1H,), 3.03 – 2.85 (m, 2H, NCH(**H**)CH_2CH_2 and), 2.71 (s, 1H,), 2.58 (dt, *J* = 12.9, 9.9 Hz, 1H, $NCCH_2CH_2H$(**H**)), 2.37 – 2.11 (m, 4H, $NCCH_2C\mathbf{H_2H}$(H) and NCH_2C**H**(H)CH_3), 1.93 (s, 3H, $C_{quat}C\mathbf{H_3}$), 1.83 – 1.65 (m, 1H, NCH_2CH(**H**)CH_3), 1.03 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 79.2 (**C**≡CH), 77.8 (C≡**C**H), 66.4 (N**C**$_{quat}$), 51.7 (N**C**$H_2CH_2CH_3$), 51.3 (N**C**$H_2CH_2CH_2$), 38.4 (NCH_2CH_2**C**H_2), 22.2 (C_{quat}**C**H_3), 19.9 (NCH_2**C**H_2CH_2), 19.0 (NCH_2**C**H_2CH_3), 11.6 (NCH_2CH_2**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{10}H_{17}N+H]^+$: 152.1434; found 152.1431. Yellow oil. 84.1 mg (90%) of 2-ethynyl-2-methyl-1-propylpyrrolidine hydrochloride (**39i'**) after acid/base workup and treatment with HCl in Et_2O.

When the product is isolated as free amine, the yield drops due to its high volatility. NMR data for 2-ethynyl-2-methyl-1-propylpyrrolidine (**39i**).

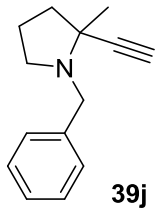


39i

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 – 3.08 (m, 1H, NC**H**(H)CH_2CH_2), 2.56 (ddd, *J* = 11.7, 9.9, 6.7 Hz, 1H, NC**H**(H)CH_2CH_3), 2.43 – 2.31 (m, 1H, NCH(**H**)CH_2CH_2), 2.26 (s, 1H, C≡C**H**), 2.25 – 2.19 (m, 1H, NCH(**H**)CH_2CH_3), 2.12 – 2.02 (m, 1H, $NCCH_2CH_2H$(**H**)), 1.86 – 1.72 (m, 3H, $NCCH_2C\mathbf{H_2H}$(H)), 1.60 – 1.41 (m, 2H, $NCCH_2C\mathbf{H_2}CH_3$), 1.36 (s, 3H, $C_{quat}C\mathbf{H_3}$), 0.93 (t, *J* = 7.4 Hz, 3H, $NCH_2CH_2C\mathbf{H_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 85.3 (**C**≡CH), 71.6 (C≡**C**H), 59.7 (N**C**$_{quat}$), 52.1 (N**C**$H_2CH_2CH_3$), 51.3 (N**C**$H_2CH_2CH_2$), 40.5 (NCH_2CH_2**C**H_2), 25.7 (C_{quat}**C**H_3), 22.4 (NCH_2**C**H_2CH_3), 20.4 (NCH_2**C**H_2CH_2), 12.2 (NCH_2CH_2**C**H_3).

1-Benzyl-2-ethynyl-2-methylpyrrolidine (**39j**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-benzylamine (53.6 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

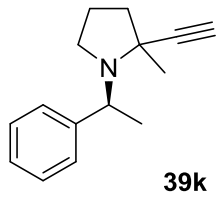


39j

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.18 (m, 5H, C**H**$_{arom.}$), 3.91 (d, *J* = 13.2 Hz, 1H, C**H**(H)Ph), 3.29 (d, *J* = 13.2 Hz, 1H, CH(**H**)Ph), 2.87 (td, *J* = 9.1, 3.2 Hz, 1H, NC**H**(H)CH_2CH_2), 2.43 – 2.35 (m, 1H, NCH(**H**)CH_2CH_2), 2.34 (s, 1H, C≡C**H**), 2.17 – 2.08 (m, 1H, $NCCH_2CH_2H$(**H**)), 1.81 (d, *J* = 6.6 Hz, 3H, $NCCH_2C\mathbf{H_2H}$(H)), 1.44 (s, 3H, $C_{quat}C\mathbf{H_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 140.2 (**C**$_{quat.,arom.}$), 128.7 (**C**H$_{arom.,ortho}$), 128.2 (**C**H$_{arom.,meta}$), 126.7 (**C**H$_{arom.,para}$), 85.2 (**C**≡CH), 71.8 (C≡**C**H), 59.6 (N**C**$_{quat}$), 54.5 (N**C**H_2Ph), 51.4 (N**C**$H_2CH_2CH_2$), 40.5 (NCH_2CH_2**C**H_2), 26.0 (C_{quat}**C**H_3), 20.3 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{14}H_{17}N+H]^+$: 200.1434; found 200.1432. Yellow oil. 71.0 mg (71%) of 1-benzyl-2-ethynyl-2-methylpyrrolidine (**39j**) after acid/base workup.

2-Ethynyl-2-methyl-1-((*S*)-1-phenylethyl)pyrrolidine (**39k**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), L-1-phenylethylamine (60.6 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

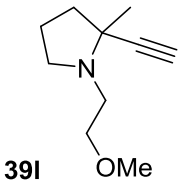


39k

Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 – 7.35 (m, 2H), 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 1H), 3.92 (q, *J* = 6.8 Hz, 1H), 3.12 (td, *J* = 9.1, 3.7 Hz, 1H), 2.80 – 2.71 (m, 1H), 2.36 (s, 1H), 2.10 – 2.03 (m, 1H), 1.86 – 1.73 (m, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 3H). Minor isomer (most of the signals are overlapping with the major diastereomer, only clear signals): **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 3.74 (q, *J* = 6.7 Hz, 1H, NC**H**CH_3). Major isomer: **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.1, 128.0, 127.5, 126.6, 86.8, 72.0, 59.6, 58.3, 49.2, 42.1, 27.8, 21.7, 20.2. **HRMS** (ESI) m/z calculated for $[C_{15}H_{19}N+H]^+$: 214.1590; found 214.1597. Yellow oil, 35 mg (33%) of 2-ethynyl-2-methyl-1-((*S*)-1-phenylethyl)pyrrolidine (**39k**) as an 75/25 mixture of diastereomers after acid/base workup.

2-Ethynyl-1-(2-methoxyethyl)-2-methylpyrrolidine (**39l**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 2-ethoxyethylamine (94 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

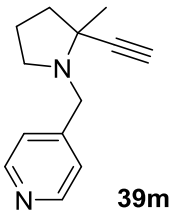


39l

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.58 – 3.45 (m, 2H), 3.37 (s, 3H), 3.17 (d, *J* = 8.4 Hz, 1H), 2.92 (ddd, *J* = 13.3, 7.6, 5.9 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.27 (s, 1H), 2.07 (d, *J* = 3.8 Hz, 1H), 1.88 – 1.74 (m, 3H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 84.9, 71.9, 71.8, 60.1, 58.8, 51.8, 49.7, 40.1, 25.6, 20.5. **HRMS** (ESI) m/z calculated for $[C_{10}H_{17}NO+H]^+$: 168.1383; found 168.1387. Yellow oil. 45 mg (54%) of 2-ethynyl-1-(2-methoxyethyl)-2-methylpyrrolidine (**39l**) after acid/base workup.

4-((2-Ethynyl-2-methylpyrrolidin-1-yl)methyl)pyridine (**39m**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 4-(aminomethyl)pyridine (54 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

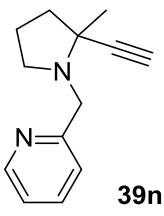


39m

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 (dd, *J* = 4.6, 1.3 Hz, 2H), 7.29 (d, *J* = 5.8 Hz, 2H), 3.91 (d, *J* = 14.4 Hz, 1H), 3.32 (d, *J* = 14.4 Hz, 1H), 2.88 (td, *J* = 9.0, 3.2 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.35 (s, 1H), 2.19 – 2.10 (m, 1H), 1.90 – 1.70 (m, 3H), 1.42 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 149.8, 149.5, 123.7, 84.4, 72.0, 59.7, 53.5, 51.6, 40.3, 26.0, 20.5. **HRMS** (ESI) m/z calculated for $[C_{13}H_{16}N_2+H]^+$: 201.1386; found 201.1392. Yellow oil. 35 mg (35%) of 4-((2-ethynyl-2-methylpyrrolidin-1-yl)methyl)pyridine (**39m**) after acid/base workup.

2-((2-Ethynyl-2-methylpyrrolidin-1-yl)methyl)pyridine (**39n**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 2-(aminomethyl)pyridine (54 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).



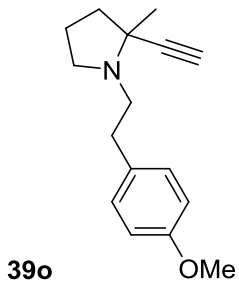
39n

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (d, *J* = 4.4 Hz, 1H), 7.63 (td, *J* = 7.6, 1.7 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.13 (dd, *J* = 6.9, 5.1 Hz, 1H), 4.03 (d, *J* = 14.0 Hz, 1H), 3.54 (d, *J* = 14.0 Hz, 1H), 2.94 (td, *J* = 9.0, 3.3 Hz, 1H), 2.50 (dt, *J* = 16.4, 8.3 Hz, 1H), 2.35 (s, 1H), 2.18 – 2.10 (m, 1H), 1.92 – 1.69 (m, 3H), 1.44 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.3, 149.2, 136.3, 122.9, 121.7, 85.0, 72.0, 59.9, 56.5, 51.7, 40.3, 25.9, 20.5. **HRMS** (ESI) m/z calculated for $[C_{13}H_{16}N_2+H]^+$: 201.1386; found 201.1384. Yellow oil. 37 mg

(37%) of 2-((2-ethynyl-2-methylpyrrolidin-1-yl)methyl)pyridine (**39n**) after acid/base workup.

2-Ethynyl-1-(4-methoxyphenethyl)-2-methylpyrrolidine (**39o**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 4-methoxyphenethylamine (76 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

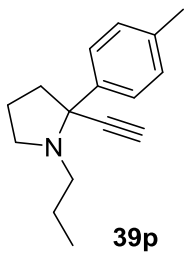


39o

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.79 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 3.24 – 3.17 (m, 1H), 2.89 – 2.66 (m, 3H), 2.54 – 2.42 (m, 2H), 2.24 (s, 1H), 2.011 – 2.05 (m, 1H), 1.91 – 1.73 (m, 3H), 1.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 157.9, 132.9, 129.6, 113.7, 85.1, 71.8, 59.8, 55.3, 52.2, 51.3, 40.4, 35.0, 25.6, 20.4. **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}NO+H]^+$: 244.1696; found 244.1693. Yellow oil. 81 mg (67%) of 2-ethynyl-1-(4-methoxyphenethyl)-2-methylpyrrolidine (**39o**) after acid/base workup.

2-Ethynyl-1-propyl-2-(*p*-tolyl)pyrrolidine (**39p**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 4-chloro-4'-methylbutyrophenone (98 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

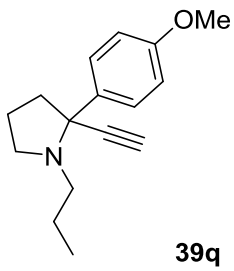


39p

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 3.36 – 3.29 (m, 1H), 2.54 (s, 1H), 2.52 – 2.45 (m, 1H), 2.34 (s, 3H), 2.29 – 2.15 (m, 3H), 2.01 – 1.85 (m, 3H), 1.50 – 1.38 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.5, 136.7, 128.8, 126.6, 74.8, 68.2, 62.4, 52.1, 50.3, 44.6, 22.0, 21.4, 21.0, 11.9. **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}N+H]^+$: 228.1747; found 228.1747. Yellow oil. 39.6 mg (35%) of 2-ethynyl-1-propyl-2-(*p*-tolyl)pyrrolidine (**39p**) after acid/base workup.

2-Ethynyl-2-(4-methoxyphenyl)-1-propylpyrrolidine (**39q**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 4-chloro-4'-methoxybutyrophenone (106 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

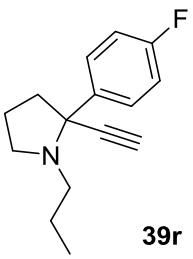


39q

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.9 Hz, 2H), 6.88 – 6.83 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.35 – 3.28 (m, 1H), 2.54 (s, 1H), 2.52 – 2.44 (m, 1H), 2.27 – 2.13 (m, 3H), 1.99 – 1.87 (m, 3H), 1.51 – 1.36 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.8, 135.1, 127.8, 113.4, 82.8, 74.9, 67.9, 55.3, 52.0, 50.3, 44.5, 22.0, 21.3, 11.9. **HRMS** (ESI) m/z calculated for $[C_{16}H_{21}NO+H]^+$: 244.1696; found 244.1700. Yellow oil. 52 mg (43%) of 2-ethynyl-2-(4-methoxyphenyl)-1-propylpyrrolidine (**39q**) after acid/base workup.

2-Ethynyl-2-(4-fluorophenyl)-1-propylpyrrolidine (**39r**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 4-chloro-4'-fluorobutyrophenone (100 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

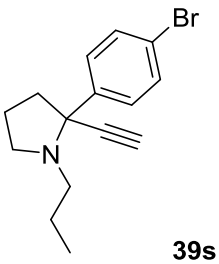


39r

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 – 7.64 (m, 2H), 7.03 – 6.96 (m, 2H), 3.39 – 3.26 (m, 1H), 2.56 (s, 1H), 2.53 – 2.44 (m, 1H), 2.27 – 2.16 (m, 3H), 2.03 – 1.85 (m, 3H), 1.51 – 1.32 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 162.1 (d, *J* = 245.8 Hz), 138.8 (d, *J* = 2.6 Hz), 128.3 (d, *J* = 8.0 Hz), 114.8 (d, *J* = 21.2 Hz), 82.5, 75.2, 67.9, 52.0, 50.3, 44.7, 22.0, 21.4, 11.9. **HRMS** (ESI) m/z calculated for $[C_{15}H_{18}NF+H]^+$: 232.1496; found 232.1493. Yellow oil. 47 mg (41%) of 2-ethynyl-2-(4-fluorophenyl)-1-propylpyrrolidine (**39r**) after acid/base workup.

2-(4-Bromophenyl)-2-ethynyl-1-propylpyrrolidine (**39s**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 4'-bromo-4-chlorobutyrophenone (131 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

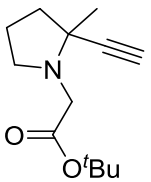


39s

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 3.36 – 3.28 (m, 1H), 2.56 (s, 1H), 2.53 – 2.44 (m, 1H), 2.27 – 2.14 (m, 3H), 2.03 – 1.84 (m, 3H), 1.53 – 1.36 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 142.5, 131.1, 128.6, 121.0, 82.1, 75.4, 68.0, 52.1, 50.3, 44.7, 22.0, 21.5, 11.9. **HRMS** (ESI) m/z calculated for $[C_{15}H_{18}NBr+H]^+$: 292.0695; found 292.0699. Yellow oil. 58 mg (40%) of 2-(4-bromophenyl)-2-ethynyl-1-propylpyrrolidine (**39s**) after acid/base workup.

Tert-butyl 2-(2-ethynyl-2-methylpyrrolidin-1-yl)acetate (**39t**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), glycine *tert*-butyl ester hydrochloride (84 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).



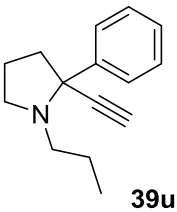
39t

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.41 (d, *J* = 16.6 Hz, 1H, NC**H**(H)), 3.41 – 3.35 (m, 1H, NC**H**(H)CH_2CH_2), 2.97 (d, *J* = 16.6 Hz, 1H, NCH(**H**)), 2.47 – 2.39 (m, 1H, NCH(**H**)CH_2CH_2), 2.29 (s, 1H, C≡C**H**), 2.11 – 2.01 (m, 1H, NCH_2CH_2C**H**(H)), 1.88 – 1.76 (m, 3H, NCH_2C**H**$_2$CH(**H**)), 1.47 (s, 9H, C(C**H**$_3$)$_3$), 1.38 (s, 3H, $C_{quat}C$**H**$_3$).**^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.8 (**C**=O), 84.6 (**C**≡CH), 80.7 (**C**$(CH_3)_3$), 72.1 (C≡**C**H), 59.9 (N**C**$_{quat}$), 53.0 (N**C**H_2C=O), 52.2 (N**C**$H_2CH_2CH_2$), 39.9 (NCH_2CH_2**C**H_2), 28.1 (C(**C**$H_3)_3$), 25.6 (NC_{quat}**C**H_3), 20.6 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{13}H_{21}NO_2+H]^+$: 224.1645; found 224.1648. Yellow oil. 22.9 mg (21%) of *tert*-butyl 2-(2-ethynyl-2-methylpyrrolidin-1-yl)acetate (**39t**) after filtration over a plug of silica and washing with DCM (50 mL).

2-Ethynyl-2-phenyl-1-propylpyrrolidine (**39u**)

In an oven-dried 10 mL microwave vessel were introduced CaC_2 (128 mg, 2 mmol), γ-chlorobutyrophenone (**33a**) (91 mg, 0.5 mmol), *n*-propylamine (74 mg, 1.25 mmol), CuI (19.05 mg, 0.1 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol). The vessel was quickly capped and placed in a preheated oil bath at 60 °C for 24 h. After 2 h, H_2O (18 mg, 1 mmol) was added. The reaction mixture turns red after a while, probably due to the formation of copper acetylide. Afterwards, the reaction mixture was quenched by addition of 2 mL water and subjected to acid-base workup; addition of 3 M HCl solution (10 mL) and extraction of the aqueous phase with MTBE (2 x 15 mL). The aqueous phase was then basified with 5 M

NaOH, forming insoluble $Ca(OH)_2$ and extracted with MTBE (3 x 15 mL). The organic phases were combined and dried over $MgSO_4.3H_2O$, and concentrated *in vacuo* to yield 52.1 mg (49%) of 2-ethynyl-2-phenyl-1-propylpyrrolidine (**39u**).

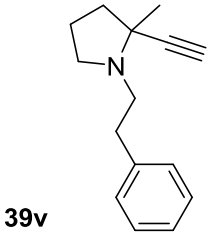


39u

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, *J* = 7.7 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.23 (m, 1H), 3.37 – 3.30 (m, 1H), 2.57 – 2.46 (m, 1H), 2.55 (s, 1H), 2.30 – 2.18 (m, 3H), 2.03 – 1.87 (m, 3H), 1.52 – 1.36 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 143.1, 128.0, 127.2, 126.7, 82.6, 75.0, 68.4, 52.1, 50.3, 44.7, 22.0, 21.5, 11.9. **HRMS** (ESI) m/z calculated for $[C_{15}H_{19}N+H]^+$: 214.1590; found 214.1586. Yellow oil.

2-Ethynyl-2-methyl-1-phenethylpyrrolidine (**39v**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), phenethylamine (61 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

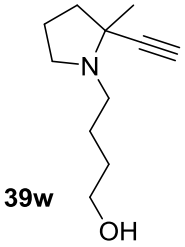


39v

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.14 (m, 5H), 3.22 (td, *J* = 8.8, 3.9 Hz, 1H), 2.93 – 2.71 (m, 3H), 2.58 – 2.43 (m, 2H), 2.24 (s, 1H), 2.12 – 2.05 (m, 1H), 1.93 – 1.74 (m, 3H), 1.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ =140.8, 128.7, 128.3, 125.9, 85.0, 71.8, 59.8, 52.0, 51.3, 40.4, 36.0, 25.6, 20.4. **HRMS** (ESI) m/z calculated for $[C_{15}H_{19}N+H]^+$: 214.1590; found 214.1594. Yellow oil. 98 mg (91%) of 2-ethynyl-2-methyl-1-phenethylpyrrolidine (**39v**) after acid/base workup.

4-(2-Ethynyl-2-methylpyrrolidin-1-yl)butan-1-ol (**39w**)

The reaction was carried out with CaC_2 (128 mg, 2 mmol), 5-chloropentan-2-one (60 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), 4-aminobutan-1-ol (45 mg, 0.5 mmol), triethylamine (76 mg, 0.75 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol).

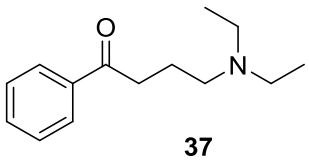


39w

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.52 (br s, 1H), 3.69 – 3.62 (m, 1H), 3.53 – 3.45 (m, 1H), 3.24 – 3.12 (m, 1H), 2.65 – 2.54 (m, 1H), 2.48 – 2.35 (m, 2H), 2.29 (s, 1H), 2.16 – 2.08 (m, 1H), 1.89 – 1.77 (m, 5H), 1.61 – 1.49 (m, 2H), 1.42 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 84.2, 72.4, 63.1, 60.0, 50.8, 50.1, 40.2, 32.6, 27.2, 24.9, 20.2. **HRMS** (ESI) m/z calculated for $[C_{11}H_{19}NO+H]^+$: 182.1539; found 182.1546. Yellow oil. 58.8 mg (65%) of 4-(2-ethynyl-2-methylpyrrolidin-1-yl)butan-1-ol (**39w**) after acid/base workup.

4-(Diethylamino)-1-phenylbutan-1-one (**37**)

In a 10 mL microwave vessel were introduced CaC_2 (64 mg, 1 mmol), γ-chlorobutyrophenone (**33a**) (91 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol) and MeCN (2 mL). The vessel was quickly capped and placed in a preheated oil bath at 60 °C for 24 h. Then, with a syringe pump 0.125 mL of 8 M H_2O in MeCN was added over two hours. The reaction mixture turns red after a while, probably due to the formation of copper acetylide. Afterwards, the reaction mixture was quenched by addition of 2 mL water and subjected to acid-base workup; addition of 3 M HCl solution (10 mL) and extraction of the aqueous phase with MTBE (2 x 15 mL). The aqueous phase was then basified with 5 M NaOH, forming insoluble $Ca(OH)_2$ and extracted with MTBE (3 x 15 mL). The organic phases were combined and dried over $MgSO_4.3H_2O$, and concentrated *in vacuo* to yield 52.1 mg (49%) of 4-(diethylamino)-1-phenylbutan-1-one (**37**).



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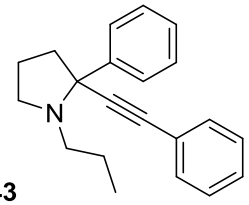
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 – 7.95 (m, 2H), 7.57 – 7.51 (m, 1H), 7.44 (m, 2H), 3.00 (t, *J* = 7.2 Hz, 1H), 2.53 (q, *J* = 7.1, 4H), 2.50 (t, *J* = 7.2, 2H), 1.89 (tt, *J* = 7.2, 7.2 Hz, 2H), 1.00 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 200.3, 137.2, 132.8, 128.5, 128.1, 52.2, 46.8, 36.5, 21.8, 11.8. **HRMS** (ESI) m/z calculated for $[C_{14}H_{21}NO+H]^+$: 220.1696; found 220.1690. Yellow oil.

2-Phenyl-2-(phenylethynyl)-1-propylpyrrolidine **(4bah)**

The reaction was carried out with CaC_2 (128 mg, 2 mmol), g-chlorobutyrophenone (91 mg, 0.5 mmol), CuI (19.05 mg, 0.1 mmol), *n*-propylamine (74 mg, 1.25 mmol), MeCN (2 mL) and H_2O (9 mg, 0.5 mmol). After two hours, another two equivalents of H_2O (18 mg, 1.0 mmol) was added. After 24 hours, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol) and iodobenzene (102 mg, 0.5 mmol) were added and the reaction mixture was stirred for an additional 4 hours at 50 °C.



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NMR/HRMS data see: W. E. Van Beek, J. Van Stappen, P. Franck and K. Abbaspour Tehrani, *Org. Lett.*, 2016, **18**, 4782 or previous chapter.

