

Review

# Azidation in the Difunctionalization of Olefins

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**Abstract:** Organic azides are key motifs in compounds of relevance to chemical biology, medicinal chemistry and materials science. In addition, they also serve as useful building blocks due to their remarkable reactivity. Therefore, the development of efficient protocols to synthesize these compounds is of great significance. This paper reviews the major applications and development of azidation in difunctionalization of olefins using azide reagents.

**Keywords:** azides; difunctionalization; olefins

## 1. Introduction

The first organic azide, phenyl azide, discovered by Griess in 1864 opened the door for the use of organic azides in synthesis [1]. Since then, numerous elegant approaches have been developed, such as the *aza*-Wittig reaction [2], Sundberg rearrangement, Curtius rearrangement [3,4], Schmidt rearrangement [5], Hemetsberger rearrangement [6] and click chemistry [7–12]. Organic azides are important building blocks and intermediates, not only due to the fact they are potential precursors of N-containing structural motifs [13–19], but also for their remarkable biological activity in pharmaceutical chemistry [20]. Moreover, organic azides have also received great attention in other fields, such as supramolecular chemistry [21–24], medicinal chemistry [25], biotechnology and materials science [26].

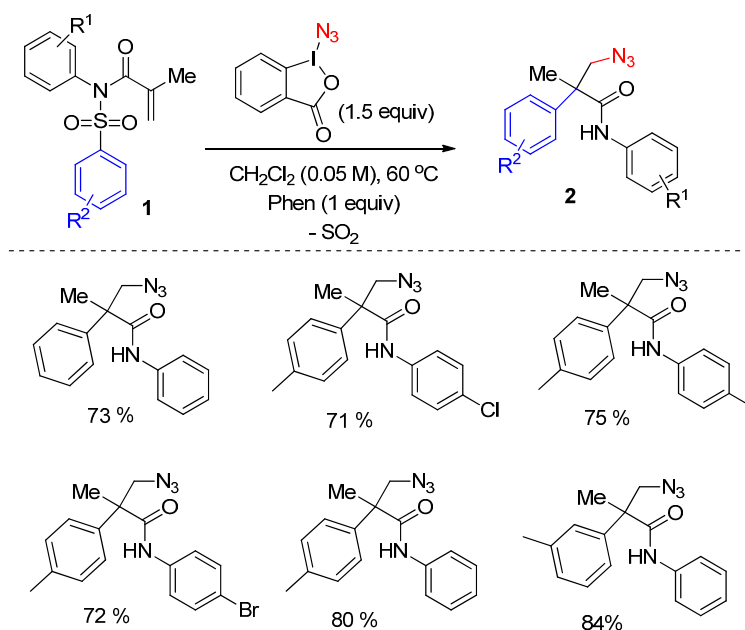
Olefins are readily available starting materials in organic synthesis. Recently, the difunctionalization of olefins [27–42] which could introduce two chemical bonds into substrates simultaneously, has attracted considerable attention. Organic azide-driven difunctionalization of olefins has been a hot topic in this area in recent years. Herein, we summarize the recent developments in the use of azidation reactions in the difunctionalization of olefins.

## 2. The Application of Organic Azides in Difunctionalization of Olefins

### 2.1. Construction of C-N<sub>3</sub> Bond and C-C Bond

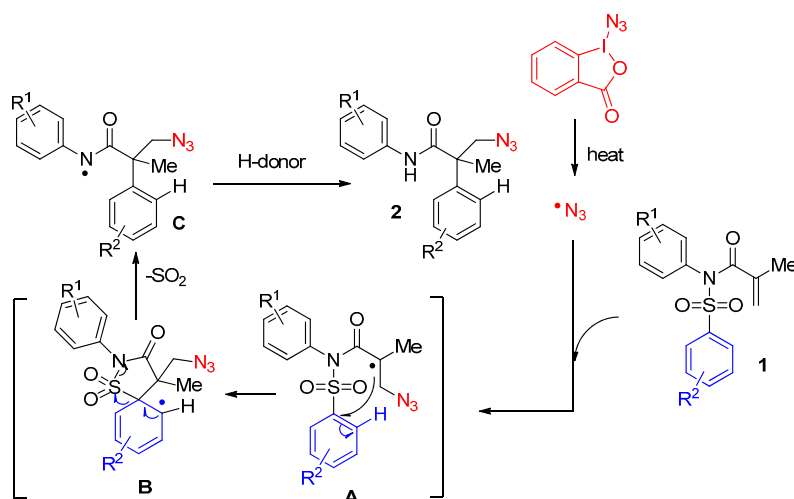
In the past decade, the hydroazidation of olefins has been significantly developed [43–48], although this kind of addition reaction has not been generally classified as a traditional difunctionalization of olefins. Therefore, we start here from the construction of C-N<sub>3</sub> bonds and C-C bonds.

An interesting radical-mediated arylazidation of activated alkenes **1** was reported by Nevado and co-workers (Scheme 1) [49]. This process involves radical addition, Csp<sup>2</sup>-Csp<sup>3</sup> and C-N bond formation, 1,4-aryl migration, and further desulfonylation, producing in good yields the corresponding products **2** bearing a quaternary stereocenter when the substituent on the nitrogen atom is an aryl group.



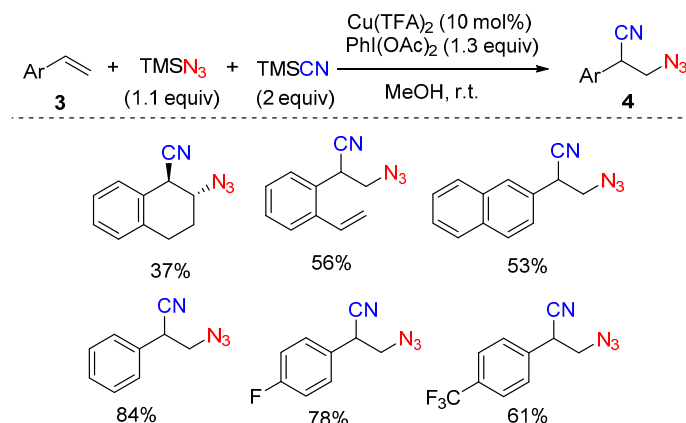
**Scheme 1.** Arylheterofunctionalization of activated alkenes.

The proposed mechanism is illustrated in Scheme 2. In the first step, the generated azido radical interacts with the activated alkene to give a new C(sp<sup>3</sup>)-N bond and an alkyl radical intermediate **A**. A 5-*ipso* cyclization then takes place on the aromatic ring generating aryl radical **B**, which leads to amidyl radical **C** upon rearomatization with concomitant desulfonation. The subsequent H-abstraction step produces the desired product **2** (Scheme 2).



