REVIEW

Copper-Catalysed Radical Reactions of Alkenes, Alkynes and Cyclopropanes with N-F Reagents

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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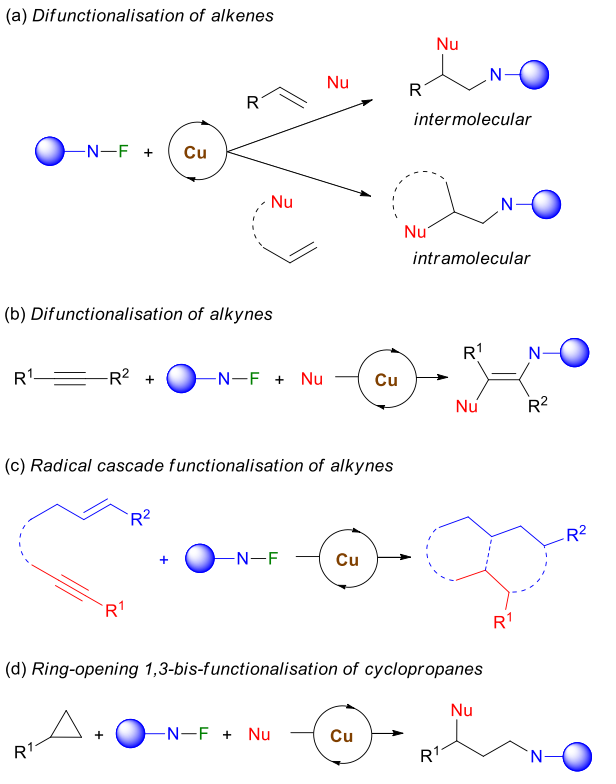
The mild generation of nitrogen-centred radicals from N-F reagents has become a convenient synthetic tool. This methodology provides access to the aminative difunctionalisation of alkenes and alkynes, and the radical ring-opening of cyclopropanes, among other similar transformations. This review article aims to provide an overview of recent developments of such processes involving radical reactions and N-F reagents using copper-based catalysts.

1. Introduction

Recent developments in catalytic radical reactions have provided access to unique reactivity with novel applications in organic synthesis.[1] Among them, transition metal-catalysed radical reactions are particularly relevant. The ability of metal complexes to generate and control different transformations are highly desirable for synthetic applications due to their chemoselectivity and the wide functional group tolerance. In this context, the use of commercially available N-F reagents, such as Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)),[2] Accufluor (1-fluoro-4-hydroxy-1,4-diazoniabicyclo-[2,2,2]octane bis(tetrafluoroborate)),[3] NFSI (N-fluorobenzenesulfonimide)[4] or NFPy (N-fluoropyridinium salts)[5] for radical reactions has become of wide interest over the past decade.

The radical additions to alkenes, alkynes and cyclopropanes have become practical methodologies to achieve the simultaneous formation of carbon–carbon and carbon–heteroatom bonds. In the case of the radical 1,2-difunctionalisation of alkenes, the reaction may consist in the simple intermolecular addition or the radical addition-cyclisation tandem process (Scheme 1a).[6] On the other hand, the alkyne functionalisation may involve the addition of functional groups across the triple bond (Scheme 1b) or the promotion of a series of cascade reactions leading to the formation of highly complex molecular skeletons in a few steps (Scheme 1c).[7] Finally, the cyclopropane derivatives, upon radical addition, undergo ring-opening reactions leading to compounds with different functional groups (Scheme 1d).[8]

In comparison to other transition metals, copper exhibits several advantages when employed as catalyst for radical reactions[9] involving alkenes or alkynes: (i) copper is inexpensive, relatively non-toxic and easy to handle; (ii) Cu(I) and Cu(II) act as good Lewis acids and, therefore, show a high affinity for alkenes and alkynes; (iii) copper promotes efficiently single-electron transfer (SET) reactions to generate alkyl radicals; (iv) copper may trap the alkyl radical intermediates producing high-valent Cu(III) species, with



Scheme 1 Examples of copper-catalysed radical reactions involving alkenes, alkynes and cyclopropanes with N-F reagents.

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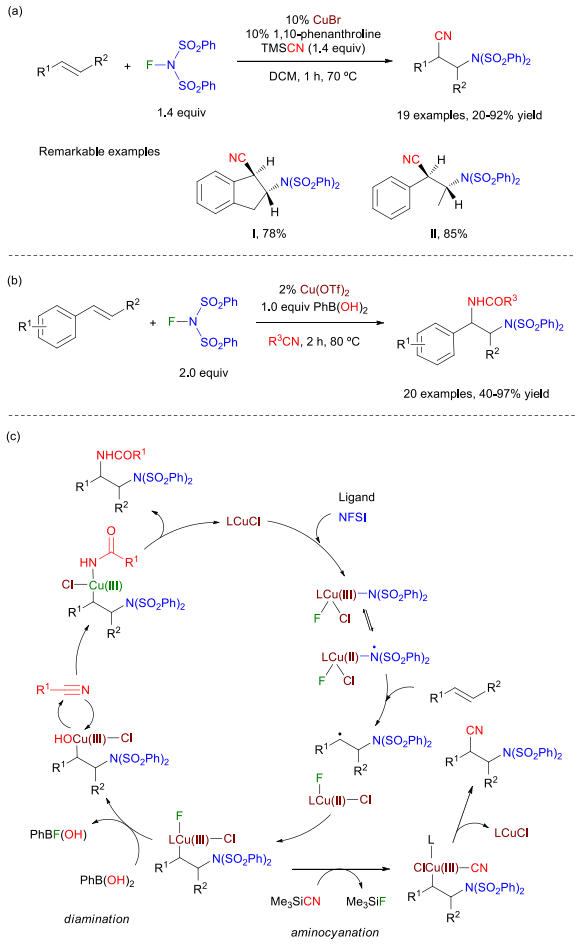
particular importance in asymmetric reactions. In this review we present the recent progress in the copper-catalysed difunctionalisation reactions of alkenes, alkynes and cyclopropanes using N-F reagents.

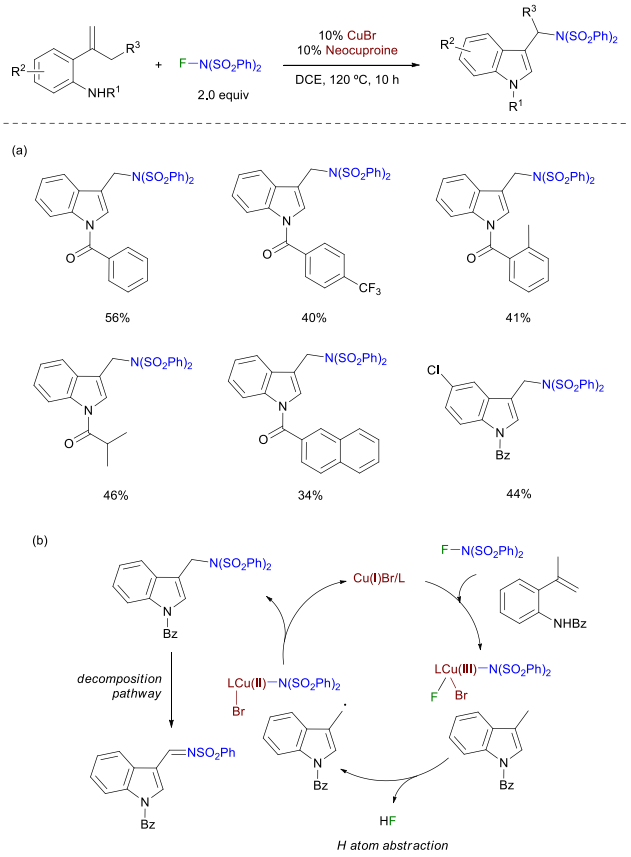
2. Radical Reactions of Alkenes

The addition of two functional groups across a double bond is a transformation with a great synthetic benefit. Accordingly, difunctionalisation reactions promoted with N-F reagents and copper-based catalysts have received considerable attention in the past decade. In this context, a variety of protocols have been described for the aminative difunctionalisation of alkenes that typically takes place by radical means, such as aminocyanation, diamination, aminotrifluoromethylation, aminoarylation, aminooxygenation, aminohalogenation, aminoazidation and aminothiolation. Moreover, the molecular complexity of the product can be enhanced through an intramolecular strategy in such a way that the amination step is followed by a ring-formation process.

In 2013, Zhang described the first copper-catalysed aminocyanation reaction of alkenes with NFSI and trimethylsilyl cyanide (TMSCN) (Scheme 2a).[10] Thus, a 1:1 mixture of copper(II) bromide and 1,10-phenanthroline served as catalyst and afforded the corresponding aminocyanation products in yields up to 92 % with high regioselectivity. Thus, the aminocyanation reaction of a 1*H*-indene derivative provided the *trans*-aminocyanation product **I** in 78 % yield.

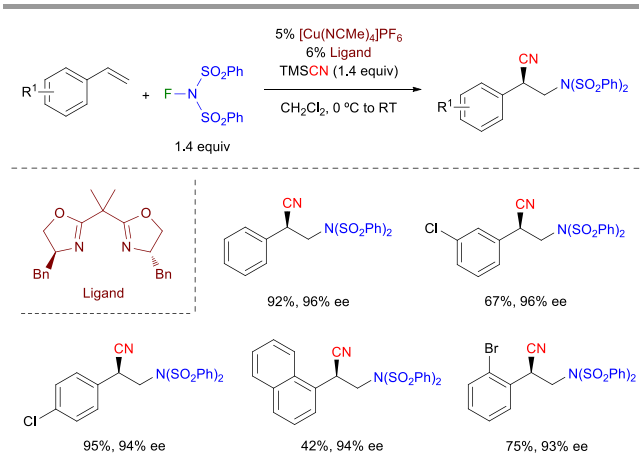


Scheme 2 Aminocyanation (a) and diamination (b) of alkenes with NFSI. Mechanistic proposal (c).



Scheme 3 Copper-catalysed sequential C(sp^2)-H and C(sp^3)-H amination of 2-vinylanilines with NFSI (a). Mechanistic proposal (b).

