Ivar Skogvik

Bachelor's thesis

How are popragylamines synthesised, how has the synthesis become greener and what are they used for?

KJ2900 - Bachelor project in chemistry

April 2023

NTNU
Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

NTNU
Norwegian University of
Science and Technology

Bachelor's thesis

2023

NTNU
Norwegian University of
Science and Technology

Ivar Skogvik

How are popragylamines synthesised, how has the synthesis become greener and what are they used for?

KJ2900 - Bachelor project in chemistry

Bachelor's thesis
April 2023

NTNU
Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

NTNU
Norwegian University of
Science and Technology

Contents

1 Abstract **1**

2 Introduction **2**
2.1 Propargylamines . . . 2
2.2 Green chemistry . . . 3

3 Synthesis of propargylamines **4**
3.1 Overview . . . 4
3.2 Substitution on propargylic structures . . . 4
3.2.1 Enantioselectivity . . . 5
3.3 Aminolysis of allenens . . . 5
3.4 Nucleophilic addition of alkyne to imines . . . 6
3.4.1 Nucleophilic addition of deprotonated alkynes . . . 6
3.4.2 Oxidation of amine to iminium ion . . . 6
3.4.3 Carbonyl amine activation . . . 7
3.4.4 Amine activation with dihaloalkanes . . . 9

4 Use of propargylamines **10**
4.1 Overview . . . 10
4.2 Propargylamines as precursour to allenes . . . 10
4.3 Propargylamines to heterocycles . . . 10
4.4 Propargylamines as bioactive compounds . . . 11

5 Evaluation of the synthesis and use of propargylamine **12**
5.1 Synthesis . . . 12
5.1.1 Criteria . . . 12
5.1.2 Substitution of propargylic structures . . . 12
5.1.3 Aminolysis of allenens . . . 12
5.1.4 Nucleophilic addition of deprotonated alkynes . . . 12
5.1.5 Oxidation of amine to iminium ion . . . 13
5.1.6 Carbonyl amine activation . . . 13
5.1.7 Amine activation with dihaloalkanes . . . 13
5.2 Use of propargylamines . . . 14
5.2.1 Synthesis from propargylamines . . . 14
5.2.2 Bioactive potential . . . 14

6 Conclusion **15**

1 Abstract

Different ways of synthesising propargylamines have been analysed and a general time line of the improvement given. Generally there are two main ways of synthesising propargylamines, first is by substitution with an amine, second is the addition between the terminal end of an alkyne and an imine. The substitution reactions are useful in cases where one wishes to maintain the terminal end of the alkyne. However it produces more waste than the alkyne imine addition. These reactions have a high atom economy, but require some sort of activation since the reaction is weak. This activation has been improved from using strong bases and oxidizers to using the reaction between an amine and carbonyl to create an iminium cation that can react. Some examples of uses of propargylamines have also been given. Their use as bioactive compounds effecting age illnesses, as precursors to chiral allenen structures and heterocycles have been briefly discussed.

2 Introduction

2.1 Propargylamines

Propargyls is a functional group in organic chemistry. It can be described as a propyn connected to the structure where it is connected via the end without the alkyne. [1] (Figure: 1) If this propargyl is bound to an amine group it is classified as a propargylamine. [1] This functional group has a wide variety of uses. It can be used in reactions and as products, therefore alot research has been put into the use and synthesis of propargylamines. [1] [2] [3] The reason is the combined abilities of alkynes to be used as an electrophilic substrate and nucleophilie. [1] Combined with the amines ability to act as a nucleophile in certain conditions. [1] Going forwards the three carbons from the simple 2-propynylamine will be named and used to explain reactions. The carbon marked 1 will be referred to as C1 when discussing potential reaction mechanisms. The carbon marked 2 is an internal end, where the end of an alkyne is connected to another carbon. Finally the carbon marked 3 is a terminal end where the alkyne is connected to a hydrogen.

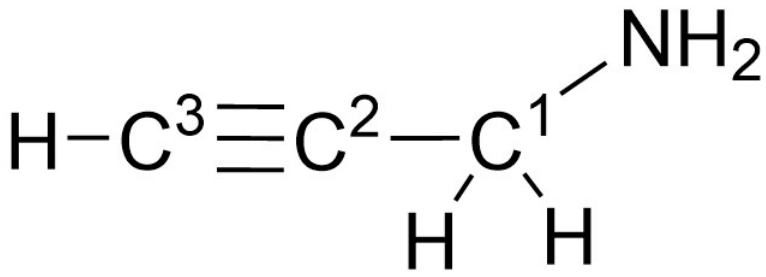

Figure 1: This is the simplest structure for a propargylamine with the IUPAC name 2-Propyn-1-amine.

Propargylamines can be used to make hetero cyclical compounds that can be aromatic.(Figure:2) [2] An example of an aromatic structure that can be created from propargylamines are pyridine structures. [2] Pyridine structures are a part of different bioactive compounds one example of a this is 2-(methyldithio)pyridine-N-oxide which has anti-bacetrial properties. [4] Pyridine structures like this are easily created by reacting a propargyl with a ketone and a catalyst in mild conditions. [5] Besides being a useful reactant they can also be a useful product by themselves, as some have been studied as a treatment for alzheimer's disease. [6] Since propargylamines can have varying substituents they can used to create many different chemicals, some of which will have valuable bioactive properties. [6] [4] Because of the wide range of applications for different propargylamines the study of improving the synthesis of these compounds is a valuable thing. Since it will be applicable for a large field synthesises. By studying how a synthesis has been improved via certain criterias, one may evaluate the current synthesis methods in order to find the one that is most applicable for the desired end product and environmental effects.

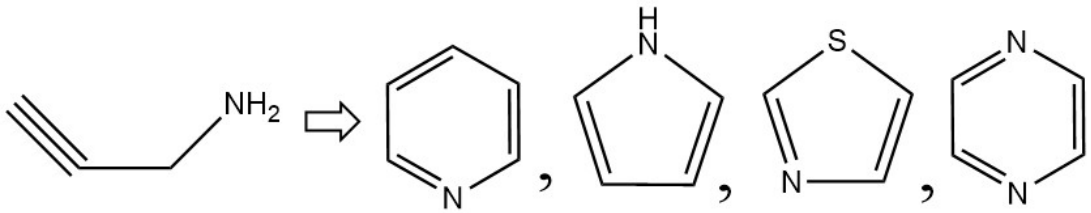

Figure 2: Illustration of some of the heterocyclic compounds that be achieved with the use of propargylamines. The respective structures are: pyridine, pyrrole, thiazole and pyrazine [2]

2.2 Green chemistry

What kinds of of criteria do we judge chemical synthesis based on? For instance the principals of green chemistry. Which is the design of chemicals and synthesises routes that seek to reduce or eliminate hazardous chemicals. In order to improve chemical reactions in accordance to green chemistry a set of principles are used, in order to judge and improve chemical synthesis. These principles focus on the environmental, health and efficiency of the synthesis. It takes into account all parts of the synthesis including reactants, solvent, byproducts, lifetime and disposal of products after their use. In order to evaluate a synthesis 12 principles of green chemistry are generally used. These 12 points were designed by Paul Anastas and John C. Warner in order to help understanding what green chemistry means. [7]