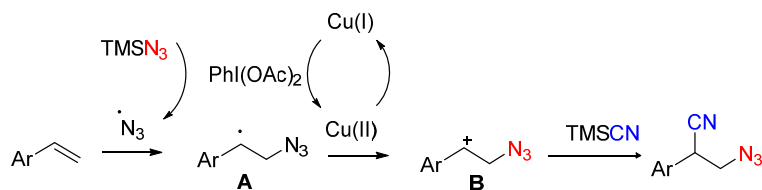
**Scheme 2.** The proposed mechanism of the arylheterofunctionalization of alkenes.

Wang and co-workers reported a copper-catalyzed intermolecular Markovnikov-type azidocyanation reaction of alkenes **3** to construct C-N<sub>3</sub> and C-CN bonds simultaneously (Scheme 3) [50], which gives a series of 3-azido-2-arylpropanenitriles **4** in moderate to good yields. These compounds may serve as potential precursors of the corresponding 3-amino-2-arylpropanoic acids. This reaction employs PhI(OAc)<sub>2</sub> as oxidant, TMSN<sub>3</sub> as N<sub>3</sub> source, TMSCN as CN source and it proceeds at room temperature. A mechanistic study revealed that the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) significantly suppressed the reaction, suggesting that a radical process may be involved in this reaction.



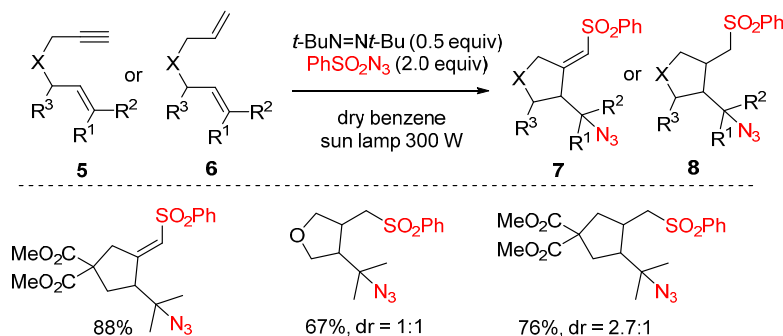
Scheme 3. Azidocyanation of aryl alkenes.

On the basis of the above results, a plausible mechanism is proposed. First, TMSN<sub>3</sub> could react with PhI(OAc)<sub>2</sub> to generate the N<sub>3</sub> radical under the standard reaction conditions. Then the radical addition to alkene gives intermediate A. In the presence of copper(II) catalyst, A could be oxidized to form the intermediate B with a carbocation center, which is trapped by TMSCN to give the final product (Scheme 4).



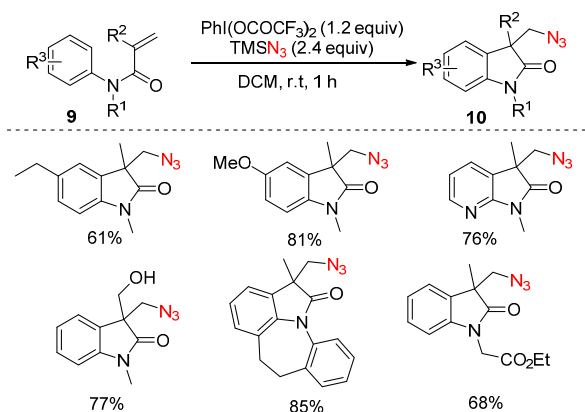
Scheme 4. Plausible mechanism of the reaction.

A radical mediated azidosulfonylation of various 1-en-6-yne **5** or 1,6-dienes **6** that are able to undergo a rapid radical rearrangement was reported by Renaud and co-workers (Scheme 5) [51]. This reaction is initiated by di-*tert*-butyldiazene upon irradiation with a 300 W sun lamp. Under the standard reaction conditions, the reaction is generally completed within 2–4 h.



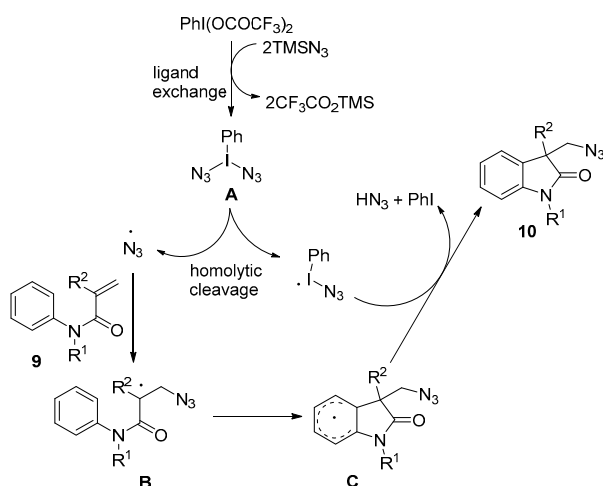
Scheme 5. Azidoarylation of alkenes.

2-Oxindoles not only have unique biological activity, but also are important building blocks in drug design and organic synthesis [52,53]. In order to synthesize these useful intermediates, a rapid approach to oxindoles through C-N<sub>3</sub> and C-C bond construction was reported by Antonchick and co-workers [54]. This chemistry proceeds under mild and metal-free conditions, giving biologically interesting 2-oxindoles **10** in good yields (Scheme 6).

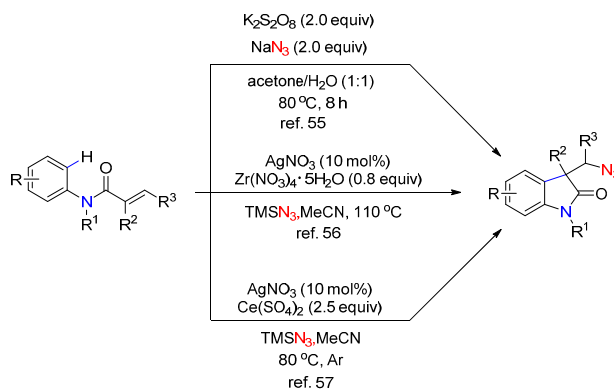


Scheme 6. Azidoarylation of alkenes.

A plausible mechanism for this transformation is illustrated in Scheme 7. This reaction begins with a double ligand exchange between  $\text{PhI}(\text{OCOCF}_3)_2$  and  $\text{TMSN}_3$  to provide intermediate **A**, which undergoes thermal homolytic cleavage to generate an azido radical. This azido radical attacks alkene **9** to give intermediate **B**, which is trapped by arene to give intermediate **C**. Rearomatization of **C** provides product **10**. Similar approaches using different catalysts and oxidants were also reported by the groups of Zhang [55], Yang [56], and Jiao [57] (Scheme 8).