Yellow oil. 54.1 mg (37%) of 2-phenyl-2-(phenylethynyl)-1-propylpyrrolidine (**4bah**) after acid/base workup.

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[4] Price calcium carbide: € 7/mol, price TMS-acetylene: € 510/mol (Prices from Sigma-Aldrich as of November 2017)

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5 Hydrazines as coupling partners in one-pot coupling reactions with ω-halogenated ketones and alkynes

In this chapter the amine component from the reaction of ω-chloroketones, amines and alkynes, as described in Chapter three, was replaced by a hydrazine. It was expected that this substitution would lead to propargylhydrazines in a similar way as in a KA² coupling, but other products were observed due to a different reactivity, where *in situ* azomethine imines are formed.

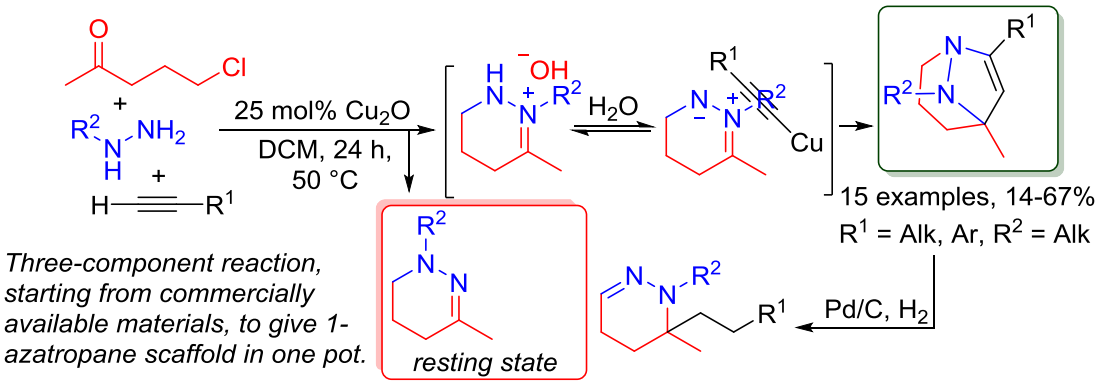


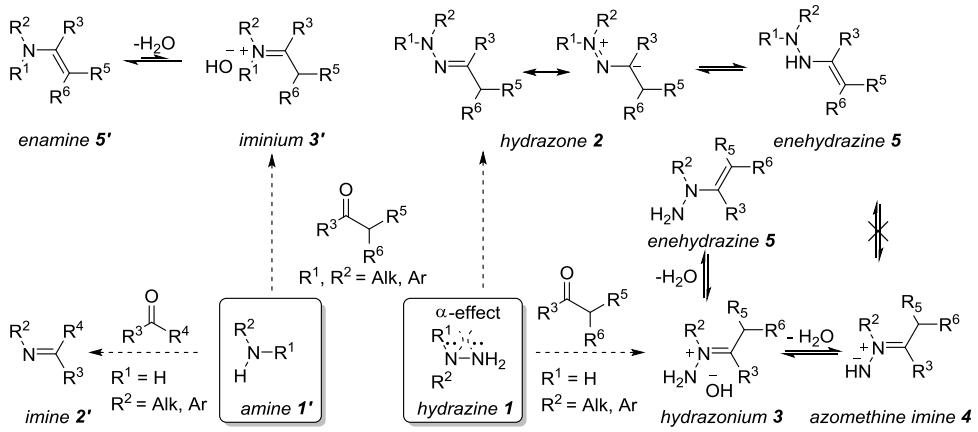
Table of Contents

5.1 Literature study: Alkynylation of hydrazones and [3+2] cycloadditions of azomethine imines and alkynes

5.1.1 Reactivity of hydrazines, hydrazones, hydrazides and azomethine imines

Hydrazines **1** as organic reagents resemble amines **1'**. Due to the presence of two electron lone pairs on the neighboring nitrogen atoms, hydrazines **1** are subject to the α-effect. Since the two lone pairs repel each other, the nitrogen atoms are more nucleophilic compared to the nitrogen atom in amines. On the other hand, amines are slightly stronger bases than hydrazines (pK_a (NH_4^+) = 9.2 and pK_a ($H_2NNH_3^+$) = 8.1).[1] In the special case where hydrazines possess an electron withdrawing carbonyl group they are named hydrazides. Extensive research has been done to address the risks associated with hydrazines **1**,[2] as they are acutely toxic and exposure (even at ppm level) may be lethal. Due to the volatile nature of hydrazines **1**, exposure by inhalation is a major risk. Hydrazines **1** are also highly flammable and explosive. Therefore, caution has to be taken when handling hydrazines **1**.

Hydrazines **1** can undergo condensation reactions with aldehydes and ketones to yield hydrazones **2** in a similar way that amines **1'** form imines **2'** (Scheme 5-1). Hydrazones **2** have enhanced stability compared to imines **2'**. This can be explained by extra resonance stabilization, in which a negative charge is delocalized onto the carbonyl atom, making the carbonyl atom less electrophilic compared to imines. This enhanced stability translates into lower reactivity towards nucleophiles (*i.e.* alkynylation reactions). As an advantageous result hydrazones **2** are therefore less prone to hydrolysis than imines **2'**.



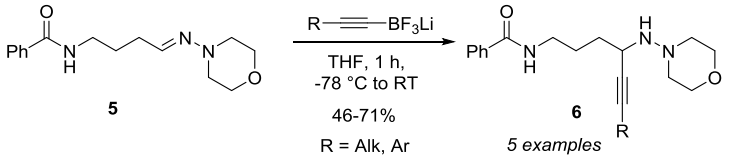
Scheme 5-1 Analogy of amines and hydrazines.

However, when an intermediate hydrazonium ion **3** is formed (similar as to the formation of an iminium ion **3'**) and the other nitrogen atom has at least one hydrogen atom attached, water can be eliminated to form azomethine imines **4** next to enehydrazines **5**.[3] This transformation can be achieved thermally[4] or acid-catalyzed[5]. In the literature, azomethine imines **4** formed from hydrazides and aldehydes or ketones are stable enough to be isolated. This can be explained by an extra resonance structure, where the negative charge of the azomethine imine is delocalized into the imidoyl carbon. On the other hand, azomethine imines **4** without stabilizing groups are not stable enough to be isolated.

In order to gain a better understanding of the reactivity of hydrazines, hydrazones and azomethine imines, a literature overview will be given of reactions involving alkynes and hydrazines, hydrazones or azomethine imines.

5.1.2 Alkynylation reactions on hydrazones

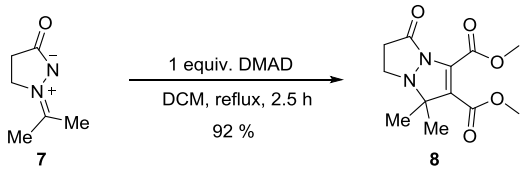
In 2016, Maulide *et al.* described the alkynylation of hydrazones **5** with lithium alkynyl trifluoroborates to form propargylhydrazines **6** (Scheme 5-2). Lithium alkynyl trifluoroborates can be synthesized in a straightforward way by deprotonation of the corresponding alkyne with *n*-BuLi in THF at -78 °C, followed by the addition of $BF_3.OEt_2$. Addition of the hydrazone **5** at -78 °C and subsequent warming to room temperature and aqueous workup gives propargylhydrazines **6**. This procedure uses a stoichiometric amount of a strong base and a stoichiometric amount of metal catalyst, while additions of alkynes to imines can typically be done with catalytic amounts of metal and without the use of strong bases. The increased difficulty is in accordance with the decreased electrophilicity of hydrazones compared to imines, as described in §5.1.1. To the best of our knowledge, this is the only example of the direct alkynylation of a hydrazone.



Scheme 5-2 Alkynylation on hydrazones with lithium alkynyl trifluoroborates.

5.1.3 Reactions of alkynes and azomethine imines: [3+2] cycloaddition or alkynylation followed by intramolecular hydrohydrazination?

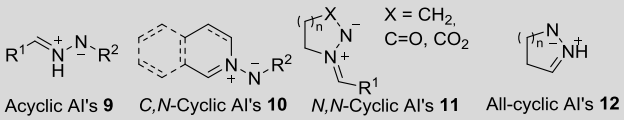
The first reports of [3+2] cycloadditions of azomethine imines and alkynes were published in 1968 by Dorn and Otto (Scheme 5-3).[6] They described the synthesis and reactivity of *N,N*-cyclic and *C,N*-cyclic azomethine imines, and showed one particular example of [3+2] cycloaddition of an *N,N*-cyclic azomethine imine **7**, derived from acetone with dimethyl acetylenedicarboxylate (DMAD) to generate bicyclic product **8**.



Scheme 5-3 The first [3+2] cycloaddition of azomethine imines with alkynes.

Interlude: Different types of azomethine imines

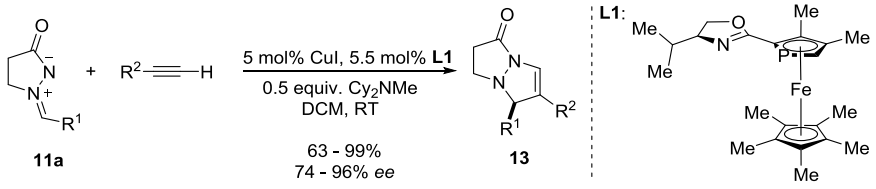
In 2003 Schantl *et al.* introduced a classification for azomethine imines, which was later in 2003 adopted in the review about azomethine imines in cycloadditions from Yus *et al.* (Scheme 5-4).[7] Four subclasses of azomethine imines (AI's) can be distinguished: acyclic AI's **9**, *C,N*-cyclic AI's **10**, *N,N*-cyclic AI's **11** and all-cyclic AI's **12**. Generally, when a carbonyl substituent is attached to the hydrazine (*e.g.* a hydrazide), azomethine imines are stable enough to be isolated. Otherwise, azomethine imines are generated *in situ* from hydrazones via 1,2-prototropy.



Scheme 5-4 Different types of azomethine imines.

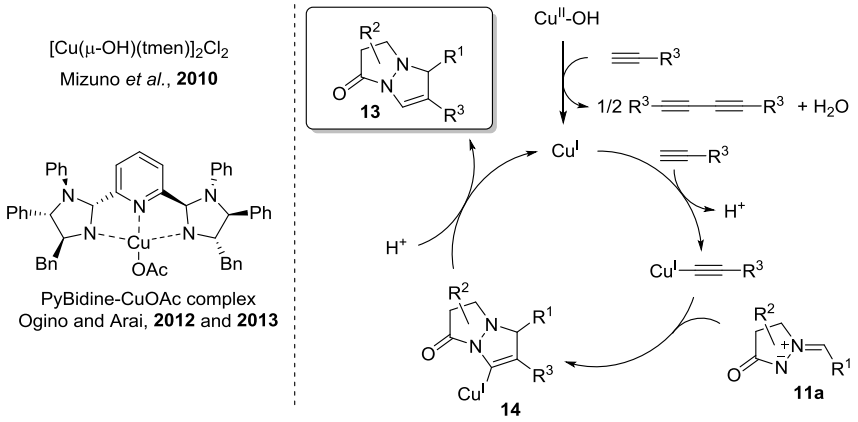
5.1.3.1 [3+2] Cycloadditions of *N,N*-cyclic azomethine imines with alkynes

In 2003, Fu *et al.* described a [3+2] cycloaddition of the same type of *N,N*-cyclic azomethine imines **11a**, derived from pyrazolidin-3-one and aldehydes, and terminal alkynes catalyzed by a Cu(I)/phosphaferrocene-oxazoline **L1** catalytic system (Scheme 5-5).[8] Yields and *ee*'s are generally high and only one regioisomer is formed. The reaction works best with electron-withdrawing groups on the alkyne. Although no reaction mechanism was shown, they presumed the *in situ* formation of copper acetylide species. At the time, this was the first Cu(I)-catalyzed coupling of alkynes and azomethine imines. Earlier Cu(I)-catalyzed reactions on 1,3-dipoles focused on azides and nitrones, yielding 1,2,3-triazoles[9] and β-lactams[10]. Later, in 2005 Fu *et al.* reported the kinetic resolution of azomethine imines **11a** based on a similar type of phosphaferrocene-oxazoline ligand.[11]



Scheme 5-5 [3+2] cycloaddition of *N,N*-cyclic azomethine imines with terminal alkynes catalyzed by a phosphaferrocene-oxazoline.

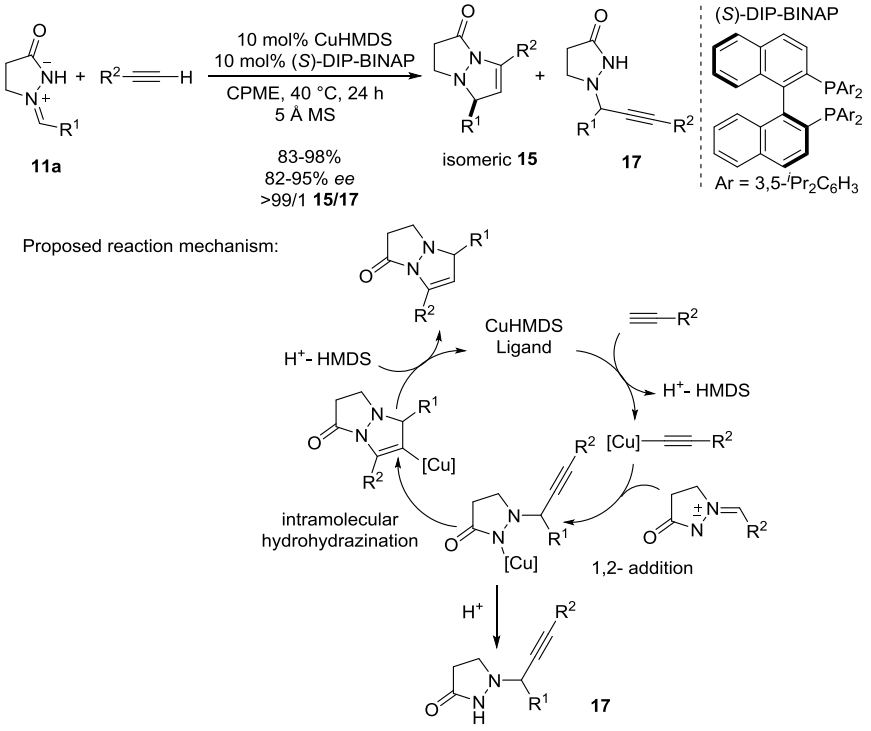
In 2010, the group of Mizuno reported a $[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$ complex to generate the same structures **13** in a racemic way describing 305 h^{-1} TOF and 860 TON values at 60°C for the [3+2] cycloaddition of **11a**, derived from benzaldehyde with methyl propiolate (Scheme 5-6).[12] In 2011, the same group reported a heterogeneous catalytic system comprising of $Cu(OH)_x/Al_2O_3$ with 46 h^{-1} TOF and 646 TON values.[13] Interestingly, they postulated a reaction mechanism. From Cu(II), the active Cu(I) species can be formed via Glazer-homocoupling of the alkyne, rendering a Cu(I) species. Cu(I) forms a copper acetylide species, which undergoes [3+2] cycloaddition with azomethine imine **11a** to form a vinyl copper species **14**. This vinyl copper species is protonated to form the target molecules **13**.



Scheme 5-6 Different catalytic systems and reaction mechanism postulated by Mizuno *et al.*

In 2011, Kobayashi *et al.* reported a CuHMDS/(*S*)-DIP-BINAP catalyzed reaction of *N,N*-cyclic azomethine imines with alkynes (Scheme 5-7).[14] The use of this specific catalytic system allowed for the synthesis of the other regioisomeric product **15** compared to the one that was reported earlier by Fu *et al.*[8] To explain this regioisomer **15** they proposed a reaction mechanism where no [3+2] cycloaddition occurs, but rather alkynylation (1,2-addition) of the

azomethine imine would occur, followed by intramolecular hydrohydrazination to form a vinyl copper species **16**, which upon protonation delivered the regioisomeric product **15**. This hypothesis was supported by the formation of trace amounts of propargyl hydrazide **17**, which can be formed from the intermediate 1,2-addition product by protonation.



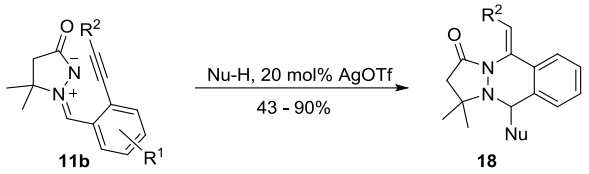
Scheme 5-7 Formation of a different regioisomeric product via CuHMDS/(*S*)-DIP-BINAP catalyzed [3+2] cycloaddition of *N*,*N*-cyclic azomethine imines with alkynes

Interlude: Intramolecular hydrohydrazination reactions

Intramolecular hydrohydrazination reactions are similar to intramolecular hydroamination reactions with the only difference being that hydrazines are more nucleophilic due to the α-effect. Therefore hydrazines should react faster than amines for a given ring-size. Intramolecular hydrohydrazinations can be Ag(I)[15], Pt(II)[16]-catalyzed and can even be combined with iodocyclization,[17] but remain much more unexplored than intramolecular hydroamination reactions.[18] Intermolecular hydrohydrazination reactions can be catalyzed by a number of metals including Ti(I), Rh(I), Ir(I), Pd(I) and can also be achieved thermally[16] or base-induced.[19]

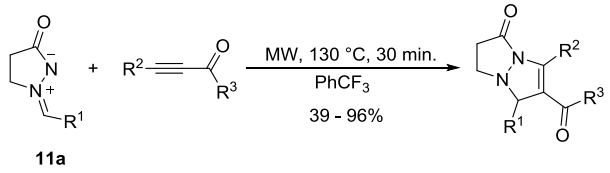
In 2012, Arai and Ogino reported the use of CuOAc and Pybidine for the synthesis of **13** in a stereoselective fashion (Scheme 5-6).[20] Although yields were generally high (58 – 99%), enantioselectivities were only moderate (32-74% *ee*). They also made similar polymer supported Cu-Pybidine catalysts.[21] The same molecules **13** could also be prepared in a racemic way via a solventless ball-milling approach, using CuI and CaF_2 as a base.[22] In 2013, Hu *et al.* described another, similar, procedure to synthesize molecules **13** in a racemic way.[23] They changed the catalyst from CuI to CuOAc claiming to avoid self-Michael addition of propiolates, while the anion is basic enough to easily form copper acetylides.

Interestingly, in 2013, Li *et al.* described an addition-cyclization reaction on *N*,*N*-cyclic azomethine imines **11b** (Scheme 5-8).[24] Although there is an alkyne function present in the azomethine imine, no intramolecular [3+2] cycloaddition occurs between the azomethine imine and the alkyne because the right conformation cannot be formed. The proposed mechanism starts with the *6-exo-dig* cyclization of the azomethine imine to the alkyne which is assisted by coordination of Ag(I) to the alkyne. This cyclization forms a hydrazonium species, which is easily attacked by a nucleophile to give products **18**.



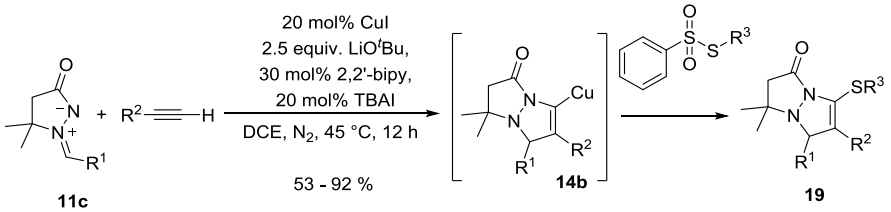
Scheme 5-8 Intramolecular hydrohydrazination of an azomethine imine, followed by nucleophile addition to the *in situ* formed hydrazonium ion.

In 2016, Cui *et al.* described a microwave-assisted, thermal [3+2] cycloaddition of *N*,*N*-cyclic azomethine imines **11a** with internal alkynes (Scheme 5-9).[25] Reactions were carried out in trifluoromethylbenzene in a microwave oven at 130 °C without the use of a metal catalyst or any other catalyst. Although the scope was limited to carbonyl-substituted alkynes, this is one of very few metal-free procedures.



Scheme 5-9 MW-assisted [3+2] cycloaddition of *N*,*N*-cyclic AI's with internal alkynes.

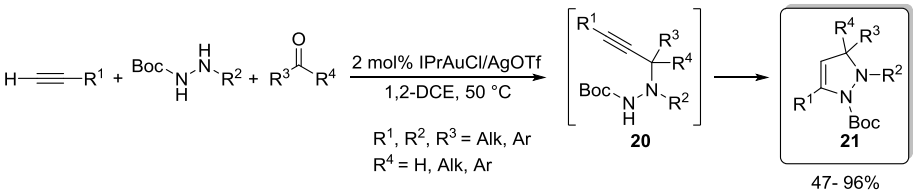
In 2017, Chen *et al.* published [3+2] cycloaddition reactions on *N*,*N*-cyclic azomethine imines **11c** with alkynes under Cu(I) catalysis and further derivatization with thiosulfonates (Scheme 5-10).[26] By using thiosulfonates as electrophiles, they were able to trap the intermediate vinyl copper species **14b**, as suggested by other groups before,[8, 13-14] to form thiolated *N*,*N*-bicyclic heterocycles **19**, upon release of an organic sulfinate.



Scheme 5-10 [3+2] Cycloaddition of *N*,*N*-cyclic azomethine imines and alkynes and trapping of intermediate vinyl copper species with thiosulfonates.

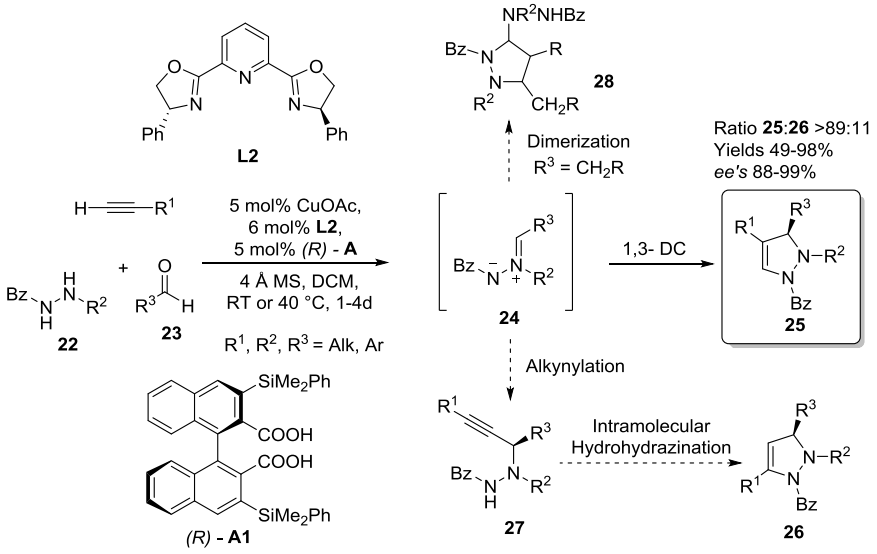
5.1.3.2 [3+2] Cycloadditions of acyclic azomethine imines with alkynes

In 2012, Ohno *et al.* described an Au/Ag-catalyzed three-component coupling of alkynes, hydrazides and aldehydes or ketones (Scheme 5-11).[27] They could prove that at room temperature propargylhydrazine **20** was formed. At 50 °C however, the Au/Ag catalytic system also catalyzed the intramolecular hydrohydrazination step which led to 3-pyrazolines **21**. Although they did not elucidate the reaction mechanism the comparison with an A^3 coupling was made, suggesting an alkynylation on the *in situ* formed hydrazone while they did not mention the possibility that alkynylation could occur on tautomeric azomethine imine.



Scheme 5-11 One-pot three-component coupling of alkynes, hydrazides and aldehydes/ketones yielding 3-pyrazolines.

