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Metal-Catalysed Azidation

Metal-Catalysed Azidation of Organic Molecules

Monalisa Goswami^{[a][‡]} and Bas de Bruin^{*,[a][‡]}

Abstract: The azide moiety is a desirable functionality in organic molecules, useful in a variety of transformations such as olefin aziridination, C–H bond amination, isocyanate synthesis, the Staudinger reaction and the formation of azo compounds. To harness the versatility of the azide functionality fully it is important that these compounds be easy to prepare, in a clean and cost-effective manner. Conventional (non-catalysed) methods to synthesise azides generally require quite harsh reaction conditions that are often not tolerant of functional groups. In the last decade, several metal-catalysed azidations have been developed in attempts to circumvent this problem. These meth-

ods are generally faster, cleaner and more functional-group-tolerant than conventional methods to prepare azides, and can sometimes even be conveniently combined with one-pot follow-up transformations of the installed azide moiety. This review highlights metal-catalysed approaches to azide synthesis, with a focus on the substrate scopes and mechanisms, as well as on advantages and disadvantages of the methods. Overall, metal-catalysed azidation reactions provide shorter routes to a variety of potentially useful organic molecules containing the azide moiety.

1. Introduction

Azides, molecules bearing the $-N=N^+=N^-$ functionality, are useful in a variety of desirable transformations. Since the discovery

of organic azides about 150 years ago, numerous synthetic protocols and applications of these energy-rich molecules have been developed.^[1] Azides are ubiquitously employed in Huisgen 1,3-dipolar cycloaddition (“click”) reactions,^[2] in which all three atoms of the azide are used to construct triazole rings. Azides can also react vigorously by releasing dinitrogen, thus leading to the formation of electron-deficient nitrenes. In the presence of transition-metal complexes, they can also form metal-bound nitrenes. As such, many frequently applied reactions involving organic azides are based on using azide functionalities as “nitrene” precursors. This involves a variety of (metal-catalysed) transformations ranging from olefin aziridination, C–H bond amination, isocyanate synthesis, the Staudinger reaction and formation of azo compounds.^[3–5] Azides have found several applications in diverse synthetic organic contexts, including peptide chemistry, combinatorial chemistry and het-

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Monalisa Goswami (1990) obtained her bachelor's degree from St. Stephen's College, Delhi University, India (2010). She then received an Erasmus Mundus scholarship to study chemistry at the University of Amsterdam (UvA), The Netherlands. She obtained her master's degree from the UvA in 2013, after which she continued her doctoral studies at the van 't Hoff Institute for Molecular Sciences, UvA, under the supervision of Prof. Dr. Bas de Bruin. Her research project deals with exploring substrate non-innocence with metalloradical catalysts.



Bas de Bruin (1971) obtained his PhD from the Radboud University in Nijmegen (Prof. A. W. Gal, 1999). He did his postdoctoral studies at the MPI für Bio-Anorganische Chemie in Mülheim a/d Ruhr (Prof. K. Wieghardt), after which he returned to Nijmegen as an assistant professor. In 2005 he moved to the University of Amsterdam, where he was promoted to associate professor in 2008 and to full professor in 2013. He is involved in various research activities, including radical organometallic chemistry, EPR spectroscopy, olefin oxygenation, polymer synthesis, mechanistic studies and computational catalysis, with a focus on the development of new (bio-inspired) catalytic transformations.

erocyclic chemistry. As such, organic azides occupy an important position at the interface between chemistry, biology, medicine and materials science.

Figure 1 provides a schematic representation of some of the different reaction types involving organic azides. An excellent review by Bräse and co-workers covers most aspects of (non-metal-catalysed) synthesis and reactivity of azide-containing molecules up to 2005.^[3]

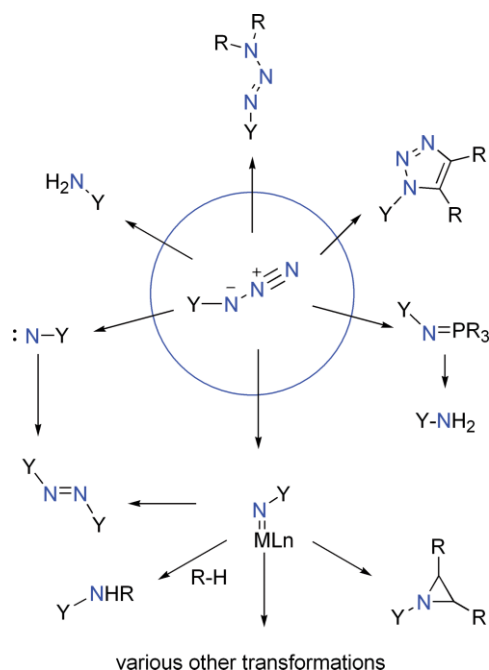


Figure 1. Different reactions in which organic azides take part.

The past few years have shown a revival in popularity of the use of organic azides in synthetic organic chemistry. Transition-metal-catalysed formation of N-containing heterocycles has been widely explored, and many of these strategies involve azides as metal-bound nitrene precursors. Just as in metal-carbene chemistry,^[6] C–H amination via metallonitrenes^[7,8] is rapidly taking centre stage as a fascinating and useful research area. This strategy involves controlled insertion of a metal-bound nitrene moiety into a C–H bond, leading to the direct formation of C–N bonds. Organic azides have several advantages over other nitrene precursors such as iminoiodanes and haloamine-Ts. They show better solubility in organic solvents of choice and are more stable, easier to use and not as over-oxidising as some iminoiodanes and haloamine-Ts can be. The strategy of using metallonitrene intermediates for N–X bond formation was first disclosed for Rh^{II} systems,^[9,10] but gradually systems based on more abundant base metals have emerged. Cobalt(II) porphyrins, for example, are successful catalysts for a variety of nitrene transfer reactions in which organic azides are used as nitrene precursors.^[11]

For the azide moiety to be fully exploited as a functional group there is a need to find protocols for synthesising azides in easy ways and without the need for the use of harsh reagents or reaction conditions. Several common methods for the construction of azides are based on classical nucleophilic substitu-

tion reactions, such as the Mitsunobu reaction with alcohols or substitution with alkyl halides. However, with these methods, protecting-group strategies or lengthy synthetic sequences are often necessary, due to chemo- and regioselectivity issues in azidation reactions of functionalised compounds. These problems can be partially overcome by using other methods, such as diazotisation of an amine followed by a Sandmeyer reaction with an alkali-metal azide, but the problem with this method is the selective azidation of one amine group in the presence of other amine groups. At the same time the harsh oxidation conditions associated with this method are not functional-group-tolerant.

The bottom line is that there is a lack of methods for azidation of molecules that contain functional groups, or what can be called *late-stage azidation*. The synthetic challenges aside, it is very important to point out the inherent dangers of working with azides or intermediate diazo compounds, especially on a large scale. As such, it is desirable to find methods in which the azide-containing compound does not need to be carried through many protection/deprotection steps to furnish the desired end product.

Thus, the scope of functionalised azides being used as substrates in a plethora of reactions having been outlined, it is obvious that the development of new (catalytic) ways to synthesise azides should provide enhanced potential for their application. In the past few years the field of metal-catalysed azidations has seen substantial progress, with many examples having been reported. A variety of metals are used to achieve efficient and selective azidations, thus functionalising molecules for further reactivity. However, a concise review of such transformations is so far lacking. This review highlights the new metal-catalysed approaches for organic azide synthesis, with a focus on applicability, substrate scopes, mechanisms and advantages and disadvantages of the applied methods. Many of these metal-catalysed reactions represent efficient synthetic methodologies for the preparation of substrates that are attractive for further (catalytic) incorporation of nitrogen atoms in organic molecules. Metal-free azidation of organic molecules is not dealt with in this review.

The review is divided into two main sections, based on the type of catalytic metal used: base metals and noble metals. This has been done in view of the distinct mechanistic pathways that are involved in the reactions depending on the type of metal. The base-metal-catalysed processes are dominated by one-electron processes and reactions involving azide radicals, whereas for the noble-metal reactions (with one exception) mostly ionic pathways are operative, involving the azide ion in nucleophilic-substitution-type reactions. This also dictates the different kinds of substrates that can be accessed. Thus, in Section 2 the activity of base metals is discussed, with subsections dedicated to specific metals such as Cu, Fe and Mn. In Section 3 noble-metal-catalysed azidation reactions are described.

2. Base-Metal-Catalysed Azidation Reactions

In this section, relevant examples of azidation reactions catalysed by the base metals Cu, Fe and Mn are discussed. Cu is

mostly used in azidation of aromatic substrates, whereas Fe and Mn prevail in azidation of aliphatic C–H bonds. The substrate specificity and applicability of other types of substrates still need to be explored in many cases. The azidating reagents are similar for most reactions. In most cases NaN_3 or tetramethylsilyl azide (TMSN_3) in combination with an oxidant or alternatively an azide-containing hypervalent iodine compound is used. In particular, cyclic hypervalent-iodine-based azidation agents have proved useful; these are reasonably stable and act both as group-transfer agents and as oxidants.^[12,13]

2.1. Copper-Catalysed Azidation

Cu-catalysed systems are by far the most intensively explored systems in metal-catalysed azidations. Most reactions result in high yields and proceed under relatively mild reaction conditions. As can be expected, the reaction conditions depend on the type of C–H bond being azidated. Most examples encountered are those taking place at aromatic substrates, but examples of azidation of substrates containing activated (allylic, benzylic, α -keto) C–H bonds have also been reported. Azidation of alkynes and alkenes is also known. Activation and azidation of aromatic C–H bonds typically does not require heating, but that of other C–H bonds typically requires elevated temperatures and longer reaction times.

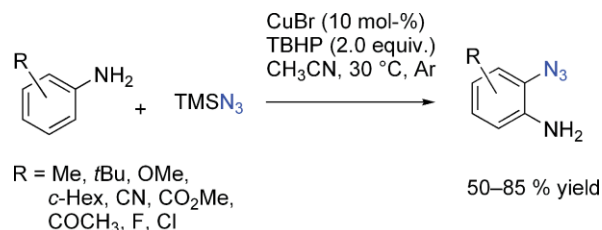
As far as azidating reagents are concerned, the use of NaN_3 or TMSN_3 in combination with an oxidising agent is most frequently encountered for systems based on Cu. The oxidants *tert*-butyl hydroperoxide (TBHP), 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO), O_2 and $\text{PhI}(\text{OAc})_2$ are often used. When the azide source itself is oxidising, the use of another oxidant is not necessary. This is the case for azide-containing hypervalent iodine compounds. In some cases, the azide-containing hypervalent iodine compound is generated in situ. Both Cu^{I} and Cu^{II} sources are encountered, but – because the reaction conditions are typically oxidative – conversion of Cu^{I} to Cu^{II} can be expected during these reactions.

Mechanistically, most of these reactions proceed through radical-type mechanisms involving formation of azide radicals (N_3^\cdot), which subsequently add to an aromatic ring, followed by hydrogen atom transfer (HAT). In some exceptional cases the

Cu^{I} catalyst is oxidised to a Cu^{II} species, followed by reductive elimination to produce the azidated product. Thus far, enantioselectivity has been reported only for one Cu-catalysed system.

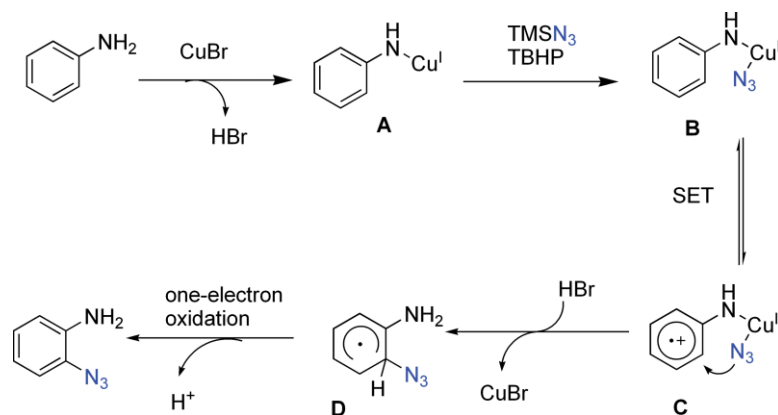
2.1.1. C–H Azidation of Anilines

Jiao and co-workers reported a Cu-catalysed aryl azidation reaction in which the amine functionality was employed as a directing group to functionalise the *ortho*-C–H bonds of anilines (Scheme 1).^[14] TMSN_3 was used as the azide source, TBHP as the oxidant and CuBr as the catalyst. Under the optimised reaction conditions (30 °C, 10 mol-% catalyst loading and 2 equiv. of TBHP), a 68 % yield of the desired product (for the *o*-phenyl-substituted aniline) was obtained within 2 h. The functional-group tolerance was demonstrated for substituents such as halogens, alkynes, and alkyl groups. The substituent R in Scheme 1 can also be an aromatic group (for phenyl substitution, 68 % yield) or a thiophene moiety (67 % yield).

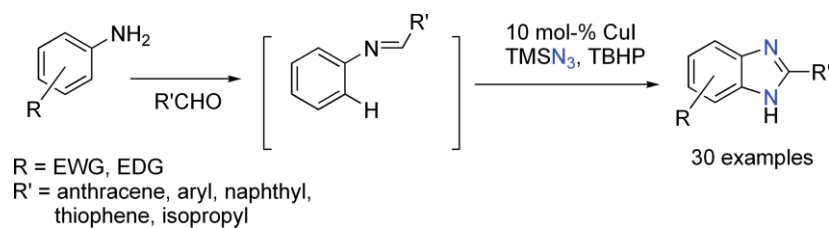


Scheme 1. C–H azidation of anilines reported by Jiao and co-workers.

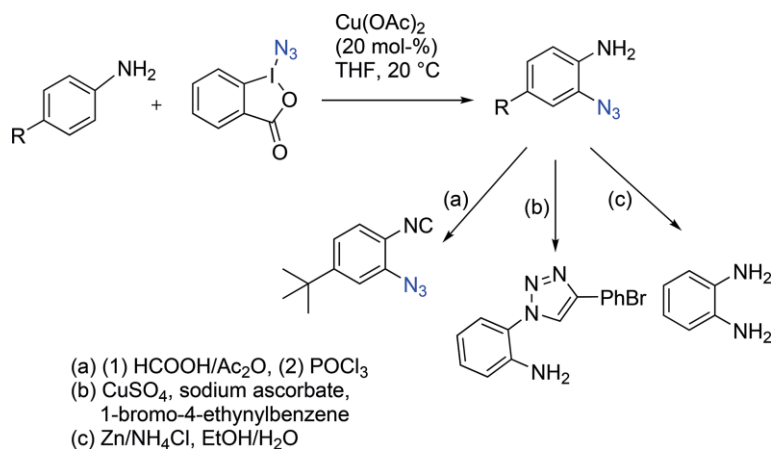
The authors showed that the reaction is completely inhibited by radical scavengers such as TEMPO and hydroquinone, thus suggesting that it follows a radical pathway. The proposed mechanism (Scheme 2) involves formation of amido intermediate **A** by reaction between the aniline substrate and CuBr, followed by formation of Cu^{II} -azide adduct **B** upon reaction with TBHP and N_3^- . Single-electron transfer (SET) from the aryl ring to the metal centre then takes place, followed by transfer of the azido ligand to the phenyl group. Subsequent release of CuBr produces intermediate **D**, which releases the azide product upon deprotonation and one-electron oxidation.



Scheme 2. Proposed mechanism of Cu^{I} -catalysed azidation of anilines.



Scheme 3. Cu^I-catalysed *o*-azidation of imines to produce benzimidazoles.



Scheme 4. *o*-Azidation of anilines with the aid of Cu(OAc)₂ and further transformations.