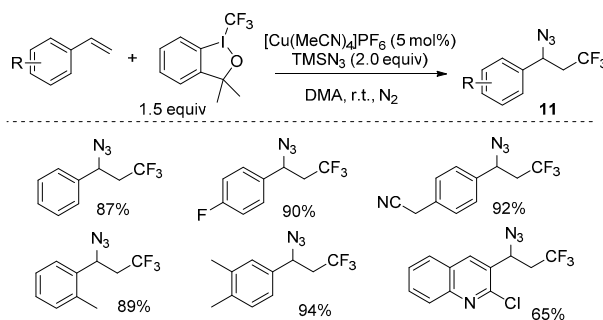


Scheme 7. Proposed mechanism for the azidoarylation of alkenes.



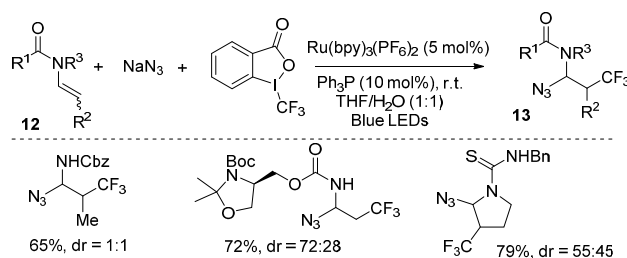
Scheme 8. Azidoarylation of alkenes.

The introduction of a trifluoromethyl group into chemical compounds is an important way to modify their activities and biocompatibilities [58]. In light of their importance in medicinal chemistry, a novel copper-catalyzed intermolecular azidotrifluoromethylation of alkenes has been developed by Liu and co-workers [59]. By using this method, various CF<sub>3</sub>-containing organoazides **11** were obtained in good yields under mild reaction conditions (Scheme 9). Besides, the resulting products can be readily transformed into other valuable CF<sub>3</sub>-containing amine compounds.



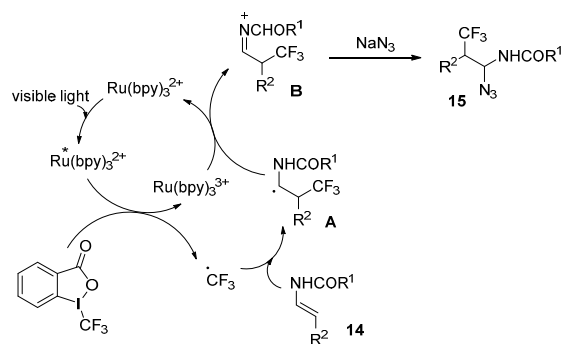
**Scheme 9.** Azidotrifluoromethylation of alkenes.

A photoredox-catalyzed azidotrifluoromethylation of enecarbamates **12** was reported by Magnier, Masson and coworkers [60]. This reaction used Tongi's reagent as CF<sub>3</sub> source, and was proposed to follow a radical/cationic pathway. Under the optimized conditions, a wide range of substrates can be readily difunctionalized (Scheme 10).



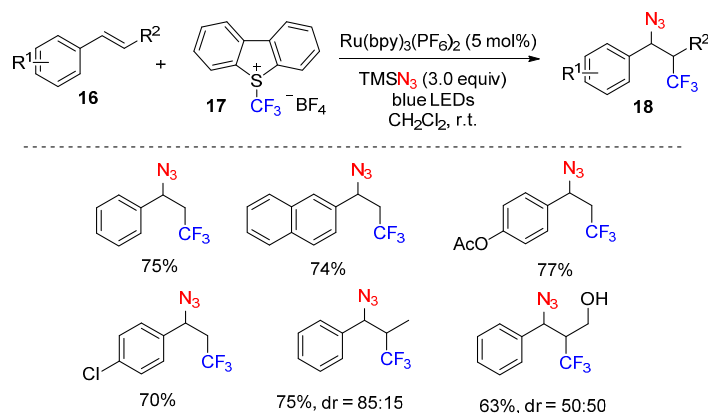
**Scheme 10.** Azidotrifluoromethylation of enecarbamates.

A possible mechanism is shown in Scheme 11. Visible light excites Ru(bpy)<sub>3</sub><sup>2+</sup> into \*Ru(bpy)<sub>3</sub><sup>2+</sup>, which is a strong reductant species that performs a SET to generate trifluoromethyl radical from Tongi's reagent. Then, addition of trifluoromethyl radical to enecarbamate **14** leads to an α-amido radical intermediate **A**, which can be oxidized into N-acyliminium cation intermediate **B** by SET process from Ru(bpy)<sub>3</sub><sup>3+</sup>. Final nucleophilic trapping by NaN<sub>3</sub> forms the products **15**.



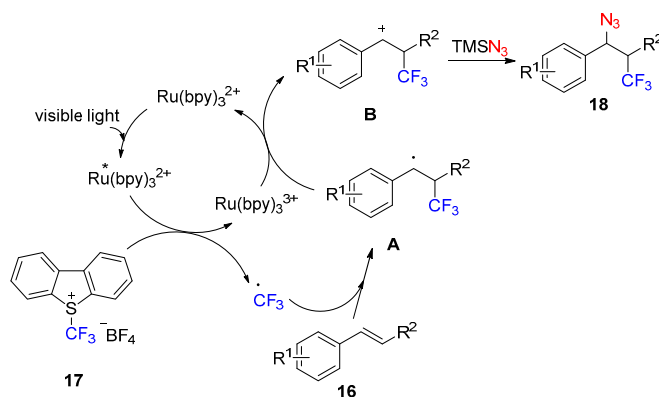
**Scheme 11.** Proposed mechanism.

Inspired by their above work, this group also developed a photoredox-catalyzed azidotrifluoromethylation of alkenes **16**. Under the optimized conditions, using Umemoto's reagent as the CF<sub>3</sub> source, a wide range of alkenes can be readily difunctionalized (Scheme 12) [61].



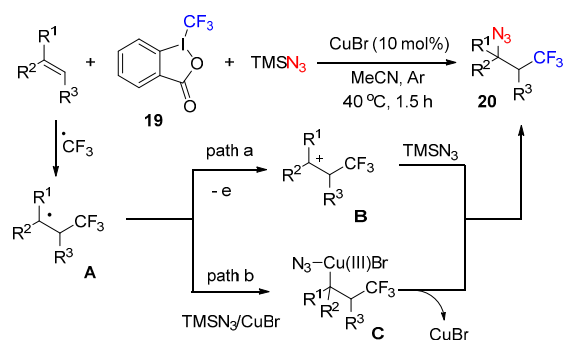
**Scheme 12.** Azidotrifluoromethylation of alkenes.