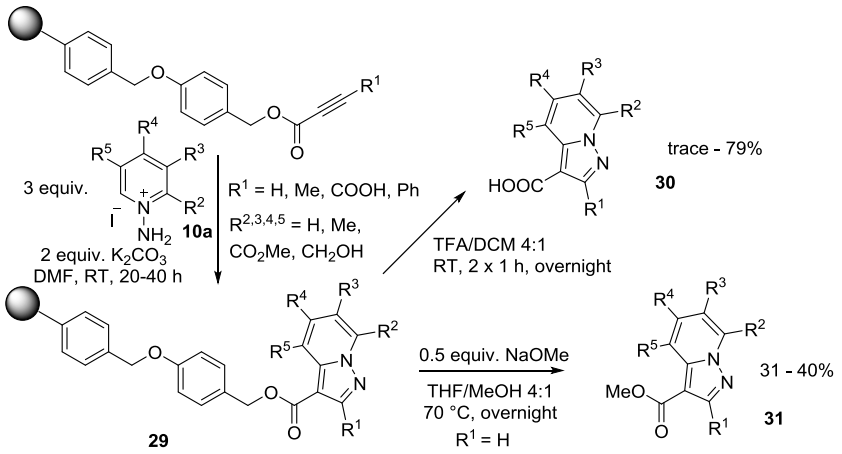
Later, in 2013, Maruoka *et al.* came up with a similar three-component reaction of alkynes, hydrazides and aldehydes (Scheme 5-12).[28] They acknowledged the fact that the combination of hydrazide **22** and aldehyde **23**, upon release of water, can generate azomethine imines **24**, rather than hydrazones. The 1,3-dipolar cycloaddition (1,3-DC) of azomethine imines **24** with alkynes can form two regioisomeric products **25** and **26**. On the other hand, 3-pyrazoline **26** can also be formed via an alkynylation followed by intramolecular hydrohydrazination path. Again, propargylhydrazine **27** was seen as by-product of this synthesis and the optimization of the reaction conditions was focused on suppressing this. The choice of catalyst, and more specifically the choice of counter ion, played a huge role on the outcome of the reaction. CuOAc was chosen as a less acidic copper source in comparison to CuCl, CuBr or CuI, since the dimerization of azomethine imine **24** to **28** was known to be acid-catalyzed. The use of catalyst *(R)* –**A1** lead via hydrogen binding with the azomethine imine to excellent yields and *ee*'s.



Scheme 5-12 Three-component coupling of alkynes, hydrazides and aldehydes for the synthesis of 3-pyrazolines.

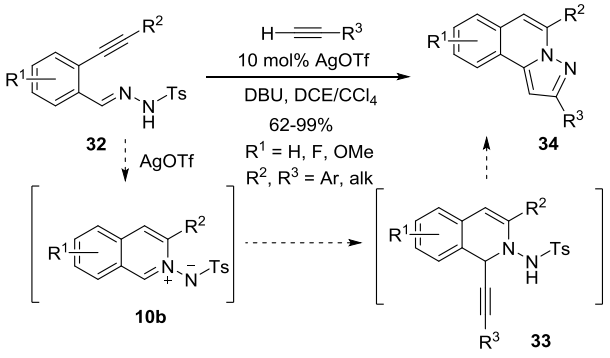
5.1.3.3 [3+2] Cycloadditions of *C,N*-cyclic azomethine imines with alkynes

In 2006, Yli-Kauhaluoma *et al.* described base-induced [3+2] cycloadditions on pyridine-derived *C,N*-cyclic azomethine imines **10a** with solid phase bound alkynes (Scheme 5-13).[29] Cleavage of the product **29** from the resin could either be done with TFA/DCM to yield the corresponding acids **30**, or with sodium methanolate to yield methyl esters **31**. Yields were generally only moderate. *C,N*-Cyclic azomethine imines **10a** have been prepared from substituted pyridines upon treatment with hydroxylamine-*O*-sulfonic acid in water, followed by basification with K_2CO_3 and subsequent treatment with HI.



Scheme 5-13 Base-induced solid-phase [3+2] cycloadditions of *C,N*-cyclic AI's.

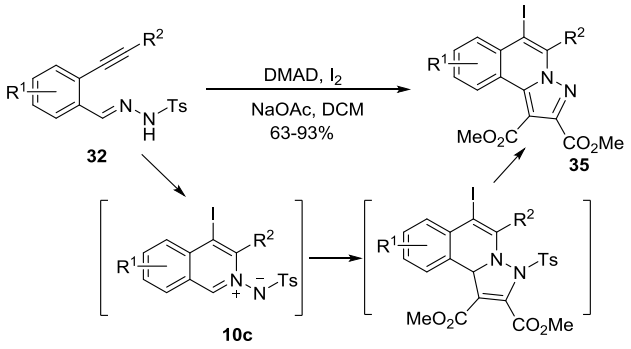
In 2009, Wu *et al.* reported on the *in situ* formation of *C,N*-cyclic azomethine imines **10a**, derived from *N*'-(2-alkynylbenzylidene)hydrazides **32** and subsequent alkynylation, intramolecular hydrohydrazination and aromatization to form compounds **34** (Scheme 5-14).[30] Although propargyl hydrazides **31** were never isolated, they postulated this reaction mechanism and did not consider a [3+2] cycloaddition of **10b** with silver acetylide and subsequent aromatization.



Scheme 5-14 Ag(I)-catalyzed [3+2] cycloaddition of *C,N*-cyclic AI's.

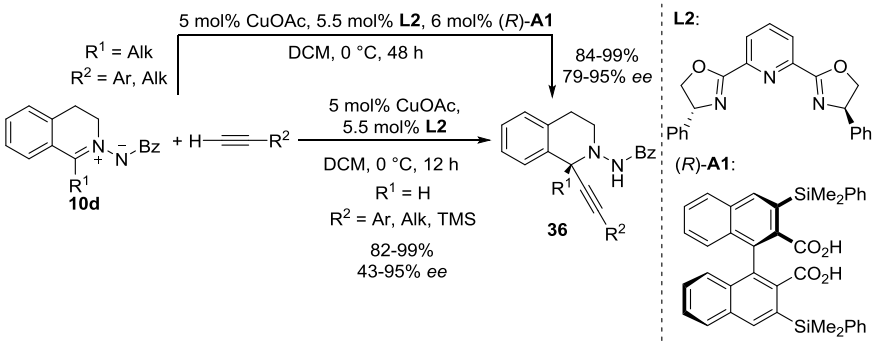
Also in 2009, Wu *et al.* reported a [3+2] cycloaddition of *in situ* formed *C,N*-cyclic azomethine imines **10c**, derived from *N*'-(2-alkynylbenzylidene)hydrazides **32** with DMAD to generate *N*-heterocycles **35** (Scheme 5-15).[31] The *in situ* formation is mediated by an electrophile (I_2) in this case. In a third report in 2009, Wu *et al.* described similar conditions and further derivatization of molecules **35** via Pd-catalyzed Suzuki cross-coupling.[32] Other reports showed similar reactions with different coupling partners (ynamides,[33]

bromoalkynes,[34] 4,4,4-trifluorobut-2-ynoate[35] and propargylamines[36]) under slightly different reaction conditions.



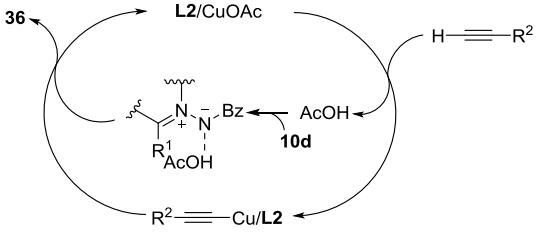
Scheme 5-15 *In situ* formation of *C,N*-cyclic azomethine imines with I_2 and [3+2] cycloaddition with DMAD.

In 2011, Maruoka *et al.* described the reaction of *C,N*-cyclic azomethine imines with alkynes under Cu(I) catalysis (Scheme 5-16).[37] Interestingly they did not observe [3+2] cycloaddition, but alkynylation of the azomethine imine moiety. When C1 unsubstituted substrates **10d** were used, the reaction is catalyzed by a copper/PyBox **L2** catalytic system, leading to excellent yields and *ee*'s of propargylhydrazine **36**. However when C1 is substituted, the yields and *ee*'s were only moderate. In the optimization of this reaction a co-catalyst (*R*)-**A1** was found that ensures good yields and *ee*'s.



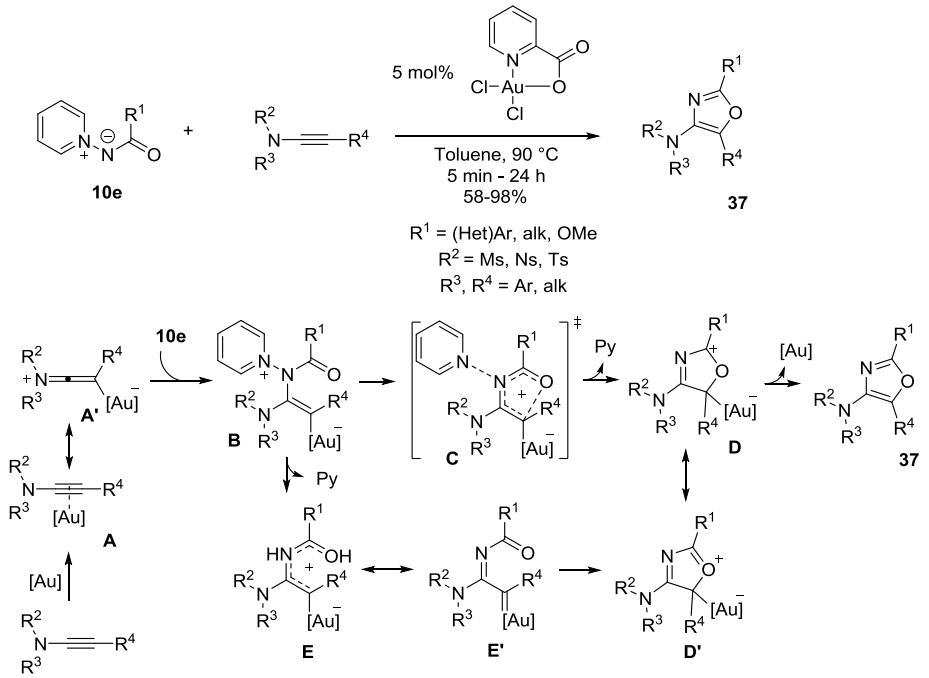
Scheme 5-16 Enantioselective alkynylation of *C,N*-cyclic azomethine imines to form propargylhydrazines.

A tentative reaction mechanism was postulated, that could explain the beneficial use of co-catalyst (*R*)-**A1** (Scheme 5-17). Upon formation of the copper acetylide species, acetic acid would be liberated, which can protonate the azomethine imine to form a hydrazonium species, which can be alkynylated. When another chiral acid is added to the reaction this can exchange for acetic acid and protonate the azomethine imine, forming a chiral hydrazonium salt. Alkynylation with copper acetylide/**L2** can then form reaction product **36**.



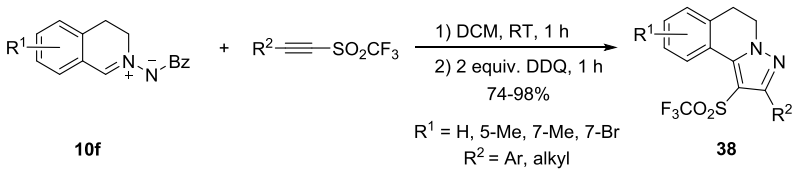
Scheme 5-17 Tentative reaction mechanism for the alkynylation of *C,N*-cyclic azomethine imines.

In 2011, Dumitrescu *et al.* described the formal [3+2] cycloaddition of *C,N*-cyclic azomethine imines **10e** with ynamides under Au(I) catalysis (Scheme 5-18). In this reaction the *N-N* bond is cleaved and pyridine is used as leaving group.[38] The reaction mechanism starts with complexation of Au(I) with ynamide to form complexes **A**/**A'** and subsequent attack of this species with azomethine imine **10e**, generating adduct **B**. Elimination of pyridine and cyclization towards end product **37** can be achieved via 4π electrocyclization of carbocation **E** or carbenoid **E'** by the acyl oxygen. Since C-O bond formation must be fast to account for the lack of 1,2-insertion reactions, carbocationic character of transition state **C** can be developed first, before elimination of pyridine.



Scheme 5-18 Formal [3+2] cycloaddition of *C,N*-cyclic azomethine imines with ynamides.

In 2012, Shibata *et al.* described a [3+2] cycloaddition of *C,N*-cyclic azomethine imines **10f** with triflyl alkynes and subsequent oxidation to form pyrazolo[5,1-*a*]isoquinoline triflones **38** (Scheme 5-19).[39] No catalyst was used, and the reaction was conducted at room temperature. One-pot oxidation with DDQ yielded pyrazolo[5,1-*a*]isoquinoline triflones **38** as a single regioisomer and in excellent yields.

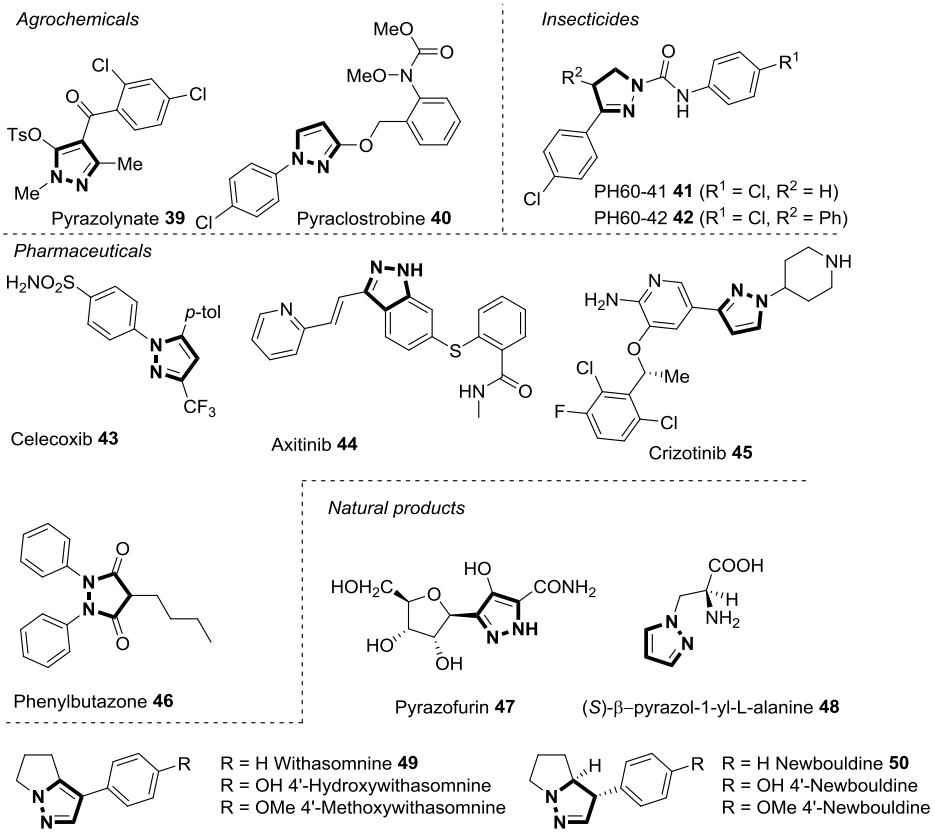


Scheme 5-19 [3+2] cycloaddition of *C,N*-cyclic azomethine imines with triflyl alkynes and subsequent oxidation.

5.2 Importance of pyrazoline scaffolds

Pyrazolidines, and related pyrazolines and pyrazoles are an important class of *N*-heterocycles and are typical products of [3+2] cycloadditions of azomethine imines and alkynes as described in §5.1. This importance is underlined by the ubiquitous examples of these scaffolds in agrochemicals, insecticides, pharmaceuticals and natural products (Scheme 5-20).[40]

Examples of pyrazole derivatives in agrochemical industry are the herbicide pyrazolynate **39**, the fungicide pyraclostrobine **40** and insecticides PH60-41 **41** and PH60-42 **42**.[41] Pyrazoles scaffolds in drugs include cyclooxygenase-2 (COX-2) inhibitors and protein kinase inhibitors such as, among others, Celecoxib **43**, Axitinib **44**, Crizotinib **45** and Phenylbutazone **46**. Pyrazole-derivatives in natural products are less common, since nature tends to have problems with synthesizing *N-N* bonds. Nevertheless, examples like pyrazofurin **47**, (*S*)-β-pyrazol-1-yl-L-alanine **48**, withasomnine **49** and newboulderine **50** (and their hydroxy- and methoxyderivatives) are known.



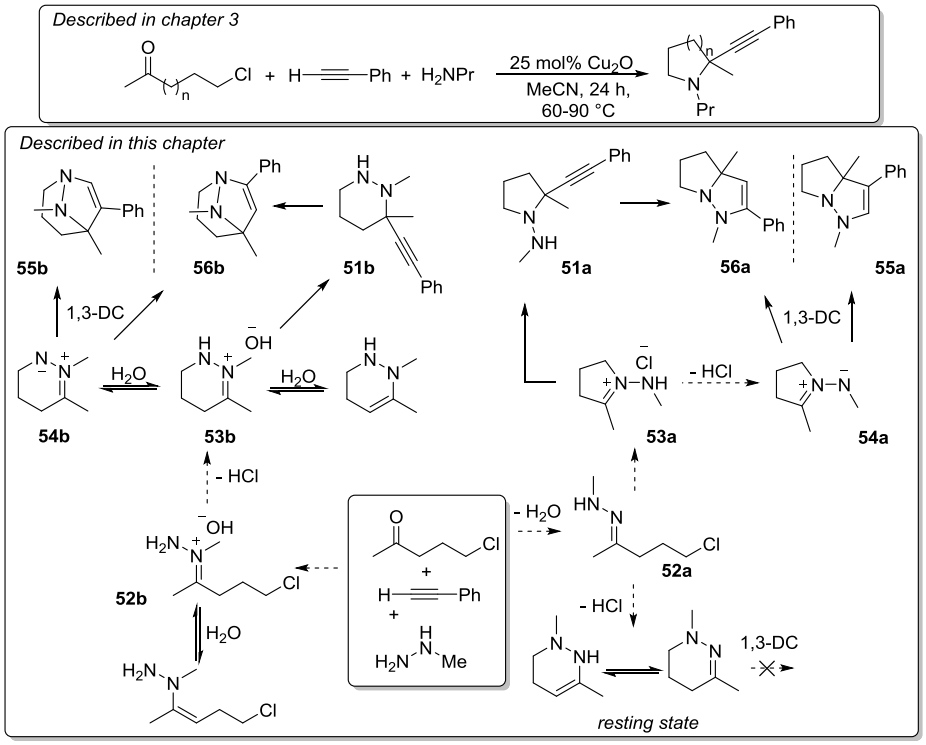
Scheme 5-20 Agrochemicals, pharmaceuticals and natural products containing pyrazole-derived scaffolds.

5.3 One-pot ketone, hydrazine, alkyne coupling

5.3.1 Initial starting point

Initially, the amine reactant of the reaction developed in chapter 3, was changed to methylhydrazine (Scheme 5-21). We were hoping that a similar reaction would occur, generating a propargylhydrazine **51a** or **51b**, depending on which nitrogen atom reacts with the carbonyl of the ketone, but instead another, single product was formed, albeit in moderate yield (40%). This product did not show any alkyne signals in the ^{13}C NMR spectrum, and could either be **56a** or **56b** (**55a** and **55b** were excluded by 2D NMR-analysis). At first sight this product could have been formed via similar alkynylation of the *in situ* formed hydrazonium **53a** or **53b**, generating propargylhydrazine **51a** or **51b**, followed by intramolecular hydrohydrazination (**51**→**56**). On the other hand, hydrazonium **53a** or **53b** could also be transformed into azomethine imine **54a** or **54b**, which could undergo a [3+2] cycloaddition with alkyne, yielding two possible regioisomers **55** or **56**. Comparison with calculated NMR data via the Small Molecule Structure Elucidation (CMC-Se) tool of the Topspin NMR program revealed that structure **56b** is more plausible than structure **56a**.

Eventually, X-ray diffraction of a crystalline example showed that product **56b** was formed (*vide infra*).



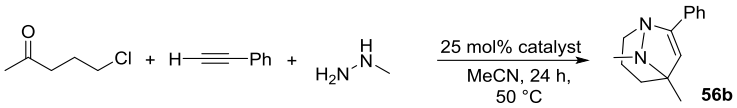
Scheme 5-21 Possible reaction pathways for the three component coupling of alkyne, halogenated ketone and hydrazine.

5.3.2 Optimization of reaction conditions

5.3.2.1 Optimization of the catalyst

Under reaction conditions, as developed in Chapter 3, the reaction of methylhydrazine (2.5 mmol), phenylacetylene (1.2 mmol) and 5-chloropentan-2-one (1 mmol) in the presence of Cu_2O (25 mol%) in MeCN at 80 °C for 24 h, delivered an isolated yield of 40% of product **56b**. In a quest to optimize this yield, we first investigated a number of catalysts which are known to be effective catalysts for alkynylation and [3+2] cycloaddition reactions of azomethine imines and alkynes. Results of this screening are summarized in Table 5-1.

Table 5-1 Screening of different catalysts.



Entry	Catalyst	Yield **56b** (%)[a]
1	$BF_3.OEt_2$	1
2	$FeCl_3$	<1
3	$Zr(acac)_4$	N.O.
4	AgOTf	6
5	AgOTf/IPrAuCl[b]	<1
6	-[c]	N.O.
7	$In(OTf)_3$	2
8	$Zn(OTf)_2$	1
9	$Yb(OTf)_3$	2
10	$Sc(OTf)_3$	2
11	Cu_2O[d]	35
12	CuOAc	37
13	CuCl	36
14	CuOTf	41
15	$CuFe_2O_2$ (magnetic nanopowder)	25
16	Cu^0	<1
17	CuO	31
18	CuC≡CPh	40
19	Cu_2O[e]	18
20	Cu_2O[f]	44
21	CuCl/LiHMDS[g]	33

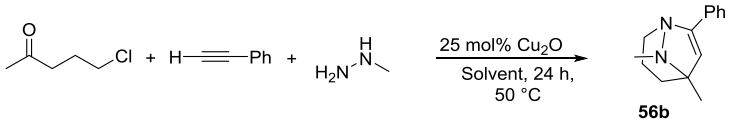
All reactions were carried out with 5-chloropentan-2-one (1 mmol), phenylacetylene (1.2 mmol), methylhydrazine (2.5 mmol) and catalyst (50 mol%) at 50 °C in MeCN (2 mL) for 24 h. [a] Yields are calculated from the ^{1}H NMR spectrum with internal standard TMB. [b] AgOTf (5 mol%) and IprAuCl (5 mol%) [c] No catalyst, trifluoromethylbenzene (2 mL), microwave irradiation for 30 min. at 130 °C [d] Cu_2O (25 mol%) [e] Cu_2O (10 mol%), 80 °C . [f] Cu_2O (50 mol%) [g] LiHMDS (60 mol%) was added as a toluene solution to CuCl (50 mol%) in DCM, and reacted for 12 h at RT, before addition of other reagents. N.O.: not observed.