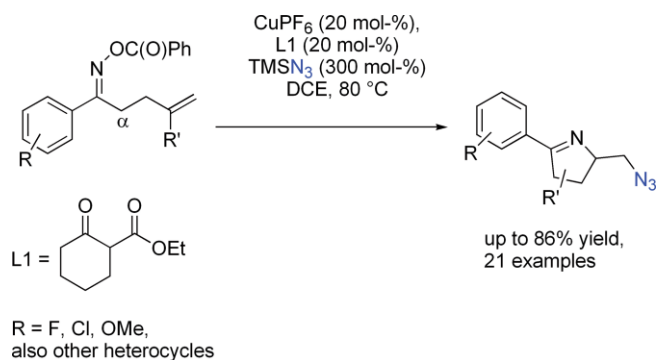
Another system that uses a directing-group strategy was reported by Punniyamurthy and co-workers (Scheme 3).^[15] In that work the authors first combined amines with aldehydes to form imines, which chelate to Cu^I salts (CuI was mainly used, although CuBr gave comparable results) and direct the azidation reactivity to the *ortho* position. Tautomerisation leads to the formation of the products. The reaction is inhibited by the presence of radical scavengers such as TEMPO, again pointing to a radical mechanism (as reported for Jiao's system). The substrate scope is broad, allowing several substituents on the aromatic ring. Various aldehydes can be used as well. The authors reported gram-scale syntheses of two of the products, which showed that reactive TMSN₃ and ligand-Cu^{III}-N₃ intermediates can even be used in larger-scale syntheses without any hazards.

Hao and co-workers demonstrated in 2014 that Cu^{II} can also be used to activate *ortho*-C–H bonds in anilines to give *o*-azido anilines.^[16] The difference from the protocol reported by Jiao and described above is that azidobenziodoxoles^[12] were used as the azide source instead of TMSN₃, circumventing the need for an external oxidant. The authors successfully combined this reagent with a Cu^{II} source to achieve aromatic azidation reactions (Scheme 4). Azidobenziodoxoles have advantages as an azide source, because they exhibit higher thermal stability and are easier to store. On the other hand, they generate higher-weight side products in the fragmentation reaction and hence are more polluting.

The authors further demonstrated the usefulness of the aromatic azidation protocol by post-synthesis functionalisation of *o*-azidoanilines. GC–MS analysis of reaction mixtures poisoned with TEMPO revealed the presence of TEMPO-azide, pointing to a radical pathway.

2.1.2. Cyclisation and Azidation of γ,δ -Unsaturated Keto-*o*-benzoyl Oximes

In 2014 Yu and co-workers reported an intramolecular imination/azidation sequence based on γ,δ -unsaturated keto-*o*-benzoyl oximes (Scheme 5).^[17] The catalyst used in this case was CuPF₆, together with a β -keto ester ligand. With the use of



Scheme 5. Cu^I intramolecular imination followed by azidation.

oximes that can be cleaved at the N–O bond by transition metals to form active iminyl intermediates, this system is able to use an azidyl group as a nucleophile to form the 5-*exo*-cyclised azidated product. In general, the cyclisation products were obtained in moderate to good yields. For 1-aryl-substituted oxime derivatives, the yields were lower when the aryl ring was an electron-rich furan or thiophene system. Better results were obtained when the substrates were disubstituted with methyl groups at the α -position. On the other hand, in the case of the α -carbon atom being tertiary, the azidation also took place at the α -position.

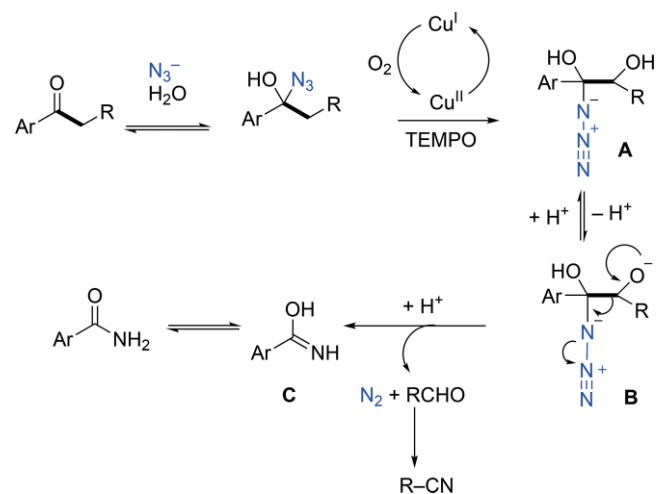
This system, however, requires 300 mol-% of TMSN₃ together with 20 mol-% catalyst and is not very selective for unsubstituted substrates. Here the substrate itself acts as an oxidant. However, for substrates with substituents next to the imine, double azidation products are obtained. The authors suspect the presence of air in the reaction mixture to be responsible for the oxidation required for the second azidation.

2.1.3. Cu-Catalysed Azidation of Carbonyl Compounds

In 2014 Jiao and co-workers disclosed a copper-catalysed protocol for aerobic oxidative C–C bond cleavage to convert alkyl aryl ketones directly into benzamides^[18] (Scheme 6). Nitrogenation of 4-phenylacetophenone with sodium azide afforded 4-phenylbenzamide in 84 % yield when the reaction was catalysed by CuCl₂ in DMF at 120 °C in the presence of TEMPO and O₂ (1 atm). Aryl ketones either with electron-donating or with electron-withdrawing substituents at the aryl ring were tolerated, and the aryl methyl ketones could be expanded to heteroaryl ketones.

Mechanistically, this is an interesting example, because the nature of the involvement of the copper catalyst in the mechanism is not obvious. To elucidate the reaction pathway, some potential intermediates such as the corresponding aldehyde, α -hydroxy ketone, α -keto aldehyde, α -keto carboxylic acid, and amide species were prepared and tested under the same reaction conditions. However, none of these substrates afforded the desired product. It was therefore postulated that nucleophilic attack of the N₃[−] anion at the carbonyl moiety of the ketone is an essential step, thus forming a geminal azido alcohol intermediate, which is oxidised to generate an α -hydroxylated intermediate of type **A** (Scheme 7). The azidation and hydroxylation steps might also be reversed. Subsequent rearrangement of intermediate **A** via **B** produces intermediate **C**, involving C–C bond cleavage. This is followed by release of molecular nitrogen and an aldehyde as byproducts. Finally, tautomerisation of **C** affords the desired amide product. The formation of a nitrile

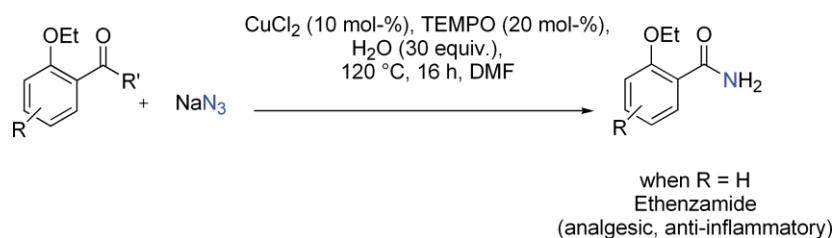
from the aldehyde (possibly by a Schmidt reaction) was detected with GC–MS. Overall, this is a useful and effective system that does not seem to have the Cu^{II} catalyst involved directly in the azidation step.



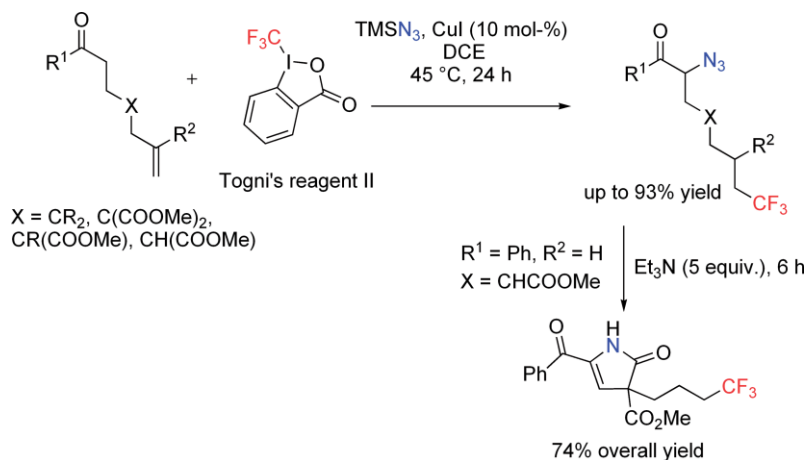
Scheme 7. Possible mechanism of the reaction depicted in Scheme 6.

A domino radical protocol for simultaneous addition of a trifluoromethyl moiety to an alkene and azidation of a remote carbonyl α -C–H position in a site-selective manner was reported by Liu and co-workers (Scheme 8).^[19] This leads to the formation of CF₃-containing α -azido ketones. These α -azido ketones could be converted into trifluoromethyl γ -lactam and spirobenzofuranone lactam scaffolds in a one-pot process in the presence of a base such as triethylamine.

Interestingly, the authors first examined the reaction under metal-free conditions, either with CF₃SiMe₃ as the CF₃ source and PhI(OAc)₂ as the oxidant, or with the Togni reagent II and *n*Bu₄NI as the CF₃ radical initiator. However, the desired product was not obtained in any of the metal-free reactions. In combination with CuI as the catalyst, though, the desired CF₃-containing α -azido ketone was obtained in 93 % yield after optimisation of the reaction conditions. The authors proposed a mechanism in which CuI plays a dual role. Besides activating the Togni reagent, CuI is also believed to catalyse the azidation step, although it is also possible that the azidation is a result of an uncatalysed nucleophilic attack of the azide anion. Gram-scale syntheses were demonstrated without the overall yield of the product being compromised, making this quite an interesting synthetic protocol.

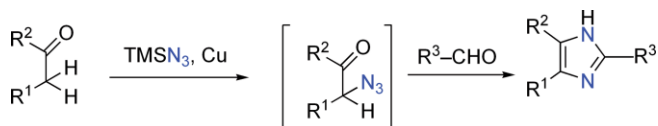


Scheme 6. CuCl₂-catalysed conversion of aryl ketones into benzamides.



Scheme 8. Trifluoromethylation-initiated azidation of carbonyl compounds.

A synthesis of 2,4,5-trisubstituted imidazoles, by a Cu-mediated three-component reaction involving ketones, aldehydes and Me_3SiN_3 , has recently been reported by Li, Zhu and co-workers (Scheme 9).^[20]

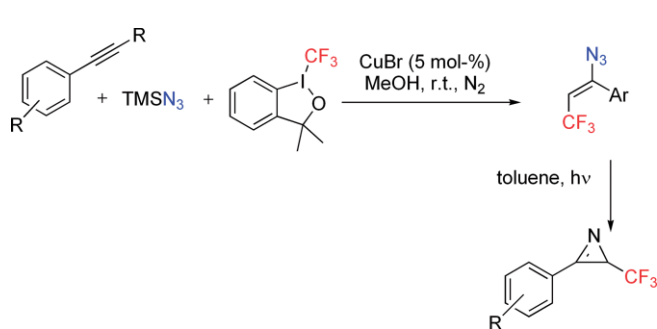


Scheme 9. Cu-catalysed C-H azidation to give imidazoles.

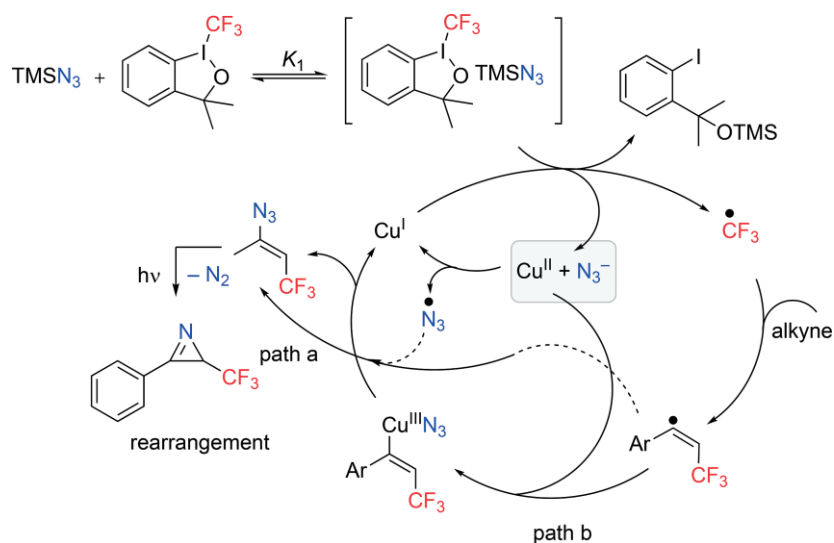
2.1.4. Copper-Catalysed Azidations with Alkynes

In an elegant recent report, Liu and co-workers reported a method for copper-catalysed trifluoromethylation/azidation of alkynes to give CF_3 -containing azido-alkenes, which could subsequently undergo photocatalysed rearrangements to give

CF_3 -containing azirines (Scheme 10).^[21] Both terminal and internal alkynes proved compatible with the reported mild reaction conditions, thus delivering the CF_3 -containing azirines in moderate to good yields. Combining the copper(I) catalyst



Scheme 10. Trifluoromethylation/azidation of alkynes with the aid of CuBr as reported by Liu and co-workers.



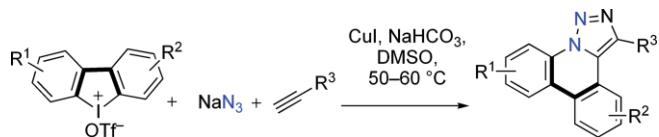
Scheme 11. Mechanistic aspects of the reaction depicted in Scheme 10.

[Cu(CH₃CN)₄]PF₆ with the Togni reagent, TMSN₃ and (4-chlorophenyl)acetylene led to the desired trifluoromethylation/azidation product in 75 % yield at room temperature under optimised reaction conditions. Cu^{II} sources also worked, but Cu^I sources seemed to give better results. The reason for this is not obvious, because oxidising conditions are used, and in the proposed mechanism (Scheme 11) Cu undergoes oxidation under the applied reaction conditions. To convert the azide into the azirine the sample was irradiated after removal of the Cu catalyst.

To discern more information about the mechanism of the reaction some mechanistic studies were performed. TEMPO was found to be detrimental in the reaction, with CF₃-substituted TEMPO being obtained, thus pointing to a radical mechanism. In addition, a competition experiment with styrene also led to CF₃-substituted species. These results revealed that a CF₃ radical is involved in the reaction; it probably adds to the alkyne to produce a CF₃-vinyl radical species. Compounds containing electron-rich aryl groups reacted more rapidly than those with electron-poor aryl groups. A significant Hammett value of $\rho = -0.29$ was measured, in agreement with a mechanism involving radical addition to the alkyne triple bond (Scheme 11).

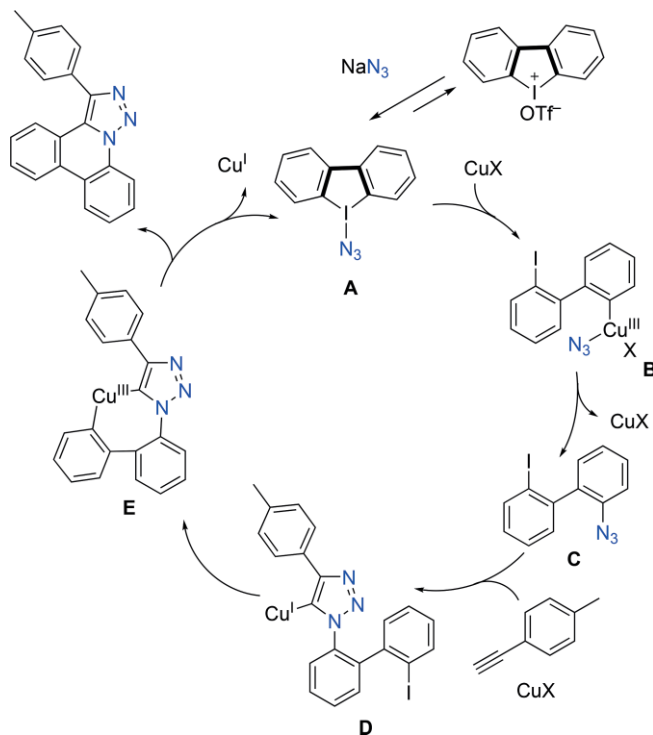
For the final C–N bond formation, there are two possibilities (Scheme 11). In path a, the azide ion released from TMSN₃ is oxidised by copper(II) to give the azide radical, which is then trapped by the CF₃-vinyl radical species to give the final product. In path b, the azide anion may coordinate to copper(II), and then the CF₃-vinyl radical is trapped by this [Cu^{II}N₃] species to form a copper(III) intermediate, which undergoes reductive elimination to yield the product. With the available experimental data, neither of these pathways could be excluded.