A similar mechanism is proposed based on their above work (Scheme 13). Firstly, visible light excites the  $\text{Ru}(\text{bpy})_3^{2+}$  into  $^*\text{Ru}(\text{bpy})_3^{2+}$ , which performs a SET to generate trifluoromethyl radical from Umemoto's reagent **17**. Then addition of trifluoromethyl radical to alkenes **16** produces carbon radical intermediate **A**, which can be oxidized into  $\beta$ -trifluoromethylated carbocation intermediate **B**. Finally, carbocation **B** is trapped by  $\text{TMSN}_3$  to form the product **18**.



**Scheme 13.** Plausible reaction mechanism.

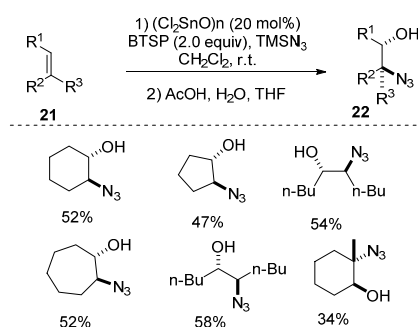
Due to the importance of these compounds, a copper-catalyzed three-component azidotrifluoromethylation of alkenes was designed by Yang (Scheme 14) [62]. This reaction proceeded under mild conditions and gave the corresponding product **20** in good yields. A possible mechanism was also proposed. Togni's reagent **19** is activated by  $\text{CuBr}$ , leading to the radical species **A** by reaction with the alkene. Then, intermediate **A** is oxidized to intermediate **B**, which is further trapped by  $\text{TMSN}_3$  to lead to the product (Path a). Alternatively, intermediate **A** reacts with  $\text{TMSN}_3$  and  $\text{CuBr}$  to afford complex **C**, further reductive elimination of complex **C** affords the product **20**.



**Scheme 14.** Azidotrifluoromethylation of alkenes.

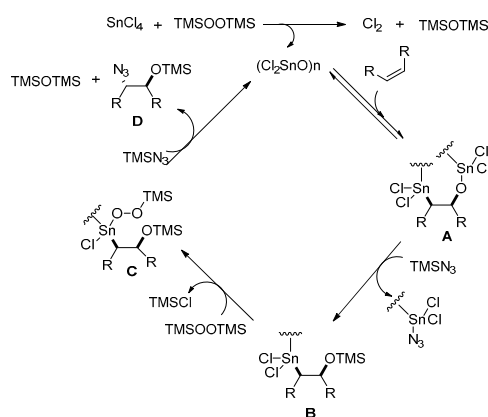
## 2.2. Construction of C-N<sub>3</sub> Bond and C-O Bond

Shibasaki and co-workers reported the first example of (Cl<sub>2</sub>SnO)<sub>n</sub>-catalyzed synthesis of *trans* β-azido alcohols by using readily available alkenes as substrates (Scheme 15) [63].



**Scheme 15.** Synthesis of *trans* β-azido alcohols.

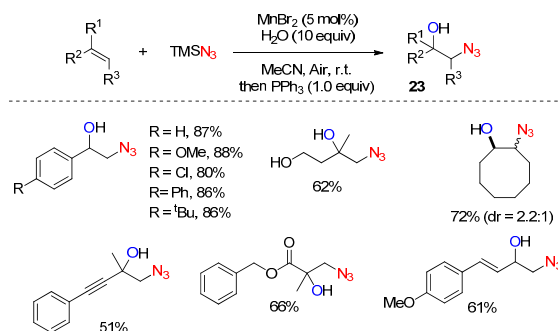
The authors proposed a catalytic cycle that involves the insertion of a C=C double bond to dichlorotin oxide to afford intermediate **A**, which could react with TMSN<sub>3</sub> to afford **B**. Subsequent nucleophilic attack of BTSP (bis(trimethylsilyl) peroxide) on Sn gives the intermediate **C**. The regeneration of (Cl<sub>2</sub>SnO)<sub>n</sub> by S<sub>N</sub>2 attack with TMSN<sub>3</sub> gives **D** as the precursor of the product (Scheme 16).



**Scheme 16.** Plausible reaction mechanism.

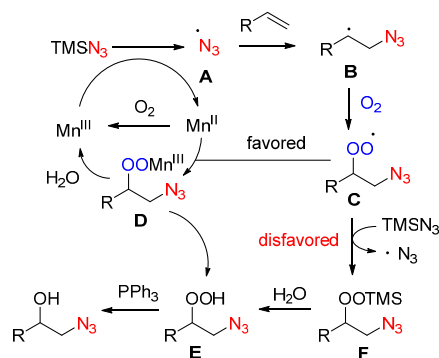
Recently, the Jiao group reported an efficient Mn-catalyzed aerobic oxidative hydroxyazidation of olefins for the synthesis of β-azido alcohols **23** using air as the oxidant (Scheme 17) [64]. This chemistry

was notable for its mild reaction conditions, broad substrate scope, and high reaction efficiency. Moreover, the resulting  $\beta$ -azido alcohols are useful precursors of  $\beta$ -amino alcohols, aziridines, and other O- and N-containing heterocyclic compounds.



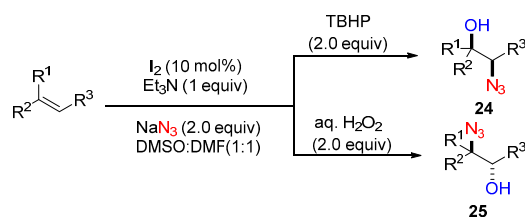
**Scheme 17.**  $\beta$ -Azido alcohol construction.

On the basis of the mechanistic study and density functional theory (DFT) calculations, a favored radical process is proposed (Scheme 18). Firstly, the  $Mn^{II}$  is readily oxidized to  $Mn^{III}$  or  $Mn^{IV}$  by molecule oxygen in the air, then  $Mn^{III}$  oxidizes  $TMSN_3$  to generate azido radical.  $Mn^{IV}$  can also oxidize  $TMSN_3$  to form the  $N_3$  radical **A** and generate  $Mn^{III}$  catalyst. Radical **A** attacks an alkene at the sterically less hindered position to form the carbon radical **B**, which is trapped by oxygen to generate the peroxy radical **C**. According to the DFT calculations, it is favored for the peroxy radical **C** to undergo Mn-participated SET and protonation processes to afford  $\beta$ -azido peroxy alcohols **E**. In comparison, the pathway through **F** is disfavored. Finally,  $\beta$ -azido peroxy alcohol **E** is reduced by  $PPh_3$  to form the  $\beta$ -azido alcohol **23**.