$BF_3.OEt_2$, $FeCl_3$ and $Zr(acac)_4$ are catalysts that are known to catalyze [3+2] cycloadditions of azomethine imines with dipolarophiles, but gave low to non-observable yields of the intended product **56b** (Entries 1-3). Other group 11 transition metals such as silver and gold also gave low yields (Entries 4 and 5). Since [3+2] cycloadditions could also be thermally activated,[25] one experiment was set up without addition of a catalyst. The high-boiling solvent trifluoromethylbenzene was used and the reaction was performed in the microwave oven at 130 °C for 30 min, but no product formation was observed (Entry 6). In(III), Zn(II)-, Yb(III)- and Sc(III) triflates were examined, since they are known to catalyze alkynylation reactions on imines, but observed yields are all very low (Entries 7-10). Since no other salts except Cu-salts seemed to work, we turned our attention to other Cu-salts. In a previous report, the importance of the counter ion in a Cu(I)-catalyzed 1,3-dipolar cycloaddition of aldehydes, hydrazides and alkynes was underlined.[28] The counter ion could be protonated, forming an acid which could catalyze the dimerization of the *in situ* formed azomethine imine (*cf.* Scheme 5-12). Other Cu(I) salts such as the acetate, chloride or triflate all gave similar results as to the oxide (Entries 11-14). With regard to the pK_a an improvement could be expected from triflic acid to hydrochloric acid, acetic acid and water, but in fact surprisingly CuOTf gave a slightly better yield of 41% in comparison to Cu_2O (35%). Since one equivalent of HCl is already formed by the ring closure of the starting material, most likely the role of the counter ion is not of much importance here, and therefore Cu_2O was selected as the catalyst of choice. Cu(II) salts such as the magnetically recoverable $CuFe_2O_2$ nanopowder and CuO gave slightly lower yields, while metallic copper only gave a trace amount of product, probably due to small quantities of oxidized copper (Entries 15-17). The use of the organocopper species copper(I) phenylacetylide did not provide improvement, giving a similar yield of 40% (Entry 18). This means that the formation of copper phenylacetylide is probably not the problematic reaction step. This is supported by the fact that the formation of copper phenylacetylide was always clearly visible as a fluffy yellow powder, which precipitates from the reaction mixture and is thus probably only partially dissolved. An advantage of this low solubility of copper phenylacetylide is that it can be recovered during workup, as it acts more like a heterogeneous catalyst than a homogeneous catalyst.

Lowering the catalyst loading from 25 mol% to 10 mol% together with an increase of the reaction temperature by 30 °C, resulted in a loss of yield to only 18% (Entry 19). Increasing the catalyst loading to 50 mol% only resulted in a small improvement to 44% (Entry 20). The use of CuHMDS, *in situ* formed from CuCl and LiHMDS resulted in a 33% yield and did not change the regioselectivity of the reaction (Entry 21) in the same way as reported earlier (Scheme 5-7).[14] Copper(I) oxide was thus selected as the optimal catalyst, and improvement of reaction conditions was hoped to be found in other reaction parameters such as solvent, ligand, or choice of additive.

5.3.2.2 Optimization of the solvent

Table 5-2 Evaluation of different solvents for the synthesis of **56b**.



56b

Entry	Solvent	Yield of **56b** (%)[a]	Polarity index
1	Acetonitrile	35	5.8
2	Toluene	20	2.4
3	DCM	51[b]	3.1
4	DCE	39	3.5
5	$CHCl_3$	34	4.1
6	DCM/HFIP 9/1[c]	53	/
7	DCM/HFIP 1/1[c]	10	/
8	THF	20	4.0
9	EtOAc	20	4.4
10	MeOH	48	5.1
11	DMF	26	6.4
12	DMSO	28	7.2
13	NEt_3	12	/
14	Neat	27	/
15	MeCN/H_2O (9/1)	47	/
16	MeOH/H_2O/HFIP (9/1/1)	20	/

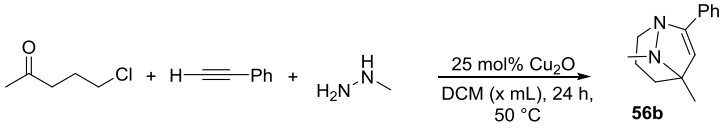
All reactions were carried out with 5-chloropentan-2-one (1 mmol), phenylacetylene (1.2 mmol), methylhydrazine (2.5 mmol) and Cu_2O (25 mol%) at 50 °C in solvent (2 mL) for 24 h. [a] Yields were calculated from the ^{1}H NMR spectrum with internal standard TMB. [b] Average of two experiments. [c] HFIP was added dropwise to the stirring reaction mixture.

A number of solvents were evaluated for this reaction (Table 5-2). The more apolar solvent toluene caused the reaction to be less efficient, rendering a 20% yield (Entry 2). From the more polar chlorinated solvents, DCM gave the best result, while DCE and chloroform performed less good (Entries 3-5). Addition of small amounts of HFIP to DCM (1/9) caused a small improvement, but addition of more HFIP to DCM (1/1) caused the reaction to shut down (Entries 6 and 7). Other, even more polar solvents such as THF and EtOAc did not improve the reaction outcome, while MeOH gave a similar result as DCM (Entries 8-10). Polar aprotic solvents such as DMF and DMSO gave a low yield (Entries 11-12). This was

surprising because from the reaction mixture it was seen that no copper phenylacetylide was precipitated. It could be that either the formation of copper phenylacetylide was obstructed by the solvent, or that the solvent completely dissolves the formed copper phenylacetylide. Using a basic solvent such as triethylamine resulted in a low yield (Entry 13). It was thought that this solvent can trap the formed HCl, and therefore avoid acid-catalyzed dimerization[28] of the azomethine imine intermediate. On the other hand, triethylamine could act as a ligand to dissolve the formed copper species, as was observed from the homogeneous reaction mixture. Unfortunately, this did not lead to an improved yield. Carrying out the reaction without solvent resulted in a sluggish reaction and low yield (Entry 14), probably caused by bad contact between reagents and copper species. Lastly, we evaluated a 9/1 MeCN/H_2O solvent system where the intermediate hydrazone could be reversibly hydrolyzed to the starting materials. The formation of the product **56b** from this equilibrium was thought to increase and compared to the initial yield of 35%, it did improve to 47% (Entry 15). Although DCM/HFIP (53% - Entry 6) gave a slightly better result than DCM (51% - Entry 3), DCM was chosen nevertheless as optimal solvent, because of cost of HFIP.

In a next optimization step, the concentration of the reaction with regard to the solvent was investigated (Table 5-3). In the previous chapter, it was determined that the rate-determining step of the reaction was the intramolecular substitution of the chlorine atom. Since the rate of an intramolecular reaction is not subject to the concentration of the reagents, it was thought that dilution would not affect the reaction rate, but rather the rate of unwanted side-reactions such as the dimerization of azomethine imines. Different volumes of DCM were evaluated ranging from 2 to 16 mL. Generally the influence of the amount of solvent did not play a big role, and 4 mL of DCM, which gave the best result (Entry 3) was chosen as optimum.

Table 5-3 Concentration screening for the synthesis of **56b**.



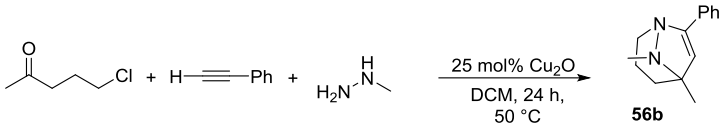
Entry	DCM (mL)	Yield **56b** (%)[a]
1	2	51
2	3	42
3	4	56
4	5	45
5	8	17
6	12	43
7	16	48

All reactions were carried out with 5-chloropentan-2-one (1 mmol), phenylacetylene (1.2 mmol), methylhydrazine (2.5 mmol) and Cu_2O (25 mol%) at 50 °C in DCM (x mL) for 24 h.
[a] Yields were calculated from the ^{1}H NMR spectrum with internal standard TMB.

In a next phase, a number of additives were tested (Table 5-4). Without extra additives, the best yield of **56b** was 56% (Entry 1). The addition of 20 mol% of phosphoric acid 1,1'-

binaphthyl-2,2'-diyl hydrogenphosphate (BNDHP), benzoic acid or methane sulfonic acid gave similar yields as without the addition of these additives (Entries 2-4), while the addition of boric acid clearly resulted in a lowered yield of **56b** (Entry 5). The addition of MeOH, as proton source, also gave a slightly lowered yield of 48% (Entry 6). The addition of a higher amount of BNDHP resulted in a lowered yield of 50% **56b**, and it can be concluded that the addition of an acid is not beneficial. To check whether the reaction mechanism could go via a radical pathway, a radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added (Entry 8). The addition of TEMPO led to a lowered yield of 42%, and thus did not completely block the reaction. In view of this, a radical pathway cannot completely be excluded. Addition of sodium bicarbonate did not improve the outcome of the reaction and only 35% of **56b** was obtained (Entry 9). Interestingly, preformation of the copper catalyst in combination with the chiral ligand (*R*)-(+)-(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine) (abbreviated as (*R*)-BINAP), was not a good catalytic system, since no reaction product **56b** was obtained. This might originate from the larger sterical hindrance caused by the ligand, around the reactive center. Sterical hindrance will later, especially when the ketone scope was investigated, proof to be a critical limiting parameter for this reaction.

Table 5-4 Screening of additives for the synthesis of **56b**.

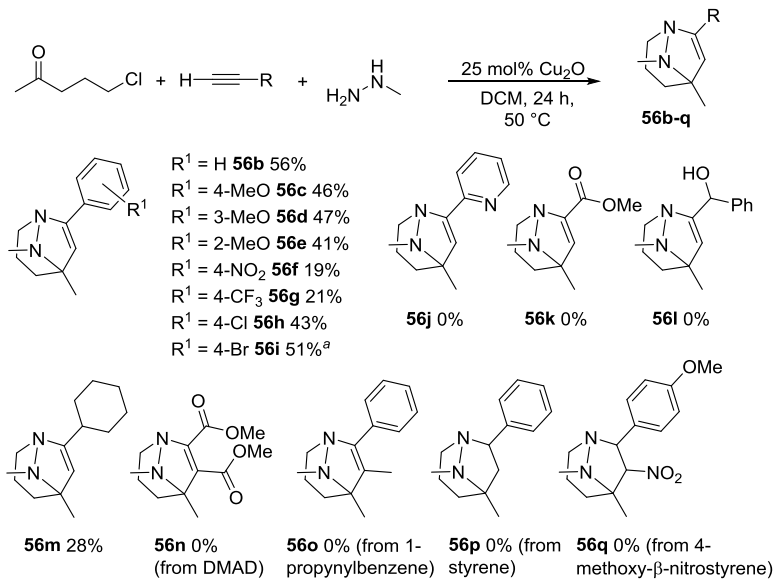


Entry	Additive (mol%)	Yield **56b** (%)[a]
1	/	56
2	BNDHP (20)	57
3	Benzoic acid (20)	56
4	Methane sulfonic acid (20)	54
5	Boric acid (20)	46
6	MeOH (20)	48
7	BNDHP (50)	50
8	TEMPO (30)	42
9	$NaHCO_3$ (100)	35
10[b]	(*R*)-BINAP (50)	0

All reactions were carried out with 5-chloropentan-2-one (1 mmol), phenylacetylene (1.2 mmol), methylhydrazine (2.5 mmol) and Cu_2O (25 mol%) at 50 °C in DCM (4 mL) for 24 h. [a] Yields were calculated from the ^{1}H NMR spectrum with internal standard TMB. [b]10 min. preactivation of Cu_2O and (*R*)-BINAP, before other reagents were added. BNDHP = 1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate.

5.3.3 Reaction scope

Next, we investigated the scope of the reaction with regard to the alkyne component (Scheme 5-22). A number of substituted terminal aryl alkynes were evaluated. Electron-donating groups were tolerated well (**56c-e**), but strong electron-withdrawing groups such as 4-nitro or 4-trifluoromethyl gave only low yields of products **56f-g**, while weak electron-withdrawing 4-chloro or 4-bromo gave similar yields of **56h** and **56i** as non-substituted phenylacetylene **56b**. The presence of heteroatoms such as nitrogen in 2-pyridinylacetylene and oxygen in methyl propiolate or 1-phenylprop-2-yn-1-ol completely blocked the reaction as no reaction products **56j-l** were observed. This can probably be explained by the fact that these alkynes are less nucleophilic. An aliphatic acetylene, such as cyclohexylacetylene, generates the product **56m** in a low yield of 28%, but illustrates that the reaction is still possible. Conducting the reaction with an internal alkyne such as DMAD, a popular dipolarophile in [3+2] cycloadditions, did not lead to any [3+2]-cycloaddition product **56n**. Although DMAD is a very good dipolarophile for [3+2] cycloadditions, it is not capable of forming a copper acetylide species, since it does not possess a terminal C(sp)-H proton. In a similar way, the use of 1-propynylbenzene, closely resembling phenylacetylene but lacking a terminal C(sp)-H proton, did not lead to any reaction product **56o**. Furthermore, other dipolarophiles, such as alkenes, did not lead to coupling products **56p** or **56q** either.



Scheme 5-22 Scope of the reaction regarding the alkyne. [a] 4 mmol reaction scale instead of 1 mmol scale for all other reactions.

A few of molecules **56** were solids, and example **56h** gave, after recrystallization from dichloromethane, suitable crystals for X-ray diffraction. After recording the structure, extensive refinement due to racemical twinning and whole-molecule disorder, resulted in an asymmetric unit containing four molecules (two (*R*)-enantiomers and two (*S*)-enantiomers), clearly showing the azatropane core (Figure 5-1, Figure 5-2). From the crystal structure, we can see that the six-membered ring clearly adopts a chair conformation.

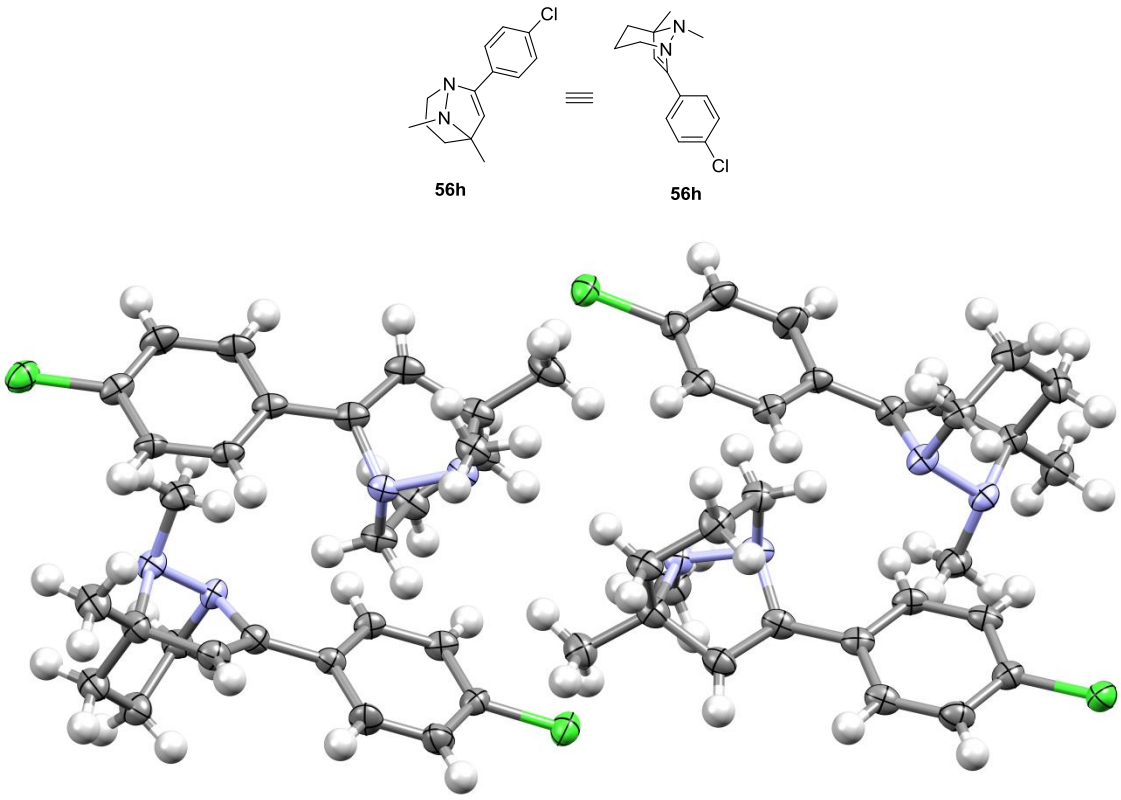


Figure 5-1 Crystal structure of the major disorder component of the asymmetric unit, containing four molecules (two times two enantiomers). Displacement ellipsoids are drawn at the 50% probability level, and hydrogen atoms are drawn as spheres of arbitrary radius.

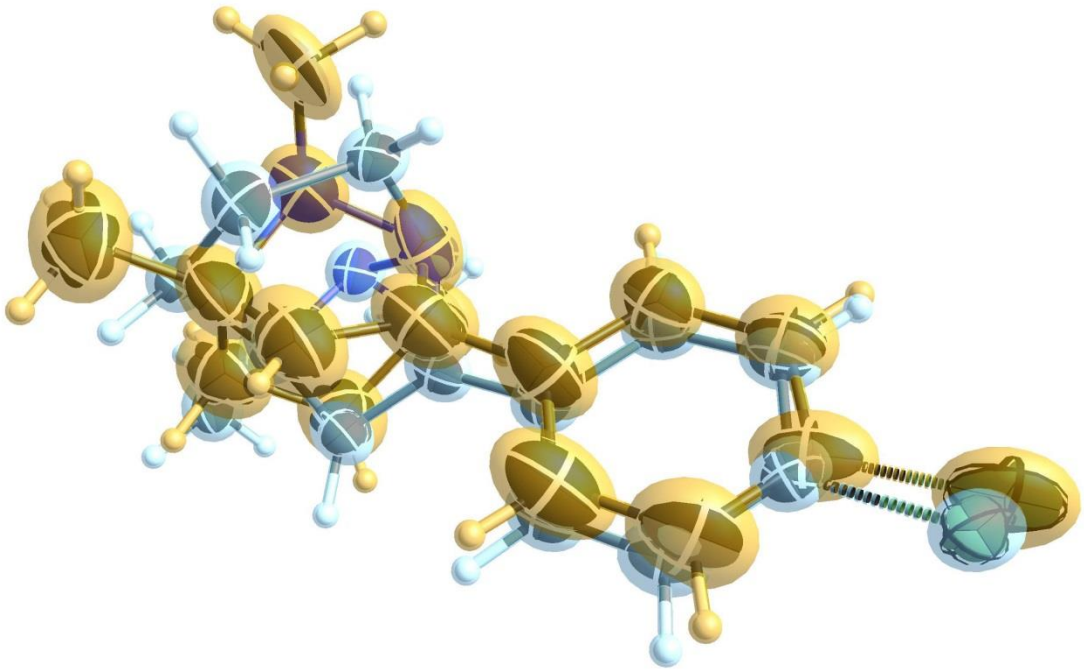
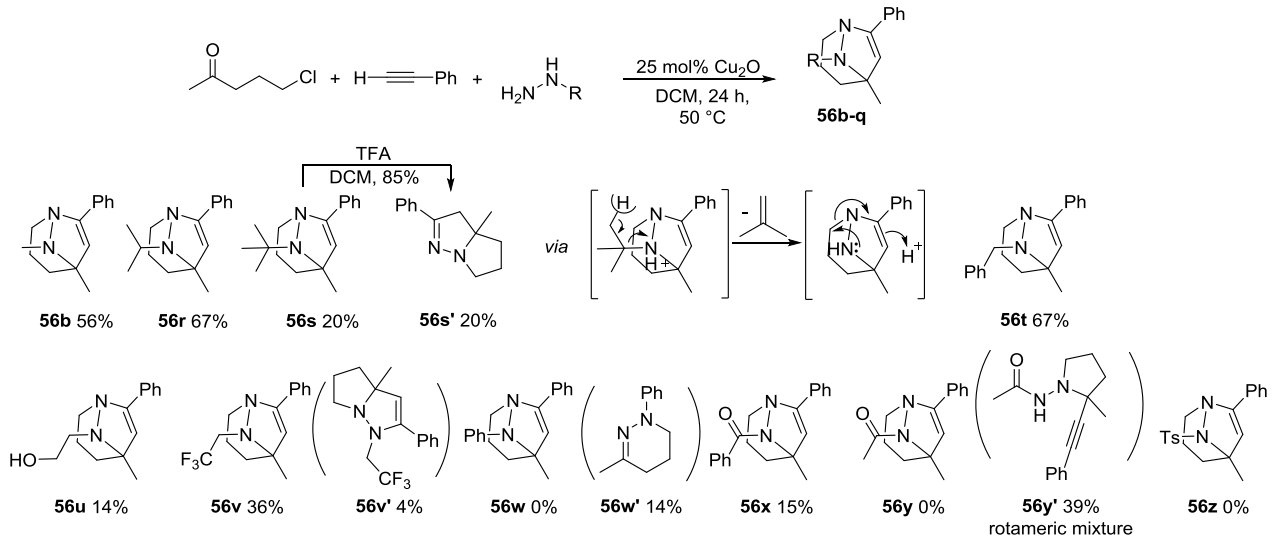


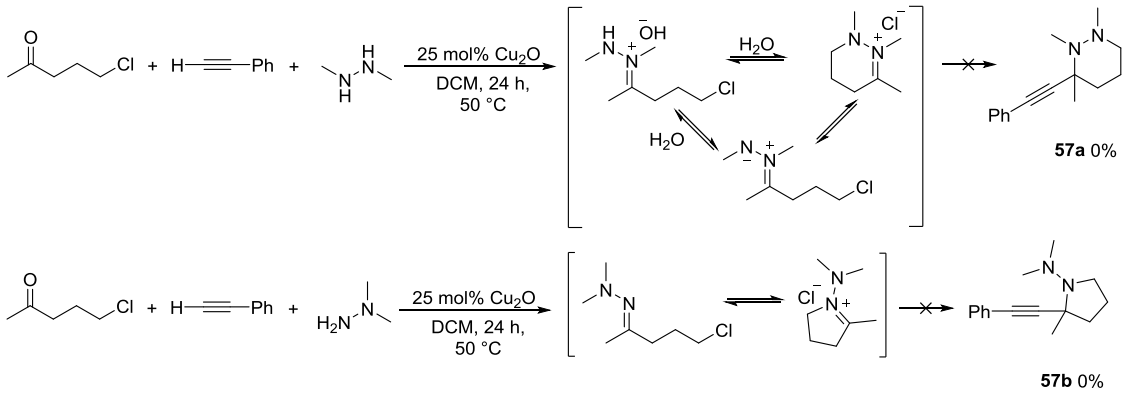
Figure 5-2 View of the molecule **56h** in residue 3 (blue) and its superimposed minor disorder component (yellow). Occupancies are respectively 78.0(6) and 22.0(6)%.

Next, the scope of hydrazines was investigated (Scheme 5-23). Other primary aliphatic hydrazines were evaluated; more sterically hindered isopropylhydrazine gave an improved yield of 67% of **56r**. Although the sterical hindrance around the reaction center increases, the nucleophilicity of the hydrazine decreases,[42] thus resulting in more difficult formation of hydrazone side product, which is beneficial for the synthesis of wanted product **56r**. When the sterical hindrance is increased to *tert*-butylhydrazine, the overall yield decreased to 40%, including the formation of a degradation product **56s'**. This product was not present after workup, but probably formed during column chromatography on silica. We reasoned that the slightly acidic nature of silica would prompt molecule **56s** to de-*tert*-butylate and rearrange to **56s'**. To test this hypothesis, product **56s** was treated with dry trifluoroacetic acid (TFA) in DCM. After basic workup, the product was completely transformed in product **56s'** in 85% yield. Mechanistically, this rearrangement probably starts with protonation of the hydrazine moiety (by either acidic silica or TFA), followed by de-*tert*-butylation with the loss of gaseous isobutene. The presence of an N-H can now provide a loss of ring strain by rearrangement of the molecule. To our delight, the use of benzylhydrazine resulted in the formation of product **56t** in a decent 67% yield. Product **56u** was formed in a low 14% yield, indicating difficulties when hydroxyl moieties were used. When trifluoroethylhydrazine was used, product **56v** was isolated, next to a very similar isomer. High-temperature NMR excluded the possibility of rotamers, and a second purification attempt provided **56v** in 36% yield. The other isomer is thought to be **56v'**, since the trifluoroethyl group probably lowers the nucleophilicity of the substituted hydrazine nitrogen atom, resulting in formation of hydrazone via the unsubstituted hydrazine nitrogen atom. This assumption should be confirmed by X-ray analysis of product **56v'**, but unfortunately no suitable crystals could be grown. When phenylhydrazine was used, no reaction product **56w** was observed, but instead cyclic hydrazone **56w'** was isolated in 14% yield. The use of phenylhydrazide resulted in a sluggish 15% yield of **56x**, while the use of acethydrazide did not lead to product **56y**. Instead, a 2-alkynylpyrrolidine **56y'** was isolated, which exhibited two sets of signals in NMR. Variable temperature NMR measurement indicated coalescence of these signals at 120 °C. These double NMR signals are therefore believed to originate from restricted rotation of the acetyl group around the O=C-N bond, because of significant double bond character, like in DMF.[43] The use of tosylhydrazide did not lead to any intended product **56z**.