In 2014 Wen and co-workers reported an example^[22] in which the Cu^I catalyst had a dual function. One role was in the context of catalysing the azidation, as in the above example from Jiao (Schemes 1 and 2), and the other was in catalysing a classical click reaction (Scheme 12). Here the authors used a cyclic iodonium triflate as an oxidising substrate, which undergoes exchange of triflate with an azide ion. The azide source in this case is NaN₃. After oxidative addition and reductive elimination, intermediate **C** (Scheme 13) is obtained, and this then undergoes a Cu-catalysed alkyne–azide cycloaddition (CuAAC) reaction to furnish the final phenanthridine product. The system is tolerant towards a variety of alkynes and also tolerates a range of different substituents on the iodonium triflate.



Scheme 12. Cu^I-catalysed azidation and click reaction to afford phenanthridines.

As such, this is an interesting three-component cascade-type reaction that is performed by combining azidation, CuAAC and Ullmann coupling, with use of a single and cheap Cu^I catalyst.

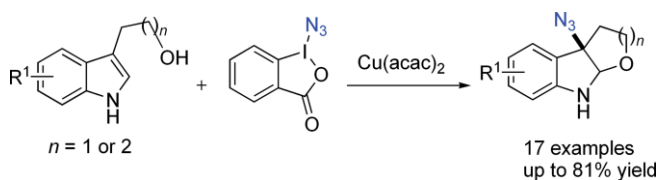


Scheme 13. Mechanism of the reaction depicted in Scheme 12.

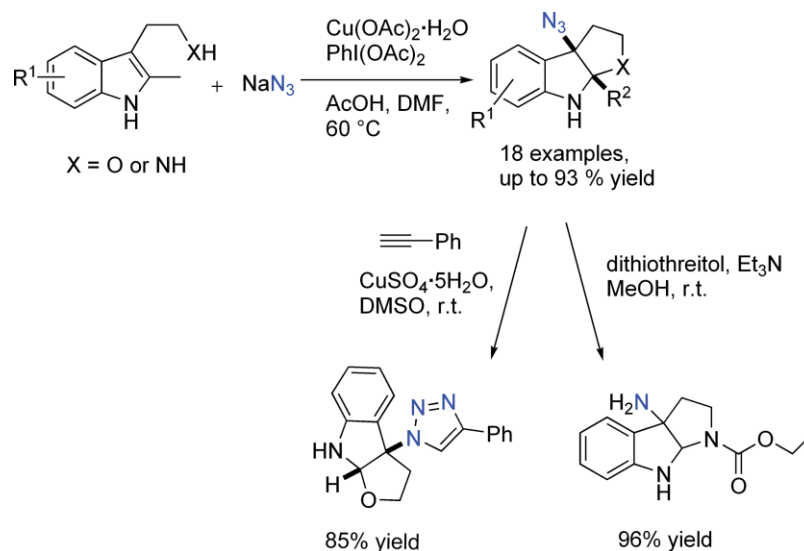
In addition, as the authors rightly point out, four new bonds (three C–N and one C–C) and two new fused rings are formed in one reaction.

2.1.5. Oxo-Azidation and Alkoxy-Azidation of Indoles, Tryptamines and Tryptophols

Dearomatisation of 3-substituted indoles has been an attractive topic in organic synthesis due to the importance of the derivatised products, such as indolenines and 2-oxindoles. This was reported by the group of Jiao, who used a Cu(acac)₂ catalyst with 3-methylindole as a model substrate and azidoiodinane as the source of azide (Scheme 14).^[23] Reasonable yields were initially also obtained when CuBr was employed as the catalyst, which indicated that copper salts might be beneficial for the reaction. Although both Cu^I and Cu^{II} sources could be employed in the transformation, best results were obtained with Cu(acac)₂, in which case the reaction times could be reduced to 90 min, with the products being obtained in yields of up to 77 %.



Scheme 14. Oxo-azidation and alkoxy-azidation of indoles catalysed by Cu(acac)₂.



Scheme 15. Azidation/cyclisation of tryptophols and tryptamines catalysed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$.

Additionally, in 2015 Wang and co-workers reported a $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ -catalysed cyclisation/azidation protocol based on tryptophols as substrates.^[24] $\text{PhI}(\text{OAc})_2$ was used as the oxidant and NaN_3 as the azide source. The reactions used an excess of both the azide and the oxidant and worked best at 60 °C (Scheme 15). The authors demonstrated post-functionalisation of the installed azide moiety producing heterocycles. Mechanistic studies revealed a radical pathway based on the formation of azide radicals.

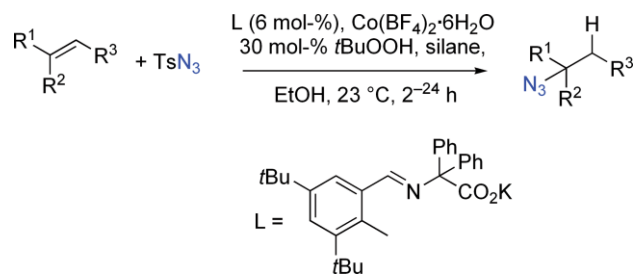
Azidations of alcohols with the aid of $\text{Cu}(\text{OTf})_2$ and TMSN_3 were described by Kumar and co-workers.^[25] The substrates were mostly benzylic alcohols, although secondary alcohols based on other heterocycles were also transformed into the corresponding azides. $\text{Cu}(\text{OAc})_2$ has also been used as a catalyst to transform arylboronic acids into the corresponding azides. In an article by Aldrich and co-workers, Chan–Lam coupling conditions^[26] were evaluated for azidation of (4-cyanophenyl)-boronic acid.^[27] Sodium azide was used as the azide source.

2.1.6. Cu-Catalysed Azidations with Alkenes

In this section we discuss the numerous reports of Cu-catalysed azidation of alkenes, which in many cases have been followed by other reactions in tandem. Jiao and co-workers have also very recently compiled such reactions with alkenes elsewhere.^[28]

One of the first examples of azidation of alkenes to give alkyl azides actually used a cobalt-based system. After the success of Co and Mn catalysis^[29] in hydrohydrazination reactions of alkenes, Carreira and co-workers explored hydroazidation of alkenes to give alkyl azides (Scheme 16).^[30] On modifying the ligand, a cobalt complex that was active in hydroazidation of a variety of alkenes could be synthesised or complexed in situ. The reaction showed Markovnikov selectivity, and the saturated

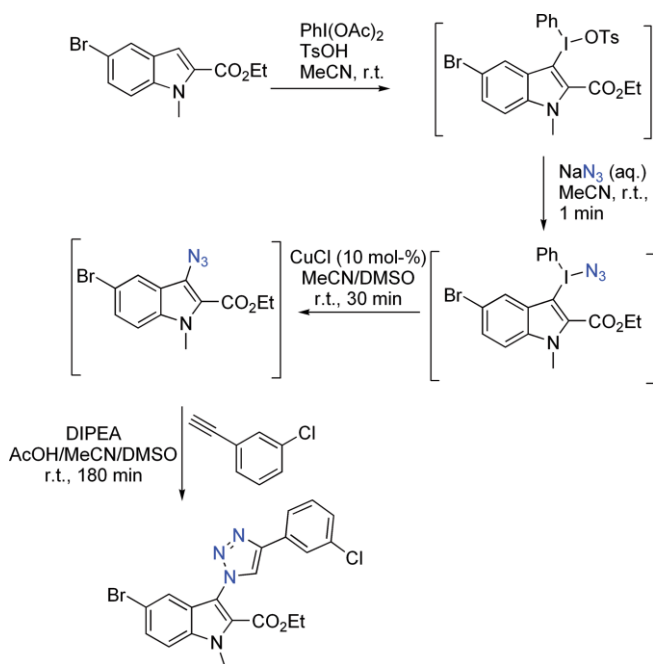
alkane was an observed side product. Better selectivity towards the azide product (20:1) was obtained with use of TMDSO (1,1,3,3-tetramethyldisiloxane) instead of PhSiH_3 , although slightly longer reaction times were required. The other remarkable aspect of this reaction is that tosyl azide could be used as the azide source. Free alcohols and styrenes were not accessible under these reaction conditions.



Scheme 16. Co-catalysed hydroazidation of alkenes.

In 2012, Suna and co-workers reported a system capable of transforming C–H bonds of electron-rich heterocycles into C–N bonds through the use of heteroaryl(phenyl)iodonium azides, which fragmented in situ to give heteroaryl azides.^[31] Use of λ^3 -iodanes can potentially lead to the formation of product mixtures in reactions with nucleophiles. Nevertheless, regiocontrol can be achieved by differentiation of electronic and steric properties of aromatic moieties. The regiocontrol over the fragmentation step of the unsymmetrical iodane is where the Cu catalyst plays a crucial role. The Cu catalyst further catalyses the cycloaddition of the azide to the acetylene. The reaction sequence is outlined in Scheme 17.

Yu and co-workers recently reported the synthesis of quinoxalines from *N*-arylenamines and TMSN_3 .^[32] In this method two oxidative C–N bond-forming processes take place in tandem

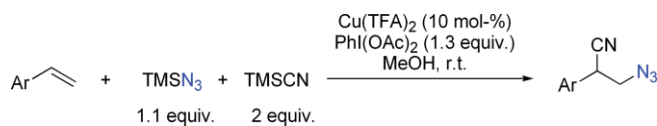


Scheme 17. C–H azidation aided by CuCl as reported by Suna and co-workers.

through the use of (diacetoxyiodo)benzene as the common oxidant. The reaction conditions are mild, and the substrates are readily accessible *N*-arylenamines. The general reaction and the mode of operation are depicted below (Scheme 18).

A procedure for azidocyanation of alkenes that was catalysed by Cu^{II}TFA and used PhI(OAc)₂ as the oxidant and TMSN₃ as the azide source was reported by Wang and co-workers (Scheme 19).^[33] TMSCN was used simultaneously as the source of CN, and the reaction could proceed at room temperature. A radical process was proposed, based on the fact that the reaction was suppressed on addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT).

A method for azidotrifluoromethylation of alkenes was reported by Liu and co-workers. In the presence of the Togni reagent and [Cu(MeCN)₄]PF₆ as the catalyst, TMSN₃ could be used as the azide source to form CF₃-containing organic azides (Scheme 20).^[34] The resulting azides could be transformed into valuable CF₃-containing amines.



Scheme 19. Azidocyanation of alkenes catalysed by Cu(TFA)₂.

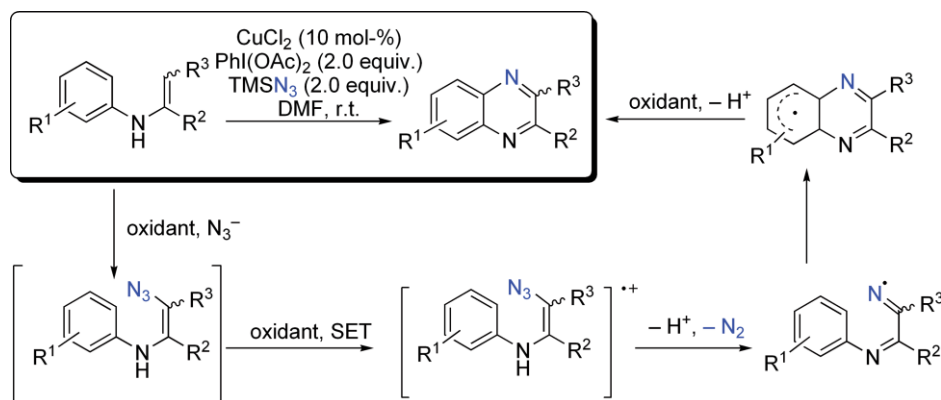
A similar transformation for aminotrifluoromethylation of alkenes has also been reported. Photoredox-catalysed azidotrifluoromethylation of alkenes in the presence of [Ru(bpy)₃](PF₆)₂ as the photocatalyst^[35] was reported by Masson, Magnier and co-workers. The same researchers also reported trifluoromethylation of enecarbamates with use of the Togni reagent as the CF₃ source.^[36]

In an elegant example from Greaney and co-workers the Zhdankin reagent^[37] was used as the azide source in light-controlled reactions involving a copper catalyst and styrene-like alkenes.^[38] Under irradiation with light, along with azidation, the addition of methanol or bromide at the benzylic position would take place. However, in the absence of light, double-azidation products were obtained. The reactions proceeded at room temperature and with 1 mol-% of loading (Scheme 21). In a follow-up study, benzylic C–H azidation was reported by the same group. Primary, secondary and tertiary azides could be synthesised with the aid of the same catalyst under irradiation with light, with excellent functional-group tolerance.^[39]

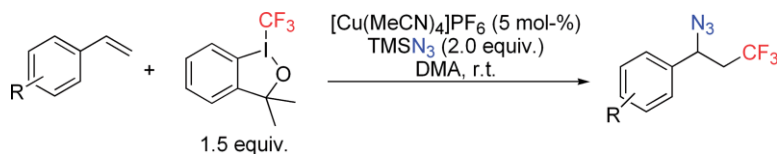
A Cu-catalysed synthesis of a wide range of chiral lactones, starting from alkene-containing carboxylic acids in the presence of a chiral ligand, was also developed by Buchwald and co-workers (Scheme 22).^[40] Remarkably, this is the only Cu-catalysed system to date that performs enantioselective azidation.

Access to isoxazolines was reported by Wang and co-workers, who used Cu(OAc)₂ as the catalyst and TMSN₃ as the azide source.^[41] The reactions proceeded under mild conditions, forming the azido-substituted isoxazolines in good yields (Scheme 23). The mechanism for this transformation remains unclear.

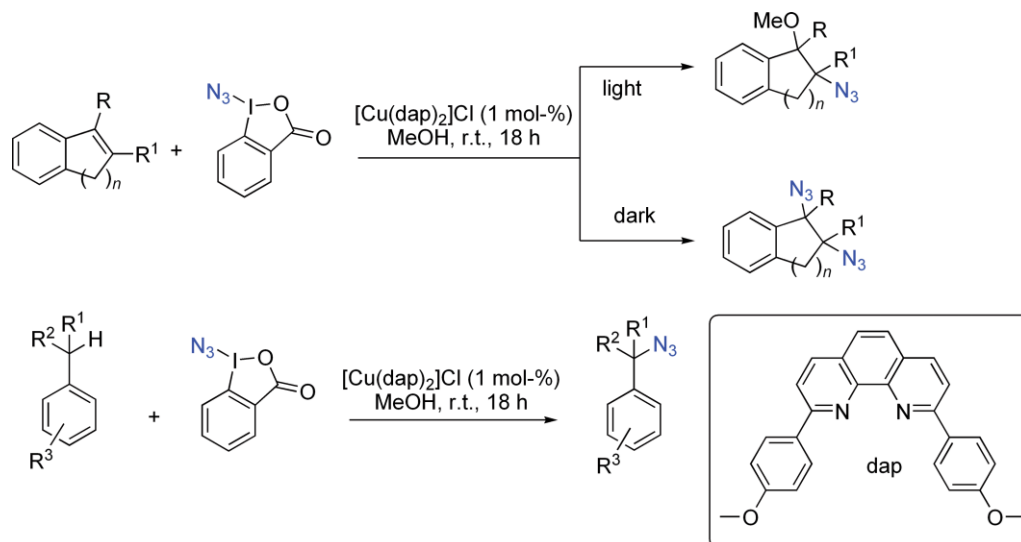
A synthesis of precursors for vicinal azides, employing a Cu^I catalyst, TMSN₃ as the source of azide and *N*-fluorobenzene-sulfonamide (NFSI) as nitrogen radical precursor, was reported by Studer and co-workers (Scheme 24). This transformation showed high diastereoselectivity in most examples.^[42]



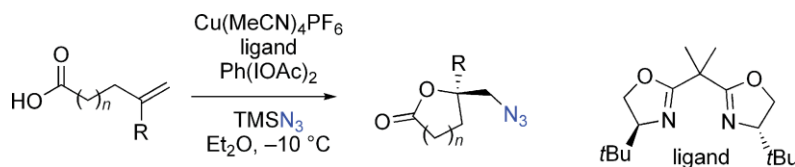
Scheme 18. Oxidative azidation/cyclisation of *N*-arylenamines to give quinoxalines.