The first point in green chemistry is to **prevent waste**. It is important to prevent waste as much as possible during chemical synthesises since it will decrease the amount of cost and resources used in the synthesis. Waste also has to be treated properly in order to reduce the harm it has on the local and global environment. A good way of preventing waste is by **reducing amount of solvent** used in chemical synthesis. This can be done by using less solvent, by running the synthesis in dry conditions if possible or by running it in a "neat condition" where there are no mediums or solvents besides the reactants themselves. [8] Closely related to preventing waste, the second point is to **maximize the atom economy** which is about maximizing the amount of atoms that go into the final product. When designing chemical synthesis it is therefore important to **avoid chemical derivatives**. This is because not all reactions will convert 100%, thus each reaction that is run will decrease the amount of product created. This decreases the yield at the end. It may also make reactions more complicated to run, since they require more steps. To get the reactions to give the maximum possible amount of the desired product it is important to use **catalysts** instead of stoichiometric. This is due to when forcing the reaction through stoichometric means, it increases the chemicals used and therefore increases waste. Catalysts are also important to increase **energy efficiency** since some chemical reactions require high temperatures, for instance between 100-200^oC, and have to be run for an extended period of time. Then it will require sufficient heating for the reaction to continue, increasing energy cost. [7]

It is not only important to think of the efficiency of the chemical synthesises, but also the safety and effects on the environment. It is therefore important to try to use **safer chemicals** for the environment and the people doing the synthesis. For long term safety one must use **degradable products** so they do not gather up in the environment and people. To make sure that people and the environment are not being harmed, one should **analyze continuously** so that one can monitor the effects and nothing unexpected goes undetected. [7]

With the principles of green chemistry the different synthesis methods for propargylamines will be evaluated to see how they have been improved, what problems they have, the use of propargylamines in further synthesis and as a product in themselves.

3 Synthesis of propargylamines

3.1 Overview

There are multiple ways of creating propargylamines.[1] One of the simplest way is by substituting an existing functional group with an amine, but that requires to have a propargyl structure first. These reactions go back to atleast 1994.[9] It has also been reported that propargylamine structures can be achieved by aminolysing a bromoallene with an amine dating back to 1991.[10] Instead of going through the process of requiring one of these structures, a more direct synthesis of propargylamines has been developed. The main idea behind these methods is the nucleophilic addition of the terminal end of an alkyne to the carbon in an imine group.[1][11][12] Due to poor nucleophilicity of the terminal alkyne and poor electrophilicty of the imine, the reaction requires activation. This can be done by either activating the alkyne or imine. Along with the activation it is required to use a catalyst for the reaction to give high yields.[1] The first of these methods is addition on an imine with a alkyne that has been deprotonated with a strong base.[13] Dating back to at least 1998[14]. The second is oxidation of an amine to an iminium cation that reacts on the terminal end of an alkyne.[11]The third is a by creating an iminium cation by reacting an amine and carbonyl together. The iminium can then react with the terminal alkyne.[15][16] The last method that will be discussed is by activating the amine with dihaloalkanes.[17][18][19] These final methods generally can be dated after the 2000s.[20] Although it is difficult to point at exact years for the use and or discovery of the reactions it gives a general idea of the development.

3.2 Substitution on propargylic structures

The most general way of synthesising structurally simple propargylamines[1] is by alkylating the amine into a propargylamine.[9][21] This can done via substitution on a propargylic halide[1], ester, acetate[9] among other groups.[1]. Such reactions have been done in different conditions such as having a temperature between 25-60^oC[9][22], using catalysts such as copper iodide,[9]nickel with a different ligands[22] in solvents such as methanol[9][12] or tert-amyl alcohol[22]. These reactions are usually done with a hydrogen on the terminal end, but can also be done with two internal end where one is an aryl group in certain conditions.[22]

The proposed reaction mechanisms varies between reactions[22][9][12], but in general the catalysts binds to the triple bond enabling the substituted group to leave the structure and creates a carbocation that is in resonance with an allene structure.[9][22][21][12] This carbocation is an electrophilic center which an amine can perform a nucleophilic attack on and create the final propargylamine.[9][21]These intermediates may be different. One example is as suggested by Watanabe et al(Figure: 3)[22] shows that the allene state is in equilibrium with the carbo cation allowing free rotation between the C1 and C2. This allowed them to reach an enatiomeric excess (ee) between 79-97%.

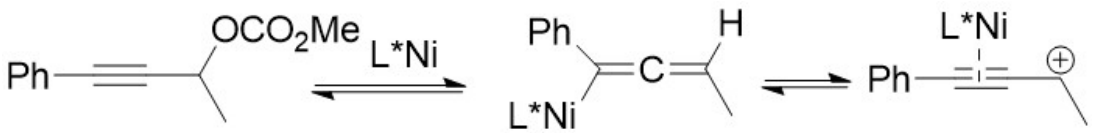

Figure 3: Shows the suggested intermediate states for the substitution reaction on propargylic carbonates. Adapted from the work of Watanabe et al[22]

It is also possible to do a substitution with a carbonyl group.[23] This way is mechanically different. It is based on the creation of an iminium cation. By the addition of amines to a carbonyl. Wherethe amine will perform a nucleophilic attack on the carbonyl group and force out water in acidic conditions.[24] This creates a propargyliminium that can be used for further reactions or reduced down to a propargylamine with hydrogen reduction mediums such as NaCNBH_3.[23] (Figure: 4)

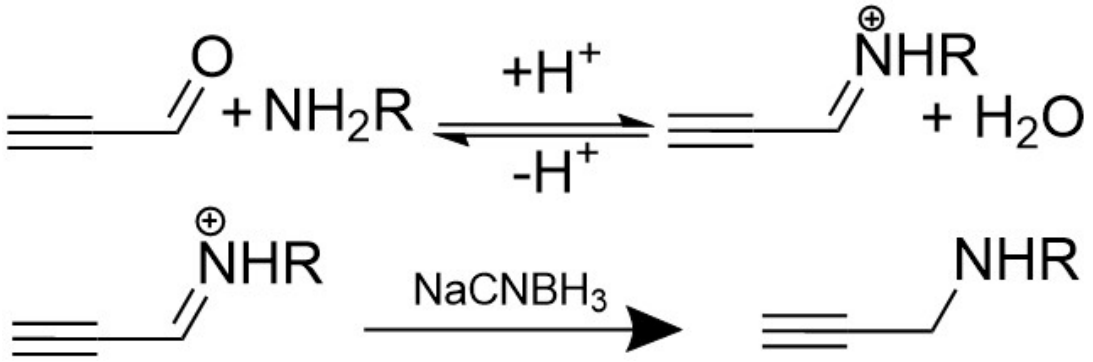

Figure 4: A method of substituting a carbonyl in order to make a propargylamine. Adapted from the work of Lauder et al [1] and Erkkilä et al [24]

3.2.1 Enantioselectivity

In certain cases a chiral center can be created on the C1 carbon and only one of the stereoisomers is desired. The work from Detz et al [12] report of the catalysed reaction of different propargylamines with a copper catalyst with organic ligands. [12] These reactions have given yields of 27-90% and an ee of 13-87% when substituting poprargylacetates. [12] Other metal catalysts such as nickel with ligands as reported by Watanabe et al [22] have been used in the amination of esters gving high ee in the range 79-95%. The yields of the reaction depend on the different propargylesters used in the reaction. [22] Alternatively to using metal-catalyst that can be toxic [25] one can use biocatalysts to create enantiomerically pure propargylamines. [1] [26] [27] One way as reported by Schmidt et al [26] by doing a synthesis with different ω-transaminases giving R or S configuration when [26] with ee of >99% with yields between 33-65%. Doing this requires different conditions than the metal catalysts pathways. [26] Instead of doing the synthesis with an enzyme, Messina et al [27] started by first creating the racemic mixture of R and S then converting it into either a pure R or S [27]. This method has been reported to have ee in the range of 22-98%. [27] It is important to note that the conversion is not universal and may vary between molecules. [1]