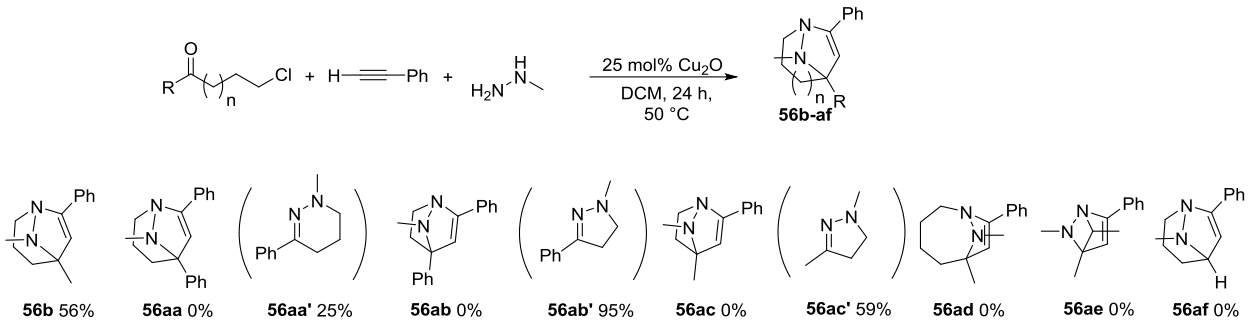
Scheme 5-23 Scope of hydrazines.

To better understand the reactivity of hydrazines in this coupling, we also briefly investigated disubstituted hydrazines (Scheme 5-24). The use of *N,N'*-dimethylhydrazine did not result in the isolation of any reaction product, although hydrazonium, cyclic hydrazonium or acyclic azomethine imine species can be formed. The use of *N,N*-dimethylhydrazine, which should easily be able to form hydrazone and via intramolecular substitution also cyclic hydrazonium species, also did not lead to the isolation of any coupling product with phenylacetylene. Although differently charged intermediates could be formed, no cyclic azomethine imine could be formed in either experiments, and thus we strongly feel that cyclic azomethine imine is the reactive intermediate for this reaction.



Scheme 5-24 The use of disubstituted hydrazines did not lead to any coupling products **57**.

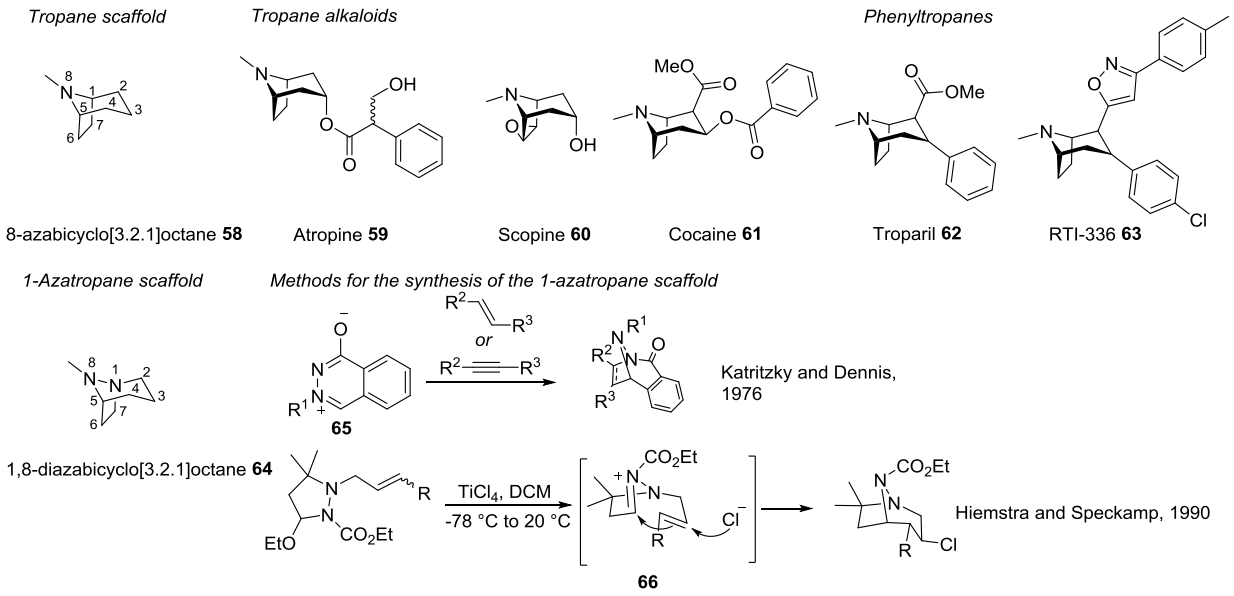
In a next phase, the scope of ketones was investigated (Scheme 5-25). The use of 4-chlorobutyrophenone, as a different substituted ketone, did not result in the formation product **56aa**. Increasing the reaction temperature to 80 °C in acetonitrile did not result in the formation of product **56aa**. However, cyclic hydrazone **56aa'** was obtained in 25% yield after column chromatography. Reducing the chain length by using γ-chlorobutyrophenone did not result in the formation of [2.2.1]bicyclic product **56ab** either, but gave a similar cyclic hydrazone **56ab'** in 95% yield after column chromatography. Interestingly, cyclic hydrazones **56aa'** and **56ab'** are stable on column chromatography, while similar cyclic imines are generally not stable and are easily hydrolyzed on acidic silica. The phenyl group compared to the methyl group blocks the reaction, probably because of sterical hindrance. Reduction of the chain length, while maintaining the methyl group by using 4-chlorobutan-2-one, surprisingly, did not lead to product **56ac**, but again cyclic hydrazone **56ac'** was formed instead. Increasing the chain length on the other hand, by using 6-chlorohexan-2-one, again did not result in the formation of intended product **56ad**, and in this case no cyclic hydrazone was obtained. The use of 3-chlorobutan-2-one did not lead to intended product **56ae** and no cyclic hydrazone was obtained. Lastly, changing the starting material 5-chloropentan-2-one to 5-chloropentanal did also not lead to the intended product **56af**, but gave a very complex reaction mixture, which was not further investigated. As a result, the ketone scope is so far limited to the use of 5-chloropentan-2-one.



Scheme 5-25 Scope of ketones.

5.3.4 Importance of (aza)tropane scaffolds

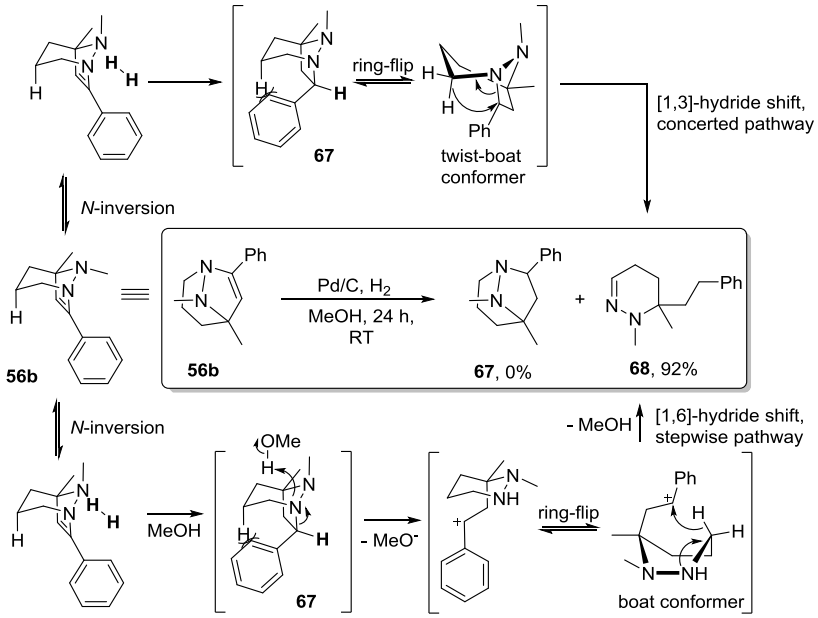
The tropane or 8-azabicyclo[3.2.1]octane scaffold **58** is an important scaffold in tropane alkaloids and are found in *Solanaceae* or nightshade plants. Examples are atropine **59**, scopine **60** and cocaine **61** (Scheme 5-26). They are used as anticholinergic drugs, deliriants and stimulants. Next to naturally occurring tropane alkaloids, some synthetic analogues of tropane alkaloids exist and are named phenyltropanes, such as Troparil **62** and RTI-336 **63**. They are used as dopamine selective reuptake inhibitors and find application in the treatment of cocaine addiction. For the discovery of new drugs, analogues of the tropane scaffold would be interesting, and scientists have synthesized in the past already some azatropanes, where one of the carbon atoms is replaced by a nitrogen atom. For instance, 1-azatropanes **64** have been synthesized earlier on, and a first report surfaced in 1976 when Katritzky and Dennis reported on the cycloaddition of alkenes and alkynes with diazinium betaines **65**.[44] They also observed rearrangements of the skeleton. A second methodology was published by Hiemstra and Speckamp firstly in 1990 via nucleophilic addition to *in situ* formed *N*-acylhydrazonium intermediates **66**.[45] The methodology was then further expanded to similar substrates in 1993,[46] and resulted in the enantioselective synthesis of the aza-analogue of cocaine in 1997.[47]



Scheme 5-26 The tropane scaffold, tropane alkaloids, phenyltropanes and 1-azatropanes.

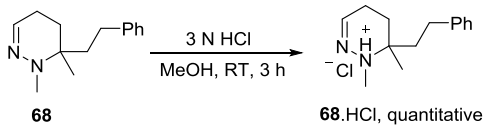
5.3.5 Reactivity of 1-azatropane products

In view of the very limited examples of 1-azatropanes in literature, an attempt was made to reduce the olefinic bond in bicyclic products **56** (Scheme 5-27). Product **56b** was dissolved in methanol and stirred for 24 hours at room temperature under one atmosphere of hydrogen with Pd/C. To our surprise, not the hydrogenated product **67** was obtained, but probably hydrazone **68** was formed as the reaction product, as this is the best fitting product obtained via Topspin's structure elucidation tool. Although this structure seems far-fetched at first sight, a logical explanation can be given for the formation of this reaction product. Two pathways are presented. The first pathway involves *N*-inversion, followed by *syn*-addition of hydrogen. The addition of hydrogen can only occur at one side of the double bond, since the other side is blocked by the phenyl ring. Molecule **67** therefore encounters strong sterical hindrance, pushing the molecule into a twisted-boat conformer from where a concerted [1,3]-hydride shift might occur, forming hydrazone **68**, although this seems very unlikely as orbitals might not overlap accordingly. A second, stepwise pathway starts also with the *syn*-addition of hydrogen to molecule **56b** to create hydrogenated product **67**. The sterical hindrance can, in this case, be lowered by breaking the N-C(Ph) bond, generating a secondary benzylic carbocation. Ring-flip to a boat conformer allows for a [1,6]-hydride shift, eventually leading to molecule **68** . The overall process is an internal redox neutral process and is closely related to reactions were the *tert*-amino effect is invoked.[48] Similar [1,6]-hydride shifts are rare but examples exist and are generally explained by the geometry of the carbocation.[49]



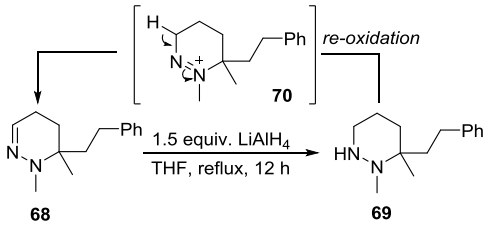
Scheme 5-27 Hydrogenation of 1-azatropane **56b** yields a rearranged cyclic hydrazone.

In order to further confirm the structure of the presumed hydrazone **68**, a methanol solution of product **68** was treated with 3 N HCl in water and stirred for three hours at room temperature (Scheme 5-28). These conditions would readily hydrolyze an imine, but it was found that hydrazone **68** was not hydrolyzed, instead the hydrochloric acid salt of **68** was isolated.



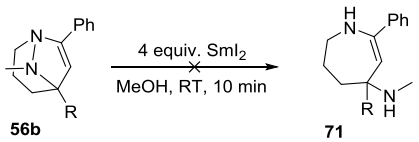
Scheme 5-28 Treatment of hydrazone with HCl gives … hydrazone.HCl.

Since hydrolysis did not result in a new product, we figured that reduction of the hydrazone would lead to the hydrazine **69** (Scheme 5-29). Reduction with sodium cyanoborohydride in methanol and acetic acid was not effective as the starting material was recovered after overnight reaction at room temperature. The use of lithium aluminum hydride as hydride donor, gave a mixture of starting material and hydrazine **69** after overnight refluxing in THF with 65% conversion. After adding another equivalent of lithium aluminum hydride and again refluxing overnight in THF, we obtained again a mixture of starting material **68** and product **69**, but this time the amount of **69** was lower and conversion was only 45%. We figured that during workup the product oxidizes again to the hydrazone. Column chromatography of this compound gave exclusively **68** inn almost quantitative yield. The existence of hydrazine **69** was clearly seen from the ^{13}C NMR spectrum of the mixture of both compounds as the signal from C=N shifted from 136.2 ppm in **68** to 47.1 ppm for C-NH in **69**. Hydrazines are known to oxidize easily, thereby generating nitrogen gas,[50] and are thus sometimes used as reductants.[51] A similar oxidation would in this case generate diazenium **70**, which cannot lose nitrogen gas, but instead tautomerizes to form hydrazone **68**.



Scheme 5-29 Reduction of hydrazone **68** gives hydrazine **69**, which spontaneously reoxidizes to hydrazone **68**.

To check the reactivity of the hydrazine **56b**, we tried to break the nitrogen-nitrogen bond (Scheme 5-30). By using SmI_2, no reaction occurred at room temperature and the starting material was recovered. In literature SmI_2 is used to cleave nitrogen-nitrogen double bonds in hydrazides, and the presence of the carbonyl group is required for the reaction to take place.[28, 37, 52]

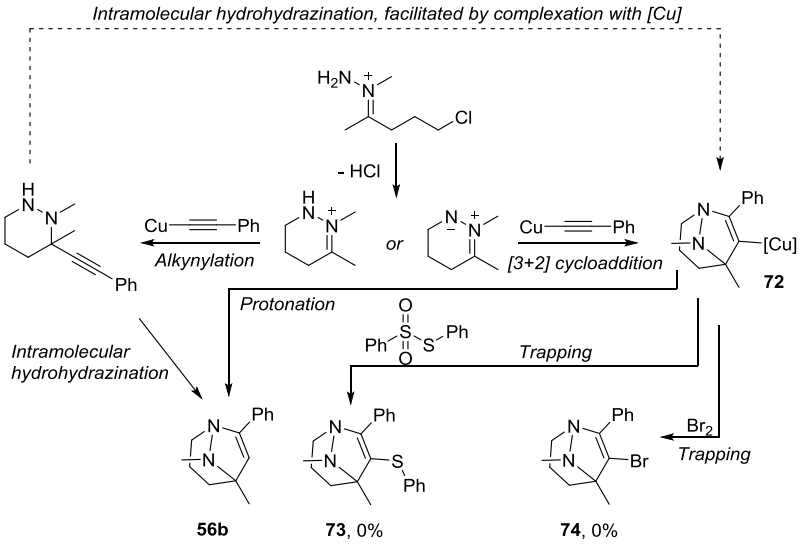


Scheme 5-30 Cleavage of the nitrogen-nitrogen bond with SmI_2 was unsuccessful.

5.3.6 Reaction mechanism proposal

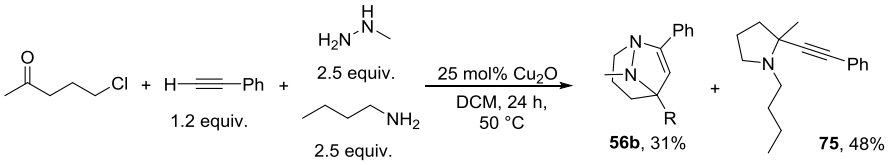
In order to present a reaction mechanism for the investigated reaction in this chapter, some additional experiments were conducted (Scheme 5-31). When a [3+2]-cycloaddition of azomethine imines with copper-acetylides is proposed, a vinylic copper species **72** can be expected to form, as suggested by other groups.[12-14] Simple protonation would generate the

end compound **56b**. However, previous literature (see Scheme 5-10) suggests that the vinylic copper species **72** can be trapped with another electrophile, *e.g.* a thiosulfonate.[26] Thus, we tried to trap the possible intermediate by adding phenyl thiosulfonate either at the beginning of the reaction or after two hours, but in both cases no other reaction product **73** was formed. Alternatively, bromine was added to the reaction mixture to form vinyl bromide **74**, but again no product **74** was observed. These two experiments in combination with the temperature independence of the reaction point in the direction of alkynylation, followed by intramolecular hydrohydrazination (Scheme 5-31 - left) and no [3+2] cycloaddition (Scheme 5-31 - right). However, one cannot exclude that intermediate **72** is formed in the alkynylation/intramolecular hydrohydrazination pathway, since the second step might be facilitated by complexation of copper to the alkyne, thus no unambiguous conclusion can be drawn from these experiments regarding the reaction mechanism. However, it is clear that vinylic intermediate **72** might be formed, but is so reactive that it immediately is protonated, as there is a proton source (formed HCl) present.



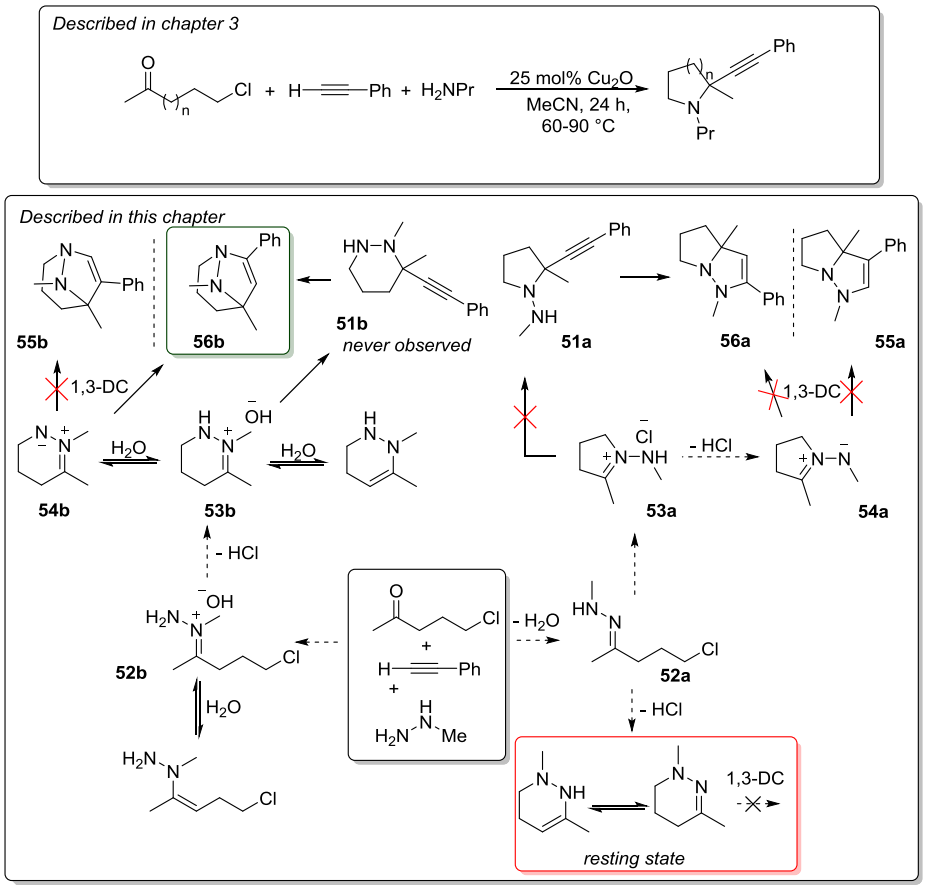
Scheme 5-31 Trapping the possible vinylic intermediate with electrophiles other than a proton. One equivalent of electrophile was added.

To get an insight in how this reaction compares to the KA² coupling as described in Chapter 3, we conducted a competition experiment where an equimolar quantity of *n*-butylamine (bp = 78 °C) and methylhydrazine (bp = 87 °C) were used (Scheme 5-32). As discussed in §5.1.1 hydrazines are better nucleophiles than amines because of the α-effect, and we thus expected that the formation of hydrazonium would be faster than the formation of imine, thus leading to more hydrazine coupled product **56b** than amine coupled product **75**, but the opposite was true. The overall low yields of product **56** can be explained by the formation of a cyclic hydrazone side product, as a result from nucleophilic attack of the other nitrogen atom in hydrazine. The hydrazone side product cannot by hydrolyzed, and no coupling product can be obtained from there. The only reason why the formation of product **75** can be explained is that the difference in nucleophilicity between methylhydrazine and *n*-butylamine must be negligible.



Scheme 5-32 Competition experiment between hydrazine and amine. Both were added as solution simultaneously.

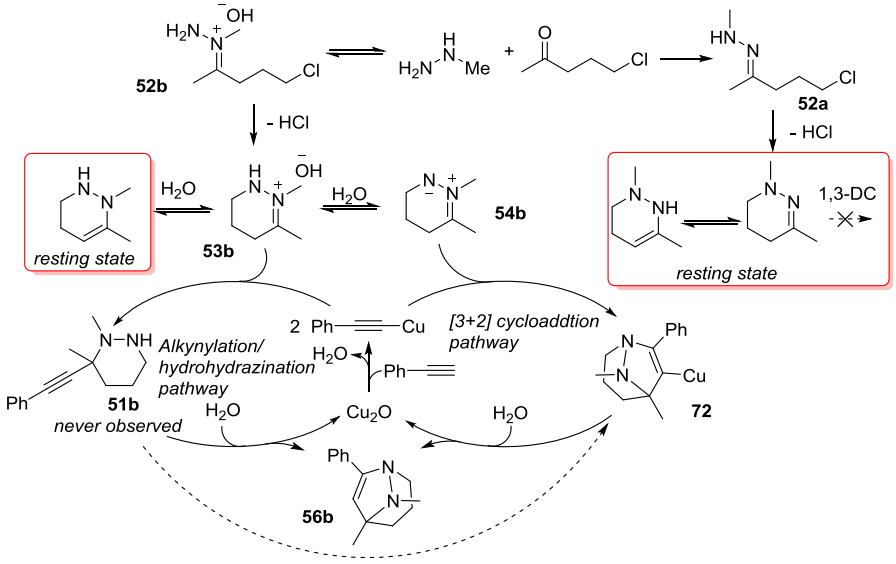
Since the additional experiments are not conclusive, and some questions remain unanswered, both reaction pathways in the formation of **56b** remain plausible, as well as the identification of the resting state (Scheme 5-33).



Scheme 5-33 Initial reaction routes revised.