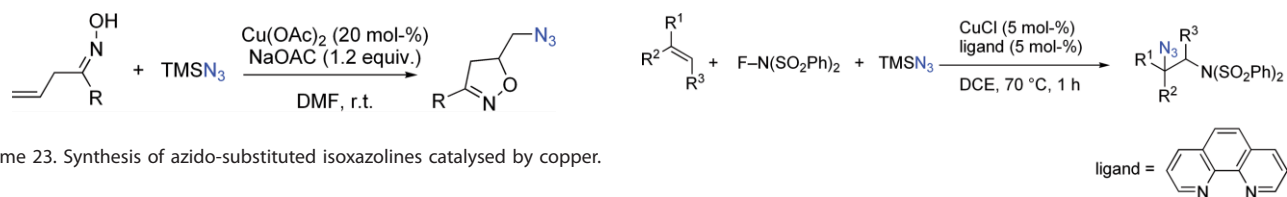
Scheme 20. Azidotrifluoromethylation of styrenes catalysed by copper.



Scheme 21. Top: light and dark reactions of styrene-like alkenes in the presence of $[\text{Cu}(\text{dap})_2]\text{Cl}$. Bottom: benzylic C–H azidation catalysed by the same catalyst.



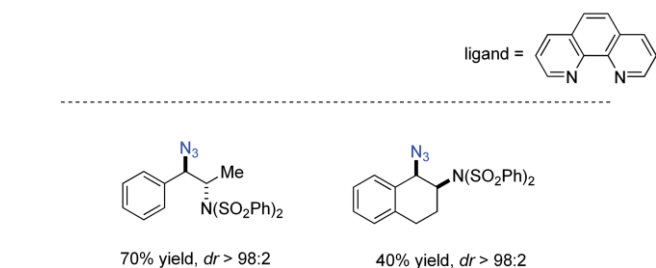
Scheme 22. Enantioselective azidation of alkenes in the presence of a chiral ligand and a Cu catalyst.



Scheme 23. Synthesis of azido-substituted isoxazolines catalysed by copper.

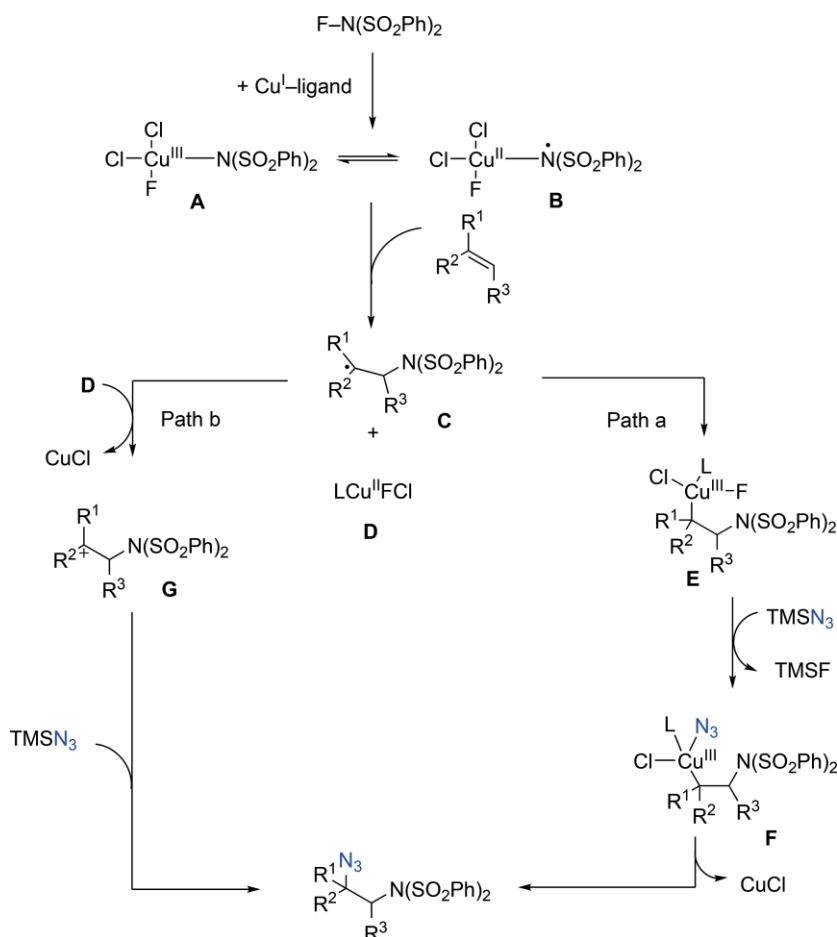
The mechanism in action here is slightly different from those of other Cu-catalysed systems, because the NFSI is believed to oxidise the Cu^{I} catalyst to a Cu^{III} species, which could exist in equilibrium with a Cu^{II} -stabilised N-centred radical (Scheme 25). This is the precursor for the bis(sulfonylamidyl) radical, which can add to the alkene in two ways. In path a, trapping of **C** with **D** can provide Cu^{III} species **E**, which can undergo ligand exchange followed by reductive elimination to give the product and regenerated catalyst. In path b, **D** can oxidise **C** to intermediate **G**, which is trapped by TMSN_3 to give the products.

A dearomative azidation of β -naphthols in the presence of CuBr as catalyst was reported. These reactions lead to highly

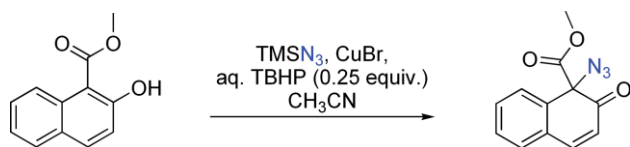


Scheme 24. Synthesis of azides from alkenes reported by Studer.

valuable naphthalenone derivatives such as quaternary azide derivatives, which can be transformed into the corresponding amines (Scheme 26).^[43]



Scheme 25. Mechanism of reaction depicted in Scheme 24.

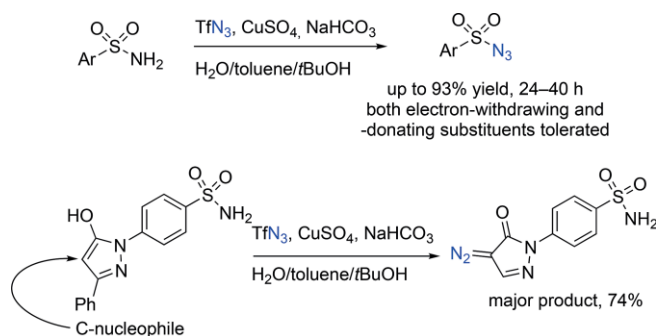


Scheme 26. Dearomative azidation of β -naphthols.

2.1.7. Cu-Catalysed Synthesis of Azide-Transfer Reagents

Sulfonyl azides are very widely used substrates in organic synthesis, as well as nitrene-transfer reagents. The method commonly used to synthesise sulfonyl azides involves the use of sulfonyl chlorides. These produce sulfonic acids in the presence of water, leading to the formation of toxic and shock-sensitive hydrazoic acid during the azidation step. To overcome these problems, a direct, mild and facile route to sulfonyl azides was reported by Fokin and co-workers.^[44] Using CuSO_4 in the presence of a base, azidation of sulfonyl amides could be performed to give the corresponding sulfonyl azide (Scheme 27). The azide source here was triflyl azide. Under the optimised reaction conditions 4 mol-% of CuSO_4 was used together with 4 equiv. of NaHCO_3 (with respect to substrate) at room temperature. The reaction times varied between 15 and 42 h. A one-pot version of this reaction that does not require the isolation of triflic azide was also devised. Use of triflic anhydride, sodium azide, NaH

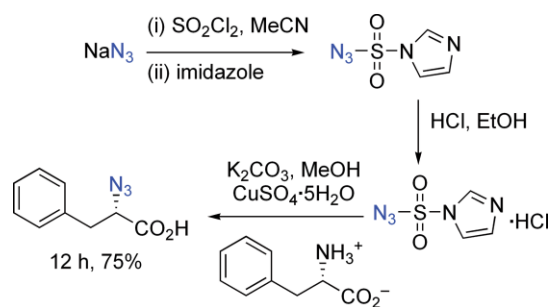
CO_3 , solvent and a reaction time of 78 h gave the sulfonyl azide in 89% yield. Electron-donating and -withdrawing substituents were tolerated, but substrates that contained carbon nucleophiles instead underwent diazotisation. No mechanistic suggestions were reported for this Cu-catalysed transformation.



Scheme 27. Top: Cu-catalysed synthesis of sulfonyl azides. Bottom: diazotisation when a C-nucleophile is present.

In another report from Goddard-Borger and co-workers,^[45] a shelf-stable imidazole-1-sulfonyl azide hydrochloride was synthesised. With this reagent in a Cu-catalysed reaction, primary amines could be converted into the corresponding azides. In the case of chiral primary amines the stereochemistry is re-

tained in the azide-transfer step (Scheme 28). This reagent could also be used to form diazo compounds from activated methylene substrates. The reactions are summarised in Scheme 28 for one particular primary amine.



Scheme 28. Top: synthesis of imidazole-1-sulfonyl azide. bottom: Cu-catalysed azide transfer to aliphatic azides by use of imidazole-1-sulfonyl azide.

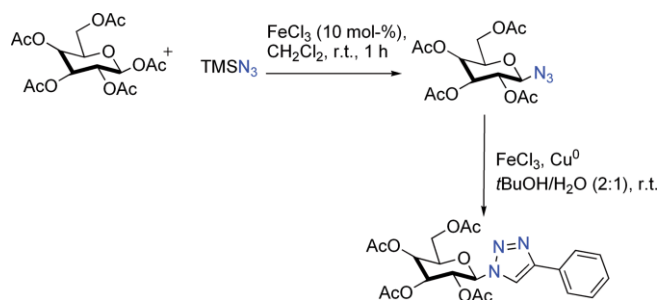
2.2. Iron-Catalysed Azidations

Unlike in the case of Cu-catalysed azidations, Fe-catalysed systems have mostly been applied in azidation of saturated C–H bonds. In many cases azidation of activated C–H bonds such as those flanked by keto/ester groups or an allylic C–H bond has been reported. However, there are also examples of azidation of non-activated aliphatic C–H bonds, such as those in decalin. Remarkable chemo-, regio- and enantioselectivities have been reported.

Mechanistically, oxidative C–H bond azidation is mostly encountered. The FeCl_3 catalyst can also act as a Lewis acid catalyst, activating the O–SiMe₃ bond in the case of azidation of silyl ethers. In case of olefin azidation in combination with TMSN_3 and an oxidant, double-azidation products are also obtained.

2.2.1. FeCl_3 in Stereoselective Synthesis of Glycosyl Azides

Azidoglycosides are important intermediates in the synthesis of many building blocks such as glycopeptides, glycosamines, glycoproteins etc. A mild method to synthesise these glycosyl azides was reported by Chen and co-workers,^[46] who used glycosyl β -peracetates as substrates (Scheme 29). Almost quantitative yields could be achieved in 6 h with use of 5 mol-% of FeCl_3 . Reaction times could be reduced to 1 h by use of 10 mol-% of the catalyst. The selectivity of this reaction was purely towards the 1,2-*trans* product. On combining the system with

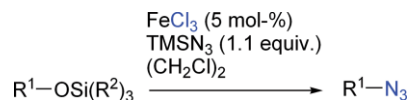


Scheme 29. FeCl_3 -catalysed synthesis of glycosyl azides.

Cu^0 , which could be oxidised by FeCl_3 to generate Cu^I , click reactions could also be accessed in the same pot. It is noteworthy that α -D-glucose was an inert substrate in this reaction.

2.2.2. FeCl_3 in Chemoselective Azidation of Benzylic Silyl Ethers

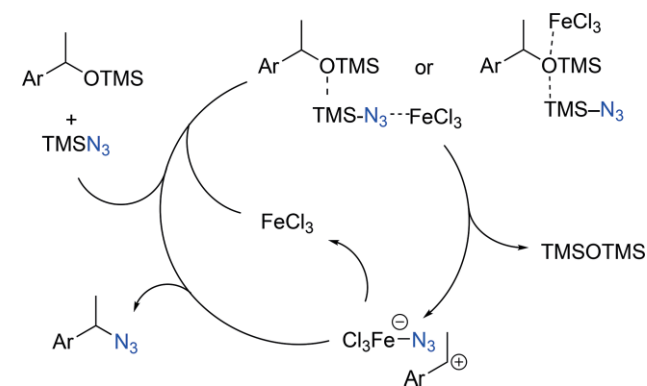
In a report by Sajiki and co-workers,^[47] secondary and tertiary silyl ethers were found to be transformed into the corresponding azides in the presence of primary benzylic silyl ethers (Scheme 30). FeCl_3 was used as the Lewis acid and the system performed best with TMSN_3 as the azide source. Use of FeBr_3 gave comparable results. However, substrates containing no benzylic secondary alkyl alcohol were unreactive. When non-protected alcohols such as phenylethanol were treated under the same reaction conditions the azide products were obtained only in very low yield (28 %). Substantial amounts of dimerised ether products were obtained. This indicates that the azidation perhaps does not involve removal of the silyl ether as the first step.



Scheme 30. Conversion of tertiary silyl ethers into the corresponding azides.

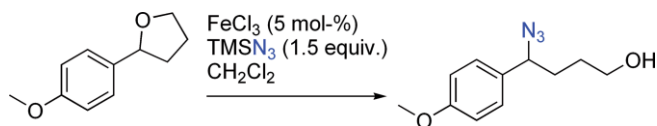
The authors further demonstrated the chemoselectivity of the system. When both secondary and primary silyl ethers were present only the secondary silyl ether underwent azidation. Interestingly, even in the presence of halides such as Cl on the aromatic ring, only the silyl ether was converted into an azide.

Because racemic azidated products were obtained when starting from an enantiopure silyl ether, a pathway involving a carbocation can be expected. On this basis a reaction mechanism was proposed (Scheme 31) in which the oxygen atom of the silyl ether could be activated either by coordination to both Lewis acids or by coordination to a complex of the Lewis acids, TMSN_3 and FeCl_3 .



Scheme 31. Mechanism of iron-catalysed azidation of silyl ethers.

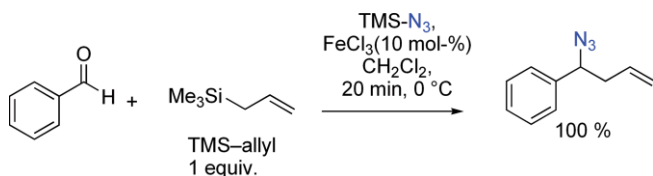
In a separate article by the same group, treatment of tetrahydrofurans with FeCl_3 and TMSN_3 was reported to cause THF ring opening, associated with azide formation at the benzylic position (Scheme 32).^[48]



Scheme 32. Ring opening of THF to give hydroxy azides.

2.2.3. FeCl₃-Catalysed Three-Component Syntheses of Homoallyl Azides

In a model reaction combining benzaldehyde, allylsilane and TMSN₃ (1:1:1), together with FeCl₃, selective formation of a homoallyl azide was reported by Ghorai and co-workers.^[49] No diazides or diallyl compounds were detected as side products (Scheme 33). Electron-deficient aldehydes were not successfully converted with this system. Here, too, like in the case of Sajiki (Scheme 30), the FeCl₃ plays the role of a Lewis acid, and a benzylic carbocation is involved as an intermediate.



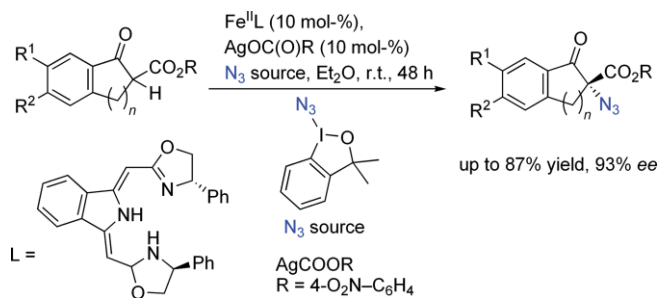
Scheme 33. Synthesis of allylic azides reported by Ghorai and co-workers.