3.3 Aminolysis of allenens

As the synthesis of propargylamines is suspected to go via an allene intermediate [9] [22](Figure: 3) The synthesis of propargylamines via allene have been shown to be possible. [10] From the work of Caporusso et al [10] they reported the synthesis of propargylamine from a bromoallene and amine. [10] (Figure: 5) They did this synthesis by reacting the bromoallene and amine in acenonitrill catalysed with copper bromide. [10] They achieved yields of 26-99% in the synthesis of different propargylamines. [10] This synthesis is not well studied, but the opposite reaction of turning propargylamine into allenes is well documented [1] [28] [3]

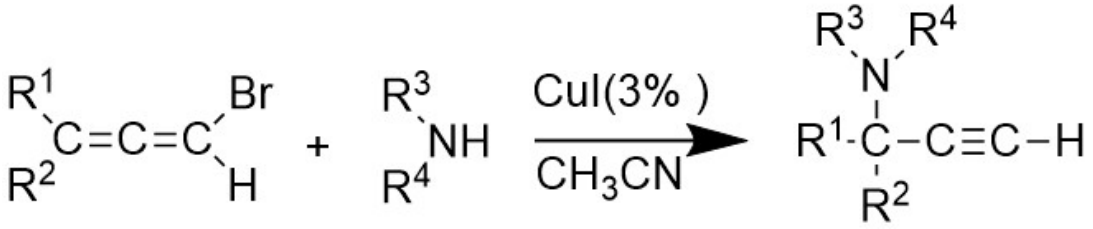

Figure 5: A reaction scheme for the synthesis of propargylamines from aminolysis of bromoallenes. Adapted from the work of Caporusso et al [10]

3.4 Nucleophilic addition of alkyne to imines

Due to alkyne's terminal hydrogen being slightly acidic, gives it an ability to act as a nucleophile when activated with a catalyst.[29] Combining this with an imine that can act as an electrophile,[24] it is possible to perform addition between these two groups in order to form a propargylamine. However due to low nucleophilicty of the alkyne and low electrophilicty of the imine the reactions needs activation to occur.[1] The activation of the alkyne or imine can be done in multiple ways.[1] [3]However even after the activation of these groups, reactions often still require a catalyst to run properly.[1]

3.4.1 Nucleophilic addition of deprotonated alkynes

Due to the slight acidity of the hydrogen on the terminal end of the alkyne it is possible to deprotonate it with a base making it a good nucleophile.[13] Then it can react with the carbon of an imine in order to create a propargylamine. Due to the acidity being between 20-24 pka, strong bases such as Lithium diisopropylamide (LDA) must be used.[1] Such reactions are usually run at low temperatures, usually -78^oC in aprotic solvents with an inert atmosphere. In order to make sure that the strong base only deprotonates the terminal hydrogen and does not react violently.[1] [13] [14]

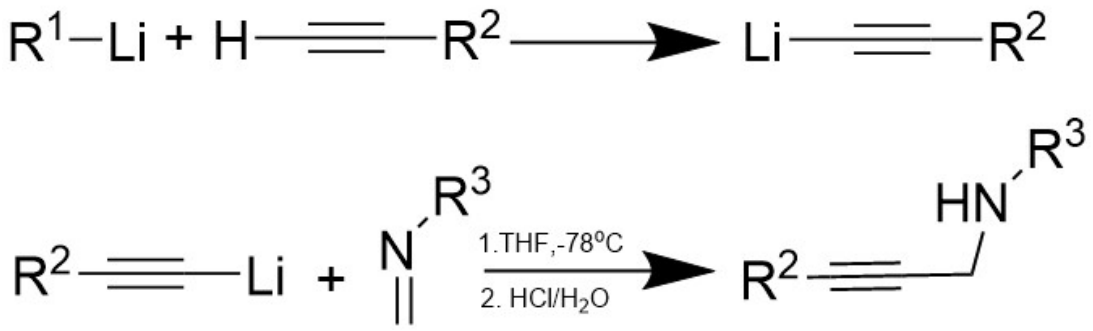

Figure 6: Shows a generalized reaction scheme for the addition of deprotonated alkynes to imines. Adapted from the work of Lauder et al[1] and Osipov et al[13]

3.4.2 Oxidation of amine to iminium ion

Instead of activating the alkyne with a strong base it is possible to do an oxidative dehydrogenation of an amine to an iminium cation.(Figure: 7)[30] [11] Thus making it a better electrophile. Then it can react with the alkyne that has been activated with a catalyst.[30] This reaction scheme is sometimes referred to as oxidative coupling.[11] [30] The oxidation of the amine can be achieved with for example with ter-butyl hydroperoxide.[30] Some reactions that have been run this way have given yields of 55-81%.[30]

Since these oxidizers may react with other functional groups, Xu et al[11] have done research looking into the use of N-oxides that can be activated, and turn into an iminium ion without an external oxidant.[11] These reactions have moderate to good yields between 53-93%.[11] With reactions times of 1-5 hours[11]

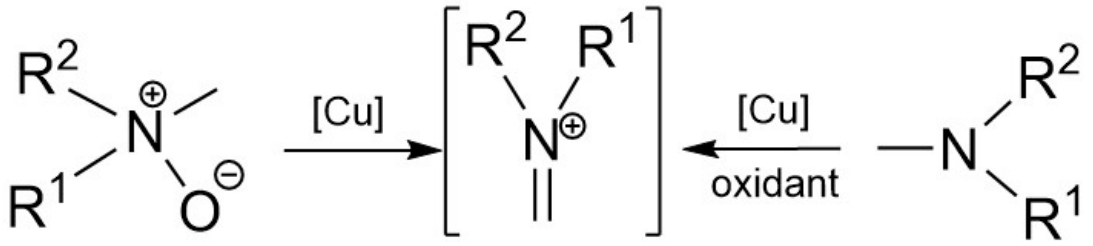

Figure 7: Shows ways of creating a iminium ion via oxidation of amine. The figure is adapted from the work of Xu et al.[11]

3.4.3 Carbonyl amine activation

Another way of turning an amine into an iminium cation, is by letting it react with a carbonyl.(Figure: 8)[24] The amine will perform a nucleophilic attack on the carbonyl and initiate a equilibrium with the iminium cation created from the carbonyl and amine.[24] Then the reaction can be performed in the same way as when an imine has been oxidized to an imium cation. This reaction scheme is sometimes referred to as Aldehyde-alkyne-amine coupling shortened to A^3-coupling[15][1][31] or Ketone-alkyne-amine shortened to KA^2-coupling.[15][1] This method of creating a propargylamine between an alkyne and amine has had alot of research put into it developing different methods[1] that can be run in a variety of conditions such as metal-free[16], microwave assisted synthesis,[31] solvent free conditions.[32] It is usually run at temperatures above 80^oC, but can be run at room temperature if the alkyne has a carboxylic acid group at the terminal end, and is mixed a boronic acid with copper iron oxide as a catalyst.[33] There has been alot of resarch in different ways of catalysing the reaction such as using, gold[20], magnesium[15], copper[34] among lots of other possible catalysts.[35]