Thus, the proposed reaction mechanism for the synthesis of 6,7-dihydro-1-azatropanes **56b** contains two pathways, as there are different factors pointing towards the two possibilities (Scheme 5-34). Both pathways start with the formation of hydrazonium salt **52b** from attack of the substituted hydrazine-nitrogen atom. Loss of HCl via an intramolecular substitution reaction generates cyclic hydrazonium **53b**. From there azomethine imine **54b** could be formed together with the tautomeric enehydrazine, which can be considered as a resting state for the reaction. On the other hand, the non-substituted hydrazine-nitrogen can react to form hydrazone **52a** which upon intramolecular substitution generates a cyclic hydrazone or enehydrazine and are considered resting states for the reaction. Independently, copper phenylacetylide is formed from copper(I) oxide with the aid of any weak base present (e.g.

methylhydrazine). Copper phenylacetylide then reacts via a [3+2] cycloaddition with azomethine imine **54b** to form vinyl copper species **72**, which is protonated to form target compound **56b**. Alternatively, copper phenylacetylide may react with cyclic hydrazonium **53b** to form propargylhydrazine **51b**, which quickly undergoes intramolecular hydrohydrazination to form target compound **56b**. Propargylhydrazine **51b**, was however never observed but could also form a π-complex with Cu^{+}, so that vinylic copper species **72** is formed, and after hydrolysis target compound **56b** can be formed.



Scheme 5-34 Proposed reaction mechanism.

5.4 Experimental

5.4.1 Instrumentation

All reactions were carried out under argon in oven dried 10 mL microwave vials. Solvents used in purification (Heptanes and EtOAc) were distilled prior to use. All ketones, hydrazines and acetylenes were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa-Aesar, Fluorochem and J&K). Products were purified on an automated column chromatography device Biotage IsoleraTM using Grace ResolvTM (12 g) columns. ^{1}H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Bruker Avance III HD spectrometer using $CDCl_3$ as solvent and TMS as the internal standard. Assignments were made using 2D (HSQC, HMBC and DEPT) spectra. Chemical shifts are given in parts per million (ppm), *J*-values are given in Hertz (Hz), and number of protons for each signal are also indicated. For high resolution mass spectrometric analysis (HRMS), samples were dissolved in CH_3OH and diluted to a concentration of approximately 10^{-5} mol/L and measured on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions $[M+H]^{+}$ are quoted.

5.4.2 Procedures and characterization data

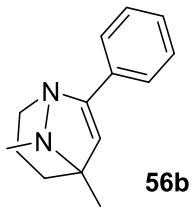
Standard experimental procedure

In an oven-dried microwave vessel (10 mL) were introduced Cu_2O (36 mg, 0.25 mmol), ketone (1 mmol), alkyne (1.2 mmol) and hydrazine (2.5 mmol) and DCM (4 mL). The vessel was flushed with Argon for 30 s, sealed and introduced in a preheated oil bath of 50 °C and

stirred during 24 hours. Afterwards, the reaction mixture was poured into 0.5 N NaOH solution (20 mL) and extracted with DCM (2 x 20 mL). The organic phases were combined and dried over $MgSO_4.3H_2O$, filtered and evaporated *in vacuo*. The crude product was then purified by automated column chromatography on a 12 g Grace column with Heptanes/EtOAc as eluting solvents.

5,8-Dimethyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56b**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).

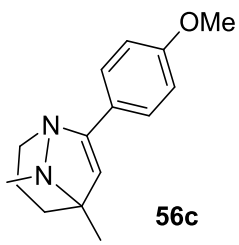


56b

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 - 7.62 (m, 2H, C**H**$_{arom., ortho}$), 7.34 - 7.26 (m, 3H, C**H**$_{arom., meta and para}$), 5.78 (s, 1H, C_{quat}C**H**C_{quat}), 3.34-3.26 (m, 1H, NC(**H**)HCH$_2$CH$_2$), 2.86 (dd, 1H, *J* = 13.3, 6.3 Hz, NC(H)**H**CH$_2$CH$_2$), 2.37 (s, 3H, NC**H$_3$**), 1.84 – 1.79 (m, 2H, NCH$_2$C(H)**H**C(H)**H**), 1.48 - 1.43 (m, 2H, NCH$_2$C**(H)**HC**(H)**H), 1.22 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.0 (**C**$_{arom., ipso}$ Ph**C**=CH), 132.1 (**C**$_{arom., ipso}$), 128.5 (**C**$_{arom., meta}$), 128.3 (**C**$_{arom., para}$), 126.6 (**C**$_{arom.,ortho}$), 115.9 (PhC=**C**H), 68.8 (CH**C**$_{quat}$(N)(CH$_2$)CH$_3$), 47.9 (N**C**H$_2$CH$_2$CH$_2$), 37.6 (N**C**H$_3$), 33.7 (NCH$_2$CH$_2$**C**H$_2$), 20.0 (C**C**H$_3$), 18.6 (NCH$_2$**C**H$_2$CH$_2$). **HRMS** (ESI) m/z calculated for $[C_{14}H_{18}N_2+H]^+$: 215.1543; found 215.1542. Yellow oil, 119.4 mg (56%) isolated yield of 5,8-dimethyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56b**) after column chromatography. R_f = 0.39 in 1/1 Hept/EtOAc.

7-(4-Methoxyphenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56c**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-ethynyl-4-methoxybenzene (159 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).

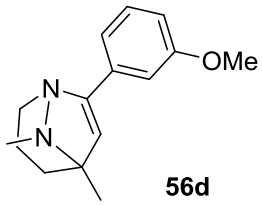


56c

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (d, 2H, *J* = 8.7 Hz, C**H**$_{arom., ortho}$), 6.87 (d, 2H, *J* = 8.7 Hz, C**H**$_{arom., meta}$), 5.62 (s, 1H, C_{quat}C**H**C_{quat}), 3.81 (s, 3H, OC**H$_3$**), 3.30 - 3.24 (m, 1H, NC(H)**H**CH$_2$CH$_2$), 2.83 (dd, 1H, *J* = 13.3, 6.1 Hz, NC(**H**)HCH$_2$CH$_2$), 2.36 (s, 3H, NC**H$_3$**), 1.86 - 1.74 (m, 2H, NCH$_2$C(H)**H**C(H)**H**), 1.44-1.39 (m, 2H, NCH$_2$C(**H**)HC(**H**)H), 1.21 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.8 (**C**$_{arom., para}$), 146.5 (Ph**C**=CH), 127.9 (**C**$_{arom., ortho}$), 124.8 (**C**$_{arom, ipso}$), 113.9 (**C**$_{arom., meta}$), 113.7 (PhC=**C**H), 68.7 (CH**C**$_{quat}$(N)(CH$_2$)CH$_3$), 55.3 (O**C**H$_3$), 47.9 (N**C**H$_2$CH$_2$CH$_2$), 37.6 (N**C**H$_3$), 33.7 (NCH$_2$CH$_2$**C**H$_2$), 20.1 (C**C**H$_3$), 18.6 (NCH$_2$**C**H$_2$CH$_2$). **HRMS** (ESI) m/z calculated for $[C_{15}H_{20}N_2O+H]^+$: 245.1648; found 248.1649. Yellow oil, 111.4 mg (46%) isolated yield of 7-(4-methoxyphenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56c**) after column chromatography. R_f = 0.33 in 1/1 Hept/EtOAc.

7-(3-Methoxyphenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56d**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-ethynyl-3-methoxybenzene (159 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).

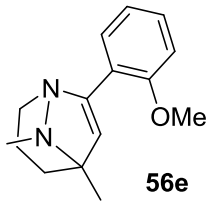


56d

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 - 7.17 (m, 3H, C**H**$_{arom.,}$), 6.86 - 6.83 (m, 1H, C**H**$_{arom.,}$), 5.78 (s, 1H, C_{quat}C**H**), 3.82 (s, 3H, OC**H$_3$**), 3.32 - 3.25 (m, 1H, NC(H)**H**CH_2CH_2), 2.86 (dd, 1H, *J* = 13.3, 6.1 Hz, NC(**H**)HCH_2CH_2), 2.37 (s, 3H, NC**H$_3$**), 1.90 - 1.76 (m, 2H, NCH_2C(H)**H**C(H)**H**), 1.47-1.41 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.21 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.8 (MeO**C**$_{arom.,}$), 146.9 (Ph**C**=CH), 133.5 (**C**$_{arom., ipso}$), 129.4 (**C**$_{arom.,}$), 119.1 (**C**$_{arom.}$), 116.3 (PhC=**C**H), 114.2 (**C**$_{arom.,}$), 111.8 (**C**$_{arom.,}$), 68.8 (CH**C**$_{quat}$(N)$(CH_2)CH_3$), 55.3 (O**C**H_3), 47.9 (N**C**$H_2CH_2CH_2$), 37.6 (N**C**H_3), 33.6 (NCH_2CH_2**C**H_2), 19.9 (C**C**H_3), 18.6 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{15}H_{20}N_2O+H]^+$: 245.1648; found 245.1641. Yellow oil, 113.7 mg (47%) isolated yield of 7-(3-methoxyphenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56d**) after column chromatography. R_f = 0.33 in 1/1 Hept/EtOAc.

7-(2-Methoxyphenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56e**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-ethynyl-2-methoxybenzene (159 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).

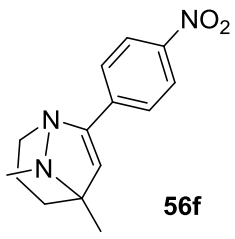


56e

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (dd, 1H, *J* = 7.7, 1.3 Hz, $CH_{arom.,}$), 7.24 (dd, 1H, *J* = 11.6, 4.3 Hz, $CH_{arom.}$),.6.97-6.91 (m, 2H, $C_{arom.}$), 6.14 (s, 1H, C_{quat}C**H),** 3.92 (s, 3H, OC**H$_3$**), 3.29 - 3.22 (m, 1H, NC(H)**H**CH_2CH_2), 2.87 (dd, 1H, *J* = 13.3, 6.0 Hz, NC(**H**)HCH_2CH_2), 2.36 (s, 3H, NC**H$_3$**), 1.83 - 1.77 (m, 2H, NCH_2C(H)**H**C(H)**H**), 1.48-1.38 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.23 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.1 (MeO**C**$_{arom.}$), 141.5 (Ph**C**=CH), 129.2 (**C**$_{arom.}$), 128.7 (**C**$_{arom.}$), 121.3 (PhC=**C**H), 120.9 (**C**$_{arom., ipso}$), 120.5 (**C**$_{arom.}$), 110.5 (**C**$_{arom.}$), 69.2 (CH**C**$_{quat}$(N)$(CH_2)CH_3$), 55.3 (O**C**H_3), 48.0 (N**C**$H_2CH_2CH_2$), 37.7 (N**C**H_3), 33.4 (NCH_2CH_2**C**H_2), 20.1 (C**C**H_3), 18.7 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{15}H_{20}N_2O+H]^+$: 245.1648; found 245.1648. Yellow oil, 101.0 mg (41%) isolated yield of 7-(2-methoxyphenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56e**) after column chromatography. R_f = 0.33 in 1/1 Hept/EtOAc.

5,8-Dimethyl-7-(4-nitrophenyl)-1,8-diazabicyclo[3.2.1]oct-6-ene (**56f**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-ethynyl-4-nitrobenzene (177 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).

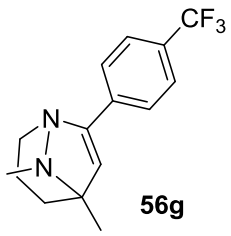


56f

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (d, 2H, *J* = 8.8 Hz, C**H**$_{arom., meta}$), 7.76 (d, 2H, *J* = 8.8 Hz, C**H**$_{arom., ortho}$), 6.08 (s, 1H, C_{quat}C**H**), 3.40 – 3.30 (m, 1H, NC(H)**H**CH_2CH_2), 2.83 (dd, 1H, *J* = 13.5, 6.1 Hz, NC(**H**)HCH_2CH_2), 2.37 (s, 3H, NC**H$_3$**), 1.85 - 1.79 (m, 2H, NCH_2C(H)**H**C(H)**H**), 1.52-1.47 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.25 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.4 (O_2N**C**$_{arom.}$), 145.6 (Ph**C**=CH), 138.3 (**C**$_{arom.,ipso}$), 127.1 (**C**$_{arom., ortho}$), 123.9 (**C**$_{arom., meta}$), 121.3 (H**C**=CPh), 69.4 (CH**C**$_{quat}$NCH_2CH_3), 47.9 (N**C**$H_2CH_2CH_2$), 37.7 (N**C**H_3), 33.4 (NCH_2CH_2**C**H_2), 19.7 (C**C**H_3), 18.5 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{14}H_{17}N_3O_2+H]^+$: 260.1394; found 260.1397. Brown solid, 50.0 mg (19%) isolated yield of 5,8-dimethyl-7-(4-nitrophenyl)-1,8-diazabicyclo[3.2.1]oct-6-ene (**56f**) after column chromatography. R_f = 0.44 in 1/1 Hept/EtOAc. T_m[°C]: 104.

5,8-Dimethyl-7-(4-(trifluoromethyl)phenyl)-1,8-diazabicyclo[3.2.1]oct-6-ene (**56g**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 4-ethynyl-α,α,α-trifluorotoluene (204 mg, 1.2 mmol) en methylhydrazine (115 mg, 2.5 mmol).

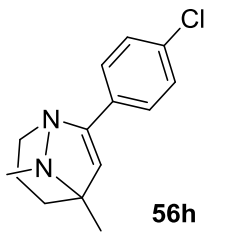


56g

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, 2H, *J* = 8.1 Hz, C**H**$_{arom., meta}$), 7.69 (d, 2H, *J* = 8.2 Hz, C**H**$_{arom., ortho}$), 5.93 (s, 1H, C_{quat}C**H**), 3.36-3.29 (m, 1H, NC(H)**H**CH_2CH_2), 2.83 (dd, 1H, *J* = 13.4, 5.8 Hz, NC(**H**)HCH_2CH_2), 2.37 (s, 3H, NC**H$_3$**), 1.84 - 1.81 (m, 2H, NCH_2C(H)**H**C(H)**H**), 1.48-1.46 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.24 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 146.0 (Ph**C**=CH), 135.5 (**C**$_{arom., ipso}$), 130.1 (q, *J* = 32.4 Hz, F_3C**C**$_{arom.}$), 126.7 (**C**$_{arom., ortho}$), 125.5 (q, *J* = 3.9 Hz, **C**$_{arom., meta}$), 125.5 (q, *J* = 271.9 Hz, **C**F_3)118.7 (PhC=**C**H), 69.1 (CH**C**$_{quat}$(N)(CH_2)CH_3), 47.9 (N**C**$H_2CH_2CH_2$), 37.7 (N**C**H_3), 33.5 (NCH_2CH_2**C**H_2), 19.8 (C**C**H_3), 18.6 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{15}H_{17}N_2F_3+H]^+$: 283.1417; found 283.1415. Yellow oil, 59.0 mg (21%) isolated yield of 5,8-dimethyl-7-(4-(trifluoromethyl)phenyl)-1,8-diazabicyclo[3.2.1]oct-6-ene (**56g**) after column chromatography. R_f = 0.45 in 1/1 Hept/EtOAc

7-(4-Chlorophenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56h**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), 1-chloro-4-ethynylbenzene (164 mg, 1.2 mmol) en methylhydrazine (115 mg, 2.5 mmol).

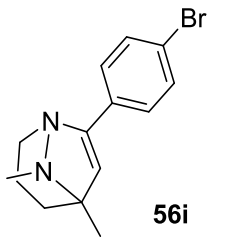


56h

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55(d, 2H, *J* = 8.5 Hz, C**H**$_{arom., meta}$), 7.30 (d, 2H, *J* = 8.5 Hz, C**H**$_{arom., ortho}$), 5.78 (s, 1H, C_{quat}C**H**), 3.33-3.26 (m, 1H, NC(H)**H**CH_2CH_2), 2.80 (dd, 1H, *J* = 13.4, 6.0 Hz, NC(**H**)HCH_2CH_2), 2.35 (s, 3H, NC**H$_3$**), 1.81 - 1.78 (m, 2H, NCH_2C(H)**H**C(H)**H**), 1.45-1.44 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.22 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 146.1 (Ph**C**=CH), 134.0 (Cl**C**$_{arom.}$), 130.6 (**C**$_{arom., ipso}$), 128.7 (**C**$_{arom., ortho}$), 127.8 (**C**$_{arom., meta}$), 116.5 (PhC=**C**H), 68.9 (CH**C**$_{quat}$(N)(CH_2)CH_3), 47.8 (N**C**$H_2CH_2CH_2$), 37.6 (N**C**H_3), 33.6 (NCH_2CH_2**C**H_2), 19.9 (C**C**H_3), 18.6 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{14}H_{17}N_2Cl+H]^+$: 249.1153; found 249.1141. Yellow oil, 108.0 mg (43%) isolated yield of 7-(4-chlorophenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56h**) after column chromatography. R_f = 0.39 in 1/1 Hept/EtOAc.

7-(4-Bromophenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56i**)

The standard experimental procedure was used with Cu_2O (143 mg, 1.0 mmol), 5-chloropentan-2-one (482 mg, 4 mmol), 1-bromo-4-ethynylbenzene (869 mg, 4.8 mmol) and methylhydrazine (461 mg, 10.0 mmol).



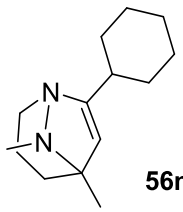
56i

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 – 7.44 (m, 4H, C**H**$_{arom.}$), 5.80 (s, 1H, C_{quat}C**H**), 3.34 – 3.23 (m, 1H, , NC(H)**H**CH_2CH_2), 2.85 – 2.75 (m, 1H, NC(**H**)HCH_2CH_2), 2.35 (s, 3H, NC**H$_3$**), 1.86 – 1.73 (m, 2H, NCH_2C(H)**H**C(H)**H**), 1.48 – 1.40 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.22 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 146.1 (Ph**C**=CH), 131.6 (**C**$_{arom., ortho}$), 131.0 (**C**$_{arom., ipso}$), 128.1 (**C**$_{arom., meta}$), 122.2 (Br**C**$_{arom.}$), 116.7 (PhC=**C**H), 69.0 (CH**C**$_{quat}$(N)(CH_2)CH_3), 47.8 (N**C**$H_2CH_2CH_2$), 37.6

(N**C**H_3), 33.5 (NCH_2CH_2**C**H_2), 19.9 (**C**CH_3), 18.6 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{14}H_{17}N_2Br+H]^+$: 290.1903; found 290.1905. Yellow oil, 597.1 mg (51%) isolated yield of 7-(4-bromophenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56i**) after column chromatography. R_f = 0.37 in 1/1 Hept/EtOAc.

7-Cyclohexyl-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56m**)

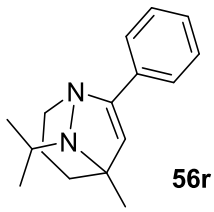
The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), cyclohexylacetylene (130 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).


56m

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.99 (s, 1H, C_{quat}C**H**), 3.26 - 3.18 (m, NC(**H**)HCH_2CH_2), 2.85 (dd, 1H, *J* = 13.4, 6.6 Hz, NC(**H**)HCH_2CH_2), 2.27 (s, 3H, NC**H$_3$**), 2.04 (d, 1H, *J* = 12.5 Hz, C**H**), 1.88 – 1.68 (m, 8H, C**H**$_{chex}$), 1.42 – 1.23 (m, 6H, $NCH_2C(H)$**H**C(H)**H** and C**H**$_{chex}$), 1.11 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.3 (Cy**C**=CH), 113.2 (CyC=**C**H), 67.6 (CH**C**$_{quat}NCH_2CH_3$), 48.0 (N**C**$H_2CH_2CH_2$), 37.3 (N**C**H_3), 36.5 (**C**H$_{chex}$), 33.7 (NCH_2CH_2**C**H_2), 32.6 (**C**H$_{chex}$), 31.3 (**C**H$_{chex}$), 26.5 (**C**H$_{chex}$), 26.4 (**C**H$_{chex}$), 26.3 (**C**H$_{chex}$), 20.5 (C**C**H_3), 18.7 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{14}H_{24}N_2+H]^+$: 221.2012; found 221.2009. Yellow oil, 60.5 mg (28%) isolated yield of 7-cyclohexyl-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56m**) after column chromatography. R_f = 0.11 in 1/1 Hept/EtOAc.

8-Isopropyl-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56r**)

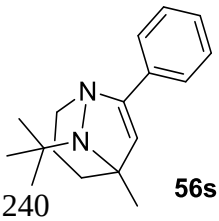
The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and isopropylhydrazine (185 mg, 2.5 mmol).


56r

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 6.8 Hz, 2H, C**H**$_{arom.,\ ortho}$), 7.35 – 7.17 (m, 3H, C**H**$_{arom.,\ meta\ and\ para}$), 4.83 (s, 1H, C=C**H**), 3.26 (septet, *J* = 6.5 Hz, 1H, NC**H**$(CH_3)_2$), 3.20 – 3.12 (m, 1H, NC**H**(H)), 3.02 – 2.92 (m, 1H, NCH(**H**)), 1.77 (dd, *J* = 12.4, 6.9 Hz, 1H, $C_{quat.}$C**H**(H)), 1.72 – 1.58 (m, 3H, $C_{quat.}$CH(**H**)C**H**$_2$), 1.31 (s, 3H, CC**H**$_3$), 1.17 (d, *J* = 6.7 Hz, 3H, NCHC**H**$_3$$(CH_3)$), 0.87 (d, *J* = 6.3 Hz, 3H, $NCHCH_3$(C**H**$_3$)). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.7 (Ph**C**=C), 133.4 (**C**H$_{arom.,\ ipso}$), 128.2 (**C**H$_{arom.,\ meta}$), 127.9 (**C**H$_{arom.,\ para}$), 127.5 (**C**H$_{arom.,\ ortho}$), 110.1 (PhC=**C**), 74.6 (**C**$_{quat.}$), 62.2 (N**C**H_2), 50.4 (N**C**H$(CH_3)_2$), 39.8 ($C_{quat.}$**C**H_2), 29.3 ($C_{quat.}$**C**H_3), 23.4 (NCH_2**C**H_2), 21.9 NCH**C**$H_3$$(CH_3)$, 16.5 $NCHCH_3$(**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{16}H_{22}N_2+H]^+$: 243.1856; found 243.1846. Yellow oil, 161.4 mg (67%) isolated yield of 8-isopropyl-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56r**) after column chromatography. R_f = 0.54 in 1/1 Hept/EtOAc.

8-(*tert*-Butyl)-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56s**)

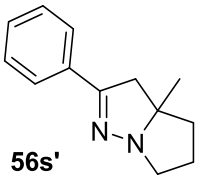
The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and *tert*-butylhydrazine (220 mg, 2.5 mmol).


56s

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.36 (m, 2H, C**H**$_{arom.,\ meta}$), 7.27 – 7.20 (m, 3H, C**H**$_{arom.,\ ortho\ and\ para}$), 4.76 (s, 1H, C=C**H**), 3.27 – 3.14 (m, 1H, NC**H**(H)), 3.04 – 2.92 (m, 1H, NCH(**H**)), 1.79 – 1.66 (m, 2H, $C_{quat.}$C**H**$_2$), 1.65 – 1.53 (m, 2H, NCH_2C**H**$_2$), 1.31 (s, 3H, $C_{quat.}$C**H**$_3$), 0.99 (s, 9H,

C($C\mathbf{H}_3$)$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.5 (Ph**C**=C), 137.5 (**C**$H_{arom.,\ ipso}$), 127.9 (**C**$H_{arom.,\ para}$), 127.6 (**C**$H_{arom.,\ ortho}$), 127.3 (**C**$H_{arom.,\ meta}$), 116.3 (PhC=**C**), 73.1 (N**C**$_{quat.}$), 62.4 (N**C**H_2), 59.6 (N**C**(CH_3)$_3$), 40.0 ($NCH_2CH_2\mathbf{C}H_2$), 28.9 ($NC_{quat.}\mathbf{C}H_3$ and NC(**C**H_3)$_3$), 22.6 ($NCH_2\mathbf{C}H_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{17}H_{24}N_2+H]^+$: 257.2012; found 257.2006. Yellow oil, 50.0 mg (20%) isolated yield of 8-(*tert*-butyl)-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56s**) after column chromatography. R_f = 0.71 in 9/1 Hept/EtOAc.