The synthesised allylic azides were explored for further reactivity such as in classical click reactions, reductions, Heck couplings etc.

2.2.4. Fe-Catalysed Enantioselective Azidation of β -Keto Esters and Oxindoles

The first Fe-catalysed enantioselective azidation of β -keto esters was reported in 2013 by Gade and co-workers, who used an I^{III} compound as the azido-transfer reagent (Scheme 34).^[50] The reacting C–H bond in the substrates is activated by the flanking keto and ester functionalities. Screening of the reaction conditions showed Fe(OOCOEt)₂ to give the best results. With use of the chiral “boxmi” pincer ligand developed by the same group, good enantioselectivities were obtained. The best enantioselectivities were obtained in combination with carboxylates. The authors therefore explored different carboxylates in the reaction. Exchanging the anionic ligand of the catalyst with silver arenecarboxylates gave better *ee* values. Finally, silver 4-nitrobenzoate gave the highest *ee* of 93 %. It is good to note that

on exchanging the anion the AgCl formed does not require isolation. The methodology was also applicable to 3-aryloxindoles with comparable enantioselectivities, although it required further optimisation. Subsequent transformation of the installed azide functionality was also demonstrated.

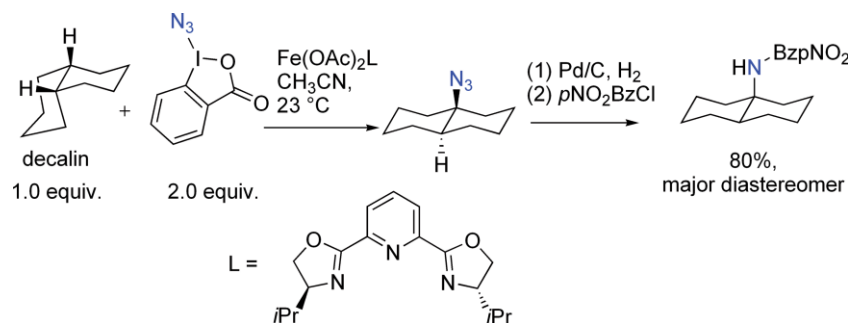


Scheme 34. Fe^{II}-catalysed enantioselective azidation of β -keto esters and oxindoles.

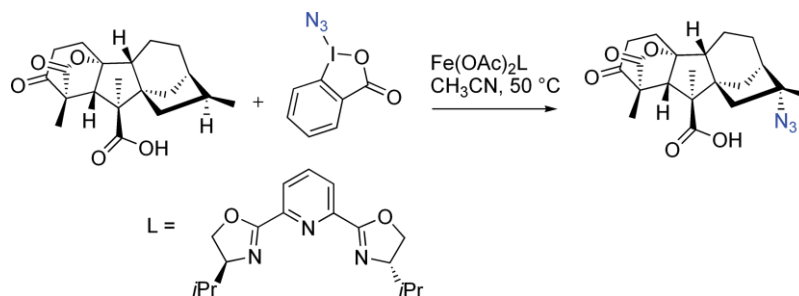
2.2.5. Fe^{II}-Catalysed Azidation of Tertiary C–H Bonds

Direct C–H functionalisation of tertiary unactivated C–H bonds is still one of the holy grails in transition-metal catalysis. Many contemporary catalytic systems can activate relatively unreactive C–H bonds under mild conditions. C–H bond functionalisation has evolved from being a curiosity to a reality for synthetic chemists.^[51,52] The C–H azidation of such bonds was reported in 2015 by Hartwig and co-workers,^[53] who used an iron catalyst based on the tridentate nitrogen ligands of the pybox family (Scheme 35). The azide-transfer reagent was an I^{III} compound. The solvent used was acetonitrile, and the reaction proceeded at room temperature. Decalin as substrate gave a 75 % yield under these conditions, and the products were formed in a 4:1 diastereomeric ratio. Better diastereomeric ratios (*trans/cis*, 6:1) could be obtained in ethyl acetate. Interestingly, electronic bias towards the more electron-rich tertiary C–H bonds was found to be inherent to the system. In cases of multiple C–H bonds, the regioselectivity was influenced by the distance of the electron-withdrawing group from the proximal tertiary C–H bond, in a way reminiscent of the regioselectivity in oxidation reactions.

The most attractive part of this transformation is the fact that it can be applied to complex molecules containing multiple tertiary C–H bonds. Irrespective of the number of tertiary C–H bonds, the azidation takes place at the most electron-rich



Scheme 35. Stereoselective C–H azidation of decalin with the aid of Fe^{II}L.



Scheme 36. Selective C–H azidation of gibberlic acid performed with the aid of the Fe^{II} catalyst with chiral ligand.

position that is sterically most accessible. This was demonstrated for gibberellic acid in an elegant example of late-stage C–H functionalisation (Scheme 36). The diastereomeric ratio of this reaction is independent of the starting compound, meaning that when starting with a mixture of diastereomers, only one diastereomer is obtained.

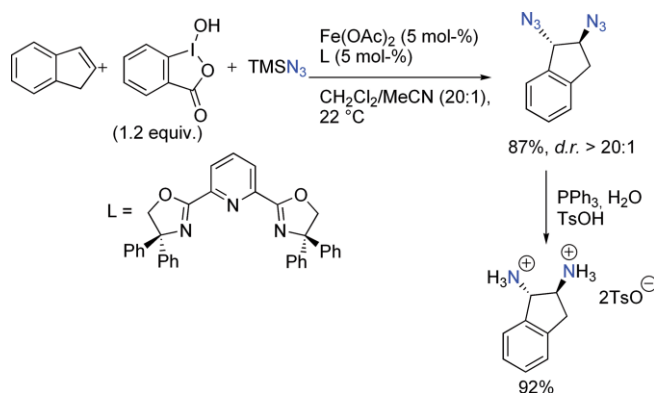
Radical-quenching experiments suggested that the reaction does involve the formation of tertiary alkyl radicals. The measured kinetic isotope effect (KIE) of ca. 5.0 in the case of [D₁₀]ethylbenzene implies that the cleavage of the C–H bond is also the rate-limiting step. Follow-up reactions of the products were also undertaken, demonstrating the formation of tetrazoles, amides, amines, N-containing heterocycles etc., which underpins the importance of azides as synthons for a variety of transformations. These elegant examples not only show the potential of late-stage azidation of C–H bonds, but the protocol also uses much milder reagents, does not involve the use of a massive excess of substrate and can be used on complex organic substrates. As such, the work has already attracted quite some attention in the form of highlights and perspectives.^[54]

Similar photoredox catalysis was reported for halogenation and azidation by Chen and co-workers.^[55] They used the Zhdankin azidoiodane reagent, Ru(bpy)₃Cl₂ and visible-light irradiation at room temperature to form C–H-azidated or -halogenated products from aliphatic substrates. These reactions are efficient, selective and compatible with complex substrates.

2.2.6. Fe^{II}-Catalysed Diazidation of Olefins

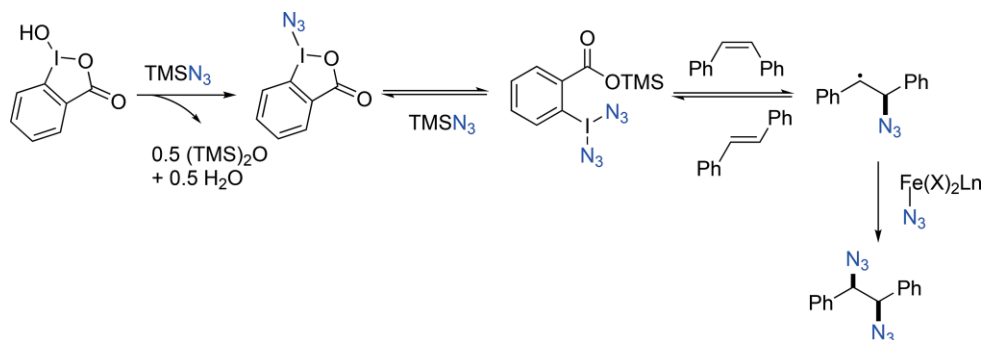
An Fe^{II}-catalysed diastereoselective olefin diazidation operative at room temperature was reported by Xu and co-workers.^[56] The reaction involves the use of TMSN₃ as the azide-transfer reagent, combined with benziodoxole as the oxidant. The

TMSN₃ is assumed to form the required I^{III}–N₃ compound in situ. The diastereomeric ratio could be modulated by changing the ligands on the iron catalyst. Indene was chosen as a test substrate, and in the presence of a bulky pybox-type ligand (similar to the one used by Hartwig and co-workers) diastereomeric ratios of up to 20:1 could be obtained. The products were obtained in 87 % yield (Scheme 37).



Scheme 37. Diastereoselective olefin diazidation of indene with the aid of a chiral Fe^{II} catalyst system.

After demonstrating the substrate scope, the authors moved on to mechanistic studies, which revealed some interesting facts. The Lewis-acidic nature of the TMS group in TMSN₃ was commented on; this may provide some understanding on why some systems work exclusively with TMSN₃ and not with NaN₃. The excess of TMSN₃ used in this system probably activates the I^{III}–N₃ compound to generate a diazido intermediate, which reversibly adds to the alkene, leading to the formation of a carbon radical species (Scheme 38). In the absence of the Fe



Scheme 38. Plausible mechanism of the reaction depicted in Scheme 37.

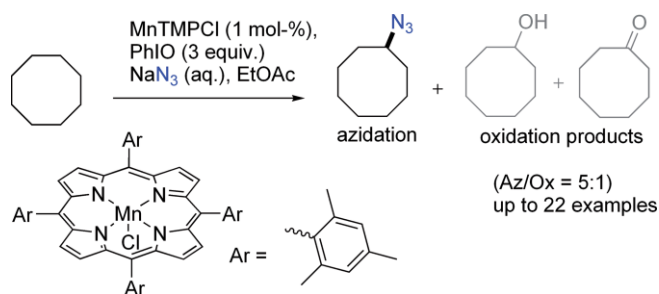
catalyst this carbon radical species undergoes elimination of N_3^- to give the *trans*-alkene. However, in the presence of the Fe catalyst the $I^{III}-N_3$ bond in the azide-transfer reagent is reductively cleaved, forming an azido radical that can further add to the carbon radical species. When this occurs in the inner sphere of the catalyst excellent diastereomeric control in the formation of the final bis(azide) product can be achieved.

2.3. Manganese-Catalysed Azidations

Mn-catalysed reactions are reported to be successful for azidation of aliphatic C–H bonds and also for alkenes; as in the case of the Fe-catalysed systems described above, this contrasts with the Cu-based systems, for which aromatic C–H bonds prevail. Typically, Mn catalysts are used in combination with an oxidant and an azide source. The mechanisms are either oxidative C–H azidation or azide radical addition to olefins. For the C–H bond azidations more sophisticated ligands such as salens and porphyrins are required, whereas for the alkenes $Mn(OAc)_2$ suffices.

2.3.1. Mn-Catalysed Azidation of Aliphatic C–H Bonds

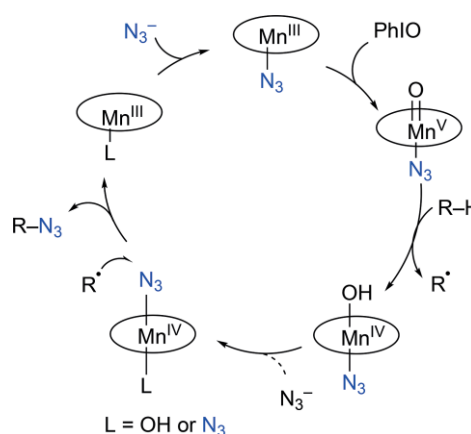
In the context of late-stage azidation Groves and co-workers recently reported an elegant Mn^{III} system capable of azidating aliphatic C–H bonds.^[57] In the development of this system, the authors were inspired by their earlier work on Mn-catalysed C–H bond fluorination.^[58,59] In that work, F-atom transfer from an $Mn^{IV}-F$ complex to free organic radicals in a rebound-type mechanism was found to have a very low barrier, and as such the authors envisioned a similar mechanism for N_3 transfer to hydrocarbons. The most successful system was found to be a manganese catalyst based on the tetramesitylporphyrin (TMP) ligand. The reaction requires a catalyst loading of 1.5 mol-% (Scheme 39). Mn–salen complexes also proved capable of catalysing this transformation. In these reactions an oxidation product is also expected, and the ratio of the azidation/oxidation (Az/Ox) products was found to be highest (5:1) when $Mn(TMP)Cl$ was used as the catalyst. The substrate scope is large and several functionalities are tolerated, such as amides, esters, ketones, carbamates, tertiary alcohols, terminal alkynes, pyridines, thiophenes etc. For the reaction between *trans*-decalin and the $Mn(TMP)Cl$ the secondary azidation was preferred. The efficiency of this process is also affected by the electronic nature of the substrate, with electron-deficient substrates performing poorly.



Scheme 39. $Mn(TMP)Cl$ -catalysed azidation of cyclooctane.

The utility of this method was demonstrated by carrying out azidations of a variety of pharmaceutically relevant complex organic molecules with different substitution patterns, such as memantine (Namenda), pregabalin (Lyrica), rasagline (Azilect), ibuprofen etc. It is noteworthy that mechanistically the $Mn^{III}TMPCl$ -catalysed reaction proceeds through a mechanism different from that followed by the systems that use $I^{III}-N_3$ compounds.

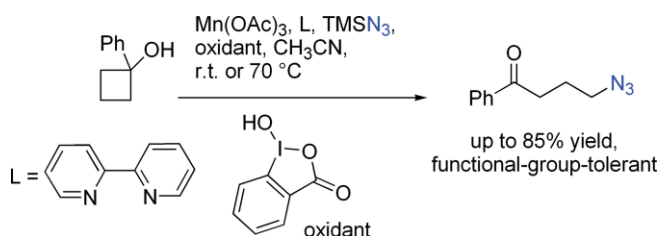
Here PhIO first oxidises the resting Mn^{III} catalyst to the hydrogen-abstrating oxo- Mn^V intermediate (Scheme 40). The substrate radical formed after hydrogen abstraction is then captured by the $Mn^{IV}-N_3$ intermediate to form the C– N_3 bond with regeneration of the catalyst. An excellent perspective article by Groves and Huang focuses on the evolution of these “tamed” azide radicals that take part in C–H bond functionalisation.^[54,60]



Scheme 40. Proposed mechanism of (TMP) $MnCl$ -mediated azidation.

The formation of $(TMP)MnN_3$ was observed by UV/Vis spectroscopy. The regioselectivity probably arises from the H-abstraction step, presumably by an oxomanganese(V) species rather than by azide radicals as commonly observed for other systems. KIE studies supported this proposal.

The oxidative azidation of cyclobutanols, with ring opening leading to the formation of alkyl azides with γ -carbonyl substituents, was reported by Zhu and co-workers.^[61] $Mn(OAc)_3$ with bidentate N-containing ligands in combination with $TMSN_3$ and benziodoxole gave the γ -keto azides in up to 85% yield (Scheme 41). Functional-group tolerance was demonstrated, and both electron-rich and electron-poor substrates were successfully converted.



Scheme 41. Oxidative azidation of cyclobutanols with the aid of $Mn(OAc)_3$.

Mechanistically, a radical pathway was suggested on the basis of the observation that TEMPO or BHT is detrimental to the reaction. Additionally, substrates containing either alkyl or aryl substituents next to the hydroxy group give mixtures of diastereomers. This also suggests a radical mechanism, because an ionic pathway should give rise to single diastereoisomers.