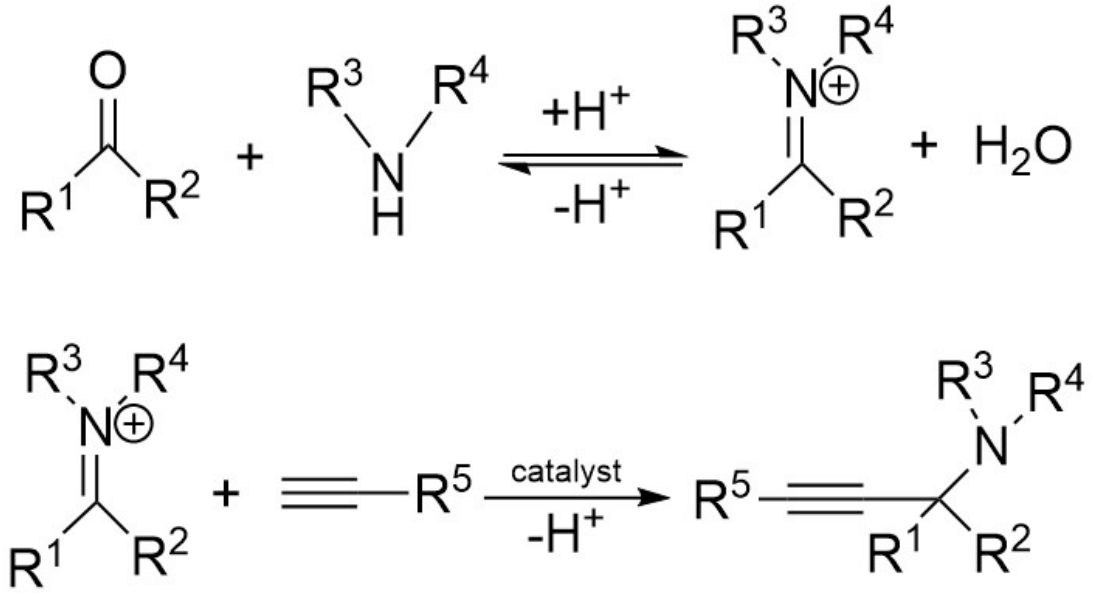

Figure 8: A reaction scheme for the synthesis of propargylamines via activating an amine with a carbonyl. Adapted from the work of

In order to run A^3-coupling metal free it is required to either use an organic or silica[16]based catalyst. It can also be done by having some other driving force that can facilitate the reaction.[16] Examples of catalysts can be a silica based nano colloidal particles.[16] An example of a reaction that can be run without a catalyst is in the case of alkynes with an acid group at the terminal end.(Figure: 9)[16] In such cases the acid can help the transformation of amine and

carbonyls into an iminium ion that then can be added on the alkynes terminal end and create a carbocation on the internal end.[16] The final step will be the splitting of the deprotonated carboxyl group going out as CO_2 and recreating the triple bond.[16] Another way without catalyst is by using salicylaldehyde as the carbonyl which can be used in A^3-coupling without a catalyst.[16]

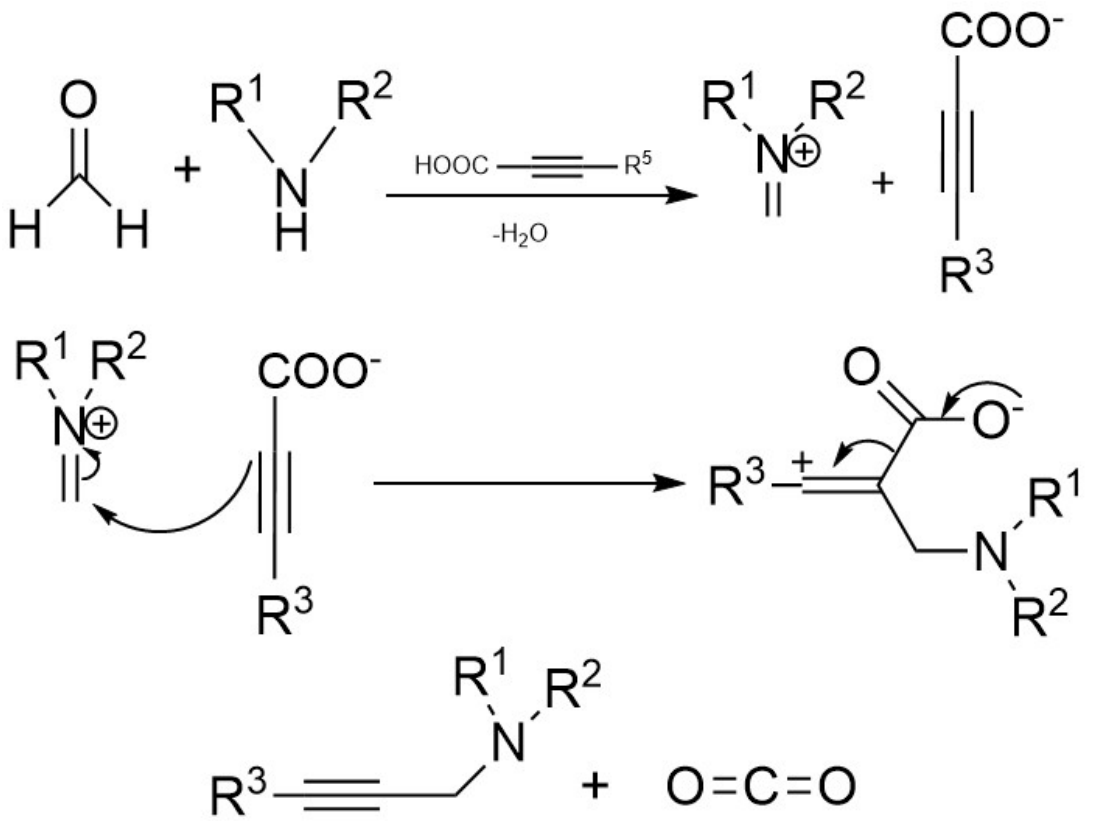

Figure 9: Shows the reaction mechanism between an amine, aldehyde and alkyne with a carboxylic acid group. Adapted from Ghosh and Biswas[16]

Along side other studies on using microwaves as an assistant in synthesis in organic chemistry[36] there has been research on it for the synthesis of propargylamines via the A^3-coupling reaction.[31]The main idea behind the use of microwaves in organic synthesis is the even spread of energy added to the system. The main draws of using microwaves are the reduced reaction time down to 15-30 minutes[31] compared to the hours[1] it takes for other reactions. Higher selectivity for certain reactions[36] and higher reproducibility.[36] Different heterogneneous copper catalysts with different supporting materials[31][37] have been used to create synthesises that have high yields of generally between 75-98%.[31][37]

The solvent free synthesis of propargylamines are done in neat conditions where the only liquids in the reaction mixture are the reactants and products themselves. Example of reactants that are liquids in A^3-coupling are benzaldehyde and formaldehyde which are liquids at standard conditions.[32] Solvent free reactions have usually the same requirements as A^3-coupling, requiring 80^oC and a catalyst to run well.[32]