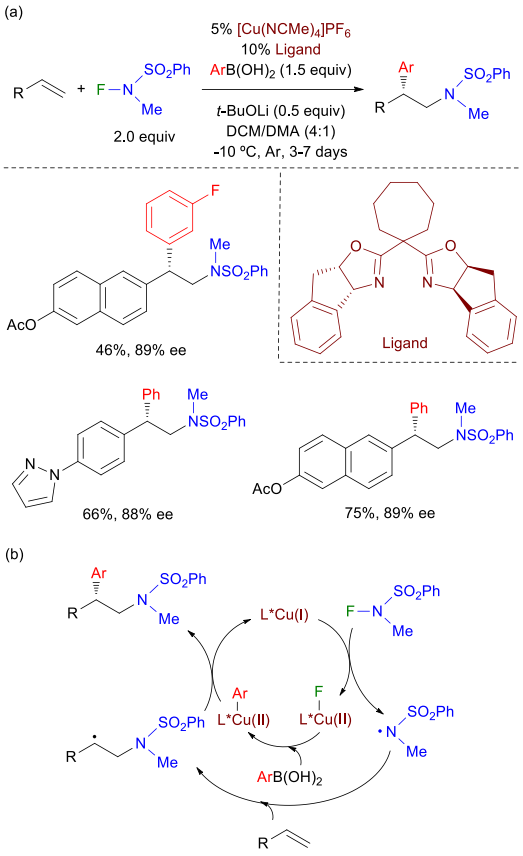
Remarkably, starting from a mixture of *E* and *Z* isomers of the



Scheme 4 Enantioselective copper-catalysed aminocyanation of alkenes with NFSI and TMSCN.

internal alkene, only the *trans*-aminocyanation product **II** was obtained (85 % yield).

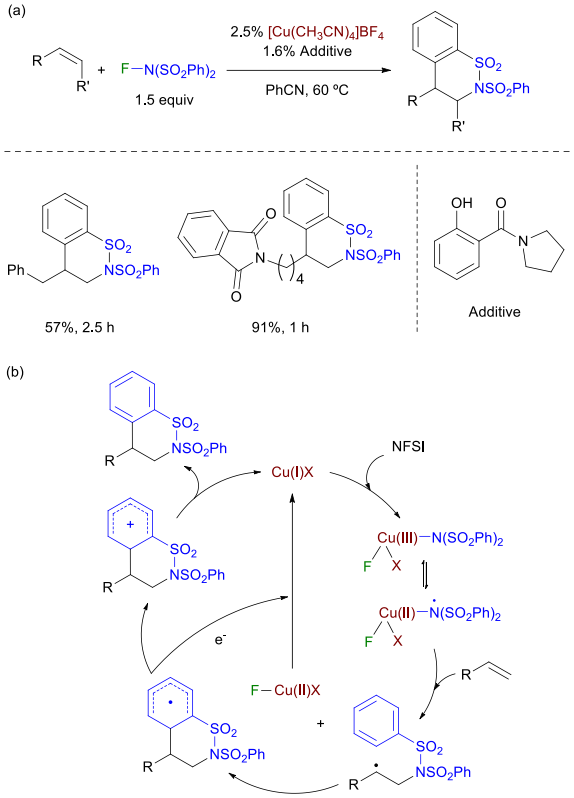
In addition, the authors reported alternative reaction conditions to achieve the copper-catalysed diamination of styrenes with NFSI and various nitriles (Scheme 2b). They provided a mechanistic proposal involving Cu(I), Cu(II), and Cu(III) species (Scheme 2c). The N-centred radicals generated from NFSI react with the olefin with high regioselectivity yielding a Cu(III) intermediate. The subsequent interaction of TMSCN or phenylboronic acid with the copper(III) fluoride complex allow the aminocyanation reaction and diamination, respectively. Very recently, a related oxidative C-H diamination strategy has been developed by Ji and Xu.[11] The reaction is formally a sequential diamination of C(sp^2)-H and C(sp^3)-H bonds of 2-vinylanilines with NFSI catalysed by a copper complex for the synthesis of indoles (Scheme 3a).



Scheme 5 Enantioselective aminoarylation of alkenes with NFAS^H (a). A plausible mechanism of olefin aminoarylation reaction (b).

Mechanistic studies revealed that NFSI plays two roles, as terminal oxidant and nitrogen source, and the reaction follows a sequential intra-/intermolecular diamination pathway (Scheme 3b). On the other hand, Liu and co-workers demonstrated the ability of chiral Box/Cu(I) complexes with NFSI and TMSCl to promote the asymmetric aminocyanation of alkenes (Scheme 4).[12]

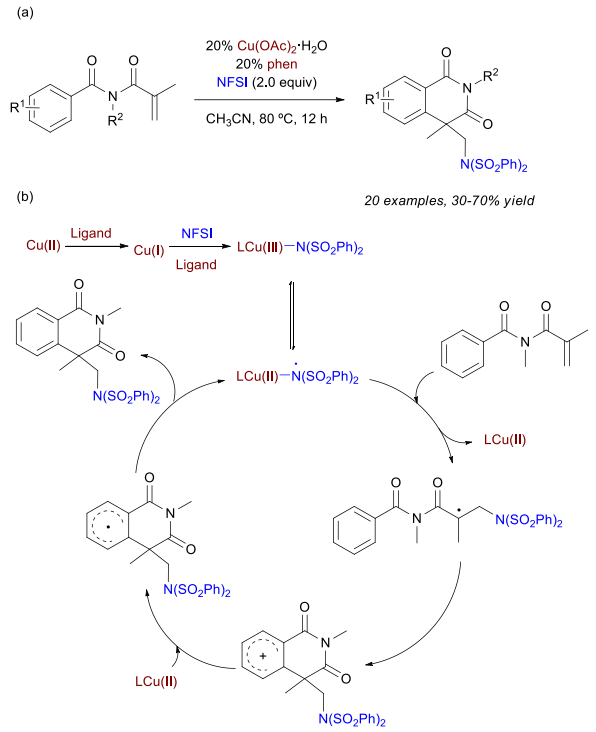
These authors have also disclosed a method for the asymmetric arylation of styrenes (Scheme 5a).[13] The catalytic system provides a useful approach to synthesize various enantiomerically enriched 2,2-diarylethylamines that were further derivatised to highly valuable chiral bioactive molecules. The descent of the reaction temperature was beneficial to enhance the enantiomeric excess. However, the reactivity decreased significantly, and a period of 3 to 7 days



Scheme 6 Intermolecular aminoarylation of aliphatic alkenes catalysed by a copper complex (a). Mechanistic proposal (b).

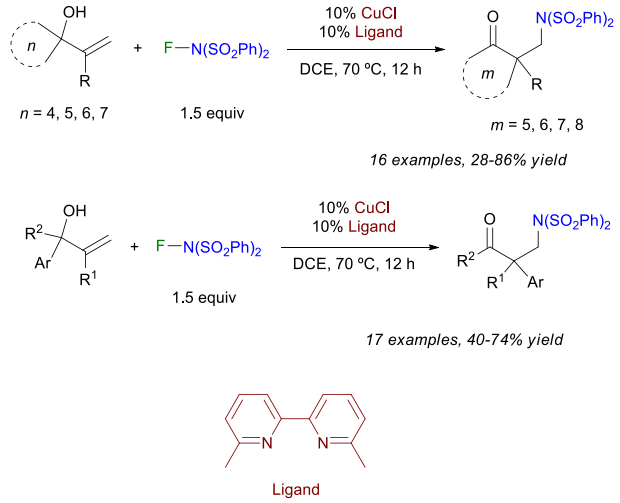
was required for reaction completion. The mechanistic proposal (Scheme 5b) shows the initial reaction of a L*Cu(I) complex with a novel *N*-fluoro-*N*-alkylsulfonamide (NFAS^H) toward the formation of *N*-centred radicals. These highly electrophilic species can react very fast with styrenes to generate benzylic radicals, whereas the interaction of a Cu(II) complex with arylboronic acids is known to be a slow process. This could eventually cause the accumulation of the benzylic radical, leading to undesired reactions. In this context, the authors have found an increase in the reactivity by the addition of *t*-BuOLi due to a favoured transmetalation step. Finally, the use of NFAS^H instead of NFSI led to the participation of less electrophilic amino radical, minimising background reactions and thus improving the reaction yield.

A related difunctionalisation process was reported by Kanai and Matsunaga.[14] The reaction consists in the intermolecular aminoarylation of aliphatic alkenes catalysed by a copper complex (Scheme 6a). This method allows the straightforward synthesis of the sultam motif, which is embedded into many biologically active compounds. Based on previous reports of related Cu-catalysed reactions,[10,15,16] the authors have proposed a mechanism in which the catalytic cycle begins with



Scheme 7 Aminocyclization of acrylamides with NFSI (a). Proposed mechanism (b).

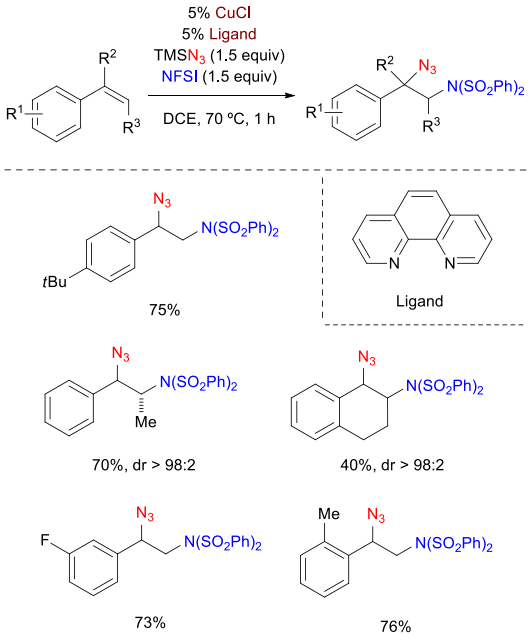
the oxidation of Cu(I) with NFSI, generating a Cu(III) species which would exist in equilibrium with Cu(II) radical species. Further interaction with the olefin provides the carbon radical intermediate that triggers an intramolecular addition to the aromatic ring. Finally, the oxidation of the resulting intermediate with the Cu(II) complex and rearomatization, leads to the sultam product while regenerating the Cu(I) catalyst (Scheme 6b). Another cyclization process was described by Xia, Liu, and co-workers in 2016.[17] The method consists in a copper-catalysed radical addition/cyclization reaction between acrylamide and NFSI (Scheme 7a), and allowed to synthesize a variety of isoquinoline-1,3-diones in moderate to good yields. Mechanistic studies, supported by DFT calculations, reveals that the oxidative addition of copper(I) to NFSI provides a copper(III) intermediate, which is able to generate a copper(II)-stabilised radical through a fast equilibrium. The interaction with the acrylamide results in a carbon-centred radical which undergoes an intramolecular addition process. The resulting radical intermediate recombines with the copper(II) species furnishing the final product (Scheme 7b).