**Scheme 18.** Proposed mechanism.

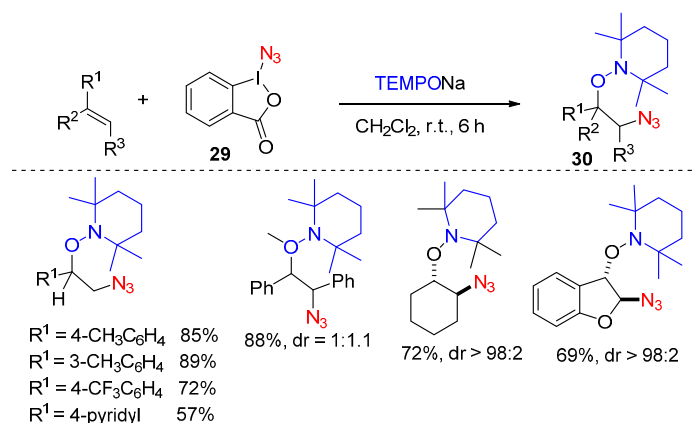
Sudalai and co-workers reported an  $I_2$ -catalyzed synthesis of 1,2-azidoalcohols by employing  $NaN_3$  as N-nucleophiles and DMF as O-nucleophiles respectively (Scheme 19) [65]. This approach displayed broad substrate scope and high reaction efficiency with regio- and stereoselectivity.  $^{18}O$  labelling studies proved that DMF served as the O-nucleophile.



**Scheme 19.** Synthesis of 1,2-azidoalcohols.

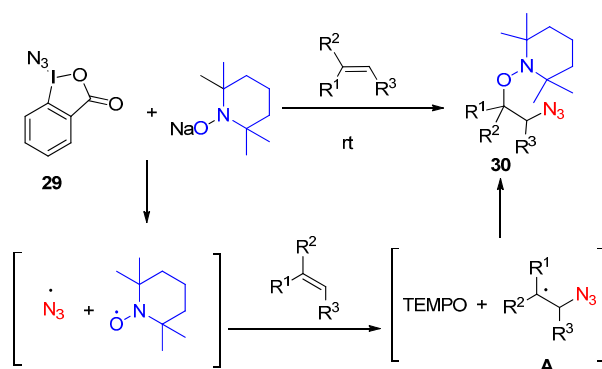






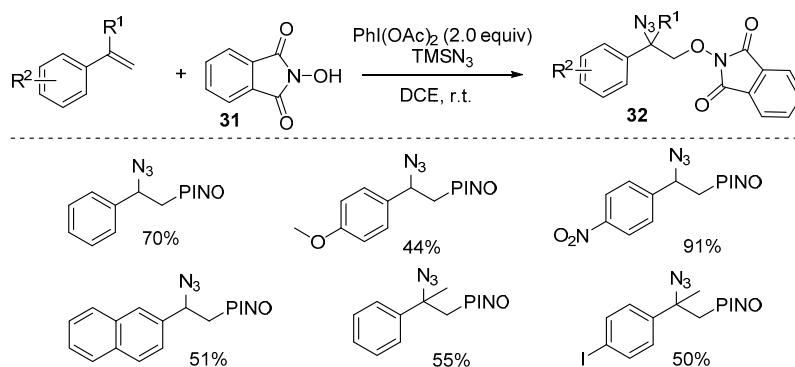
Scheme 22. Oxyazidation of alkenes.

Inspired by their previous work that TEMPONa could reduce CF<sub>3</sub>-iodine reagent (Togni reagent) to generate CF<sub>3</sub>-radical [68], a radical process was suggested by the authors (Scheme 23). Under the standard reaction conditions, TEMPONa reduced Togni reagent to generate an N<sub>3</sub> radical, and release TEMPO, then the N<sub>3</sub> radical is trapped by an olefin to generate species A, which reacts with TEMPO to form products 30.



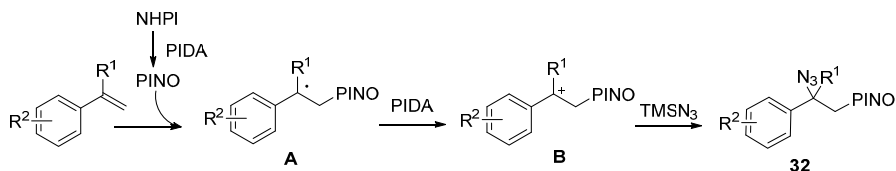
Scheme 23. Radical oxyazidation of alkenes.

Recently, an efficient oxyazidation of alkenes under metal-free conditions was reported by Xia and co-workers. This reaction could form C-O and C-N bonds in one step by using N-hydroxyphthalimide as an oxygen-radical precursor and TMSN<sub>3</sub> as the N<sub>3</sub> source. A number of aryl-substituted alkenes was tolerated in this transformation (Scheme 24) [69].



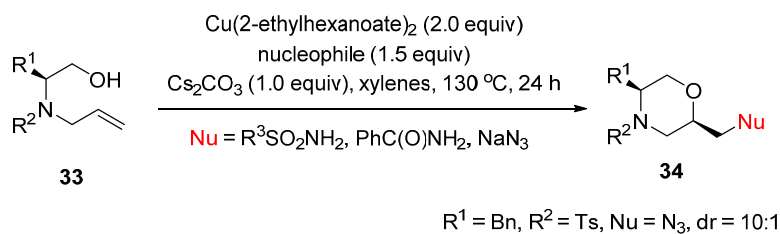
Scheme 24. Oxyazidation of alkenes.

A possible mechanism is outlined in Scheme 25. In the presence of PIDA, N-hydroxyphthalimide (NHPI) **31** could be oxidized to generate an N-oxyl (PINO) radical, which attacks alkenes to form intermediate **A**. Intermediate **A** can be further oxidized to cation intermediate **B** by PIDA. Finally, intermediate **B** is trapped by  $\text{TMSN}_3$  to give products **32**.



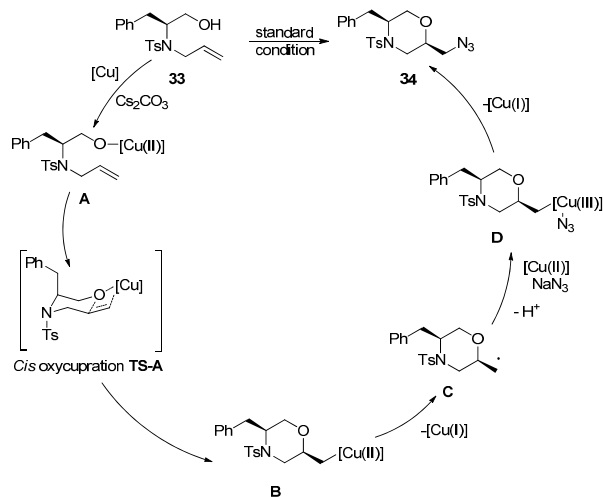
Scheme 25. Possible mechanism.