3.4.4 Amine activation with dihaloalkanes

It is possible to create a propargylamine by using a dihaloalkanes to activate either the alkyne[18] [17] with a metal catalyst(Figure: 10)[17] or by activation of the amine group[18] which can be done without a metal catalyst.[18] Examples of dihaloalkanes that can be used to perform these reactions are dihalomethanes[18] and benzal halides.[19] In this reaction hydrogenhalides will be produced as a byproduct.[18] [19] These reactions have moderate to high yields of 50%-95%.[18] [19]

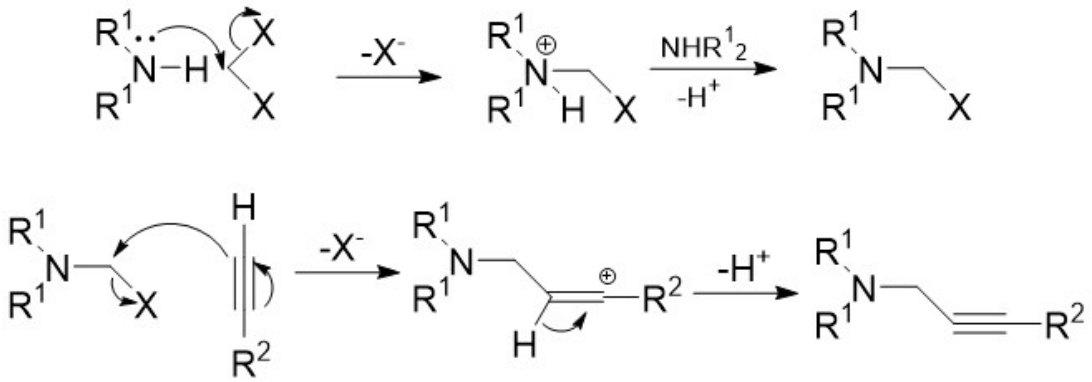

Figure 10: Shows how a dihalomethane can activate an amine such that it can be added on the terminal end of an alkyne. Adapted from Ghosh and Biswas[16]

4 Use of propargylamines

4.1 Overview

Molecules with propargylamine structures can serve as a good precursor to a wide range nitrogen containing heterocycles and chiral allenes with different substituents. [28] [2] Some reactions from propargylamines may require harsh condition, but may still be valuable if the reactions give good results. [28] Propargylamines may have more uses in synthesis than for heterocycles and allenes, but only these uses will be highlighted. Other than to be used in further synthesis propargylamines also have been shown to have medicinal benefits against some age related illnesses. [6] [38] [39] Bioactive propargylamines often maintain a terminal end with a hydrogen. [6] [38] [39]

4.2 Propargylamines as precursour to allenes

It is possible to use propargylamines as a pathway to create an allene structure where two double bonds are connected. These structures have the ability to be chiral and are also an important building block for bioactive compounds. [40] The synthesis of allenes can be difficult requiring high temperatures and complex structures. [28] In the synthesis reported by Periasamy et al [28], they created a propargylamine with 2-benzyl morpholine or N-methyl camphanyl piperazine. This propargylamine was then turned into into an allene by heating it to 120^oC in toulen with 50mol% $ZnBr_2$. [28] The yield of the propargylamine was between 23-89% and the conversion to an allene was between 71-89% with ee up to 99%. [28]

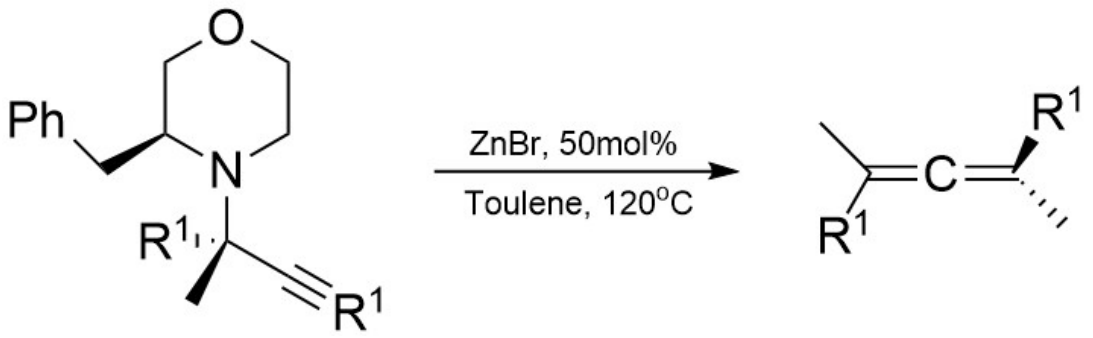

Figure 11: Shows the synthesis of a chiral allene from a propargylamine. This reaction have been run with yields between 71-89% with enatiomeric excess of up to 99% as reported by Periasamy et al [28]

4.3 Propargylamines to heterocycles

Propargylamines are useful for creating a wide range of heterocyclic compounds. [2] Since heterocyclic compounds are useful in many fields such as drugs, pigments, antibiotics and in vitamins. [2] Some specific examples of creating compounds containing heterocycles such as pyridine, pyrazine and pyrroles are given from the work of Budi et al. [2]

The first example is the synthesis of dihydropyridine derivatete.(Figure: 12) This can be done with a combination of a proaprgylamine/ester with a propargylester to form dihydropyridine derivatives by reacting them with a gold catalyst at 80^oC in dichloroethane triethylamine. [2]

The second example is the synthesis of pyrazine rings with different substitutions.(Figure: 13) This can be achieved from an unsubtituted propargylamine by mixing a propargylamine with an aldehyde creating a tetrasubstiuted pyrazine ring structure. [2] This reaction was run in the presence of 5 mol% gold catalyst in dicloroethane with 5 equivelents of water at room temperature yielding between 56-95% depending on the the type of aldehyde used. [2]

One final example is the synthesis of tetrasubstitued pyrroles.(Figure: 14) This synthesis requires a propargylamine and imine which react in the presence of LiHMDS or PMDTA in THF

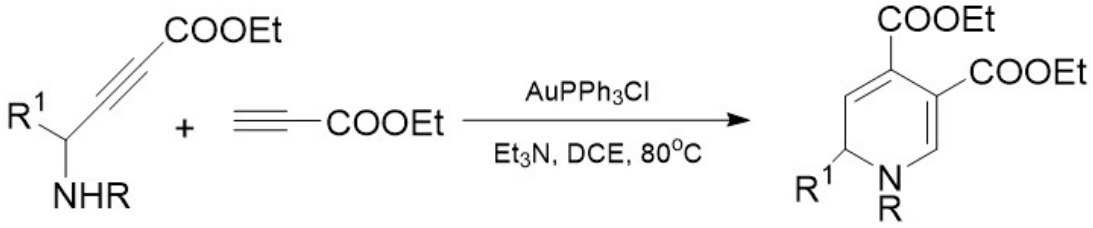

Figure 12: Shows a synthesis of a pyridine structure with multiple substituents by reacting two propargylic structures together. Adapted from the work of Budi et al [2]

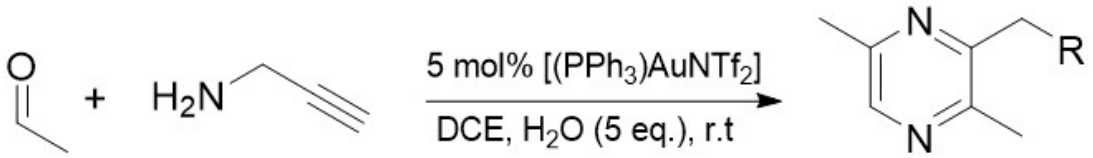

Figure 13: Shows a synthesis of a pyrazine structure with multiple substituents by reacting a propargylamine and aldehyde together. Adapted from the work of Budi et al [2]

at -78^oC for 10 hours, then at room temperature for 1 hour. Giving yields between 50-86% depending on the reactants used. [2]