Scheme 8 Amination-induced 1,2-rearrangement of allylic alcohols.

A different method for the aminative 1,2-difunctionalisation of alkenes catalysed by copper complexes was reported by Zhang's group (Scheme 8).[18] They employed NFSI to generate nitrogen-centred radicals which then undergo addition across the double bond of an allylic alcohol. The resulting carbon-centred radical then experiences a 1,2-rearrangement, providing access to α-quaternary Mannich bases bearing an all-carbon quaternary centre. This methodology can be applied to the amination/ring expansion or to the amination/1,2-migration of aryl groups. An alternative catalytic system was described later by Li, Zhang, and co-workers for the same transformation.[19]

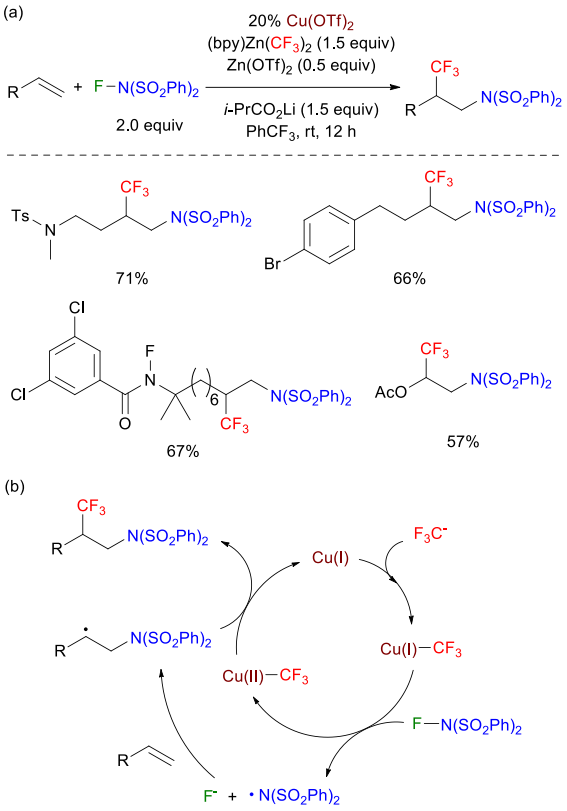
The simplicity and synthetic utility of copper-catalysed difunctionalisation reactions have been demonstrated by



Scheme 9 Aminoazidation of alkenes with NFSI and $TMSN_3$.

Studer and Zhang. They have described an accessible and practical catalytic system based for the aminoazidation of alkenes using the commercially available NFSI and $TMSN_3$ as reagents (Scheme 9).[20] The aminoazidation products can be obtained in good to high yields with excellent diastereoselectivity. To illustrate the synthetic usefulness of the protocol, the reaction products were derivatised into a triazole, a monoprotected 1,2-diamine.

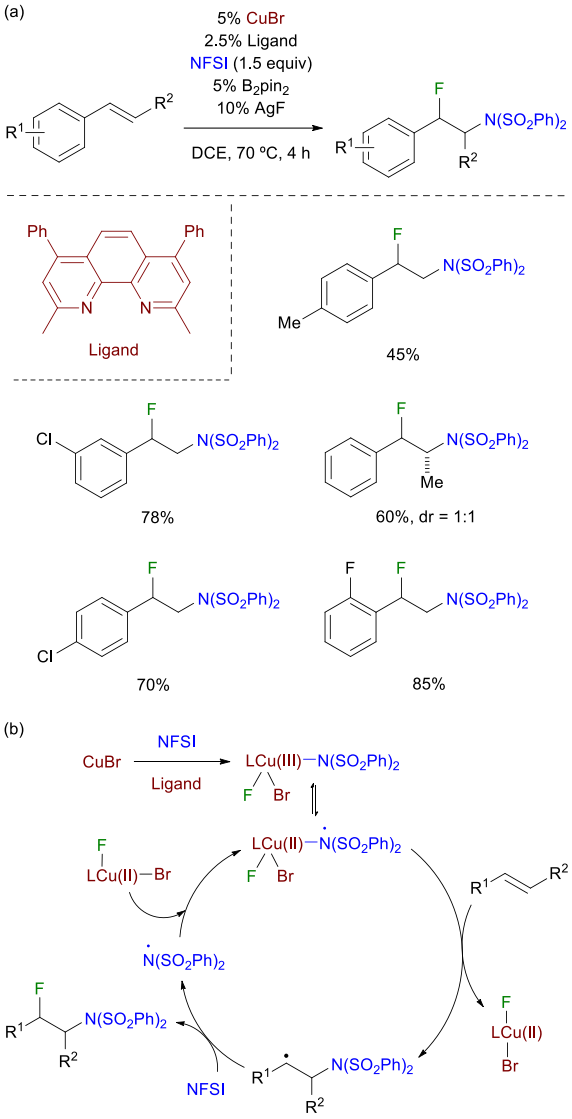
Fluoroalkyl groups are highly useful structural motifs in numerous pharmaceutical compounds. Recently, Li developed



Scheme 10 Aminotrifluoromethylation of alkenes with NFSI and $(bpy)Zn(CF_3)_2$ (a). Mechanistic proposal (b).

the copper-catalysed aminotrifluoromethylation of alkenes with NFSI as *N*-radical precursor and $(bpy)Zn(CF_3)_2$ (bpy = 2,2′-bipyridine) as the CF_3 source (Scheme 10a).[21] The method exhibits a broad scope, including activated and inactivated olefins, and excellent functional group tolerance. Based on mechanistic studies, the authors proposed a catalytic cycle which starts with the transmetalation of the CF_3 anion from zinc to copper (Scheme 10b). A single electron transfer from the Cu(I)–CF_3 intermediate to NFSI could then generate a N-centred radical. The addition of this radical across the olefin C-C bond generates a C-centred radical intermediate, which can be then intercepted by a Cu(II)–CF_3 complex, leading to the final product and restarting the catalytic cycle.

Although NFSI is one of the most commonly used electrophilic fluorination agent,[22] it can be used either as fluorine or nitrogen source. Thus, in 2014, Zhang and co-workers described the first example of copper-catalysed aminofluorination reactions employing NFSI (Scheme 11a).[23] Interestingly, the process takes place with regioselectivity opposite to that found in previous examples based on palladium catalysts and control reactions without catalyst.[24]

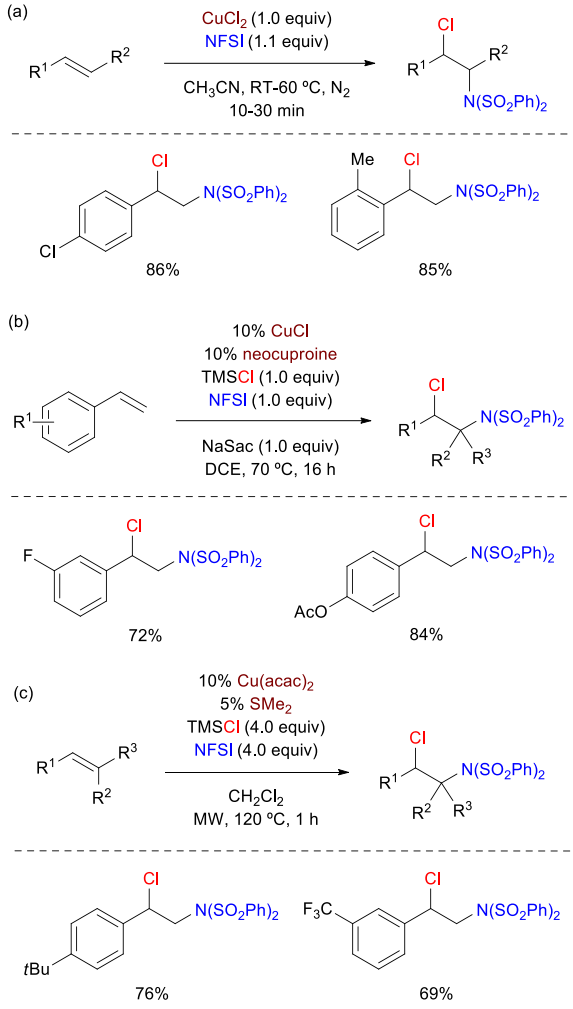


Scheme 11 Aminofluorination of alkenes with NFSI (a). Mechanistic proposal (b).

The reactions were performed using CuBr and bathocuproine (BC) as the ligand, and the yields were improved using bis(pinacolato)diboron (B_2pin_2) and AgF as additives. The effect of the former might be attributed to the interaction between copper and boron, whereas the latter was used to eliminate halide ions. Mechanistic studies and DFT calculations suggest that the initial oxidative addition of Cu(I) to the N-F bond could generate a Cu(III) intermediate in equilibrium with a Cu(II)-stabilised radical. Subsequent addition of the imidyl radical to

the double bond generates a benzylic radical intermediate. A final fluorine transfer from NFSI provides the aminofluorination product (Scheme 11b).