2.3.2. Mn-Catalysed Azidation of Alkenes

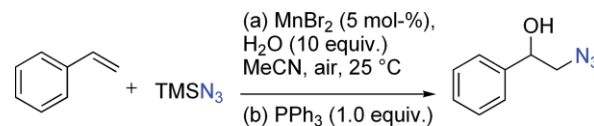
Mn^{III}-mediated phosphonation/azidation of alkenes with the aid of a simple Mn(OAc)₃ catalyst and TMSN₃ as the azide source has been reported.^[62] In this reaction a P–C bond and a C–N bond are formed in a single transformation. With diethyl *H*-phosphonate and styrene as the reaction partners yields up to 88 % could be obtained, although the amount of Mn(OAc)₃ used is stoichiometric (Scheme 42). The transformation could also be scaled up to about 1 g.



Scheme 42. Phosphonation/azidation of alkenes in the presence of Mn(OAc)₃.

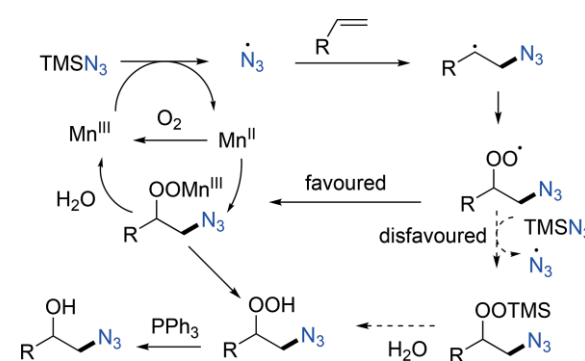
In another report, Jiao and co-workers^[63] developed a catalytic reaction based on aerobic oxidative generation of azido radicals that add to alkenes. This leads to the formation of β -azido alcohols, which can later be converted into aziridines, β -amino alcohols or N- or O-containing heterocycles. Use of styrene as the model substrate and performing the reaction in air in the presence of MnBr₂ and TMSN₃ gave the desired product in up to 88 % yield (Scheme 43). It is noteworthy that Mn^{III} sources also gave the desired products but in lower yields, despite the oxidative conditions of the reaction. MnBr₂ plays a dual role here, both generating the azido radical and stabilising the peroxy radical. Terminal alkenes can also be azidated and so were internal alkenes. Various aliphatic alkenes could be hydroxy-azidated by use of this protocol.

The use of O₂ from air as the oxidant is an advantage of this system, because it prevents over-oxidation of other functional groups. This makes this system quite functional-group-tolerant. The azido precursor here is TMSN₃, which is oxidised by air, meaning that it does not need to be pre-prepared as in the case of halo-azides and hypervalent I^{III}–N₃ reagents.



Scheme 43. Oxidative azidation of styrene to give the corresponding β -azido alcohol.

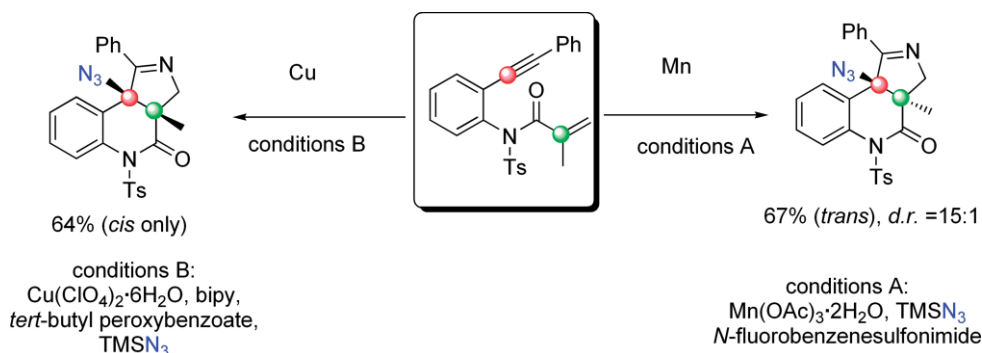
Mechanistically, Mn^{II} is first oxidised to Mn^{III/IV} by O₂ (Scheme 44). Mn^{III} then oxidises TMSN₃ to form an azido radical. This subsequently attacks the alkene at a sterically favoured position, leading to the formation of a carbon radical, which can then be trapped by molecular oxygen to form the peroxy radical. This then undergoes Mn-mediated SET and protonation to give the β -azido peroxy alcohol. Finally, PPh₃ reduces the peroxy alcohol to give the final β -azido alcohol.



Scheme 44. Mechanism of the reaction depicted in Scheme 43.

2.3.3. Diastereodivergent Radical Cyclisation/Azidation of 1,7-Enynes

Selective synthesis of both *cis*- and *trans*-pyrrolo[3,4-*c*]quinolines through the use of two sets of catalysts and ligand systems was reported by Wan and co-workers.^[64] In the transformation of *N*-sulfonyl-tethered 1,7-enynes the Mn(OAc)₃-catalysed reaction yielded the *trans* product with high selectivity, whereas the Cu-catalysed system gave the *cis* product with high selectivity. The transformation is summarised in Scheme 45. Also in this case a radical process is operative; the reactions do not proceed in the presence of TEMPO or BHT.



Scheme 45. Summary of the diastereodivergent cyclisation/azidation of 1,7-enynes catalysed by Mn and Cu catalysts.

3. Noble-Metal-Catalysed Azidations

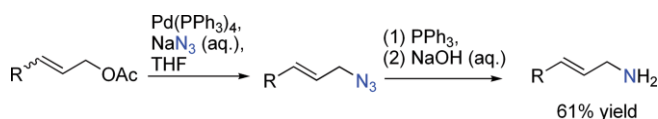
As well as base metals, there are also several interesting reports of azidation reactions that are performed by noble metals. Whereas base-metal-catalysed azidations appear to be dominated by radical-type reactions involving generation of azide radicals, noble-metal-catalysed azidation reactions predominantly proceed by (ionic) non-radical pathways in which N_3^- acts as a nucleophile. Aliphatic C–H bonds do not seem to be accessible as reaction partners in most noble-metal catalysts reported to date. The only substrates thus far reported to be susceptible to noble-metal-catalysed azidation are allyl acetates, alkenes, allenes, aromatic C–H bonds and alkynes. Mechanistically they mostly proceed by allylic azidation and oxidative addition and reductive elimination pathways. Some enantioselective azidations have been reported in the case of Pd. Chiral catalysts for Ag, Au and Rh systems have apparently not yet been successful or have not yet been explored intensively.

3.1. Palladium-Catalysed Reactions

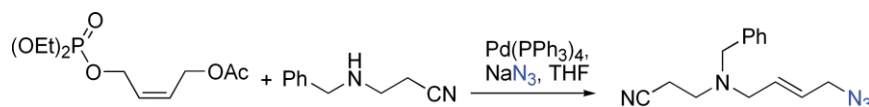
Although azidation reactions today are dominated by reactions mediated by Cu, Mn and Fe, the first examples of catalytic azidation reactions were based on palladium. However, examples are limited to allyl acetates. Both Pd^0 and Pd^{II} complexes have been used. In some cases, very high catalyst loadings were needed. However, enantioselective azidation is possible with palladium, and this has been used in the total synthesis of some natural products. The Pd systems are dominated by ionic pathways: that is, allylic azidation and “traditional” oxidative addition and reductive elimination elementary steps.

3.1.1. Palladium(0)-Catalysed Azidations

In 1986 Taniguchi and co-workers reported the Pd-catalysed azidation/amination of allyl acetates.^[65] In a one-pot protocol, with $\text{Pd}(\text{PPh}_3)_4$ as the catalyst and NaN_3 as the azide source acting as a nucleophile, allyl acetates were converted into allylamines, via allyl azide intermediates (Scheme 46). In each case the (*E*) isomer was obtained. Conversion of the allyl azide into the allylamine requires the presence of additional PPh_3 and 2 *N* NaOH and acidic workup. An example of a case in which the substrate is the (*Z*) isomer but the obtained product is the (*E*) isomer is shown in Scheme 47.

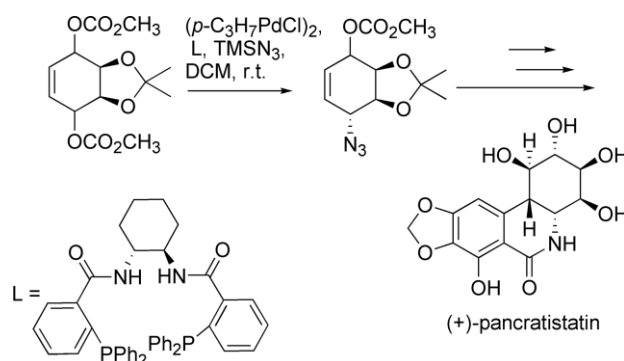


Scheme 46. $\text{Pd}(\text{PPh}_3)_4$ -catalysed azidation of allyl acetates followed by reduction to corresponding amines by PPh_3 .



Scheme 47. Pd-catalysed azidation of a (*Z*)-allyl acetate to give the (*E*) product.

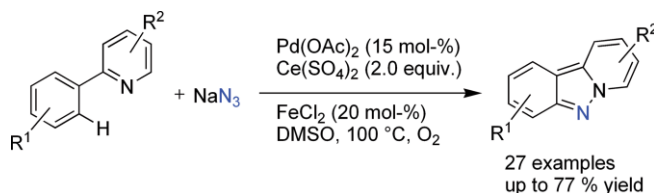
This Pd^0 strategy for azidation of esters was also used in an enantioselective variant in the first reported total synthesis of (+)-pancratistatin,^[66] reported by Trost and co-workers in 1995. By use of a Pd–allyl complex together with a chiral ligand the carbonate ester could be stereoselectively converted into the azide, which was then derivatised in multiple steps to form (+)-pancratistatin (Scheme 48). The same strategy was also used for the desymmetrisation step in the total synthesis of (–)-epibatidine, another natural product.^[67]



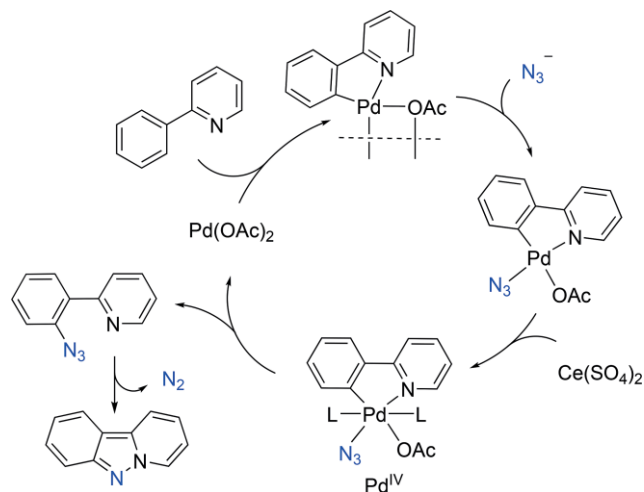
Scheme 48. Part of the total synthesis of (+)-pancratistatin that employed Pd-catalysed azidation.

3.1.2. Palladium(II)-Catalysed Azidation

Tandem Pd-catalysed C–H azidation and N–N bond formation in arylpyridines, promoted by a $\text{Pd}(\text{OAc})_2$ catalyst, was reported by Jiao and co-workers in 2013 (Scheme 49).^[68] Here, C–H activation of the aromatic ring first takes place through chelation-directed cyclopalladation to form a cyclopalladium(II) dimeric species. Ligand exchange with the azide anion (NaN_3 being the azide source), oxidation [$\text{Ce}(\text{SO}_4)_2$] and subsequent reductive elimination generates the C–H-activated *ortho*-azidated product with regeneration of the Pd^{II} catalyst (Scheme 50). The methodology does not work with TMSN_3 and is also sensitive to solvent. Overall this is a concise method for the synthesis of pyrido[1,2-*b*]indazoles from readily available arylpyridines. The catalyst loadings were, however, as high as 15 %.

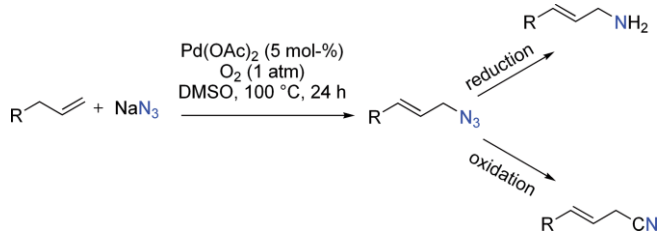


Scheme 49. C–H azidation of arylpyridines and subsequent N–N bond formation in the presence of Pd^{II} .



Scheme 50. Mechanism of the reaction depicted in Scheme 49.

Pd^{II} -catalysed allylic C–H azidation, which also uses NaN_3 as the azide source and works under oxygen (atmospheric pressure), has also been reported.^[69] The Pd^{II} source used is $\text{Pd}(\text{OAc})_2$. The methodology uses DMSO as the solvent and works at the rather high temperature of 100 °C (Scheme 51). The formed products can be further transformed into triazoles by use of a Cu catalyst in the same pot. The installed azide moiety can also be reduced to give allylic amines or oxidised to give allyl nitriles.



Scheme 51. Pd^{II} -catalysed allylic C–H azidation.

3.2. Ag-Catalysed Azidations

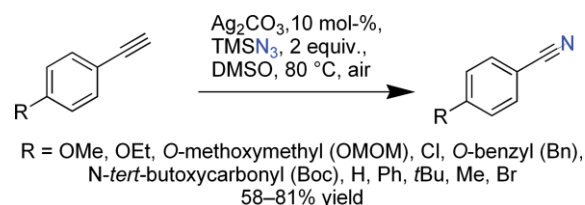
All examples of silver-catalysed azidations involve unsaturated bonds – in alkynes, diynes and ethynyl carbinols, for example – and the reactions proceed via intermediate vinyl azides. The formation of *trans*-alkenyl complex of silver with alkynes is quite different from the corresponding reaction behaviour of gold π complexes. This also leads to different reaction products with similar substrates. There is, however, one exception in which a decarboxylative azidation is mediated by a silver catalyst in a free-radical process. Mechanistically, this seems so far to be the only noble-metal-catalysed azidation reaction that proceeds through a SET process.

3.2.1. Ag-Catalysed Functionalisation of Alkynes by Azidation

In 2013 Jiao and co-workers reported the direct conversion of alkynes into nitriles through C \equiv C bond cleavage.^[70] Although the azide moiety is not retained in this reaction, the corre-

sponding nitrile product is formed via an azide intermediate. Nitriles are commonly encountered structural motifs in nature and are also widely found in agricultural chemicals, medicines, dyes etc. By combining an alkyne azidation step with a silver catalyst Jiao and co-workers were able to show that the silver catalyst leads to the formation of a *trans*-alkenyl–metal complex, in a way mechanistically distinct from that observed with gold salt π -acid catalysts.

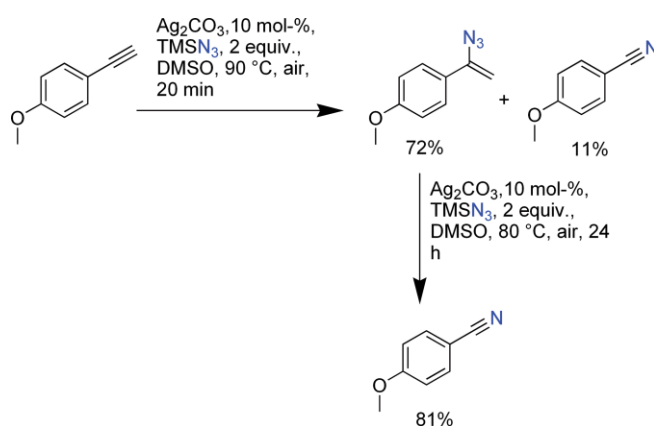
Initially, the nitrogenation of (*para*-methoxyphenyl)acetylene was investigated in the presence of Ag_2CO_3 and TMSN_3 in DMF as the solvent. This led to the formation of the corresponding nitrile in 58 % yield. On changing the solvent to DMSO the same product was obtained in 81 % yield (Scheme 52). The use of DMSO as the solvent and TMSN_3 as the nitrogen source was crucial for the success of the reaction. At the same time, increasing the reaction temperature from 80 °C to 130 °C led to lowering of the yield.



Scheme 52. Ag-catalysed synthesis of nitriles from alkynes by azidation.