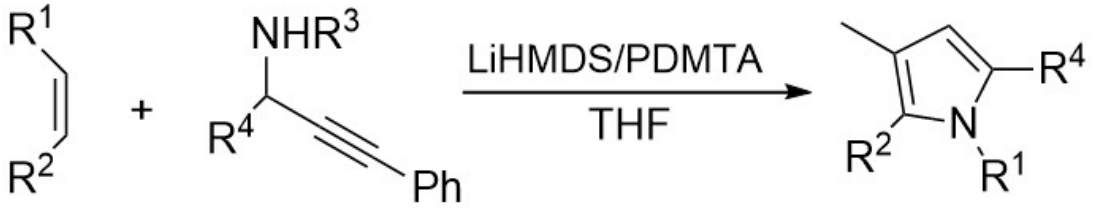

Figure 14: Shows a synthesis of a pyrrole structure with multiple substituents by reacting a propargylamine and aldehyde together. Adapted from the work of Budi et al [2]

4.4 Propargylamines as bioactive compounds

Some propargylamines have beneficial bioactive abilities that have been tested on humans to help prevent or mitigate certain diseases such as parkinsos and alzheimers. [6] Some of the compounds that have been tested as preventative medicine for parkinsons or alzheimers are selegiline, pargyline and rasagiline. [39] [38] In study from Carreiras et al [6] from 2020, they studied the potential of different propargylamines and they report that they could be: "[...]acting as inhibitors of both cholinesterases and monoamine oxidases, they show improvement of cognitive impairment, antioxidant activities, [...] ". [6]

5 Evaluation of the synthesis and use of propargylamine

5.1 Synthesis

5.1.1 Criteria

How well do these different synthesises for the proaprgylamines comply with the ideals of green chemistry? As analyzing the feed stocks for the synthesis of different propargylamines is extensive and other points such as analyzing continuously depends on the chemists doing the synthesis, the analysis will be focused on the waste, atom economy, energy efficiency and the chemical hazards of doing the synthesising of propargylamines in the methods previously described.

5.1.2 Substitution of propargylic structures

In these types of reactions, one first needs to get a propargyl with a good leaving group. In order to run the reaction. Since this is the case, creating it will increase the total waste during the synthesis. This is because waste is produced for making the start material and some part of the molecule is splitted of. On the other hand, the conversion from the propargyl to propargylamine can be done in mild conditions. Such that it is not too much of a hazard and being run at slightly higher temperatures than room temperature makes it relatively energy efficient. Despite being wasteful, this way of synthesising propargylamines will still be a valuable. Since other methods mostly rely on reacting the terminal end of an alkyne with an imine. This means that the end product can not have a terminal alkyne end. Unless the alkyne has two terminal ends which only acetylene has, which is a gas at standard conditions and may be difficult to work with and get to react. So substitution of functional groups to make propargylamines is a method that should be utilized when it is desired to maintain the terminal end of an alkyne, but it produces more waste products. As there are many different studies on such reactions it can be assumed that the idea behind it is a valid idea, however validity of individual studies should always be questioned.

5.1.3 Aminolysis of allenens

The aminolysis of bromoallenes may serve as another way of creating propargylamines with a terminal end, but due to it not being well researched by the fact it is not included in different reviews of propargylamine synthesis [1] [3] and the inverse reaction of propargylamine to allene seemingly being a more useful reaction strategy. This synthesis may be useful, but it is not well documented.

5.1.4 Nucleophilic addition of deprotonated alkynes

This method is theoretically very simple, but it uses very strong bases that needs to be handled carefully and in a isolated environment. A problem with creating propargylamines in this way is that it is limited to less complex molecules. For instance if the amine functional group is in a larger molecule that has another acidic proton such as in $\alpha - position$ to a carbonyl group. The deprotonated terminal alkyne might deprotonate it or be added on the carbonyl carbon. In addition, depending on the base used, for instance LDA, the protonated base must be removed from the final product, thus creating waste. Generally another method should be preferred to avoid the use of strong base, but in cases where reactivity is low it might serve as a useful alternative.

5.1.5 Oxidation of amine to iminium ion

The oxidation of amines to iminium ions as a way of activating them for reactions with the terminal end of a alkyne. It has the same problems as the deprotonation of the alkyne. The oxidation mediums must be used with care and may react with other functional groups in larger and more complicated molecules, but the research from Xu et al [11] may serve as a way of getting around this. Where the N-oxide is created in the larger structure and then can be activated without and external oxidizer avoiding the oxidation of other functional groups. Still, this method requires another chemical that is not incorporated into the final structure increasing the total waste while being dangerous for the person doing the synthesis. There are multiple reports talking about the oxidation of amines so the idea appears to be good, but the suggested methods from Xu et al may require more research.

5.1.6 Carbonyl amine activation

By far one of the most promising ways of synthesising different propargylamines. This method can be performed in mild conditions and does not suffer from the fact that other hydrogens can be deprotonated instead of the one on the terminal alkynes, or another functional group getting oxidized. This method can be used to have different substituents on the amine, C1 carbon or the end of the alkyne. The reactivity and yields of the reaction have been shown to result in good yields. When such reactions are run in neat conditions the atom economy is high while the only byproduct created in the synthesis is water. Many different ways of running such reactions have been reported so the idea behind the reaction appears to be good and trustworthy, but individual reports should be looked at critically.

The different sub sections such as metal free synthesis and microwave synthesis are currently being studied and improved. The metal- and catalyst-free synthesis that were highlighted, require an acid group connected to the alkyne which may prove difficult to make. Such that this reaction may only be reserved for synthesises where metal free conditions are vital. Something that might be a problem with activating amine with carbonyl is that the synthesis may be sterically hindered. In cases where the carbonyl and amine are integrated in large molecules. This fact may also be used in further study of these reactions in order to have a carbonyl or amine with steric hindrance that may increase selectivity for certain synthesises.

In terms of future improvements it will be to the catalysts in order to reduce the temperature needed for the reaction to run while decreasing reaction time. Microwave synthesis may prove to be a good way of reducing the reaction time, although it requires special equipment and the validity may be questioned. Since microwave assisted synthesis have been controversial [41], but since it has been continuously studied for years. It can be thought that the studies are trustworthy. Although one should always question the validity of individual reports. Alternatively to further improvements to microwave synthesis some new discovery might outshine this reaction technique with respect temperature and time.

5.1.7 Amine activation with dihaloalkanes

Amine activation can serve as a metal free way of synthesising propargylamines. A large problem with the reaction is the use of dihaloalkanes such as dicloromethane. Which have been know to be toxic for animals and people for a long time. [25] The reaction would also produce hydrogen chloride which is a strong acid that needs to be removed from the final product. As it can be a problem for other reaction and is not desired to have in high concentrations in potential medicine. It could potentially be easy to remove by washing it with water, given that the product is hydrophobic. Still the problem remains that it uses and creates hazardous chemicals.