A second (degradation) product was obtained after column chromatography and was identified as 3a-methyl-2-phenyl-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-*b*]pyrazole (**56s'**).

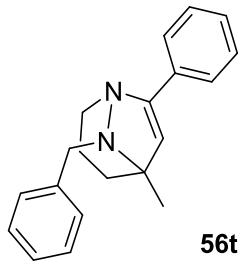

56s'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 – 7.60 (m, 2H, C**H**$_{arom.,\ ortho}$), 7.38 – 7.27 (m, 3H, C**H**$_{arom.,\ meta\ and\ para}$), 3.71 – 3.62 (m, 1H, NC**H**(H)), 3.37 – 3.26 (m, 1H, NCH(**H**)), 3.21 (d, *J* = 16.4 Hz, 1H, N=CC**H**(H)), 2.92 (d, *J* = 16.4 Hz, 1H, N=CCH(**H**)), 1.84 – 1.6 (m, 4H, $NCH_2C\mathbf{H}_2C\mathbf{H}_2$), 1.41 (s, 3H, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 152.5 (**C**=N), 133.2 (**C**$H_{arom.,\ ipso}$), 128.8 (**C**$H_{arom.,\ para}$), 128.4 (**C**$H_{arom.,\ meta}$), 126.2 (**C**$H_{arom.,\ ortho}$), 72.3 (N**C**$_{quat.}CH_3$), 53.0 ($N\mathbf{C}H_2CH_2CH_2$), 46.9 (N=C**C**H_2), 37.3 ($NCH_2CH_2\mathbf{C}H_2$), 26.3 (**C**H_3), 24.4 ($NCH_2\mathbf{C}H_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{13}H_{16}N_2+H]^+$: 201.1386; found 201.1381. Yellow oil, 40.1 mg (20%) isolated yield of 3a-methyl-2-phenyl-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-*b*]pyrazole (**56s'**) after column chromatography. R_f = 0.64 in 1/1 Hept/EtOAc.

Product 8-(*tert*-butyl)-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56s**) (38.0 mg, 0.148 mmol) was dissolved in DCM (1 mL) and treated with TFA (17 mg, 0.148 mmol) in DCM (1 mL). The reaction mixture was stirred for two hours at room temperature. Afterwards, the reaction mixture was washed with 0.5 N NaOH solution, dried over $MgSO_4.3H_2O$ and concentrated *in vacuo* to obtain 25.3 mg (85%) of 3a-methyl-2-phenyl-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-*b*]pyrazole (**56s'**). No further purification was necessary.

<u>8-Benzyl-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56t**)</u>

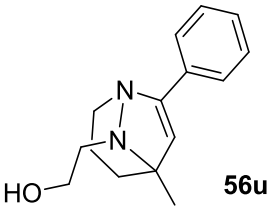
The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and benzylhydrazine (305 mg, 2.5 mmol).


56t

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, 2H, *J* = 7.0 Hz, PhC**H**$_{arom.,\ ortho}$), 7.39 (d, 2H, *J* = 7.0 Hz, BnC**H**$_{arom.,\ ortho}$), 7.30 - 7.20 (m, 6H, C**H**$_{arom.,\ meta\ and\ para}$), 5.88 (s, 1H, PhC=C**H**), 3.77 (d, 1H, *J* = 13.3 Hz, PhC**H**(H)N), 3.53 (d, 1H, *J* = 13.3 Hz, PhCH(**H**)N), 3.19-3.12 (m, 1H, NC(H)**H**CH_2CH_2), 2.75(dd, 1H, *J* = 13.2, 6.0 Hz, NC(**H**)HCH_2CH_2), 1.92 - 1.81 (m, 2H, $NCH_2C(H)\mathbf{H}C(H)\mathbf{H}$), 1.48-1.44 (m, 2H, $NCH_2C(\mathbf{H})HC(\mathbf{H})H$), 1.26 (s, 3H, $C_{quat}C\mathbf{H_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.6 (Ph**C**=CH), 141.0 (**C**$_{arom.,\ ipso,\ benzyl}$), 132.2 (**C**$_{arom.,\ ipso,\ phenyl}$), 129.1 (**C**$_{arom.,\ ortho,\ benzyl}$), 128.4 (**C**$_{arom.,\ meta,}$), 128.2 (**C**$_{arom.,\ para}$), 127.8 (**C**$_{arom.,\ meta}$), 126.7(**C**$_{arom.,\ ortho,\ phenyl}$), 126.1 (**C**$_{arom.,\ para}$), 116.7 (PhC=**C**H), 68.8 (CH**C**$_{quat}NCH_2CH_3$), 53.6 (N**C**H_2Ph), 47.8 ($N\mathbf{C}H_2CH_2CH_2$), 34.2 ($NCH_2CH_2\mathbf{C}H_2$), 20.6 (C**C**H_3), 18.8 ($NCH_2\mathbf{C}H_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{20}H_{22}N_2+H]^+$: 291.1856; found 291.1847. Orange solid, 198.4 mg (68%) isolated yield of 8-benzyl-5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-ene (**56t**) after column chromatography. R_f = 0.55 in 9/1 Hept/EtOAc. T_m[°C]: 66.

2-(5-Methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-en-8-yl)ethan-1-ol (**56u**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and 2-hydroxyethylhydrazine (190 mg, 2.5 mmol).

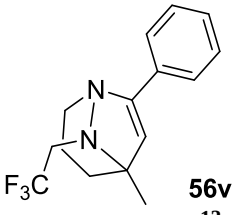


56u

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 - 7.52 (d, 2H, *J* = 7.1 Hz, $CH_{arom., ortho}$), 7.34 - 7.32 (m, 3H, $CH_{arom., meta and para}$), 5.94 (s, 1H, PhC=C**H**), 4.76 (s, 1H, O**H**), 3.97 - 3.95 (m, 1H, HOC**H**(H)CH_2), 3.84 - 3.81 (m, 1H, HOC**H**(H)CH_2), 3.37 - 3.31 (m, 1H, NC(H)**H**CH_2CH_2), 2.93 – 2.89 (dd, 1H, *J* = 13.2, 5.9 Hz, NC(**H**)HCH_2CH_2), 2.71 - 2.66 (m, 1H), 2.60 - 2.55 (m, 1H), 1.86 - 1.83 (m, 2H, $NCH_2C(H)$**H**$C(H)$**H**), 1.47-1.45 (m, 2H, NCH_2C(**H**)HC(**H**)H), 1.22 (s, 3H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 145.8 (**C**$_{arom., ipso}$), 131.2 (Ph**C**=CH), 128.7 (**C**$_{arom., meta}$), 128.6 (**C**$_{arom., para}$), 126.2 (**C**$_{arom., ortho}$), 117.9 (H**C**=CPh), 68.6 (CH**C**$_{quat}$(N)$(CH_2)CH_3$), 63.2 (HO**C**H_2), 48.6 (HOCH_2**C**H2N), 47.9 (N**C**$H_2CH_2CH_2$), 33.5 (NCH_2**C**H_2CH_2), 20.1 (NCH_2CH_2**C**H_2), 18.6 (C**C**H_3). **HRMS** (ESI) m/z calculated for $[C_{15}H_{20}N_2O+H]^+$: 245.1648; found 245.1645. Brown oil, 33.8 mg (14%) isolated yield of 2-(5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-en-8-yl)ethan-1-ol (**56u**) after column chromatography. R_f = 0.38 in 1/1 Hept/EtOAc.

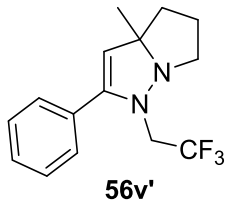
5-Methyl-7-phenyl-8-(2,2,2-trifluoroethyl)-1,8-diazabicyclo[3.2.1]oct-6-ene (**56v**) and 3a-methyl-2-phenyl-1-(2,2,2-trifluoroethyl)-3a,4,5,6-tetrahydro-1*H*-pyrrolo[1,2-*b*]pyrazole(**56v'**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and 2,2,2-trifluoroethylhydrazine (285 mg, 2.5 mmol).



56v

8/1 mixture of constitutional isomers. Major isomer (presumed **56v**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.49 (d, 2H, *J* = 6.5 Hz, C**H**$_{arom., ortho}$), 7.36 - 7.31 (m, 3H, C**H**$_{arom., meta and para}$), 5.17 (s, 1H, PhC=C**H**), 3.50 – 3.44 (m, 1H, NC**H**(H)CF_3), 3.38 - 3.28 (m, 2H, NC(H)**H**CH_2CH_2 and NCH(**H**)CF_3), 3.03 – 2.99 (m, 1H, NC(**H**)HCH_2CH_2), 1.90 – 1.84 (m, 1H, $NCH_2CH_2C(H)$**H**), 1.73 - 1.66 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.36 (s, 1H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 147.3 (Ph**C**=CH), 131.5 (**C**$_{arom., ipso}$), 128.7 (**C**$_{arom., para}$), 128.6 (**C**$_{arom., meta}$), 127.4 (**C**$_{arom., ortho}$), 125.0 (q, *J* = 278.0 Hz, **C**F_3), 113.3 (PhC=**C**H), 75.6 (CH**C**$_{quat}NCH_2CH_3$), 59.5 (N**C**$H_2CH_2CH_3$), 57.4 (q, *J* = 30.2 Hz, N**C**H_2CF_3), 38.1 (NCH_2CH_2**C**H_2), 31.4 (C_{quat}**C**H_3), 23.1 (NCH_2**C**H_2CH_2).

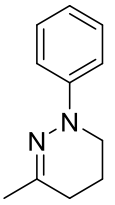


56v'

Minor isomer (presumed **56v'**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.62 (d, 2H, *J* = 7.2 Hz, C**H**$_{arom., ortho}$), 7.36 - 7.31 (m, 3H, C**H**$_{arom., meta and para}$), 5.84 (s, 1H, PhC=C**H**), 3.40 – 3.28 (m, 1H, NC**H**(H)CF_3), 3.21 - 3.09 (m, 2H, NC(H)**H**CH_2CH_2 and NCH(**H**)CF_3), 2.83 (dd, 1H, *J* = 13.3, 5.9 Hz, NC(**H**)HCH_2CH_2), 1.90 – 1.84 (m, 1H, $NCH_2CH_2C(H)$**H**), 1.73 - 1.66 (m, 3H, NCH_2C**H**$_2$C(**H**)H), 1.25 (s, 1H, C_{quat}C**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 148.4 (Ph**C**=CH), 131.5 (**C**$_{arom., ipso}$), 128.7 (**C**$_{arom., para}$), 128.6 (**C**$_{arom., meta}$), 126.7 (**C**$_{arom., ortho}$), 125.7 (q, *J* = 277.0 Hz, **C**F_3), 116.0 (PhC=**C**H), 68.6 (CH**C**$_{quat}NCH_2CH_3$), 51.5 (q, *J* = 30.1 Hz, N**C**H_2CF_3), 47.5 (N**C**$H_2CH_2CH_3$), 34.0 (NCH_2CH_2**C**H_2), 20.3 (C_{quat}**C**H_3), 18.6 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for mixture of isomers $[C_{15}H_{17}N_2F_3+H]^+$: 283.1417; found 283.1417. Yellow oil, 113.3 mg (40%) isolated yield of mixture of isomers after column chromatography. R_f = 0.37 in 95/5 Hept/Acetone.

3-Methyl-1-phenyl-1,4,5,6-tetrahydropyridazine (**56w'**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-1-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and phenylhydrazine (270 mg, 2.5 mmol).

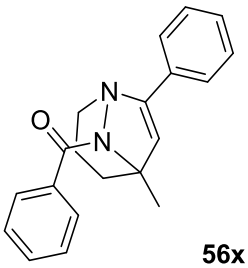


56w'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (t, *J* = 7.6 Hz, 2H, C**H**$_{arom., ortho}$), 7.18 (d, *J* = 8.4 Hz, 2H, C**H**$_{arom., meta}$), 6.82 (t, *J* = 6.9 Hz, 1H, C**H**$_{arom., para}$), 3.46 (t, *J* = 5.6 Hz, 2H, NC**H**$_2$), 2.16 (t, *J* = 6.6 Hz, 2H, $NCH_2CH_2C\mathbf{H}_2$), 2.07 – 1.99 (m, 2H, $NCH_2C\mathbf{H}_2CH_2$), 1.98 (s, 3H, N=CC**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 148.4 (**C**$_{arom., ipso}$), 143.6 (**C**=N), 128.9 (**C**$_{arom., ortho}$), 119.2 (**C**$_{arom., para}$), 113.6 (**C**$_{arom., meta}$), 42.3 ($N\mathbf{C}H_2CH_2CH_2$), 25.6 ($NCH_2CH_2\mathbf{C}H_2$), 24.3 (C**C**H$_3$), 19.1 ($NCH_2\mathbf{C}H_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{11}H_{14}N_2+H]^+$: 175.1230; found 175.1231. Yellow oil, 25.0 mg (14%) isolated yield of 3-methyl-1-phenyl-1,4,5,6-tetrahydropyridazine (**56w'**) after column chromatography. R_f = 0.58 in 9/1 Hept/EtOAc.

(5-Methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-en-8-yl)(phenyl)methanone (**56x**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and benzoylhydrazine (340 mg, 2.5 mmol).

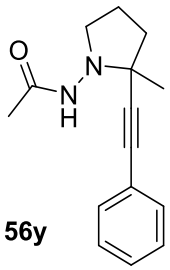


56x

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 - 7.25 (m, 10H, C**H**$_{arom.}$), 5.71 (s, 1H, PhC=C**H**), 3.57-3.53 (m, 1H, NC(H)**H**CH_2CH_2), 3.05 – 3.00 (m, 1H, NC(**H**)HCH_2CH_2), 2.09 (m, 1H, $NCH_2C(H)HC(\mathbf{H})H$), 1.78 – 1.75 (m, 3H, $NCH_2C(\mathbf{H})\mathbf{H}C(H)\mathbf{H}$) 1.24 (s, 3H, $C_{quat}C\mathbf{H_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 173.3 (**C**=O), 141.6 (Ph**C**=CH) , 136.3 (C=O**C**H$_{arom}$), 132.4 (**C**H$_{arom}$), 131.5(**C**H$_{arom}$), 130.5 (**C**H$_{arom}$), 128.3 (**C**H$_{arom}$), 128.2 (**C**H$_{arom}$), 128.0 (**C**H$_{arom}$), 127.7 (**C**H$_{arom}$), 126.3 (**C**H$_{arom}$), 122.2 (H**C**=CPh), 75.0 ($CH_3\mathbf{C}_{quat}$), 57.2 ($N\mathbf{C}H_2CH_2CH_3$), 35.0 ($NCH_2CH_2\mathbf{C}H_2$), 25.2 (C**C**H$_3$), 22.2 ($NCH_2\mathbf{C}H_2CH_2$). **HRMS** (ESI) m/z calculated for $[C_{20}H_{20}N_2O+H]^+$: 305.1648; found 305.1651. Yellow solid, 44.6 mg (15%) isolated yield of (5-methyl-7-phenyl-1,8-diazabicyclo[3.2.1]oct-6-en-8-yl)(phenyl)methanone (**56x**) after column chromatography. R_f = 0.64 in 1/1 Hept/EtOAc. T_m[°C]: 134.

N-(2-Methyl-2-(phenylethynyl)pyrrolidin-1-yl)acetamide (**56y**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 5-chloropentan-2-one (121 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and acethydrazide (185 mg, 2.5 mmol).



56y

7/3 mixture of rotamers. Major rotamer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 - 7.38 (m, 2H, C**H**$_{arom.}$), 7.36 - 7.26 (m, 3H, C**H**$_{arom.}$), 6.38 (br s, 1H, N**H**), 3.27-3.19 (m, 1H), 2.87 – 2.78 (m, 1H), 2.27 – 2.15 (m, 1H), 2.12 (s, 3H, C=OC**H**$_3$) 1.95 – 1.75 (m, 3H, $NCH_2C(\mathbf{H})\mathbf{H}C(H)\mathbf{H}$) 1.44 (s, 3H, $C_{quat}C\mathbf{H_3}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 174.6 (**C**=O), 131.8, 128.4, 128.3, 122.3, 87.9, 86.5, 62.5 ($CH_3\mathbf{C}_{quat}$), 53.9 ($N\mathbf{C}H_2CH_2CH_3$), 37.4 ($NCH_2CH_2\mathbf{C}H_2$), 25.0 (C**C**H$_3$), 19.9, 18.7.

Minor rotamer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 - 7.38 (m, 2H, C**H**$_{arom.}$), 7.36 - 7.26 (m, 3H, C**H**$_{arom.}$), 6.34 (br s, 1H, N**H**), 3.44-3.37 (m, 1H), 2.77 – 2.68 (m, 1H), 2.27 – 2.15 (m, 1H), 1.99 (s, 3H, C=OC**H**$_3$) 1.95 – 1.75 (m, 3H, $NCH_2C(\mathbf{H})\mathbf{H}C(H)\mathbf{H}$) 1.47 (s, 3H, $C_{quat}C\mathbf{H_3}$).

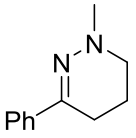
^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.7 (**C**=O), 131.8, 128.6, 128.4, 122.4 87.3, 86.6, 62.9 (CH_3**C**$_{quat}$), 53.7 (N**C**$H_2CH_2CH_3$), 37.0 (NCH_2CH_2**C**H_2), 24.8 (C**C**H_3), 21.7, 18.9.

VT NMR: All peaks coalescent at 120 °C **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.51 - 7.45 (m, 2H, C**H**$_{arom.}$), 7.41 - 7.33 (m, 3H, C**H**$_{arom.}$), 7.07 (br s, 1H, N**H**), 3.21-3.13 (m, 1H), 2.95 – 2.86 (m, 1H), 2.24 – 2.14 (m, 1H), 1.97 (s, 3H, C=OC**H**$_3$) 1.95 – 1.75 (m, 3H, NCH_2C(**H**)**H**C(H)**H**) 1.41 (s, 3H, $C_{quat}C$**H$_3$**). **^{13}C NMR** (100 MHz, DMSO-d_6) δ = not detected (**C**=O), 130.9, 127.6, 127.5, 121.9, 89.1, 84.6, 61.1 (CH_3**C**$_{quat}$), 52.2 (N**C**$H_2CH_2CH_3$), 37.1 (NCH_2CH_2**C**H_2), 23.9 (C**C**H_3), 19.3, 18.2.

HRMS (ESI) m/z calculated for $[C_{15}H_{18}N_2O+H]^+$: 243.1492; found 243.1487. White solid, 95.4 mg (40%) isolated yield of *N*-(2-methyl-2-(phenylethynyl)pyrrolidin-1-yl)acetamide (**56y**) after column chromatography. R_f = 0.19 in 1/1 Hept/EtOAc. T_m[°C]: 72.

1-Methyl-3-phenyl-1,4,5,6-tetrahydropyridazine (**56aa'**)

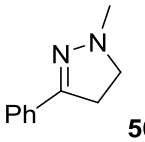
The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 4-chloro-1-phenylpropan-1-one (182 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).


56aa'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 - 7.65 (d, 2H, *J* = 7.3 Hz, C**H**$_{arom., ortho}$), 7.33 - 7.24 (m, 3H, C**H**$_{arom., meta and para}$), 2.95 (s, 3H, NC**H$_3$**), 2.84 (t, 2H, *J* = 5.6 Hz, NC**H$_2$**CH_2CH_2), 2.49 (t, 2H, *J* = 7.0 Hz, NCH_2CH_2C**H$_2$**), 2.11 – 2.05 (m, 2H, NCH_2C**H$_2$**CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 143.0 (**C**=N), 139.0 (**C**$_{arom., ipso}$), 128.1 (**C**$_{arom., meta}$), 127.6 (**C**$_{arom., para}$), 124.4 (**C**$_{arom., ortho}$), 48.8 (N**C**$H_2CH_2CH_2$), 46.5 (N**C**H_3N**C**$H_2CH_2CH_2$), 21.4 (NCH_2CH_2**C**H_2), 20.1 (NCH_2**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{11}H_{14}N_2+H]^+$: 175.1230; found 175.1223. Brown oil, 42.8 mg (25%) isolated yield of 1-methyl-3-phenyl-1,4,5,6-tetrahydropyridazine (**56aa'**) after column chromatography. R_f = 0.21 in 1/1 Hept/EtOAc.

1-Methyl-3-phenyl-4,5-dihydro-1*H*-pyrazole (**56ab'**)

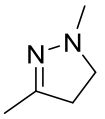
The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 3-chloro-1-phenylpropan-1-one (169 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).


56ab'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 - 7.61 (m, 2H, C**H**$_{arom., ortho}$), 7.33 - 7.36 (m, 3H, C**H**$_{arom., meta and para}$), 3.15 - 3.10 (dd, 2H, *J* = 14.1, 5.0 Hz, NCH(**H**)CH(**H**)), 2.97 – 2.92 (dd, 2H, *J* = 14.4, 5.1, NC**H**(H)C**H**(H)), 2.90 (s, 3H, NC**H$_3$**). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 151.7 (**C**=N), 133.0 (**C**$_{arom., ipso}$), 128.5 (**C**$_{arom., para}$), 128.4 (**C**$_{arom., meta}$), 125.8 (**C**$_{arom., ortho}$), 56.2 (N**C**H_2CH_2), 43.5 (N**C**H_3), 33.4 (N=C**C**H_2CH_2). **HRMS** (ESI) m/z calculated for $[C_{10}H_{12}N_2+H]^+$: 161.1073; found 161.1080. Yellow oil, 151.9 mg (95%) isolated yield of 1-methyl-3-phenyl-4,5-dihydro-1*H*-pyrazole (**56ab'**) after column chromatography. R_f = 0.36 in 1/1 Hept/EtOAc.

1,3-Dimethyl-4,5-dihydro-1*H*-pyrazole (**56ac'**)

The standard experimental procedure was used with Cu_2O (36 mg, 0.25 mmol), 4-chloro-butan-2-one (107 mg, 1 mmol), phenylacetylene (123 mg, 1.2 mmol) and methylhydrazine (115 mg, 2.5 mmol).

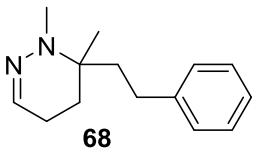


56ac'

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.94 (t, *J* = 9.2 Hz, 2H, NC**H**$_2$), 2.75 (s, 3H, NC**H**$_3$), 2.56 (t, *J* = 9.2 Hz, 2H, NCH$_2$C**H**$_2$), 1.95 (s, 3H, N=CC**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 153.1 (**C**=N), 56.4 (N**C**H$_2$CH$_2$), 43.9 (N**C**H$_3$), 37.7 (N=C**C**H$_2$CH$_2$), 16.2 (N=C**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_5H_{10}N_2+H]^+$: 99.0917; found 99.0909. Yellow oil, 58.0 mg (59%) yield of 1,3-dimethyl-4,5-dihydro-1*H*-pyrazole (**56ac'**) after basic workup with 0.5 N NaOH. The yield was recalculated for the presence of phenylacetylene.

1,6-Dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine (**68**)

In a 10 mL microwave vessel were introduced Pd on carbon (39.1 mg, 0.368 mmol), product (**56b**) (78.8 mg, 0.368 mmol) and MeOH (4 mL). The vial was capped, and a balloon filled with H_2 was pierced through the septum of the microwave vial. The reaction mixture was stirred at room temperature for 24 hours under H_2 atmosphere. Afterwards, the reaction mixture was diluted with EtOAc (20 mL) and filtered over a layer of Celite. The reaction mixture was concentrated *in vacuo* to obtain the product 1,6-dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine (**68**) as a yellow oil. No further purification was necessary.