The simultaneous addition of oxygen and nitrogen across an alkene is a convenient way to construct the precursor of 2-aminomethylmorpholines **34**. Remarkably, through copper-catalyzed oxyamination of alkene, a novel synthetic method for the preparation of **34** was reported by Chemler and co-workers [70]. Under the reaction conditions, **34** was obtained in good yields with excellent diastereoselectivity (Scheme 26).



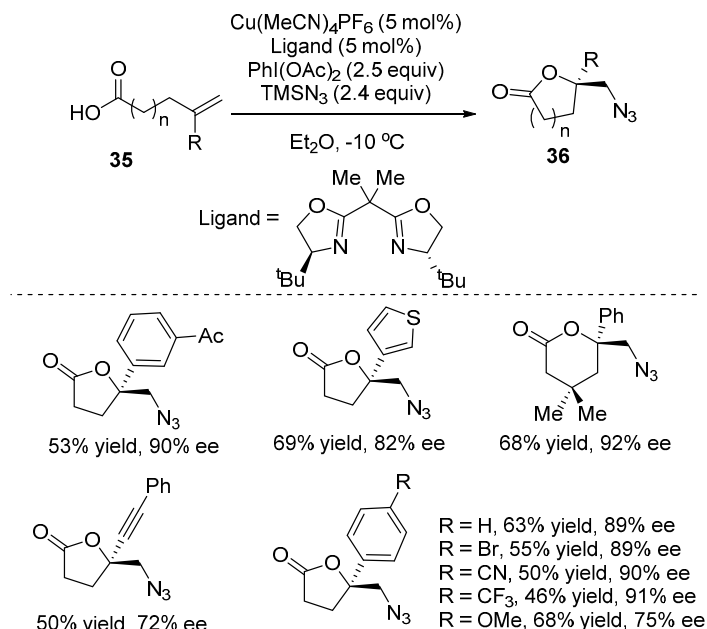
Scheme 26. Oxyazidation of alkenes.

A plausible mechanism is illustrated in Scheme 27. Coordination of alcohol **33** to copper(II) 2-ethylhexanoate gives monomer **A**. Thermal conditions promote *cis*-oxycupration via **TS-A**, then give the copper(II) intermediate **B**. The diastereoselectivity is rationalized by a chair-like transition state where vicinal tosyl and benzyl substituents adopt pseudoaxial positions. Intermediate **B** undergoes C-Cu(II) homolytic cleavage to give carbon radical **C**. In the presence of an azide nucleophile, an organocopper(III) intermediate **D** is formed, which can undergo reductive elimination to form the product **34**.



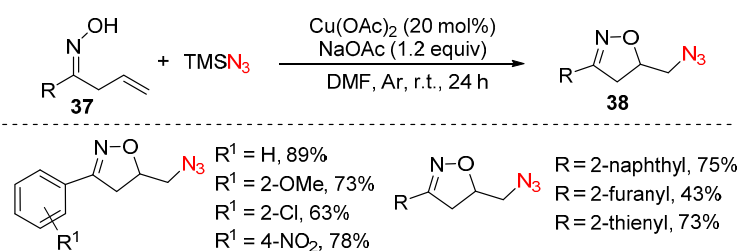
Scheme 27. Proposed oxyamination reaction mechanism.

A new approach to synthesize a wide range of chiral lactones **36** based on Cu-catalyzed enantioselective radical oxyfunctionalization of alkenes was developed by Buchwald and co-workers [71]. This method provides a straightforward approach to various lactone building blocks containing tetrasubstituted stereogenic centers, which are hard to access through traditional methods (Scheme 28).



**Scheme 28.** Synthesis of chiral lactones.

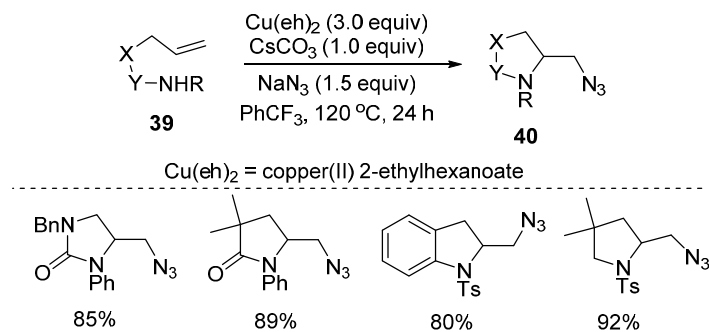
Isoxazolines are useful building blocks in organic chemistry [72]. Recently, an efficient Cu(OAc)<sub>2</sub>-catalyzed oxyazidation of alkenes **37** was developed by Wang, Xu and co-workers (Scheme 29) [73]. This reaction occurs under mild conditions, forming the azido-substituted isoxazolines **38** in good yields, although the mechanism of this chemistry is still unclear.



**Scheme 29.** Oxyazidation of alkenes.

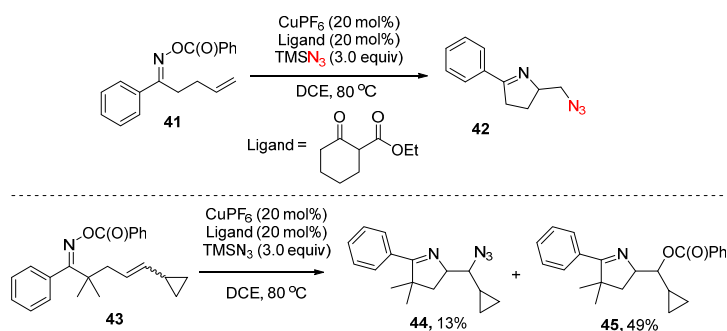
### 2.3. Construction of C-N<sub>3</sub> Bond and C-N Bond

Olefin diamination methods provide powerful access to vicinal diamines that are useful in chemical biology, medicinal chemistry and materials science. Recently, a novel copper(II)-promoted intramolecular azidoamination of alkenes **39** was reported by Chemler and co-workers (Scheme 30) [74]. This method could tolerate a wide range of internal and external amine sources for the formation of differently functionalized nitrogen heterocycles **40**.

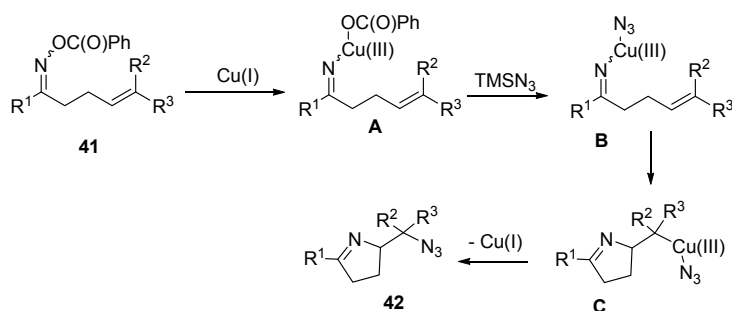


Scheme 30. Intermolecular alkene azidoamination.