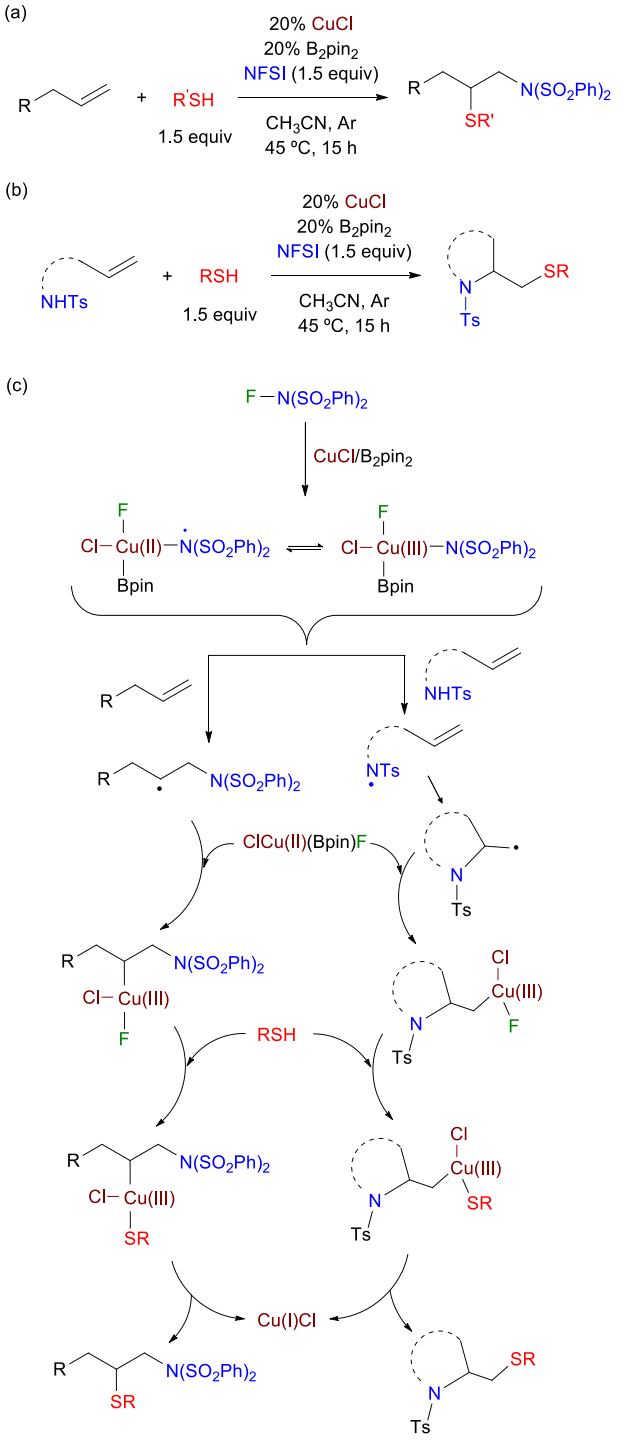
The copper-mediated aminochlorination of inactivated alkenes was developed by Liu, Li, and co-workers (Scheme 12a).[25] In



Scheme 12 Different methods for aminochlorination of alkenes with NFSI: stoichiometric reaction (a), catalytic reaction using TMSCl as reagent (b), microwave assisted catalytic reaction using TMSCl.

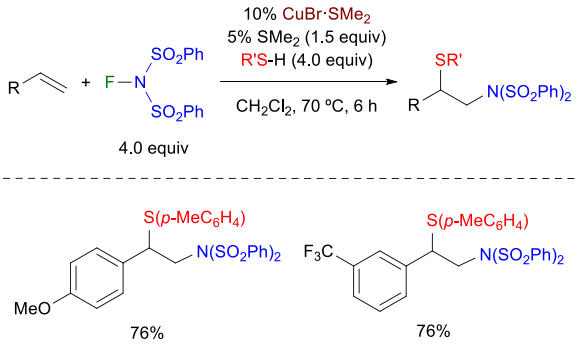
this report, the authors also extended the protocol to the aminochlorination of alkynes (see Section 3). The methodology allows the construction of functionalised chloroamines in good to high yields. Additionally, two catalytic systems have been reported by means of a copper complex, NFSI as the nitrogen source, and chlorotrimethylsilane (TMSCl) as the chlorination reagent. The first one, by E. G. Pérez and co-workers, used CuCl and neocuproine to achieve the regioselective aminochlorination of a series of styrenes in moderate to high yields under relatively mild conditions (Scheme 12b).[26] The second method has been recently reported by Iwasaki and Nishihara and requires a mixture of $Cu(acac)_2$ and SMe_2 as the catalyst, and 1h at 120 °C by means of microwave heating (Scheme 12c).[27]

The construction of C-S bonds has also been accomplished. Zhu and co-workers reported an efficient method for the regioselective 1,2-thioamidation of terminal alkenes, catalysed by copper in the presence of NFSI and thiols (Scheme 13a).[28] Interestingly, the generation of *N*-centred radicals, by the



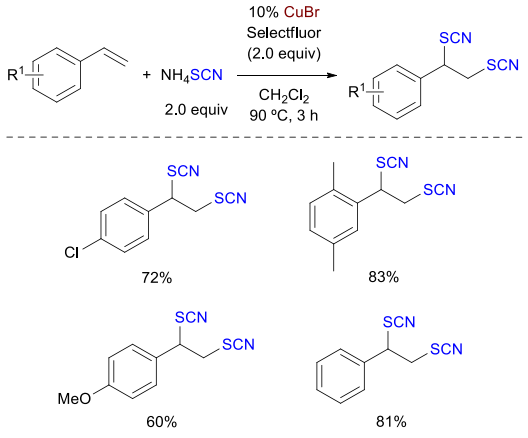
Scheme 13 Regioselective 1,2-thioamidation of terminal alkenes with NFSI and thiols (a). Intramolecular thioamidation of alkenes (b). Mechanistic proposal for inter- and intramolecular processes (c).

reaction of a copper complex with NFSI, provided a reverse regioselectivity compared to that observed in previously reported methods which proceed with the participation of sulphur radical or cationic intermediates. Thus, the nitrogen atom is always linked to the terminal carbon of the olefin generating the more stable secondary carbon radical intermediates. The intramolecular thioamidation process was also accomplished with alkenes containing an amido N–H moiety with the same reaction conditions. Thus, a variety of pyrrolidines and one piperidine derivatives were obtained in



Scheme 14 Regioselective 1,2-thioamidation of alkenes with NFSI and thiols.

moderate to high yields (Scheme 13b). The mechanism for both inter- and intramolecular reactions was proposed based on the radical inhibiting experiments and previous literature reports (Scheme 13c). Initially, the oxidation of the complex $CuCl/B_2Pin_2$ with NFSI provides a Cu(III)-species, which is in equilibrium with a Cu(II)-species. The decomposition of such complexes generates amido radicals, which can then follow

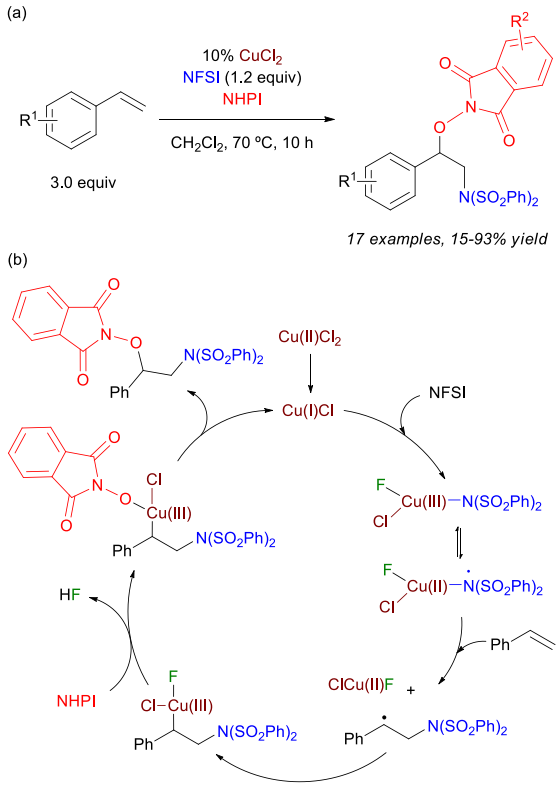


Scheme 15 Dithiocyanation of styrenes with ammonium thiocyanate and Selectfluor.

two possible routes for inter- or intramolecular process. In path a, the addition of such radicals across the olefin generates a C-centred radical intermediate, which can be then intercepted by a Cu(II) complex to yield a Cu(III) complex. The latter evolves by ligand exchange with a thiol, followed by the reductive elimination step to afford the targeted product and the initial oxidation state of the copper complex. In path b, the former *N*-centred radicals undergo a hydrogen atom transfer process from the amido N-H moiety before the intramolecular addition across the olefin *via* 5-*exo*-trig cyclization takes place. A similar Cu(III) complex was then formed, followed by ligand exchange and reductive elimination.

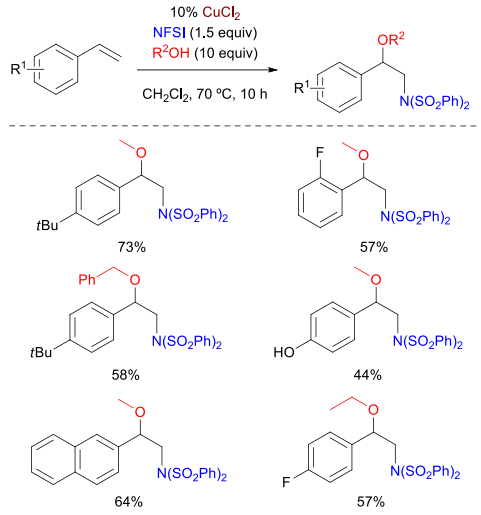
Very recently, Iwasaki and Nishihara have reported an improved method for the 1,2-thioamidation of alkenes.[29] The use of a copper catalyst and dimethyl sulfide efficiently promotes the regioselective aminothiolation of alkenes with NFSI and thiols (Scheme 14). The scope of the reaction has been extended to terminal aromatic and aliphatic alkenes and internal alkenes, which can be transformed into the corresponding aminothiolation adducts in good yields. Mechanistic investigations led the authors to pose a similar proposal to the previously postulated by Zhu (see Scheme 13c).