5.2 Use of propargylamines

5.2.1 Synthesis from propargylamines

Propargylamines have shown good potential to be used in the synthesis of allenens and different heterocycles while maintaining the ability to react further. The synthesis of allenens from the propargylamines that Periasamy et al [28] created in their synthesis gave good ee and can result in good yields. However this reaction used a significant amount of catalyst at 50mol%. While also splitting of a large part of the starting reactant, making it not so atom economically efficient. It might still be a good reaction compared to alternative methods since it had such a good ee. However such an evaluation is beyond the scope of this text.

Propargylamines have great potential to be used in the synthesis of different heterocycyles. From the examples that have been highlighted from Budi et al [2] one can see that the synthesises have a good atom economy. Incorporating most of the reactants used into the final product, but not 100%. However for two of the synthesis namely the dyhydropyridine (Figure:12) and pyrrole example(Figure:14) are run with a gold ligand bearing catalyst. These catalyst are most likely going to be difficult to manufacture and expensive making this reaction less green.

5.2.2 Bioactive potential

Propargylamines have been shown to have potential as medicine. So there might be more chemicals bearing a propargylamine structure that may act as good bioactive chemicals. As many of the synthesises of propargylamines require metal catalysts. Lots of different metal catalyst have been shown to be toxic to animals. [25] So the problem is that trace amounts of these catalysts may end in the final product, in what is intended to be medicine and may harm the patient taking it. Therefore there has been research into the metal free synthesis of propargylamines. These reactions have their own drawbacks as discussed in the synthesis section.

6 Conclusion

The synthesis of propargylamines can be divided into two main groups. These consist of substitution of another propargylic structure and the addition between an alkyne and imine. These reactions can be run in many different conditions and have their own benefits and drawbacks. When it is important to create a propargylamine that maintains a terminal end, it can be done by substituting a functionalised propargylic structure with an amine. This requires the start propargyl to be synthesised, increasing the total waste, but can be done in mild conditions. A more direct and less wasteful process is the addition between an alkyne and imine, but this reaction uses the terminal end of an alkyne to create a bond. The addition between an alkyne and imine is a weak reaction, therefore requiring some type of activation. This can be done by deprotonating the alkyne or creating an iminium cation. The creation of an iminium cation can be achieved in different ways such as oxidizing an amine or by reacting an amine with a carbonyl. The addition reactions can be run in different conditions such as: solvent free, microwave assisted or metal free in the right conditions. It is also possible to create propargylamines via activating with a dihaloalkyne or by the aminolysis of bromoallene, but these reactions may be situational. So the synthesis of propargylamines has become greener by first creating a more atom efficient synthesis via the addition of an alkyne to an imine. The activation that is required has been made less hazordous by using a carbonyl and amine instead of strong bases or oxidizers. Which also decreases the total waste created from the synthesis, as the parts of the carbonyl will be incorporated into the structure while only producing water as a byproduct.

Propargylamines have good potential for use in the synthesis of different heterocycles and chiral allenens. Being able to give high enatiomeric excess in the synthesis of allenens. Although some of these reactions require either a complex catalyst or large amount of them.

References

[1] Lauder K, Toscani A, Scalacci N, Castagnolo D. Synthesis and Reactivity of Propargylamines in Organic Chemistry. Chem Rev. 2017 12;117:14091-200. Available from: https://pubs.acs.org/doi/abs/10.1021/acs.chemrev.7b00343.

[2] Budi HS, Mustafa YF, Al-Hamdani MM, Surendar A, Ramezani M. Synthesis of heterocycles from propargylamines. Taylor Francis forensic sci ser. 2021;51:3694-716. Available from: https://www.tandfonline.com/doi/abs/10.1080/00397911.2021.2001660.

[3] Sheng X, Chen K. Review Syn thesis Recent Advances in Reactions of Propargylamines. Synthesis. Available from: https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0039-1690684.

[4] O'Donnell G, Poeschl R, Zimhony O, Gunaratnam M, Moreira JBC, Neidle S, et al. Bioactive pyridine-N-oxide disulfides from allium stipitatum. J Nat Prod. 2009 3;72:360-5. Available from: https://pubs.acs.org/doi/full/10.1021/np800572r.

[5] Meng YY, Kang WF, Si XJ, Song YY, Li YJ, Xu F. HKUST-1-Catalyzed Formation of C–C and C-N Bonds: Rapid Assembly of Substituted Pyridines from Propargylamine and Carbonyl Compounds. ChemistrySelect. 2018 8;3:8793-6. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/slct.201801799.

[6] Do M, Carreiras C, Ismaili L, Marco-Contelles J. Propargylamine-derived multitarget directed ligands for Alzheimer's disease therapy. Bioorganic Med Chem Lett. 2020;30:126880. Available from: https://doi.org/10.1016/j.bmcl.2019.126880.

[7] Basics of Green Chemistry | US EPA;. Available from: https://www.epa.gov/greenchemistry/basics-green-chemistry.

[8] Sarkar A, Santra S, Kundu SK, Hajra A, Zyryanov GV, Chupakhin ON, et al. A decade update on solvent and catalyst-free neat organic reactions: a step forward towards sustainability. Green Chem. 2016;18. Available from: https://doi.org/10.1039/C6GC01279E.

[9] Imada Y, Yuasa M, Nakamura I, Murahashi SI. Copper(I)-Catalyzed Amination of Propargyl Esters. Selective Synthesis of Propargylamines, l-Alken-3-ylamines, and (Z)-Allylamines. J. Org. Chem.; 1994. Available from: https://doi.org/10.1021/jo00088a004.

[10] Caporusso AM, Geri R, Polizzi C, Lardicci L. Copper catalyzed aminolysis of bromoallenes as a new efficient route to propargylamines. Tetrahedron Lett. 1991 12;32:7471-2. Available from: https://doi.org/10.1016/0040-4039(91)80138-V.

[11] Xu Z, Yu X, Feng X, Bao M. Propargylamine Synthesis by Copper-Catalyzed Oxidative Coupling of Alkynes and Tertiary Amine N-Oxides. J Org Chem. 2011;76:6901-5. Available from: https://doi.org/10.1021/jo201059h.

[12] Detz R, Delville Miemstra H, vanMaarseveen J. Enantioselective Copper-Catalyzed Propargylic Amination. Angew Chem, Int Ed. 2008 5;47:3777-80. Available from: https://onlinelibrary.wiley.com/doi/10.1002/anie.200705264.

[13] Osipov SN, Golubev AS, Sewald N, Burger K. New efficient syntheses of -difluoromethyl- and -trifluoromethyl-ornithine. Tetrahedron Lett. 1997 8;38:5965-6. Available from: https://doi.org/10.1016/S0040-4039(97)01344-0.

[14] Rodriques KE, Basha A, Summers JB, Brooks DW. Addition of aryllithium compounds to oxime ethers. Tetrahedron Lett. 1988;29:3455-8. Available from: https://doi.org/10.1016/0040-4039(88)85188-8.

[15] Neofotistos SP, Tzouras NV, Pauze M, Gómez-Bengoa E, Vougioukalakis GC. Manganese-Catalyzed Multicomponent Synthesis of Tetrasubstituted Propargylamines: System De-

velopment and Theoretical Study. Adv Synth Catal. 2020. Available from: https://doi.org/10.1002/adsc.202000566.

[16] Ghosh S, Biswas K. Metal-free multicomponent approach for the synthesis of propargylamine: a review. RSC Adv. 2021. Available from: https://doi.org/10.1039/D0RA09392K.