Yu and co-workers reported an intramolecular azidation reaction through copper-mediated N-O cleavage and subsequent C-N bond forming 5-*exo* cyclization. The forming intermediate is subsequently azidated to afford the corresponding dihydropyrroles (Scheme 31) [75]. To understand this reaction mechanism, compound **43** was treated under standard reaction conditions. However, in this case **44** and **45** are mainly obtained with only trace amounts of ring opening product formation, suggesting that the cyclization step is unlikely a free radical process. Based on these results, a reaction mechanism is proposed (Scheme 32). The first step involves the oxidative addition of Cu(I) to the N-O to give intermediate **A**, which undergoes ligand exchange and then intramolecular cyclization to afford intermediate **C**, followed by reductive elimination to afford products **42**.

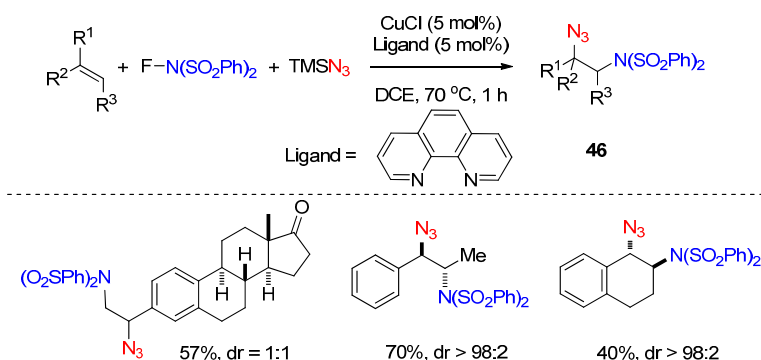


Scheme 31. Azidation of unsaturated O-acyl oximes and radical clock experiments.



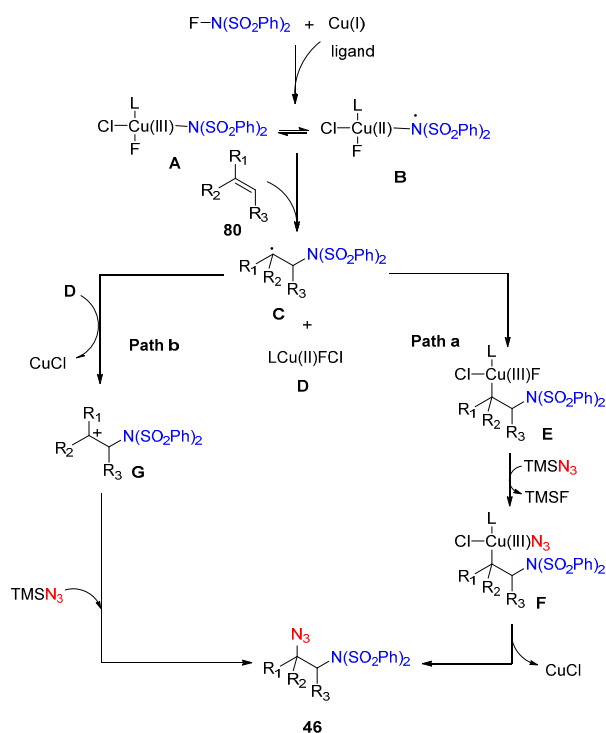
Scheme 32. Proposed mechanism.

Studer and co-workers described a novel methodology for the efficient synthesis of the precursors of vicinal amino azides **46** (Scheme 33) [76], which can easily be transformed into other important amine derivatives. This chemistry employed Cu(I) as catalyst, TMSN<sub>3</sub> as N<sub>3</sub> source and available N-fluorobenzenesulfonimide (NFSI) as nitrogen-radical precursor leading to the desired products in moderate to excellent yields with high diastereoselectivity.



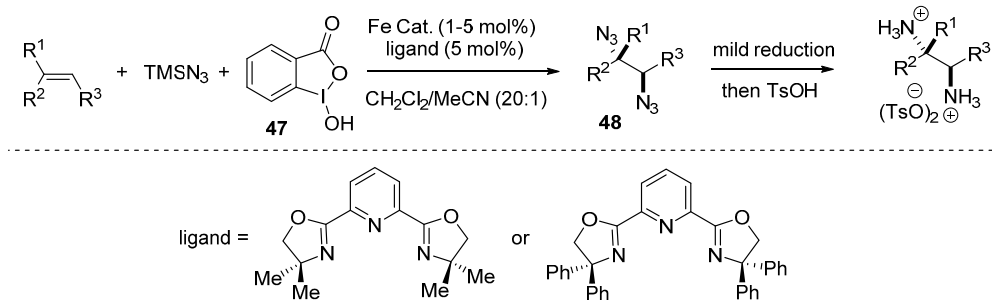
Scheme 33. Aminoazidation of alkenes.

A plausible reaction mechanism based on the reported processes is outlined in Scheme 34 [77,78]. Firstly, Cu(I) reacts with NFSI to form Cu(III) species **A**, which could exist in equilibrium with a Cu(II)-stabilized N-centered radical **B**. It is the precursor of bis-sulfonylamidyl radical, which adds to the alkene to generate carbon radical **C** and Cu(II) species **D**. Also **B** species could react as N-radicals with the alkene. Then two pathways are suggested. In path a, trapping of **C** with **D** provides Cu(III) species **E**, which exchanges ligand with TMSN<sub>3</sub> to give Cu(III) complex **F**. Reductive elimination of **F** affords the products along with the regeneration of the Cu(I) catalyst. In path b, **D** oxidizes **C** to cationic intermediate **G**, which is trapped by TMSN<sub>3</sub> to form the products.



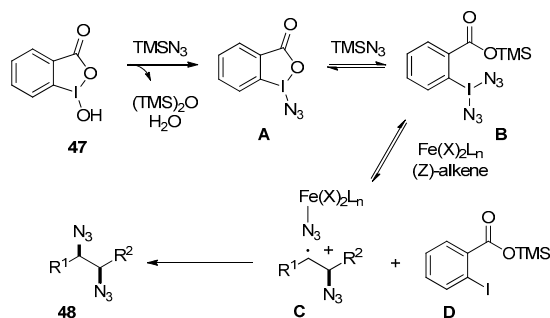
Scheme 34. Proposed reaction mechanism.

Snider and co-workers reported a Mn(OAc)<sub>3</sub>-mediated diazidation of alkenes and glycals for the formation of 1,2-diazides compounds [79]. Very recently, Xu and co-workers reported a novel iron-catalyzed diastereoselective olefin diazidation method which tolerates a broad range of olefins (Scheme 35) [80]. This method also provides a convenient approach to vicinal primary diamines and other synthetically valuable nitrogen-containing compounds.