The dithiocyanation of alkenes was also accomplished with a copper catalyst and N-F reagents. Particularly, Zhang and co-workers reported the synthesis of dithiocyanates *via* Cu-catalysed reaction of different styrenes, ammonium thiocyanate, and Selectfluor as oxidant (Scheme 15).[30] This methodology showed a wide range of functional groups tolerance in styrenes with different substituents in the aromatic ring. Preliminary mechanistic investigations supported the participation of radical species such as a benzylic radical which was trapped by TEMPO.



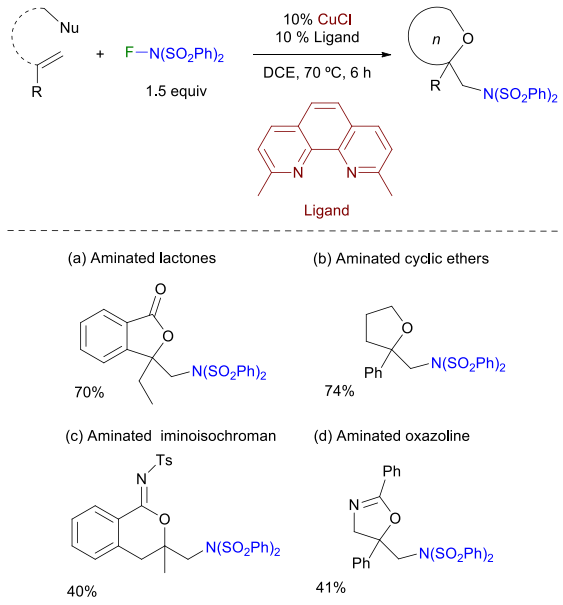
Scheme 16 Aminooxygenation of styrenes with NFSI and *N*-hydroxyphthalimide derivatives.

In 2015, Zhang and co-workers developed the copper-



Scheme 17 Aminooxygenation of styrenes with NFSI and simple alcohols.

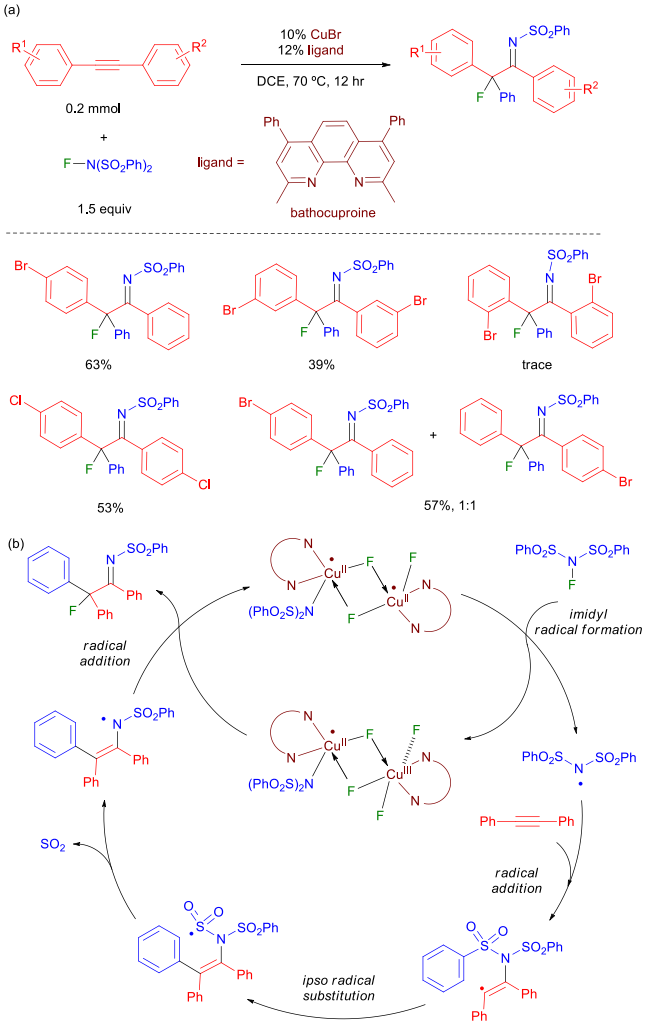
catalysed aminooxygenation of styrenes with NFSI and *N*-hydroxyphthalimide derivatives (Scheme 16a).[31] Interestingly, the aminooxygenation product could be readily converted into the corresponding alcohol or free amine through the cleavage



Scheme 18 Intramolecular aminooxygenation of alkenes with NFSI.

of the N–O or C–N bond of the NHPI moiety. In addition, the authors proposed a plausible mechanism for the reaction (Scheme 16b). Initially, the oxidative addition of NFSI to a Cu(I) complex provides a Cu(III) species in equilibrium with a copper(II)-stabilised *N*-centred radical. Next, the addition of such species across the olefin produces a benzylic radical which is then trapped by the complex F-Cu(III)-Cl, affording an alkyl-Cu(III) complex that undergoes a ligand exchange process with NHPI. Finally, the reductive elimination step provides the final product and the initial oxidation step of the catalyst.

On the other hand, E. G. Pérez and co-workers reported another method for the aminoalkoxylation of styrenes using NFSI and simple alcohols (Scheme 17).[32] The Cu-catalysed reaction is regioselective and takes place under simple and mild conditions; NFSI acts as the oxidant and nitrogen source and alcohols such as MeOH, EtOH, and benzyl alcohol can be used as the alkoxy sources. The authors proposed the participation of radical species into a mechanism similar to that described before by Zhang's group. The intramolecular version of these aminooxygenation processes was described by Qui and Zhang (Scheme 18).[33] The synthesis of a variety of saturated oxygen heterocycles was achieved using a copper



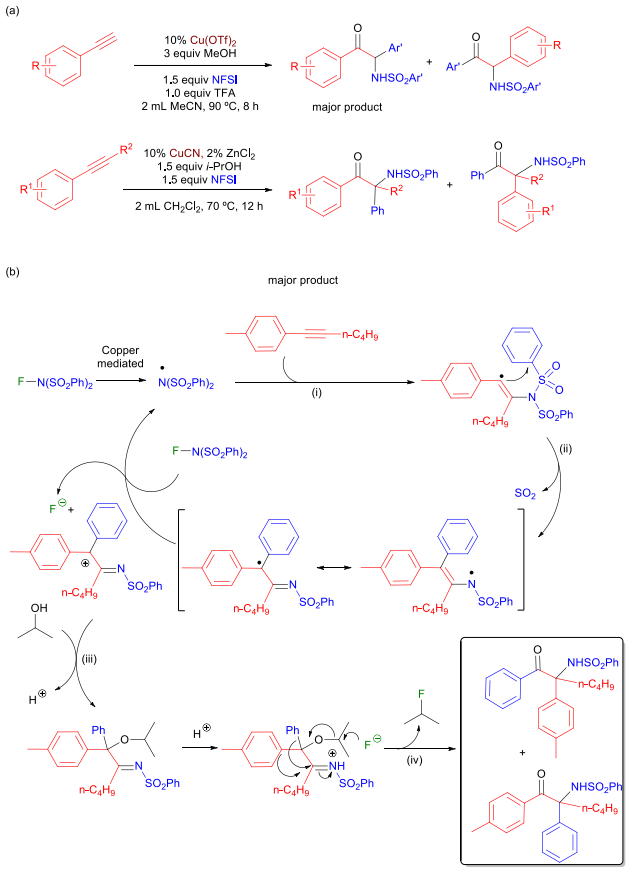
Scheme 19 Synthesis of α-fluoroimines by copper-catalyzed reaction of diarylacetylenes and *N*-fluorobenzenesulfonimide (a). Mechanistic proposal (b).

complex and NFSI as the amination reagent.

3 Radical Additions to Alkynes

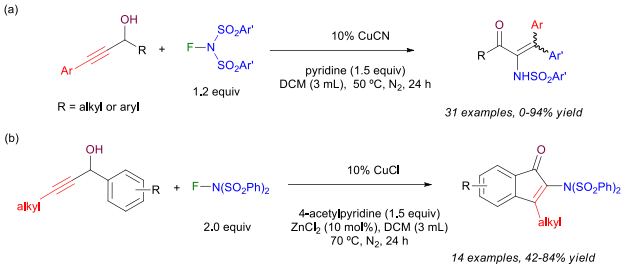
The examples of reactions of alkynes and N-F reagents are scarce when compared to olefins as substrates. However, those transformations involve higher diversity since they include not only difunctionalisation of the triple carbon-carbon bond, but also cascade and tandem processes. Regarding to the difunctionalisation reactions, Murakami and Itami[34] reported the copper-catalysed synthesis of α-fluoroimines from diarylacetylenes and NFSI (Scheme 19a). The proposed mechanism involves the formation of Cu(II)-Cu(II) and Cu(II)-Cu(III) dinuclear species and the generation of imidyl radical, which reacted with alkyne leading to the formation of the product (Scheme 19b). The imine group could easily be transformed into other functional groups.