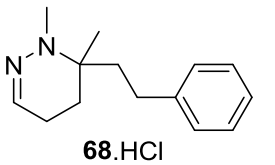


68

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.22 (m, 2H, C**H**$_{arom., ortho}$), 7.21 – 7.15 (m, 3H, C**H**$_{arom., meta and para}$), 6.67 (br t, *J* = 2.5 Hz, 1H, N=C**H**), 2.83 (s, 3H, NC**H**$_3$), 2.68 – 2.49 (m, 2H, PhC**H**$_2$), 2.21 – 2.13 (m, 2H, N=CHC**H**$_2$), 2.01 – 1.83 (m, 2H, H(**H**)CC$_{quat.}$C**H**(H)CH$_2$Ph), 1.69 (ddd, *J* = 14.0, 11.6, 6.3 Hz, 1H, C$_{quat.}$CH(**H**)CH$_2$Ph), 1.63 – 1.51 (m, 1H, **H**(H)CC$_{quat.}$CH(H)CH$_2$Ph), 1.08 (s, 3H, CC**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 142.5 (**C**$_{arom., ipso}$), 136.2 (**C**=N), 128.5 (**C**$_{arom., ortho}$), 128.3 (**C**$_{arom., meta}$), 125.8 (**C**$_{arom., para}$), 54.2 (**C**$_{quat.}$), 39.1 (PhCH$_2$**C**H$_2$), 37.9 (N**C**H$_3$), 29.6 (Ph**C**H$_2$CH$_2$), 29.0 (C=NCH$_2$**C**H$_2$), 22.0 (C=N**C**H$_2$CH$_2$), 19.3 (C**C**H$_3$). **IR** (ATR, cm^{-1})= ν_{max} = 1603. **HRMS** (ESI) m/z calculated for $[C_{14}H_{20}N_2+H]^+$: 217.1699; found 217.1689. Yellow oil, 73.1 mg (92%) isolated yield of 1,6-dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine (**68**) after workup. R_f = 0.51 in 1/1 Hept/EtOAc.

1,6-Dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine hydrochloric acid salt (**68**.HCl)

In an NMR vial were introduced 1,6-dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine (**68**) 49.0 mg, 0.227 mmol) in MeOH (0.5 mL) and 3 N HCl in water (1 mL). The vial was capped and the reaction mixture was stirred at room temperature for 3 hours. Afterwards, the reaction mixture was concentrated *in vacuo* to obtain the product 1,6-dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine hydrochloric acid salt (**68**.HCl). No further purification was necessary.

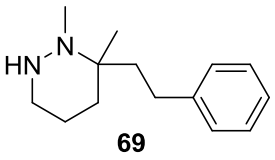


68.HCl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.57 (br s, 1H, N**H**), 7.69 (br t, *J* = 2.5 Hz, 1H, N=C**H**), 7.33 – 7.27 (m, 2H, C**H**$_{arom., ortho}$), 7.24 – 7.15 (m, 3H, C**H**$_{arom., meta and para}$), 3.13 (s, 3H, NC**H**$_3$), 2.70 – 2.58 (m, 4H, PhC**H**$_2$ and C=NC**H**$_2$), 2.22 – 2.11 (m, 1H, PhCH$_2$C(H)**H**), 2.04 – 1.93 (m, 2H, H(**H**)CC$_{quat.}$C**H**(H)CH$_2$Ph), 1.92 – 1.83 (m, 1H, C$_{quat.}$CH(**H**)CH$_2$Ph), 1.32 (s, 3H, CC**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 151.2 (**C**=N), 140.4 (**C**$_{arom., ipso}$), 128.8 (**C**$_{arom., ortho}$), 128.2 (**C**$_{arom., meta}$), 126.5 (**C**$_{arom., para}$), 59.0 (**C**$_{quat.}$), 37.3 (PhCH$_2$**C**H$_2$), 36.0 (N**C**H$_3$), 29.3 (Ph**C**H$_2$), 26.1 (C=NCH$_2$**C**H$_2$), 21.5 (C=N**C**H$_2$CH$_2$), 19.6 (C**C**H$_3$). **HRMS** (ESI) m/z calculated for $[C_{14}H_{20}N_2+H]^+$: 217.1699; found 217.1689. Yellow oil, 57.0 mg (99%) isolated yield of 1,6-dimethyl-6-phenethyl-1,4,5,6-tetrahydropyridazine hydrochloric acid salt (**68**.HCl) after workup.

1,6-Dimethyl-6-phenethylhexahydropyridazine (**69**)

In a 10 mL microwave vessel were introduced $LiAlH_4$ (12,8 mg, 0.337 mmol), product (**68**) (48.6 mg, 0.225 mmol) and dry THF (1 mL) at 0°C. The reaction mixture was stirred at reflux for 12 hours under Argon atmosphere. Afterwards, the reaction mixture was diluted with Et_2O (10 mL) and washed with 0.5 N NaOH solution, the organic phases were dried over $MgSO_4.3H_2O$ and concentrated *in vacuo* to obtain a 65/35 mixture of product **69** and starting material **68**. Repetition of the reaction with this mixture gave a 45/55 mixture of product **69** and starting material **68**, which was eventually purified to give 31.5 mg (65%) of the starting material **68**.



69

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.22 (m, 2H, C**H**$_{arom., ortho}$), 7.21 – 7.15 (m, 3H, C**H**$_{arom., meta and para}$), 3.04 – 2.92 (m, 2H, NC**H**$_2$), 2.68 – 2.49 (m, 2H, PhC**H**$_2$), 2.37 (s, 3H, NC**H**$_3$), 1.93 – 1.66 (m, 2H, NCH_2CH(**H**), C**H**$_2CH_2$Ph), 1.56 – 1.46 (m, 3H, NCH_2C**H**(H)C**H**$_2$), 1.07 (s, 3H, CC**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 142.9 (**C**$_{arom., ipso}$), 128.5 (**C**$_{arom., ortho}$), 128.3 (**C**$_{arom., meta}$), 125.9 (**C**$_{arom., para}$), 56.2 (**C**$_{quat.}$), 47.1 (N**C**H_2), 39.0 ($PhCH_2$**C**H_2), 38.0 (N**C**H_3), 33.8 (NCH_2**C**H_2), 30.1 (Ph**C**H_2CH_2), 22.7 (NCH_2CH_2**C**H_2), 19.3 (C**C**H_3). No HRMS data could be collected due to instability of the product.Yellow oil, 31.5 mg (65%) yield of mixture of starting material (**68**) and product 1,6-dimethyl-6-phenethylhexahydropyridazine (**69**) after workup.

XRD measurement of 7-(4-chlorophenyl)-5,8-dimethyl-1,8-diazabicyclo[3.2.1]oct-6-ene

Crystals for X-ray structure determination were grown by slow evaporation of a saturated dichloromethane solution. A light yellow prism-shaped fragment of 0.3 x 0.25 x 0.08 mm was mounted on an Oxford Diffraction SuperNova four circle goniometer with Atlas CCD detector. The crystal was flash-cooled by a 100K nitrogen stream. Diffraction data were collected with Cu Kα radiation (1,54184 Å) by making ω-scans. Full data completeness was achieved up to 67,68° in θ. All other parameters related to the crystal, data collection and structure refinement can be obtained from the table on the next page.

Crystal data	
Chemical formula	$C_{14}H_{17}ClN_2$
M_r	249.38
Crystal system, space group	Monoclinic, *I*2
Temperature (K)	100
a, *b*, *c* (Å)	19.7998 (6), 7.5312 (2), 35.9484 (12)
β (°)	103.862 (4)
V (Å3)	5204.4 (3)
Z	16
μ (mm^{-1})	2.42
Crystal size (mm)	0.30 × 0.25 × 0.08
Data collection	
Absorption correction	Multi-scan *CrysAlis PRO* 1.171.38.41r (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.848, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	21223, 8448, 7086
R_{int}	0.051
$(\sin\theta/\lambda)_{max}$ ($Å^{-1}$)	0.630
Refinement	
R[$F^2 > 2\sigma(F^2)$], *wR*(F^2), *S*	0.058, 0.141, 1.05
No. of reflections	8448
No. of parameters	1198
No. of restraints	889
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)	0.28, −0.35
Absolute structure	Refined as an inversion twin.
Absolute structure parameter	0.41 (3)
Computer programs	CrysAlis PRO 1.171.38.41r (Rigaku OD, 2015), SHELXT 2014/5 (Sheldrick, 2014),[53] SHELXL2016/4 (Sheldrick, 2016),[54] WinGX (Farrugia, 1999),[55] ShelXle (Hübschle, 2011),[56] DSR (Kratzert, 2014),[57] Mercury 3.9 (CCDC, 2016).[58]

As evidenced from the *Z*-value, the crystal contains 4 molecules in the asymmetric unit. *I*2 is a chiral space group, and the 4 independent molecules are 2 (*S*)-enantiomers and 2 (*R*)-enantiomers that are not related by crystallographic symmetry. All of the molecules display whole-molecule disorder, by which an enantiomer in the crystal structure is replaced by its mirror image. In this way, the crystal structure resembles a structure with a much smaller cell

in the space group C2/c, which would be an exact fit if the disorder would be evenly spread out over the two sets of molecules. Here, however, the refined occupancies of the major conformers are 78.0(6)%, 79.3(5)%, 84.7(5)% and 84.9(5)%, and this is the only setting which fits the structure.

In addition, the crystal is racemically twinned to the tune of 40%, which was also refined.

After initial recognition of the disorder in the crystal structure, DSR[59] was used to turn one of the major conformers into a fragment, which was then applied to the structure to fit the disordered electron density. Restraints were placed on 1,2 and 1,3 distances to make them equal to the corresponding distances in the superimposed major conformer. Restraints were also placed on the displacement ellipsoids of the minor conformers according to the 'rigid bond' principle within 0.01 s.d., and an additional constraint for sphericity of the displacement ellipsoids of C in the minor components was implemented to within 0.015 s.d., for Cl to within 0.1 s.d. Some extra constraints were placed on specific atoms (C10B, C11B, C12C, Cl1C) to prevent them going non-positive-definite (n.p.d.)

Overall, this reduced $\Delta\rho_{max}$, $\Delta\rho_{min}$ to the values given in the table, +0.28 and -0.35.

The remaining issues are situated around Cl1C at an occupancy of just 15%, and it is evident that the heaviest atoms (Cl) will have the largest Fourier cut-off ripples located around them. Cl1C is probably just unfortunately situated with respect to a ripple, which makes its displacement ellipsoids go n.p.d.

5.5 References

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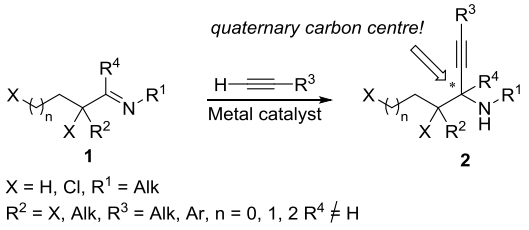
6 General conclusions & outlook

In this PhD thesis a number of alkynylation strategies were developed. Chapter one gave a literature overview of alkynylation reactions on imines and the one-pot three-component A³ coupling variant. It is clear that in recent years a number of heterogeneous catalysts were developed, and that the metal of choice for A³ couplings is, in most cases, copper. Although heterogeneous catalysts are being developed, the actually used heterogeneous catalyst will largely depend on the characteristics of the A³ coupling to be catalyzed. For the replacement of components in the A³ coupling, most of the straightforward replacements were investigated. Nevertheless, the scope of these reactions can still be expanded (*vide infra*). Similarly, specific A³ couplings such as the redox-A³ or decarboxylative coupling might be further expanded scope-wise. More importantly, design and application of new ligands for asymmetric A³ couplings will probably be of interest for years to come because of the particularity of the catalyst-ligand interaction with the substrate. Therefore, new classes of ligands will have to be discovered in a quest for high enantioselectivity (>99% *ee*), and fine-tuning of the ligand for a specific application will probably always be a topic of interest.

As a second in row the synthetic utility of propargylamines will be a topic of interest for many more years, since the substrate scope of A³ couplings is still expanding. Although there already exists a plethora of reactions involving propargylamines as discussed in §1.4, new highly functionalized propargylamines will probably create opportunities for new reactions to be developed.

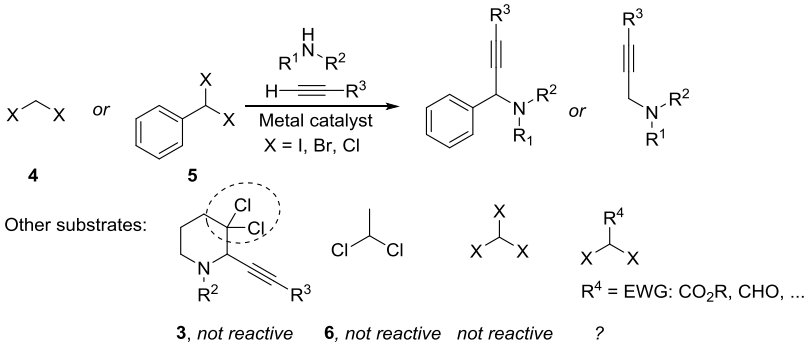
In chapter two $In(OTf)_3$ was identified as the catalyst of choice for alkynylation of polychlorinated aldimines. It would be interesting to evaluate the alkynylation of different polychlorinated ketimines **1**, especially in the case of α-chloroketimines, which might be less prone to hydrolysis (Scheme 6-1). Obtained products would have a quaternary carbon center. Control of the stereocenter in molecules **2** by addition of a chiral ligand would be very interesting. Addition of a chiral ligand was evaluated for the synthesis of propargylamines from α,α-dichloroaldimines but the combination of $In(OTf)_3$ with a number of popular chiral ligands did not result in good enantioselectivities (not in this thesis).



Scheme 6-1 Alkynylation of polychlorinated ketimines.

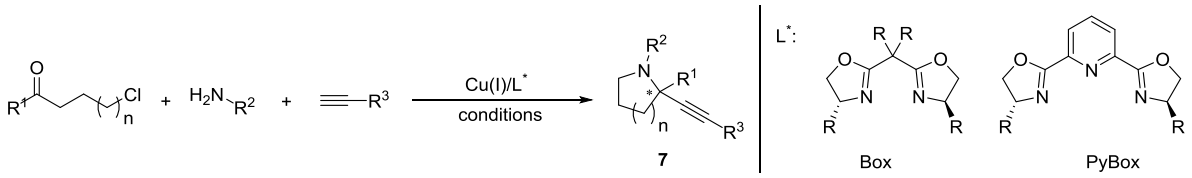
An initial plan was to use the dichloromethylene group, often present in alkynylated products **3** from polychlorinated aldimines, in AHA couplings (Scheme 6-2). However, the scope of dihaloalkanes in the AHA coupling was so far limited to dihalomethane **4** and dibenzalhalides **5**. A better understanding of the reaction mechanism might lead to expansion of the scope, since now it is not obvious why only those substrates are reactive. Initial experiments to use 2-alkynyl-3,3-dichloropiperidines **3** in AHA couplings resulted in no reaction, thus in §2.6.2 we investigated the three-component coupling of amines, alkynes and dichloroethane **6**. Dichloroethane **6** was chosen as it closely resembles dichloromethane and benzal chloride,

however no coupling was observed. Instead of using dichloroethane, which adds an electron-donating methyl group to the dichloromethylene function it might be better to add electron-withdrawing substituents as is the case with benzal chloride.



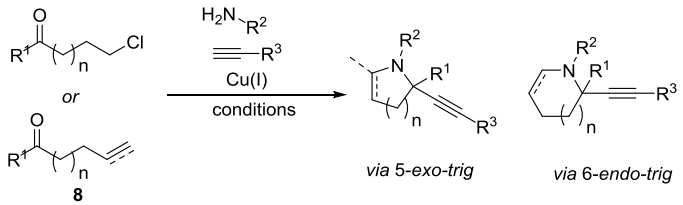
Scheme 6-2 AHA reactions with different substrates.

In chapter three, the coupling of ω-chlorinated ketones, primary amines and alkynes was developed (Scheme 6-3). A logical expansion would be to control the stereocenter formed in the reaction by addition of a chiral ligand. The combination of Cu and chiral ligands such as Box and PyBox is well known and could in certain cases catalyze the stereoselective addition of alkynes to imines. So far a few experiments were tried using these ligands, but no chiral induction was observed (not in this thesis).



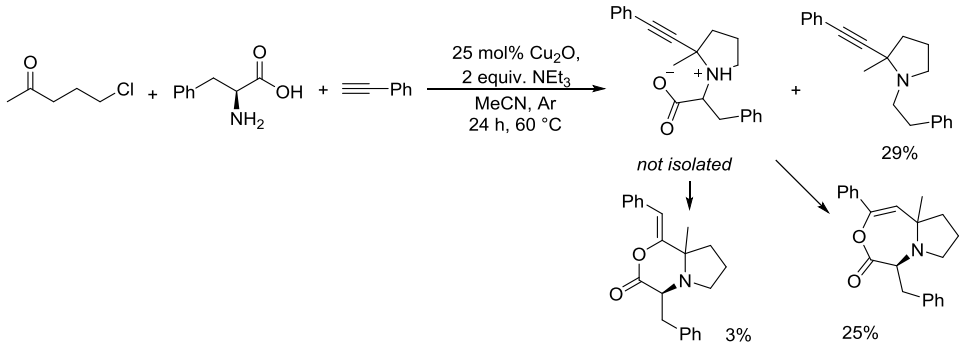
Scheme 6-3 Addition of chiral ligands to control the stereocenter in molecules **7**.

Furthermore, the substrate scope of the ketone component could be further exploited, as this scope was mostly limited to the use of commercially available ketones. It would be interesting to expand this scope to the use of more functionalized ketones.
Although the KA² reaction only generates one equivalent of water and one equivalent of hydrochloric acid as waste products, it would be useful to evaluate the reactivity of ω-ene or -yne ketones **8**, as no hydrochloric acid would be formed from the intramolecular hydroamination in a 5-*exo-trig* or 6-*endo-trig* cyclization instead of intramolecular substitution (Scheme 6-4).



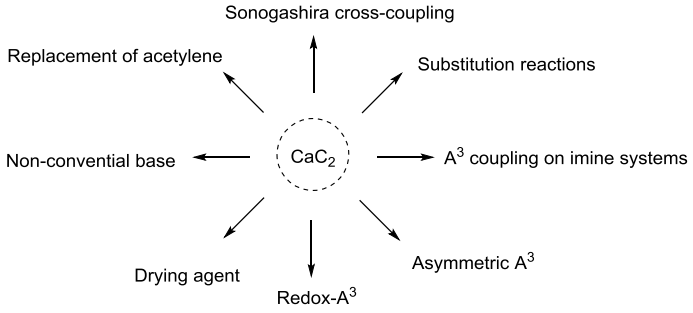
Scheme 6-4 ω-Ene or –yne ketones could undergo similar KA² reactions, thereby avoiding the formation of hydrochloric acid as side-product.

In the special case where amino acids are used as coupling partners, different reaction products were obtained (Scheme 6-5). It would be very interesting if amino acids could be used as coupling partners, as this coupling could have applications in peptide synthesis. The formed propargyl amino acids could be excellent substrates for high-yielding alkyne-azide click reactions, which are very popular in peptide synthesis. For the KA² coupling to produce selectively one product, the reaction probably needs to be re-optimized.



Scheme 6-5 KA² coupling using amino acids.

In chapter four calcium carbide was used as acetylene source in KA² couplings. As calcium carbide is only recently receiving more attention in organic chemistry, its application still has to be evaluated in many different reactions (Scheme 6-6). For example, all A³ reactions developed with terminal alkynes could be expanded when calcium carbide is used. So far, addition of calcium carbide mediated by a transition metal is limited to iminium systems. Expansion to imine systems would be very interesting and our preliminary results in §4.3.3 show that this should be possible.

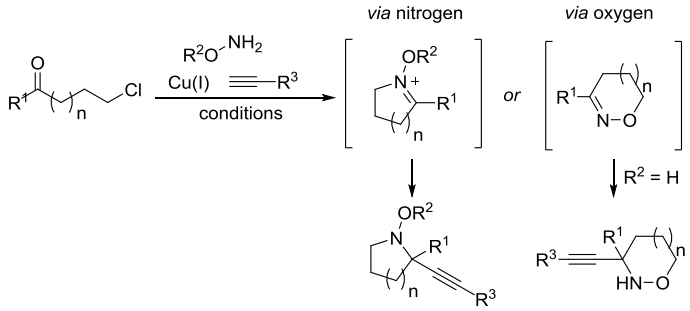


Scheme 6-6 Possible reactions involving calcium carbide.

Moreover, calcium carbide should be evaluated in all reactions were acetylene is used. Calcium carbide could possess interesting properties as irreversible and cheap drying agent because it is known for its quick hydrolysis. We also experienced that calcium carbide can act as a (strong) base, so it might be used as non-conventional base. Together with its basic properties, its nucleophilic properties could be further evaluated in different reactions next to the Sonogashira reaction of aliphatic halides as was the subject of §4.3.4 (*e.g.* substitution).

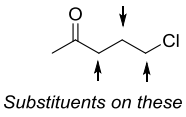
In chapter five, hydrazines were used as alternative coupling partners for amines in KA² couplings with ω-chlorinated ketones and alkynes. A logical expansion would be to use

hydroxylamines and generate *in situ* oximes, depending on intramolecular substitution with oxygen or nitrogen, different products could be obtained (Scheme 6-7).



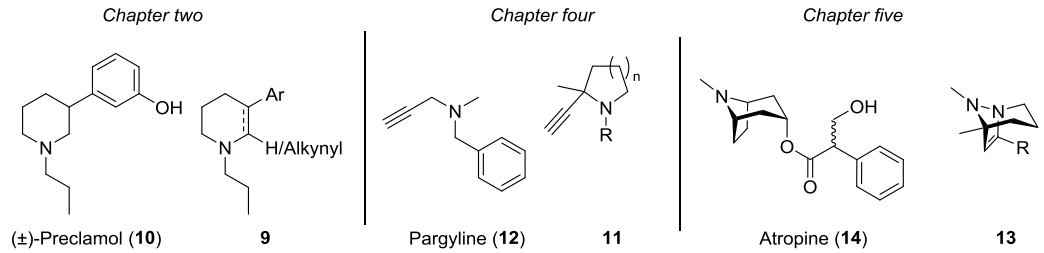
Scheme 6-7 Replacement of the amine component in KA² couplings with hydroxylamines.

The scope of ω-chlorinated ketones is very narrow, but could possibly be extended by using 3-, 4- or 5-substituted 5-chloropentan-2-ones (Scheme 6-8). Furthermore, the reactivity of 6,7-dihydro-1-azatropanes should be further exploited in order to fully understand the behavior of these substrates.



Scheme 6-8 Placing substituents on position 3,4 or 5 of 5-chloropentan-2-one.

Lastly, some of the synthesized molecules in this thesis closely resemble known pharmaceuticals (Scheme 6-9). For example a number of 3-subsituted piperidines **9**, as synthesized in chapter two are closely related to (±)-Preclamol (**10**) and could thus exhibit similar antipsychotic effects. The terminal alkynes **11** synthesized in chapter four could possess similar properties as Monoamine Oxidase B (MAO-B) inhibitors such as pargyline (**12**). As an advantage the molecule is held in a specific conformation as a result of its cyclic structure, which could lead to enhanced properties if the orientation of pharmacophores is right. The synthesized 1-azatropanes **13** from chapter five are aza-analogues of tropane alkaloids such as atropine (**14**) and could have similar anticholinergic properties. Molecules **9**, **11** and **13** could be tested for similar biological activity as their lookalike drugs **10**, **12** and **14** or might be used in broad-spectrum screening for biological activity. However, these screenings were not subject of this thesis.



Scheme 6-9 Synthesized molecules **9**, **11**, **13** could possess biological activity.