Scheme 35. Diazidation of olefins.

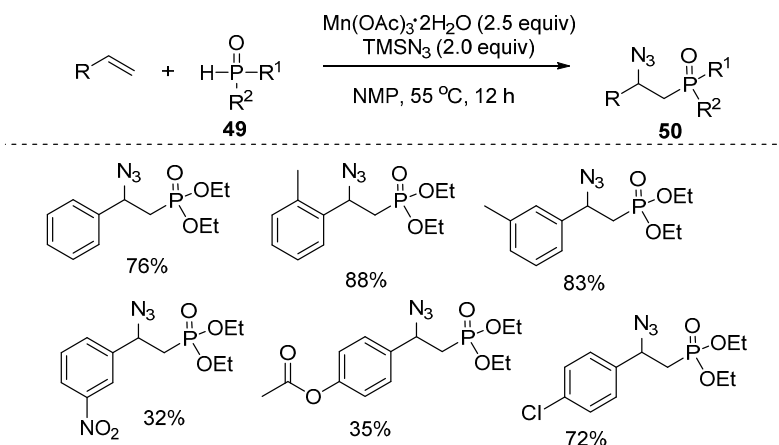
A proposed mechanism is shown in Scheme 36. TMSN<sub>3</sub> reacts with **47** to give intermediate **A**, which is further activated by TMSN<sub>3</sub> to generate intermediate **B**. In the presence of iron catalysts, intermediate **B** reacts with alkene to afford intermediate **C** and release intermediate **D**. It is likely that the high-valent iron species may be further oxidize intermediate **C** through inner-sphere azido ligand transfer to afford the diazide product.



Scheme 36. Possible mechanism.

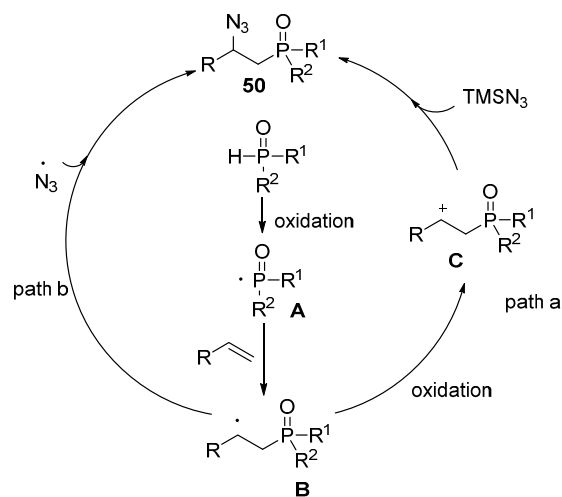
#### 2.4. Construction of C-N<sub>3</sub> Bond and C-P Bond

An efficient method for the synthesis of β-azidophosphonates **49** through Mn(OAc)<sub>3</sub>-mediated radical oxidative phosphonation-azidation of alkenes under relatively mild reaction conditions was reported by Tang and co-workers. This reaction displayed a broad substrate scope and can be easily scaled up. The products can be obtained in a one-pot operation (Scheme 37) [81].



Scheme 37. Phosphonation-azidation of alkenes.

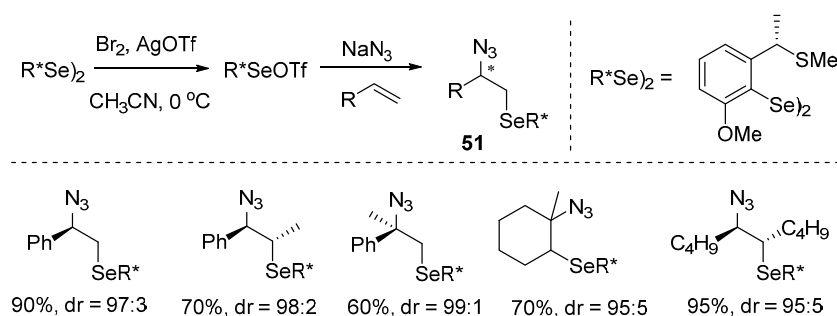
Based on their previous studies in P–C bond formation, and reaction of organophosphorus radicals [82], a possible mechanism was proposed (Scheme 38). The reaction is initiated by the addition of phosphorous radical **A** to alkene to generate radical **B**, which undergoes further oxidation to afford cationic intermediate **C**. The intermediate **C** is then trapped by TMSN<sub>3</sub> to afford the final product **50** (path a). Alternatively, the radical **B** could be directly trapped by an azido radical to form the product **50** (path b) (Scheme 38).



Scheme 38. Possible reaction pathways.

### 2.5. Construction of C–N<sub>3</sub> Bond and C–Se Bond

Tiecco and co-workers reported the first example of a highly asymmetric electrophilic azidoselenenylation of olefins for the preparation of azido selenium derivatives **51**. This reaction occurs with a high level of facial selectivity, which was made possible by the use of chiral, non-racemic selenium reagents (Scheme 39) [83].

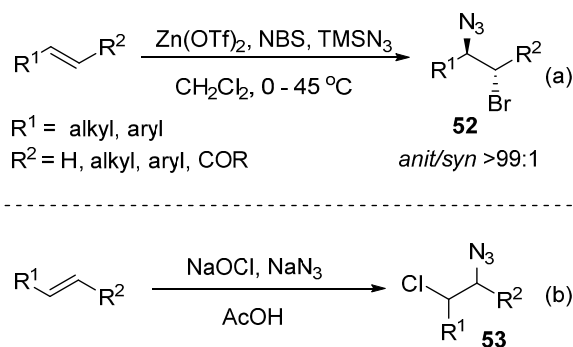


Scheme 39. Azidoselenenylation of alkenes.

### 2.6. Construction of C–N<sub>3</sub> Bond and C–Halogen Bond

1,2-Haloazidation of alkenes represents an important transformation in organic synthesis. By using Zn(OTf)<sub>2</sub> as catalyst, a metal-catalyzed bromoazidation of alkenes was reported by Hajra and co-workers. The corresponding bromoazidation products were obtained in good yields by using this protocol (Scheme 40a) [84]. Phukan's group also achieved the bromoazidation of alkenes by using other bromine sources [85,86]. Moreover, a route to 1,2-azidochlorides from alkenes was developed by Finn and co-workers (Scheme 40b) [87].





**Scheme 40.** Bromoazidation or chloroazidation of alkenes.

### 3. Conclusions

In conclusion, this review has summarized recent difunctionalization reactions of olefins with organic and inorganic azides through C-N<sub>3</sub> bond formation. An oxidative single electron transfer (SET) process is involved in most cases. These approaches provide efficient protocols for the preparation of various organic azido compounds, which can then be further applied in many transformations to synthesize various valuable nitrogen-containing compounds.

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