Zhang and co-workers[35] reported the efficient synthesis of α-amino-α-aryl ketones by a cascade radical aminative multifunctionalisation reaction of terminal and internal arylalkynes using NFSI (or related *N*-fluoroarylsulfonimides) and simple alcohols (Scheme 20a). The proposed mechanism involved the following steps: (i) regioselective nitrogen-centred radical addition to the alkyne leading to the formation



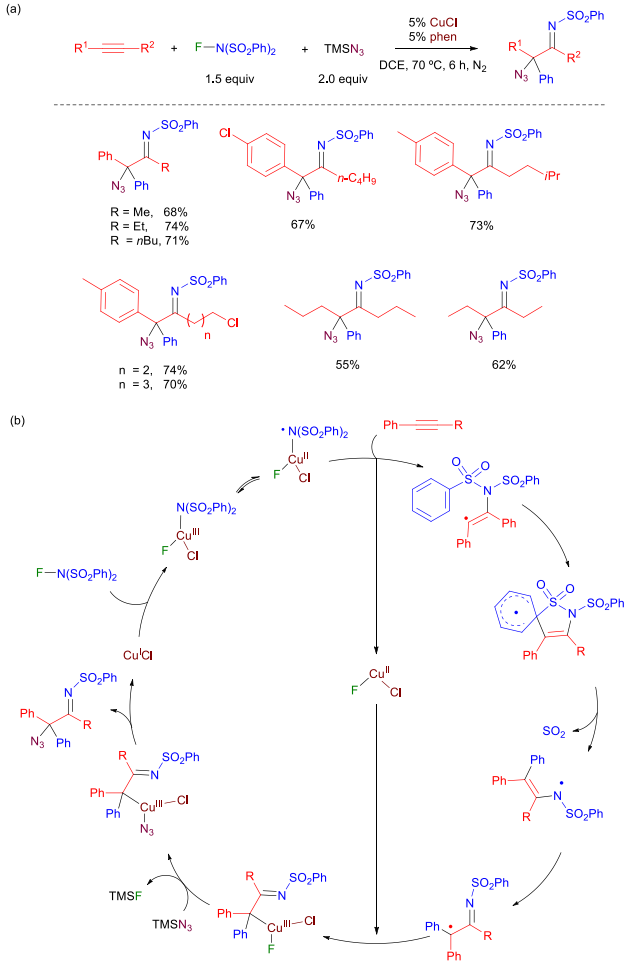
Scheme 20 Synthesis of α-amino-α-aryl ketones (a). Proposed mechanism (b).

of vinyl radicals; (ii) subsequent migration of the aryl group from the nitrogen source followed by efficient desulfonylation, (iii) oxygenation, and (iv) semi-pinacol rearrangement (Scheme 20b).



Scheme 21 Synthesis of α-amino-β-aryl unsaturated carbonyl compounds (a) and indenones (b).

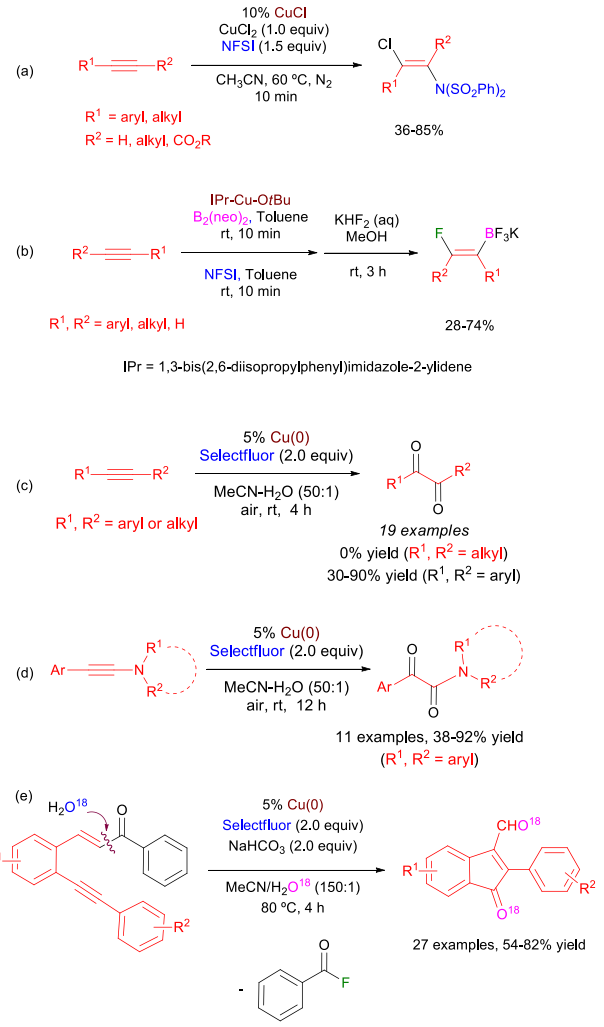
With a similar system, Li[36] described the synthesis of α-amino-β-aryl unsaturated carbonyl compounds and 2-amino-1H-inden-1-one depending on the substituent on the alkyne moiety (alkyl or aryl). The aminoarylation reaction of aryl/alkyl alkynes took place using NFSI as aminoarylation or amination



Scheme 22 Synthesis of α-azido-α-aryl imines (a). Mechanistic proposal (b).

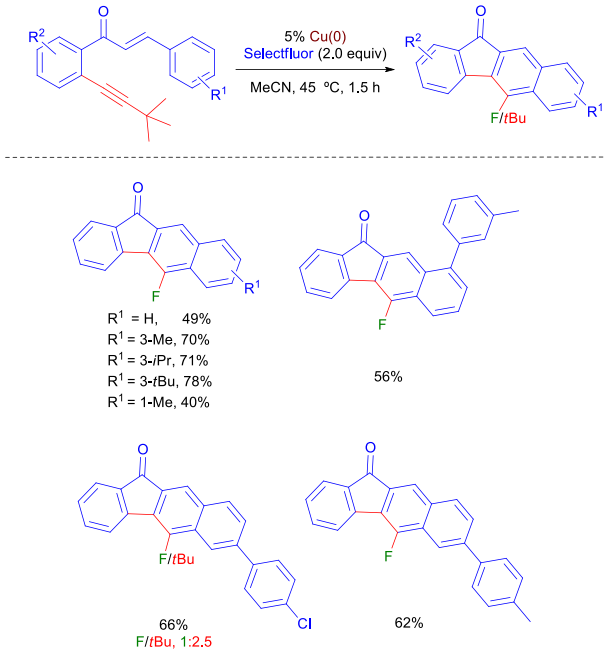
reagent whereas the hydroxyl group acted as the directing group (Scheme 21a and b). A complex mechanism was proposed, where the initial step was common for both types for substrates.

The same group[37] achieved the copper-mediated synthesis of α-azido-α-aryl imines using NFSI as both nitrogen source and aryl source and trimethylsilyl azide ($TMSN_3$) as azido source (Scheme 22a). In this case, the proposed catalytic cycle involved the imidyl radical addition to alkynes and subsequent 1,4-aryl migration. In this system, the authors postulated that copper(I) reacted with NFSI by oxidative addition generating an equilibrium involving Cu(III) and Cu(II) species. The reaction of the copper(II) intermediate with the alkyne leads to the



Scheme 23 Synthesis of chloroenamines by the reactions of alkynes and NFSI in the presence of $CuCl_2$ (a). Copper(I)-mediated borofluorination of alkynes (b). Cu(0)–Selectfluor-mediated 1,2-dicarbonylation of alkynes (c) and ynamides (d). Synthesis of 3-formyl-1-indenone derivatives catalyzed by Cu(0) in the presence of Selectfluor (e).

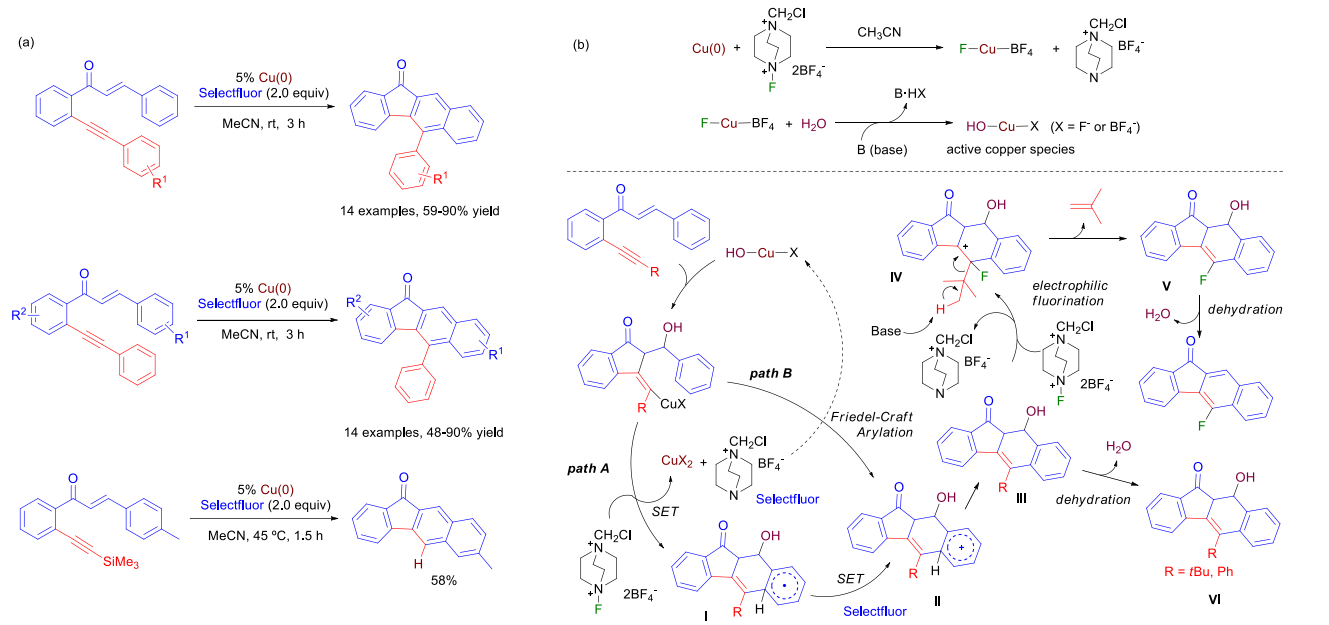
formation of a vinyl radical. A subsequent 1,4-aryl migration/desulfonylation step provides an alkyl radical, which reacts with Cu(II) species to afford a Cu(III) species acting as the precursor of a Cu(III)–N_3 azido complex (Scheme 22b), formed by transmetalation with $TMSN_3$. A final reductive elimination step gives the α-azido-α-aryl imine.