The substrate scope of this reaction is remarkable. Both electron-donating and halogen substituents on the phenyl ring gave the corresponding aromatic nitriles in moderate to excellent yields. Even substituents with unprotected reactive groups such as NH_2 and NH gave satisfactory yields. Heteroaryl compounds were also tolerated in this reaction. At the same time, aliphatic alkynes were also suitable candidates for this transformation.

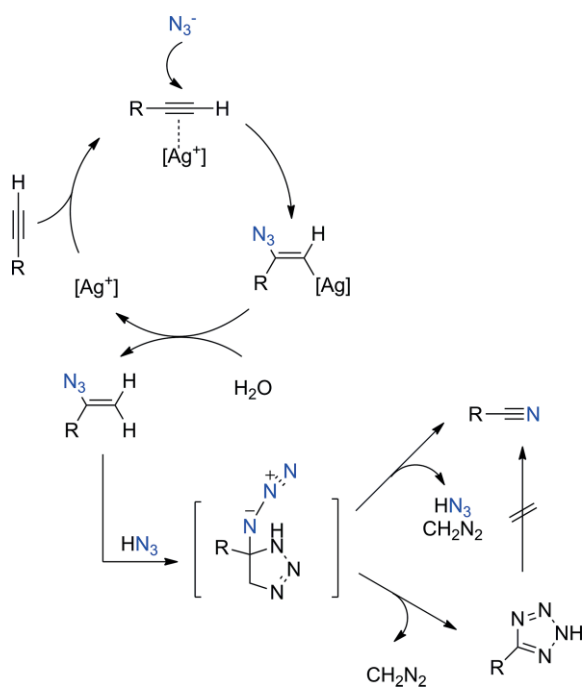
Mechanistically, a free-radical pathway was ruled out, because addition of TEMPO was not detrimental to the efficiency of this reaction. However, during the reaction a key vinyl azide intermediate was observed and characterised (Scheme 53). In the presence of more TMSN_3 and Ag_2CO_3 the vinyl azide intermediate was smoothly converted into the corresponding nitrile.



Scheme 53. Isolation of the vinyl azide intermediate and further reaction with TMSN_3 and Ag_2CO_3 to give the nitrile product.

This shows that more than 1 equiv. of TMSN_3 is required for the successful conversion of the alkyne into the nitrile. Additional mechanistic insight was gained by performing the reaction in $[\text{D}_6]\text{DMSO}$ and monitoring the reaction by ^1H NMR spectroscopy. The peaks of the vinyl azide species could be assigned, and these increased and decreased over time as the nitrile product was generated.

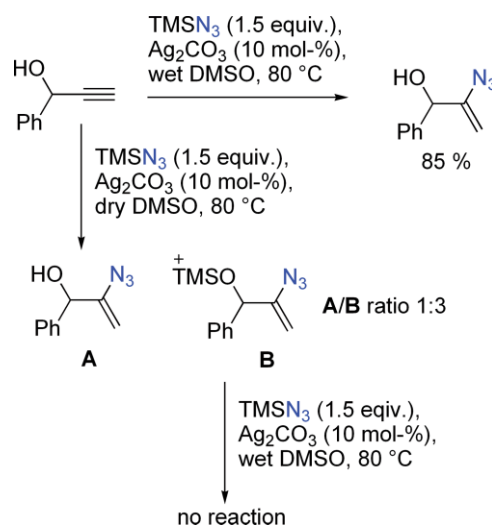
The proposed mechanism is depicted in Scheme 54. The alkyne is first activated by the silver catalyst, followed by attack of the azide anion. This leads to the formation of the *trans*-alkenyl complex. Protonation of this *trans*-alkenyl complex generates the vinyl azide, which likely involves the presence of trace amounts of water in the DMSO. The vinyl azide then cyclises with another azide as in a traditional click reaction to form the triazole intermediate. This triazole could either form a tetrazole by release of diazomethane or transform directly into the nitrile under the applied standard reaction conditions. Because a control experiment starting from the tetrazole under the standard reaction conditions did not produce the nitrile product, this pathway could be ruled out. Thus, the reaction involves fast rearrangement of the triazole that releases HN_3 and CH_2N_2 in the process.



Scheme 54. Proposed mechanism of the reaction depicted in Scheme 52.

Whereas in the previous example by Jiao and co-workers the azidation of alkynes led to the formation of a triazole intermediate that rearranged to give the corresponding nitrile in the same reaction pot, Bi and co-workers demonstrated that by installing a hydroxy group next to the alkyne functionality the azide product could be stabilised to give the vinyl azide as the final product.^[71] The hydroxy group also dictates the regioselectivity of this reaction involving terminal alkynes, because no 2-hydroxy-2-phenylacetonitrile was detected by ^1H NMR spectroscopy, unlike in the reactions reported by Jiao (Scheme 52).

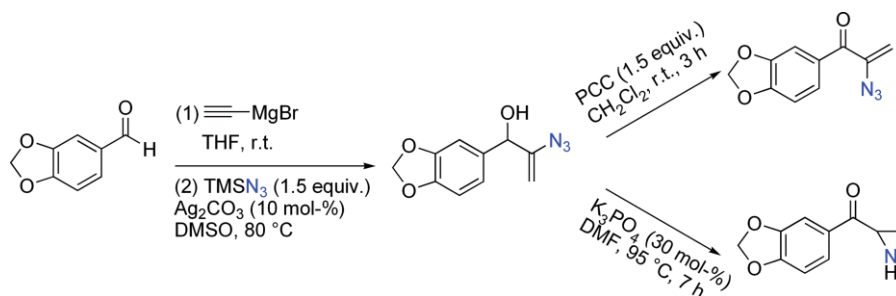
Under the standardised reaction conditions with ethynyl carbinol as the substrate, Ag_2CO_3 (10 mol-%) gave the best yields with TMSN_3 (1.5 equiv.) as the azide source and DMSO as the solvent. The substrate scope was demonstrated to be very broad. Substituents with bulky groups required longer reaction times (up to 8 h). Both electron-rich and electron-deficient (hetero)aryl and alkyl groups were tolerated. Other reactive functionalities such as alkenyl, alkynyl and cyclopropyl moieties were also tolerated. By attempting to perform the reaction in dry DMSO, the authors established the importance of residual water in the solvent. Under absolutely dry conditions the desired vinyl azide **A** was formed together with the *O*-trimethylsilylated product **B** in a 1:3 ratio (Scheme 55). Furthermore, on subjection of the *O*-trimethylsilylated product to the standardised reaction conditions it remained intact, showing that the TMS product does not undergo hydrolysis to give the vinyl azide product.



Scheme 55. Hydro-azidation of ethynyl carbinols.

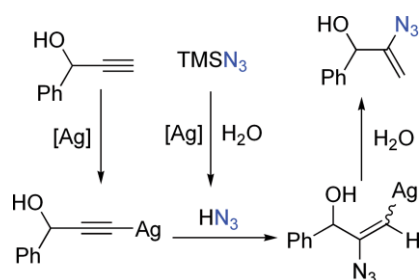
Additionally, the authors demonstrated gram-scale synthesis of the vinyl azide product starting from the aldehyde, which is remarkable. This product could be transformed into the α -carbonyl vinyl azide by use of pyridinium chlorochromate (PCC) as the oxidant. In addition, by use of potassium phosphate (K_3PO_4) the vinyl azide could be directly converted into the NH aziridine, a transformation not reported elsewhere. By this methodology other substituted vinyl azides were also converted into the corresponding NH aziridines (Scheme 56).

Mechanistically a free-radical pathway was excluded by means of experiments conducted in the presence of TEMPO free radical. Instead, formation of a silver acetylide complex was proposed, based on the observation that when starting from the silver acetylide the vinyl azide was obtained in the presence of TMSN_3 under the standardised reaction conditions without any additional Ag_2CO_3 . Also, internal alkynes do not react under these conditions. The importance of the OH group was underlined by an experiment in which the OH moiety was replaced by an OBn substituent. This led to loss of selectivity, because now the nitrile product was also formed. Moreover, when D_2O was added to the reaction mixture the isolated product had



Scheme 56. Synthesis of vinyl azides and azirines starting from the aldehyde in a gram-scale reaction.

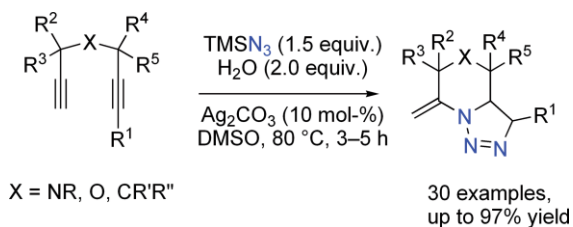
93 % deuterium incorporated, thus showing the importance of the residual water in the solvent. These observations led to the tentative mechanism depicted in Scheme 57.



Scheme 57. Proposed mechanism for the Ag-catalysed hydroazidation of ethynyl carbinols.

After formation of the silver acetylide complex, the species reacts with hydrazoic acid (HN_3) formed from the silver-catalysed reaction between TMSN_3 and water. This gives a vinyl silver intermediate, which undergoes protonation from residual water to produce the desired azide.

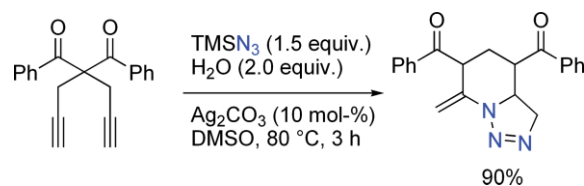
In a follow-up study, Bi and co-workers employed a variety of diynes and TMSN_3 in a silver-catalysed reaction to perform a tandem hydroazidation/alkyne–azide cycloaddition sequence to give 1,5-fused 1,2,3-triazole frameworks.^[72] These 1,5-fused 1,2,3-triazoles are biologically active compounds. The general reaction is depicted in Scheme 58.



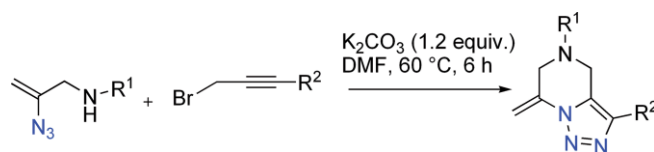
Scheme 58. Ag-catalysed reaction of diynes to give fused triazoles.

In the reaction of the diyne depicted in Scheme 59 with TMSN_3 , 2 equiv. of H_2O and Ag_2CO_3 the triazole product was obtained unexpectedly, in 90 % yield. On investigation of the substrate scope the symmetrical diynes showed good reactivity, with yields between 80 and 90 %. The yields were also satisfactory for unsymmetrical diynes, thus showing a broad tolerance to different substituents. The mechanism was confirmed to be a sequence involving hydroazidation followed by alkyne–azide cycloaddition of the diynes with TMSN_3 . This was done by first

synthesising the vinyl azide in a silver-catalysed step and then treating it with propargyl bromides (Scheme 60) under basic conditions. The desired product was formed in excellent yields, thus establishing that the silver takes part only in the hydroazidation step.

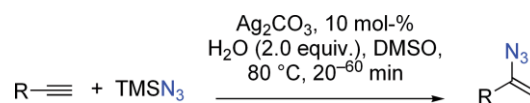


Scheme 59. Standardised reaction conditions for the reaction depicted in Scheme 57.



Scheme 60. Experiment establishing the non-involvement of Ag in the cyclisation step of the reaction depicted in Scheme 59.

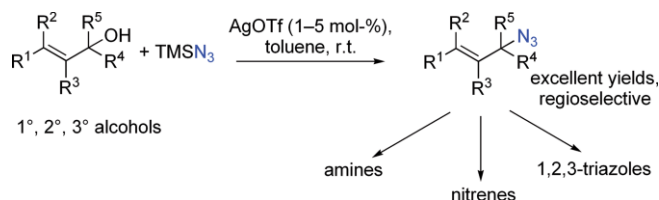
A more general route to vinylic azides by hydroazidation of terminal alkynes with TMSN_3 in the presence of Ag_2CO_3 was reported by Bi and co-workers.^[73] Stoichiometric amounts of H_2O were used in the reaction to avoid dependence on the hydroxy group, as in the case of ethynyl carbinols. With 2 equiv. of water full conversion of 1-bromo-4-ethynylbenzene into the corresponding vinyl azide was achieved under catalytic conditions (Scheme 61). Aryl, alkyl and alkenyl terminal alkynes gave good yields. Propargyl compounds were also successfully converted into the vinyl azides. The method was therefore quite general and worked well for unactivated terminal alkynes. The vinyl azide products are interesting substrates for the synthesis of triazoles, amino ketones etc.



Scheme 61. Ag-catalysed azidation of alkynes to give vinyl azides.

Direct catalytic azidation of allylic alcohols in the presence of AgOTf as the catalyst was reported by Rueping and co-work-

ers^[74] (Scheme 62). Allylic azides are interesting substrates for a variety of reactions involving nitrenes. The conditions were mild: with use of 5 mol-% of the catalyst and TMSN₃ as the azide source, high yields could be obtained at room temperature with reaction times ranging between 4 and 16 h. Primary, secondary and tertiary alcohols were all accessible. Functional-group tolerance was also demonstrated.



Scheme 62. Ag-catalysed azidation of allylic alcohols.

3.2.2. Silver-Catalysed Decarboxylative Azidation of Carboxylic Acids

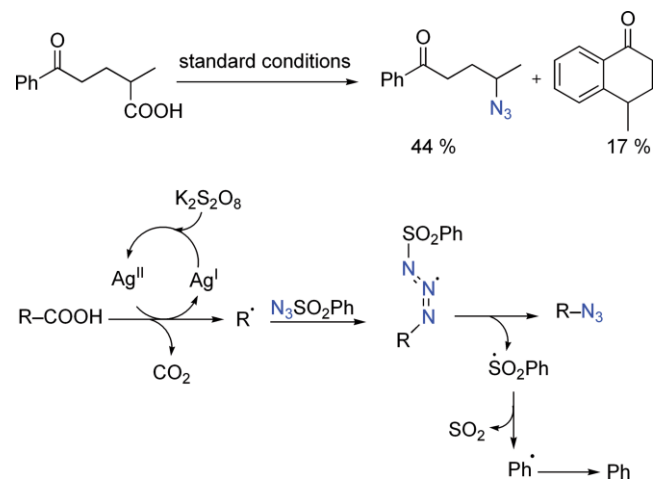
Decarboxylative nitrogenation of aliphatic carboxylic acids for the synthesis of alkyl azides was reported independently and almost simultaneously by Li and co-workers^[75] and by Jiao and co-workers.^[76] In this methodology K₂S₂O₈ is used as an oxidant, AgF or AgNO₃ as the catalyst and PhSO₂N₃ as the azide source. Interestingly, the mechanism is believed, on the basis of EPR and DFT calculations, to involve an alkyl radical formed after decarboxylation of the carboxylic acid moiety. The alkyl azide can be tertiary, secondary or primary. Previously, alkyl substrates had been encountered only for base metals, such as Hartwig's Fe-catalysed example or Groves' Mn-catalysed system. For a noble metal this example is an outlier, in the sense that it is effective for alkyl substrates and appears to proceed by a single-electron-transfer mechanism. These are features encountered more typically for base-metal catalysts (Scheme 63).



Scheme 63. Ag-catalysed decarboxylative azidation of carboxylic acids.

After screening of the reaction conditions, the most effective system proved to be a combination of AgNO₃ or AgF, PhSO₂N₃ as the azide source and K₂S₂O₈ as the oxidant (72 % yield). Other azide sources such as NaN₃ or Togni-N₃ gave no products. AgF was chosen as the catalyst of choice because of its higher photostability. The reaction is most effective for tertiary aliphatic carboxylic acids, followed by secondary and primary acids. However, the aromatic benzoic acid does not react under these conditions at all. In this case the addition of 2 equiv. of TEMPO was detrimental to the reaction, and no azide product was detected. Additionally, treatment of 2-methyl-5-oxo-5-phenylpentanoic acid under the applied standard reaction conditions gave a cyclic byproduct, which also hints at the formation of a carbon radical that undergoes cyclisation (Scheme 64, top). A carbon radical was also detected by EPR spectroscopy

in a sample of the reaction mixture after 50 min under standard reaction conditions. DFT calculations revealed more information about the SET process. The reaction barriers predicted by DFT are in line with the fact that TMSN₃ is not effective in this reaction. The overall mechanism is depicted in Scheme 64 (bottom).