[17] Tang Y, Xiao T, Zhou L. Cobalt-catalyzed alkyne–dihalomethane–amine coupling: an efficient route for propargylamines. Tetrahedron Lett. 2012 11;53:6199-201. Available from: https://doi.org/10.1016/j.tetlet.2012.08.136.

[18] Rawat VS, Bathini T, Govardan S, Sreedhar B. Organic Biomolecular Chemistry Catalyst-free activation of methylene chloride and alkynes by amines in a three-component coupling reaction to synthesize propargylamines †. Org Biomol Chem. 2014;12:6725. Available from: https://doi.org/10.1039/C4OB00986J.

[19] Lin Z, Yu D, Zhang Y. Propargylic amines constructed via copper-catalyzed three-component coupling of terminal alkynes, benzal halides and amines. Tetrahedron Lett. 2011 9;52:4967-70. Available from: https://doi.org/10.1016/j.tetlet.2011.07.099.

[20] Wei C, Li CJ. A Highly Efficient Three-Component Coupling of Aldehyde, Alkyne, and Amines via C-H Activation Catalyzed by Gold in Water. J Am Chem Soc. 2003. Available from: https://doi.org/10.1021/ja0359299.

[21] Zou Y, Zhu FL, Duan ZC, Wang YH, Zhang DY, Cao Z, et al. Enantioselective Cu-catalyzed decarboxylative propargylic amination of propargyl carbamates. Tetrahedron Lett. 2014 3;55:2033-6. Available from: https://doi.org/10.1016/j.tetlet.2014.02.030.

[22] Watanabe K, Miyazaki Y, Okubo M, Zhou B, Tsuji H, Kawatsura M. Nickel-Catalyzed Asymmetric Propargylic Amination of Propargylic Carbonates Bearing an Internal Alkyne Group. Org Lett. 2018. Available from: https://doi.org/10.1021/acs.orglett.8b02325.

[23] Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD. Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures 1; 1996. Available from: https://doi.org/10.1021/jo960057x.

[24] Erkkilä A, Majander I, Pihko PM. Iminium Catalysis. Chem Rev. 2007. Available from: https://doi.org/10.1021/cr068388p.

[25] Egorova KS, Ananikov VP, Zelinsky ND. Toxicity of Metal Compounds: Knowledge and Myths. Organometallics. 2017. Available from: https://doi.org/10.1021/acs.organomet.7b00605.

[26] Schmidt NG, Simon RC, Kroutil W. Biocatalytic Asymmetric Synthesis of Optically Pure Aromatic Propargylic Amines Employing w-Transaminases. Adv Synth Catal. Available from: http://dx.doi.org/10.1002/adsc.201500086.

[27] Messina F, Botta M, Corelli F, Schneider MP, Fazio F. Resolution of (()-1-Aryl-2-propynylamines via Acyltransfer Catalyzed by Candida antarctica Lipase. J Org Chem. 1999. Available from: https://doi.org/10.1021/jo982513i.

[28] Periasamy M, Reddy PO, Satyanarayana I, Mohan L, Edukondalu A. Diastereoselective Synthesis of Tetrasubstituted Propargylamines via Hydroamination and Metalation of 1-Alkynes and Their Enantioselective Conversion to Trisubstituted Chiral Allenes. J Org Chem. DOI:101021/acsjoc5b02554, 2016. Available from: https://doi.org/10.1021/acs.joc.5b02554.

[29] Wang M, Gao B, Huang H. Catalytic nucleophilic addition of terminal alkynes to ,-unsaturated--lactams. Chinese J Catal. 2016 4;37:476-83. Available from: https://doi.org/10.1016/j.tchem.2022.100007.

[30] Dang GH, Nguyen DT, Le DT, Truong T, Phan NTS. Propargylamine synthesis via direct oxidative CC coupling reaction between N,N-dimethylanilines and terminal alkynes under metal-organic framework catalysis. J Mol Catal A Chem. 2014;395:300-6. Available from: https://doi.org/10.1016/j.molcata.2014.08.034.

[31] Shah AP, Sharma AS, Jain S, Shimpi NG. Microwave assisted one pot three component synthesis of propargylamine, tetra substituted propargylamine and pyrrolo[1,2-: A] quinolines using CuNPs@ZnO-PTh as a heterogeneous catalyst. New J Chem. 2018;42:8724-37. Available from: https://doi.org/10.1039/C8NJ00410B.

[32] Manujyothi R, Aneeja T, Anilkumar G. Solvent-free synthesis of propargylamines: an overview. RSC Adv. 2021. Available from: https://doi.org/10.1039/D1RA03324G.

[33] Zhang JY, Huang X, Shen QY, Wang JY, Song GH. Room temperature multicomponent synthesis of diverse propargylamines using magnetic CuFe2O4 nanoparticle as an efficient and reusable catalyst. Chin Chem Lett. 2018 1;29:197-200. Available from: https://doi.org/10.1016/j.cclet.2017.05.012.

[34] Nakamura S, Ohara M, Nakamura Y, Shibata N, Toru T. Copper-Catalyzed Enantioselective Three-Component Synthesis of Optically Active Propargylamines from Aldehydes, Amines, and Aliphatic Alkynes. Chem Eur J. Available from: https://doi.org/10.1002/chem.200903550.

[35] Nasrollahzadeh M, Sajjadi M, Ghorbannezhad F, Sajadi SM. A Review on Recent Advances in the Application of Nanocatalysts in A 3 Coupling Reactions. Chem Rec. 2018;18:1409-73, DOI:10.1002/tcr.201700100. Available from: https://doi.org/10.1002/tcr.201700100.

[36] Kumar A, Kuang Y, Liang Z, Sun X. Microwave chemistry, recent advancements, and eco-friendly microwave-assisted synthesis of nanoarchitectures and their applications: a review. Mater Today Nano. 2020 8;11. Available from: https://doi.org/10.1016/j.mtnano.2020.100076.

[37] Xiong X, Chen H, Zhu R. Highly efficient and scale-up synthesis of propargylamines catalyzed by graphene oxide-supported CuCl2 catalyst under microwave condition. Catal Commun. 2014 9;54:94-9. Available from: https://doi.org/10.1016/j.catcom.2014.05.030.

[38] Pålhagen S, Heinonen E, Hägglund J, Kaugesaar T, Mäki-Ikola O, Palm R. Selegiline slows the progression of the symptoms of Parkinson disease. Neurology. 2006 4;66:1200-6. Available from: https://doi.org/10.1212/01.wnl.0000204007.46190.54.

[39] Tardos L, Janvari-Kanyo E. Pharmacology of selegiline. Neurology. 1996 12;47:137S-145S. Available from: https://doi.org/10.1212/wnl.47.6_suppl_3.137s.

[40] Wang JY, Zhang S, Yu XY, Wang YH, Wan HL, Zhang S, et al. Organocatalytic asymmetric synthesis of bioactive hexahydropyrrolo[2,3-b]indole-containing tetrasubstituted allenes bearing multiple chiral elements. Tetrahedron Chem. 2022 3;1:100007. Available from: https://doi.org/10.1016/j.tchem.2022.100007.

[41] Nüchter M, Ondruschka B, Bonrath W, Gum A. Microwave assisted synthesis-a critical technology overview. Green Chem. Available from: https://doi.org/10.1039/B310502D.