Scheme 24 Synthesis of fluorinated benzo[b]fluorenones and *tert*-butyl-substituted benzo[b]fluorenones from *tert*-butylethynyl-substituted 1,6-enynes catalyzed by Cu(0)/Selectfluor

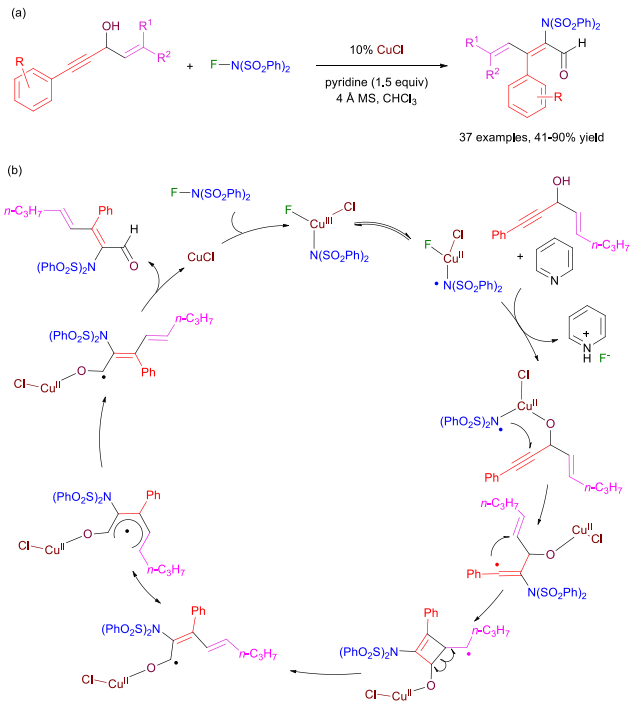
As already commented in the previous section, Liu, Li, and co-workers[25] described a methodology for the regio- and stereoselective aminochlorination of inactivated alkynes with NFSI in the presence of $CuCl_2$ (Scheme 23a), which allowed the synthesis of functionalised chloroenamines in good to high yields. Additionally, Sadighi[38] reported the stoichiometric difunctionalisation of alkynes by the reaction of *in situ* generated (NHC)Cu(I)-boryl complexes with alkynes, followed by treatment with NFSI. Thus, alkynes were converted into *cis*-(β-fluorovinyl)boronates (Scheme 23b). The reaction of the N-F reagent and the alkyne could induce cascade processes. For instance, in 2013 Liu group[39] applied the Cu(0)/Selectfluor catalytic system to the 1,2-dicarbonylation of alkynes under mild conditions using water and dioxygen (Scheme 23c,d). In this contribution, the authors proposed that the redox reaction of copper powder with Selectfluor originates the copper(II) active catalytic species, XCuOH, that induces the activation of the alkyne moiety by coordination. The same group used the same combination of Cu(0)/Selectfluor for the synthesis of 3-formyl-1-indenone derivatives by oxidative cyclization of 1,5-enynes with concomitant C–C bond cleavage (Scheme 23e).[40]

Liu and co-workers also developed the preparation of benzo[b]fluorenone[41] derivatives by annulation reaction of 1,6-enynes. Importantly, the product obtained depended on the substituent on the alkyne moiety. Thus, in the case of *tert*-butylethynyl-substituted 1,6-enynes, fluorinated benzo[b]fluorenones were obtained as major products and



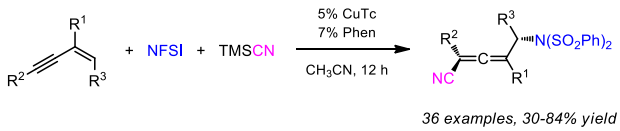
Scheme 25 Synthesis of 5-aryl-substituted benzo[b]fluorenones (and 11H-benzo[b]fluoren-11-ones (a) and mechanistic proposal for the formation of 5-aryl-substituted benzo[b]fluorenones (b).

tert-butyl-substituted benzo[b]fluorenones were the minor products (Scheme 24). However, arylethynyl-substituted 1,6-enynes gave 5-aryl-substituted benzo[b]fluorenones, and the reaction with (trimethylsilyl)ethynyl-substituted 1,6-enynes, delivered 11H-benzo[b]fluoren-11-ones (Scheme 25a). As in the previous systems,[35,36] the authors proposed the formation of the active copper(II) species XCuOH (X = F or BF_4) generated by the reaction of Cu(0) powder and Selectfluor in the presence of water. The benzo[b]fluorenones underwent oxycupration by XCuOH species leading to the formation of an alkenyl copper intermediate (Scheme 25b). Two possible pathways could then occur. In path A, the alkenyl-copper(II) complex suffered a double SET to give a cationic species, **II**. Alternatively, through path B, the alkenyl-copper(II) complex could give **II** through a Friedel–Crafts arylation process under oxidative conditions. One way or the other, intermediate **III** is formed by proton abstraction from **II**. The dehydration of **III** delivered benzo[b]fluorenone **VI** (R = tBu or Ph). In the case of *tert*-butylethynyl-substituted 1,6-enynes, **III** may undergo an electrophilic fluorination by Selectfluor to give intermediate **IV**, which suffered a C–C bond cleavage en route to intermediate **V**. Dehydration of the latter afforded the fluorinated product. For the (trimethylsilyl)ethynyl-substituted 1,6-enynes, the alkenyl-copper complex could undergo desilylation, with the aid of F^-, leading to an alkenyl complex lacking the trimethylsilyl group. An annulation process of this intermediate and subsequent dehydration would give the final 11H-benzo[b]fluoren-11-one.



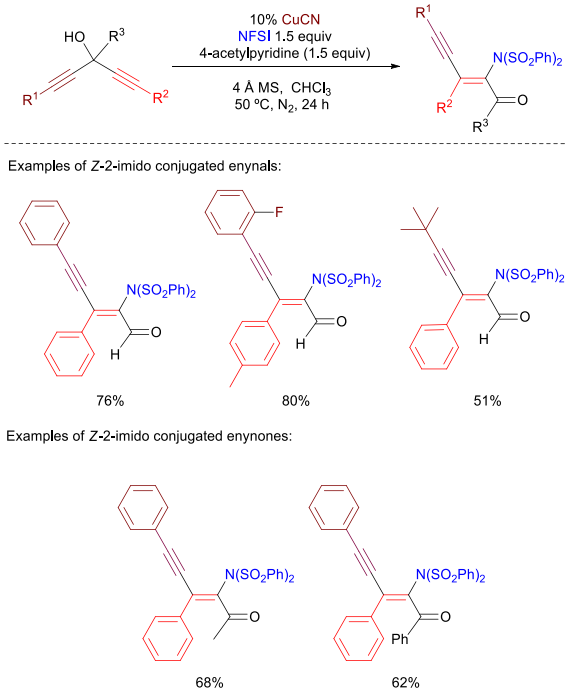
Scheme 26 Imidovinylation of alkynes with copper as catalyst and NFSI (a). Mechanistic Proposal (b).

Very recently Bao, Zhang and co-workers have reported the 1,4-sulfimidocyanation of 1,3-enynes with NFSI and TMSCN catalysed by copper(I)-thiophene-2-carboxylate (CuTc) and 1,10-phenanthroline (Scheme 27).[42] This method allows to synthesize a variety of multisubstituted allenes with high regioselectivity. These compounds can be easily transformed into synthetically useful molecules. Based on mechanistic investigations the authors propose a Cu(I)/Cu(II) mechanism with the participation of allenyl radicals.

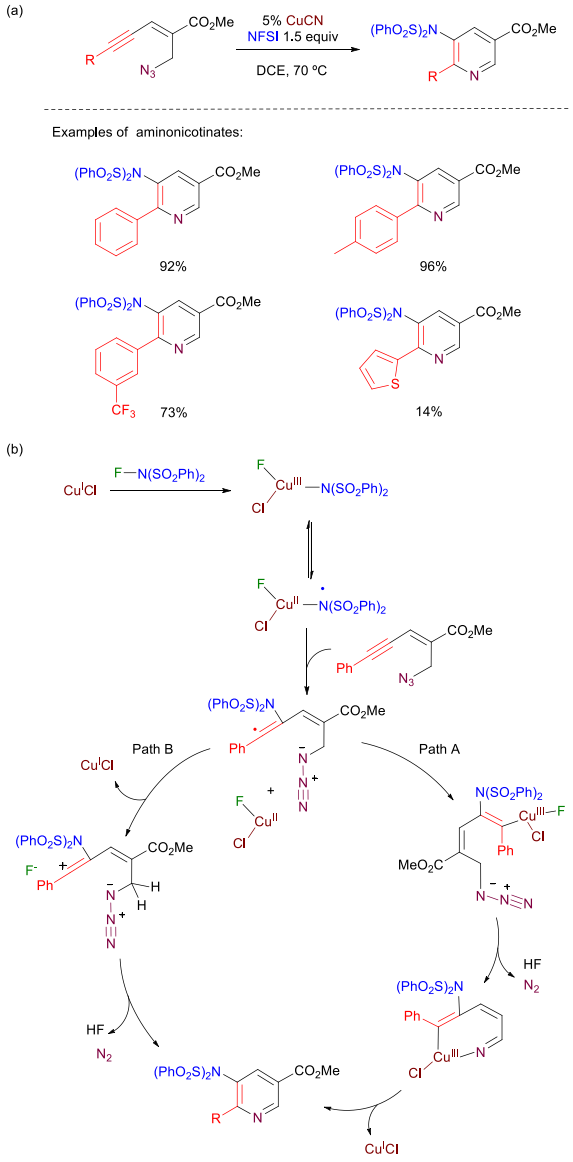


Scheme 27 Synthesis of multisubstituted allenes by 1,4-sulfimidocyanation of 1,3-enynes with NFSI and TMSCN.