Scheme 64. Top: formation of a cyclised side product confirming the involvement of a carbon radical. Bottom: proposed mechanism for decarboxylative azidation in the presence of Ag.

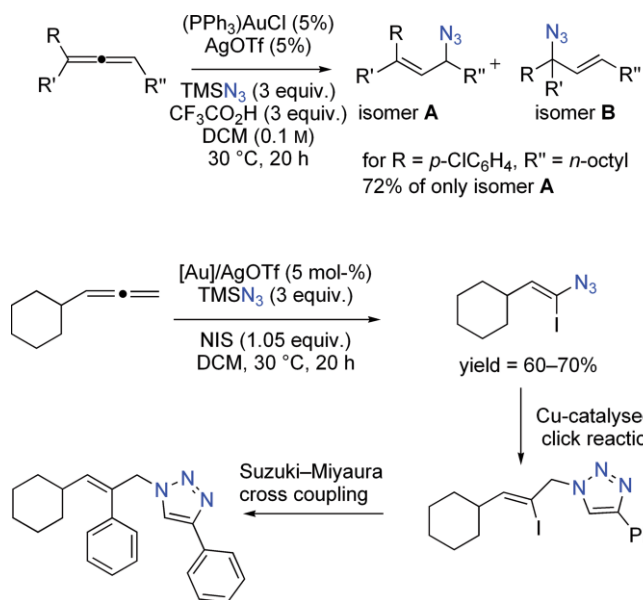
3.3. Au-Catalysed Azidations

Allenes and alkynes are widely used substrates in gold chemistry. In gold-catalysed azidation reactions, too, these are commonly encountered substrates. Au^IPPh₃ complexes are used in two of the reactions discussed below, whereas in the other JohnPhos/gold(II) catalyst is used. The azidating reagent is TMSN₃ in all cases. These reactions require no external oxidants. The azide ion simply works as a nucleophile. The products of some of these azidations (an iodo-azide and amides generated by azidation of alkynes, and tetrazoles formed by C–C bond cleavage) are unique to these systems.

3.3.1. Au-Catalysed Azidation of Allenes

A gold-catalysed allene azidation protocol was developed by Muñoz and co-workers in 2014. The authors used (PPh₃)AuCl/AgOTf as the catalyst, TMSN₃ as the nucleophile and cyclohexylallene as a test substrate.^[77] Full conversion was achieved to produce the anticipated allyl azide and its regioisomer. Allyl trifluoroacetate was also obtained, together with the corresponding acetamide as an unexpected product. To make the reaction more selective, [(PhO)₃P]AuCl was used as the catalyst (Scheme 65). Additionally, water was used as an additive, and temperatures were lowered. The regioselectivity of the reaction was found to be dictated by the electronic nature of the allenes. A phenyl group close to the allene gave only one regioisomer, and the selectivity was reduced as the phenyl group moved further away from the allene. The synthetic utility of this system was demonstrated by the synthesis of iodinated allyl azides. The azide could be used in a further reaction to give a triazole,

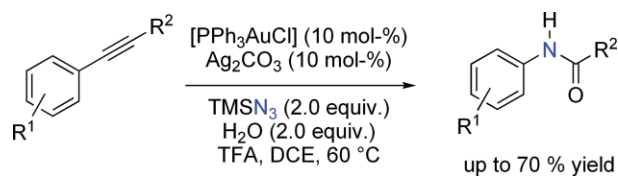
and the iodo functionality could be utilised for cross-coupling. The mechanism of this reaction requires more attention; NMR studies suggested that a complex equilibrium seems to exist.



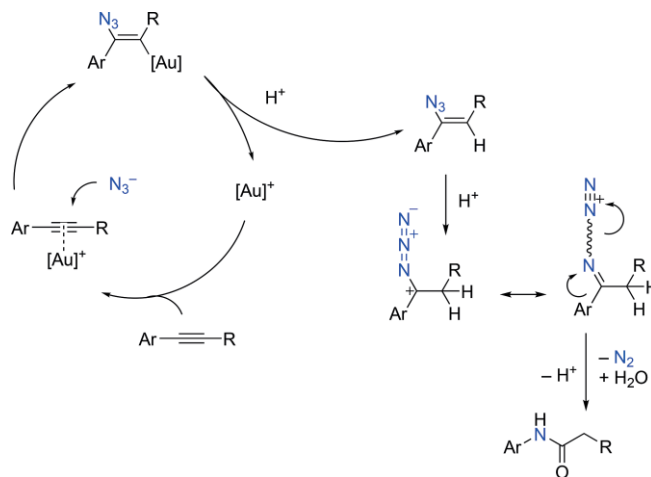
Scheme 65. Gold-catalysed azidation of allenes and further functionalisation.

3.3.2. Au-Catalysed Formation of Amides from Alkynes by Azidation

In a rare example of aryl–alkyne C–C bond cleavage, Jiao and co-workers reported the formation of amides^[78] directly from substrates such as 1,2-diphenylethyne with use of TMSN_3 as nitrogen source (Scheme 66). $(\text{PPh}_3)\text{AuCl}/\text{Ag}_2\text{CO}_3$ was found to be efficient, and $\text{Ag}(\text{CF}_3\text{CO}_2)$ proved to be the best chloride ion abstractor in this case. The diaryl substitution at the alkyne was not a necessity, but aryl substitution gave better results. An ester-substituted phenylacetylene derivative gave no useful conversion. On monitoring the reaction by NMR spectroscopy the authors were also able to elucidate a mechanism in which activation of the alkyne by the catalyst is the first step, followed by nucleophilic attack of the azide anion to produce a *trans*-alkenyl–gold complex. In agreement with this hypothesis, (1-azidovinyl)benzene also yielded the expected amide product. This substrate also gave the product in the absence of the catalyst, thus confirming that the Au catalyst is involved only in the first steps of the reaction (i.e., activation of the alkyne and subsequent nucleophilic attack of the azide anion). The proposed mechanism is depicted in Scheme 67.



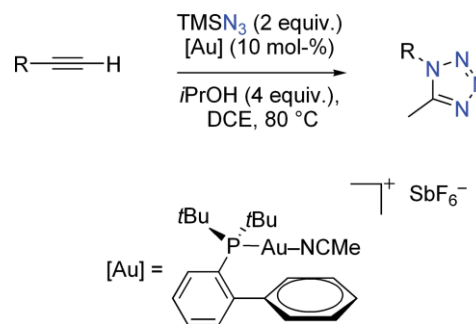
Scheme 66. Gold-catalysed reaction of aryl–alkynes to give amides by azidation.



Scheme 67. Mechanism of the reaction depicted in Scheme 66.

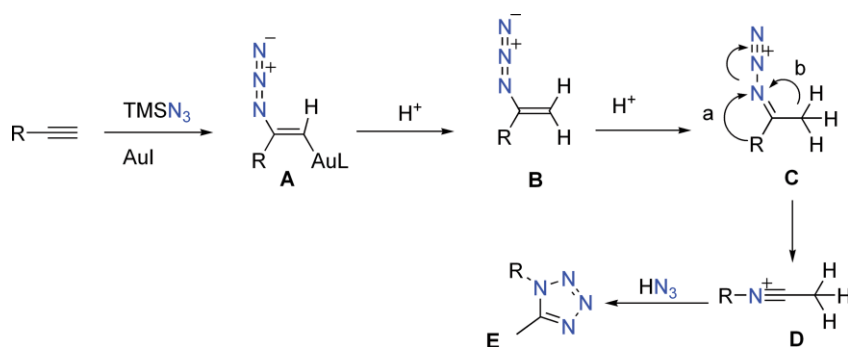
3.3.3. Au-Catalysed Synthesis of Tetrazoles from Alkynes

The reported Au-catalysed reaction of alkynes to give amides as discussed above involves the cleavage of the aryl–alkyne bond in the alkyne by the action of $[\text{Au}(\text{PPh}_3)\text{Cl}]$ and Ag_2CO_3 in the presence of water and trifluoroacetic acid. In a follow-up study Echavarren and co-workers reported the use of a JohnPhos/gold(I) catalyst that takes part in reactions with alkynes in the absence of Ag_2CO_3 .^[79] The gold catalyst in this reaction plays a dual role, firstly by activating the alkyne towards nucleophilic attack and secondly by generating the Brønsted acid required for the final transformation of the alkenyl azide into the tetrazole (Scheme 68).



Scheme 68. Au-catalysed synthesis of tetrazoles from alkynes by use of the JohnPhos/Au system.

Initially the transformation was attempted in a stoichiometric reaction in which an alkyne, TMSN_3 , the neutral Au complex and AgSbF_6 were mixed in dichloromethane at room temperature. This gave the tetrazole product still coordinated to the Au complex, thus implying that release of the product from Au might be challenging under the applied catalytic conditions. However, on increasing the temperature and performing the reaction in *i*PrOH the reaction could indeed be made catalytic. For electron-poor alkynes the yields were lower, and for internal alkynes the reaction was not successful. Aliphatic alkynes could also be employed in the reaction. The proposed mechanism is outlined in Scheme 69.

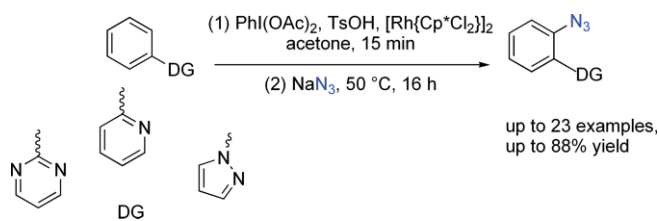


Scheme 69. Proposed mechanism of the Au-catalysed synthesis of tetrazoles from alkynes.

The reaction can be explained in terms of a mechanism that proceeds by reaction between an $(\eta^2\text{-alkyne})\text{gold(I)}$ complex and HN_3 , formed in situ from TMSN_3 and $i\text{PrOH}$, to give **A**, which undergoes protodeauration to form **B** (Scheme 68). Protonation of **B** would give the iminodiazonium cation **C**, which could evolve to form the nitrilium cation **D** by migration of the R group (path a). Competitive migration of the methyl group (path b) is also possible. Finally, a formal 1,3-dipolar cycloaddition of HN_3 to **D** provides product **E**.

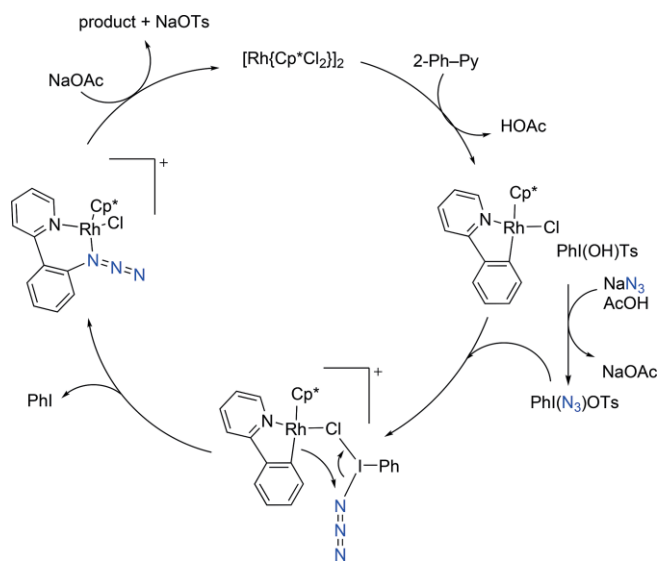
3.4. Rhodium-Catalysed Azidation

In 2013 Li and co-workers reported on the *o*-azidation^[80] of 2-phenylpyridine in the presence of $[\text{RhCp}^*\text{Cl}_2]$ as the catalyst. A hypervalent iodine source – $\text{PhI}(\text{OAc})_2$ – was used as the oxidant and NaN_3 as the azide source (Scheme 70). This methodology is reminiscent of the aniline system used by Jiao and co-workers, in which an oxidant and a directing group (DG) also used to achieve selective azidation of the aniline^[14] at the *ortho* position.



Scheme 70. Rh-catalysed azidation of arenes. DG = directing group.

In contrast with the base-metal-catalysed reactions described in Section 2, this reaction does not involve the formation of azide radicals. The proposed mechanism of the reaction involves Rh^{III} species, with cyclometallation of 2-phenylpyridine with the initial Rh dimer complex taking place first (Scheme 71). The active azidation reagent – $\text{PhI}(\text{N}_3)\text{OTs}$ – then reacts with this intermediate. In the next step electrophilic azidation takes place via a proposed five-membered TS involving a rhodacycle. Subsequently, PhI is eliminated, leading to release of the azidated product. The selectivity of the reaction can be attributed to the pyridine directing group and chelation of the substrate on the metal atom.



Scheme 71. Mechanism of the Rh-catalysed azidation reactions of arenes depicted in Scheme 70.

4. Conclusions

This review highlights metal-catalysed approaches to azide synthesis, with the main focus on the substrate scopes, mechanisms and applicability. Metal-catalysed reactions that introduce azide moieties into organic compounds are relatively new in the field of catalysis. Most examples in this review date from the last decade if not the last five years, which is rather surprising in view of the frequent use of organic azides in a variety of organic synthetic transformations.

Quite a few examples involve direct functionalisation of C–H bonds. They include aromatic and activated (allylic, benzylic, α -carbonyl) C–H bonds, but quite a few examples involving azidation of aliphatic C–H bonds are also described. These reactions appear to involve reactive azide radicals in the C–H bond azidation process, and yet proceed quite selectively in many cases. Nucleophilic substitution reactions involving the N_3^- anion as the nucleophile are other frequently encountered strategies used to introduce the azide moiety. Notably, reactions proceeding through azide radical formation are frequently encountered for Cu-, Fe- and Mn-catalysed reactions, whereas azidation reactions mediated by the late transition metals Pd, Rh and Au seem

to proceed mostly by ionic pathways, such as allylic azidation and/or "traditional" oxidative addition and reductive elimination elementary steps. This is in line with the commonly observed $1e^-$ reactivity of base metals in contrast to the $2e^-$ reactivity of noble metals.

Directing-group strategies are also frequently encountered in these catalytic reactions, in which advantage is taken of the chelating effect of nitrogen-containing substituents to achieve selective azidation of *o*-positions in aromatic rings. Azidation of aromatic C–H bonds proceeds at relatively low reaction temperatures and typically has relatively short reaction times. For aliphatic C–H bonds, higher reaction temperatures are typically required. Undoubtedly, the most impressive C–H bond azidation is that achieved with Hartwig's Fe "boxmi" system, in which tertiary C–H bonds are selectively azidated at room temperature in a chemo-, regio- and enantioselective manner. Late-stage azidation is therefore no longer only a desirable reaction, but truly made possible. In many examples, follow-up functionalisation reactions of the installed azide functionality proved to be orthogonal with the azidation protocol, thus enabling interesting one-pot transformations.

In terms of the viability of these transformations there are a few issues that will need to be addressed in order to make azidation reactions applicable in larger-scale reactions. It is clear that most of these transformations use $TMSN_3$ or NaN_3 as azide sources, and these are infamous for their toxic and potentially explosive nature. Similarly, the azide products are not harmless either (explosion limit depends on the C/N ratio). Thus, caution needs to be taken in trying to upscale these reactions. As such these reactions are perhaps good contenders for flow chemistry to address safety issues. Nonetheless, in some examples discussed in this review gram-scale synthesis was achieved. Another common element in many of the reactions discussed in this review is the need to use a hypervalent iodine compound, which produces stoichiometric amounts of halogen-containing waste. This needs to be tackled, perhaps by use of milder oxidants or recovery of the waste and reuse. On the bright side, in some examples oxygen/air could be used as an oxidant and this is perhaps the path forward.

Overall, despite some issues that need to be addressed in the future, recent advances made in transition-metal-catalysed azidation reactions provide access to a wide variety of interesting organic azides, ready for subsequent functionalisation reactions. This field can definitely be expected to aid the organic synthetic community in making a variety of products of interest.

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Keywords: Azides · Transition-metal catalysis · Noble-metal catalysis · Radical reactions · Synthetic methods · C–H activation

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