Zhang and Li[43] described the imidovinylation of alkynes with copper as catalyst and NFSI as imidation reagent (Scheme 26a). The reaction involved a 1,3-carbon migration of propargylic alcohols and their derivatives *via* vinyl migration. As proposed by these authors for other systems,[10,23,36] the catalytic cycle initiated by the oxidative addition of NFSI to the CuCl to generate a Cu(III) complex, which was in equilibrium with a radical Cu(II) species (Scheme 26b). This copper(II) complex reacted with propargylic alcohol, through pyridine assisted HF removal, to form an alkoxo-Cu(II) intermediate. Subsequently, a nitrogen-cantered radical added selectively to the C≡C bond to generate a vinyl radical, which afforded an alkyl radical bearing a cyclobutenyl fragment. Successive carbon-carbon bond cleavage and 1,3-vinyl migration generated (2*Z*,4*E*)-radical, which further transformed into the more stable alkoxo (2*E*,4*E*)-radical. Homolysis of the Cu–O bond gave the (*E*)-2-imido-2,4-dienal and regenerated the Cu(I) species. Li group applied also this type of methodology to the preparation of (*Z*)-2-amino conjugated enynals/enynones by cascade aminoalkynylation–oxidation of propargylic alcohols



Scheme 28 Synthesis of (*Z*)-2-amino conjugated enynals/enynones by cascade aminoalkynylation–oxidation of propargylic alcohols with copper as catalyst and NFSI.



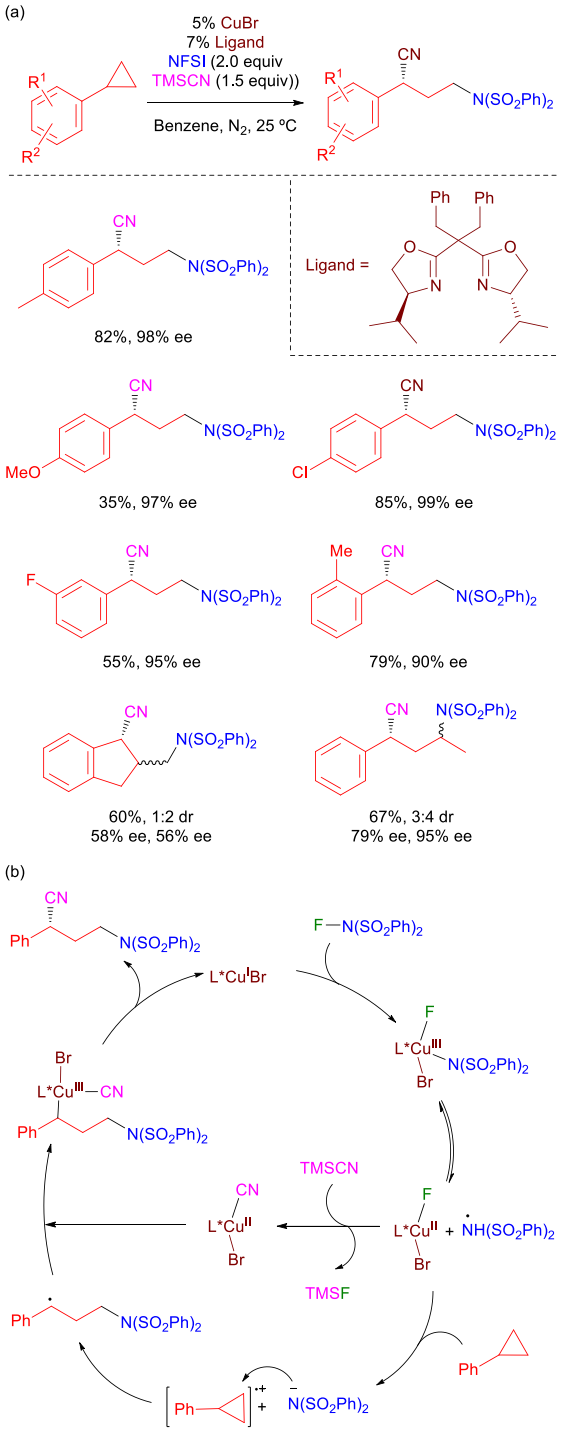
Scheme 29 Synthesis of aminonicotinates (a). Proposed mechanism (b).

using NFSI and its derivatives as amination reagent (Scheme 28).[44] A gram-scale production of one conjugated enynal was conducted in 69 % yield to demonstrate the synthetic utility of the method. The proposed mechanism was very similar to previous system reported by these authors.[36,43]

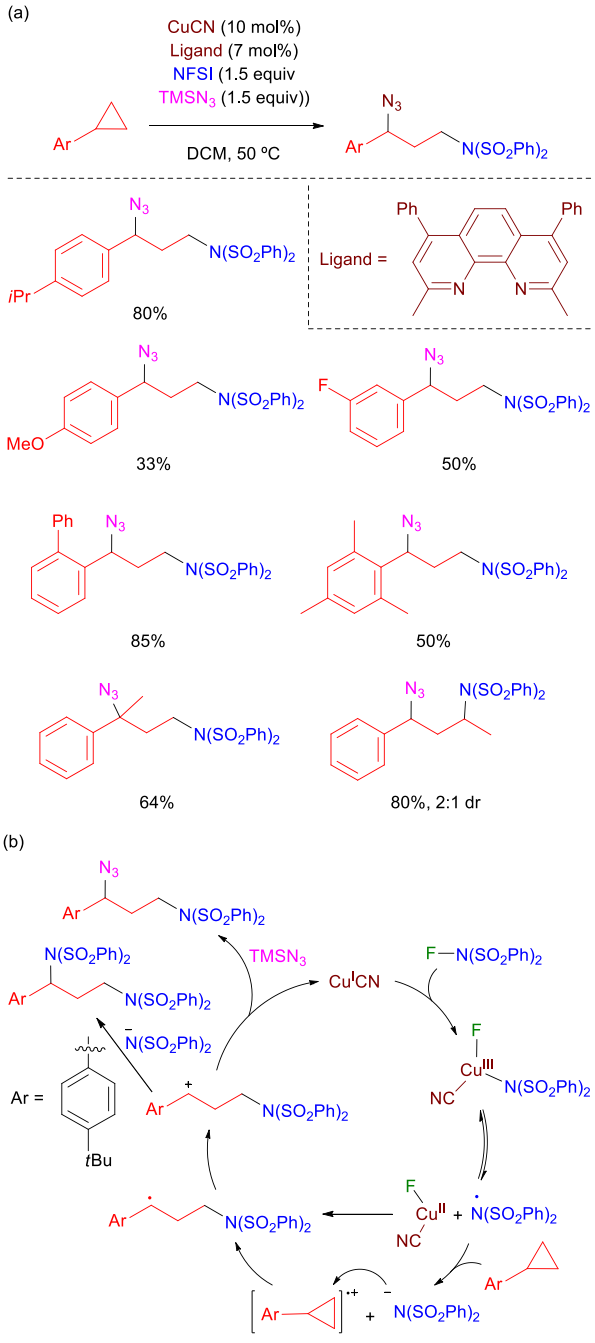
Based on Li´s findings, Ranjan and co-workers developed a method for the synthesis of amino nicotinates[45] by aminative aza-annulation of enynyl azides using NFSI (Scheme 29a). The reaction took place by regioselective inter-/intramolecular diamination: one nitrogen atom from the NFSI and the other from the azide. The proposed catalytic cycle (Scheme 29b) was based on the experiments carried out and some literature precedents.[20,33,46] Thus, the initial steps were identical to those postulated by Li. However, Ranjan proposed two possible pathways, one of them occurring through the Cu(III) species, and, alternatively, a second pathway involving the formation of cationic species by oxidation of the vinyl radical with Cu(II).

4 Ring-opening 1,3-Bisfunctionalisation of Cyclopropanes

Based on the literature precedents about the copper-catalysed asymmetric radical relay[47] and on their investigations of copper catalysed radical reactions,[10,48] Li and co-workers[49] developed the synthesis of highly enantiopure γ-amino nitriles by amino-cyanation of arylcyclopropanes using NFSI as the nucleophilic nitrogen source and oxidant, TMSCN as the other nucleophile and a chiral bisoxazoline ligand (Scheme 30a). The mechanistic proposal was similar to those for other related catalytic systems reported by this group, involving the formation of an equilibrium between Cu(III)-N and Cu(II)-species, and the generation of Cu(II)-CN and Cu(III)-CN species. The latter complex undergoes reductive elimination to afford enantioselectively γ-amino nitrile (Scheme 30b). The aryl group



Scheme 30 Synthesis of γ-amino nitriles (a). Mechanistic proposal (b).



Scheme 31 1,3-aminoazidation of arylcyclopropanes with NFSI and $TMSN_3$ (a). Catalytic cycle (b).

was necessary for the reaction, possibly as stabilizer of the alkyl radical.

Li group extended this methodology also to the preparation of 1,3-diamine derivatives by 1,3-aminoazidation of arylcyclopropanes with NFSI and $TMSN_3$ (Scheme 31a),[50] that is, by simultaneous introduction of two different nitrogen sources. The catalytic cycle was very similar to that postulated by the same group for the amino-cyanation of arylcyclopropanes, although differently the reaction of the benzyl radical with the F-Cu^{II}-CN species leads to the formation of benzyl cation, which reacted with $TMSN_3$ to generate the product. In the case of *p*-*t*Bu-phenyl derivative, the nucleophilic attack of excess amide anion to benzyl cation could lead to the formation of a small amount of the diaminated byproduct (Scheme 31b).

5 Conclusion

We have described herein the advances on the copper-catalysed radical difunctionalisation reactions of alkenes, alkynes and cyclopropanes using N-F reagents. The reactions involve radical addition, radical addition–cyclization, or cascade processes to accomplish high-value transformations. The practical applicability of some catalytic systems has been demonstrated by gram scale reactions. One of the main drawbacks is the use of a considerable catalyst loading, thus the development of more active catalysts and subsequent low catalyst loadings must be considered a target in the next future. In addition, since the applicability of these processes is almost limited to alkenes, alkynes and cyclopropanes bearing an aryl group, more active catalysts which augment the yet scarce examples of alkyl-substituted substrates are also required.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Ministerio de Economía y Competitividad (MINECO) (CTQ2017-82893-C2-1-R) and Universidad de Huelva (PO FEDER 2014-2020 UHU-1254043) for grants.

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