Recent Advances in Copper-Catalyzed Radical C-H Bond Activation Using N-F Reagents

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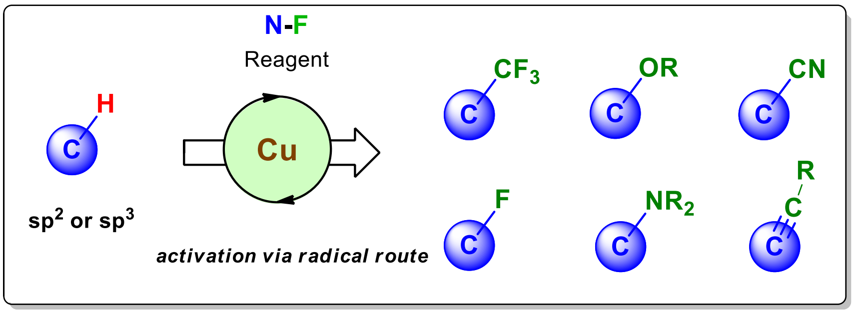


Received:
Accepted:
Published online:
DOI:

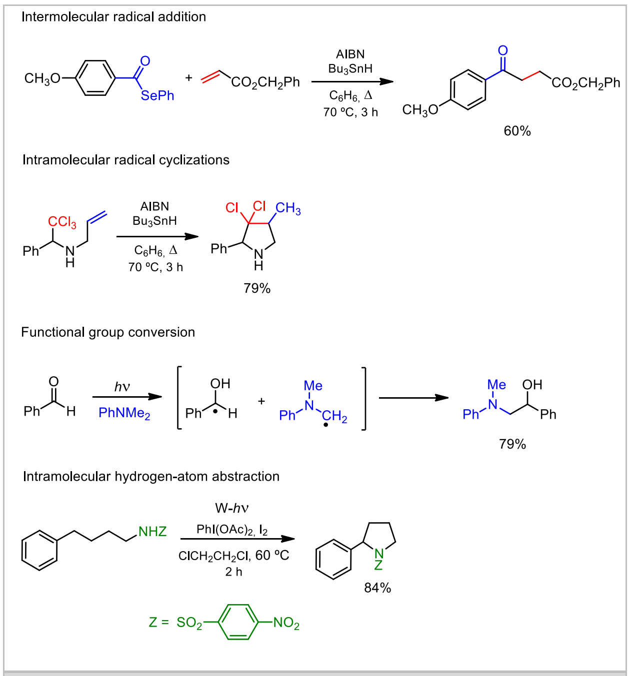
Abstract This review is aimed at giving an update in the area of copper catalyzed C-H functionalization involving nitrogen-centered radicals generated from substrates containing N-F bonds. These processes include intermolecular Csp^3-H bond functionalization, remote Csp^3-H bond functionalization via intramolecular hydrogen atom transfer (HAT) and Csp^2-H bond functionalization, which might be of potential use in industrial applications in the future.

Key words copper catalysis, C–H bond functionalization, amination, nitrogen-fluorine bond, radical fluorination

1 Introduction

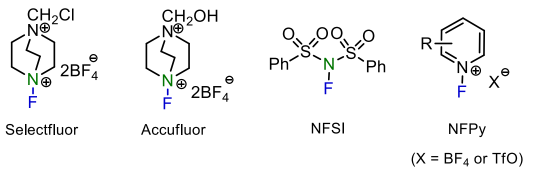
Reactions involving alkyl radicals are fundamental in organic synthesis, due to their chemoselectivity or the wide functional group tolerance, among other features.[1] Particularly interesting reactions are the intermolecular radical addition reactions, the intramolecular radical cyclizations, the functional group conversion and the intramolecular hydrogen-atom abstraction (Scheme 1).[2] The former transition metal-mediated radical reactions have proven quite useful as a synthetic protocol since the metal complexes can exert a certain control in the activity of the radical species, regulating the appearance of undesired side reactions.[3] Toward that end, copper has been widely used mainly due to its low cost and toxicity. It is worth mentioning that the four different oxidation states of copper (Cu(0), Cu(I), Cu(II), and Cu(III)) may be involved in the mechanism of Cu-catalyzed radical reactions.

The use of commercially available N-F reagents,[4] such as Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)),[5] Accufluor (1-fluoro-4-hydroxy-1,4-diazoniabicyclo-[2,2,2]octane bis(tetrafluoroborate)),[6] NFSI (*N*-fluorobenzenesulfonimide)[7] or NFPy (*N*-fluoropyridinium salts)[8] for radical-driven reactions has been extensively developed in the last decade (Scheme 2). Thus, they have been employed as fluorination[9] and/or amination[10] reagents, and as versatile intermediaries for the preparation of other N-F reagents or catalysts for several other types of functionalization or transformations of organic derivatives.[9f]



Scheme 1 Several examples of radical reactions in organic synthesis

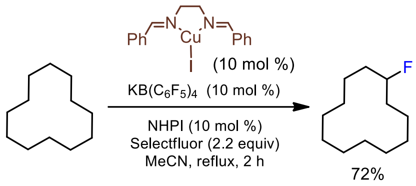
One of the most studied copper-catalyzed transformations promoted using N-F reagents involves the activation of C-H bonds, either intermolecular Csp^3-H or Csp^2-H bond functionalization (amination, fluorination, cyanation, alkylation, arylation, etc) or cyclization by intramolecular Csp^3-H bond activation. The aim of this contribution is to present the recent advances in copper-mediated radical processes in which N-F reagents are involved.



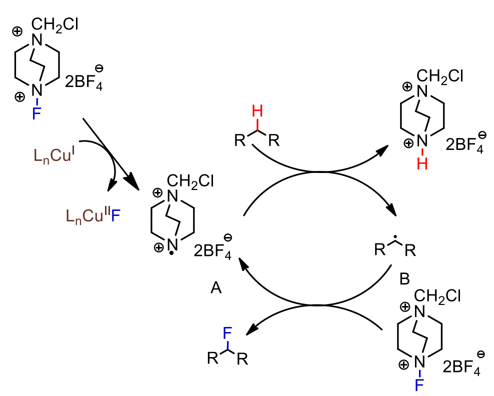
Scheme 2 Commonly used N-F reagents

2 Intermolecular Csp^3-H Functionalization

The above N-F reagents can be used to transfer either the fluorine atom (fluorination) or the amine moiety (amination reactions) by copper-mediated radical transformations en route to C-H bond activation. In 2012, Lectka and co-workers reported the mild, catalytic Csp^3–H fluorination of alkanes by an interplay between copper(I) and Selectfluor (Scheme 3).[11] A series of aliphatic, benzylic, and allylic substrates was fluorinated using a copper(I) bisimine complex as the catalyst, Selectfluor, *N*-hydroxyphthalimide (NHPI) as the radical initiator and (KB(C$_6$F$_5$)$_4$) as anionic phase-transfer agent. The authors proposed a radical chain mechanism in which copper acts as the initiator, instead of as the catalyst, promoting an inner-sphere SET from copper(I) to Selectfluor (Scheme 4).[12] Gram-scale synthesis of monofluorinated products were also described. For instance, 1-fluorocyclododecane was obtained in 50% yield after 8 h.

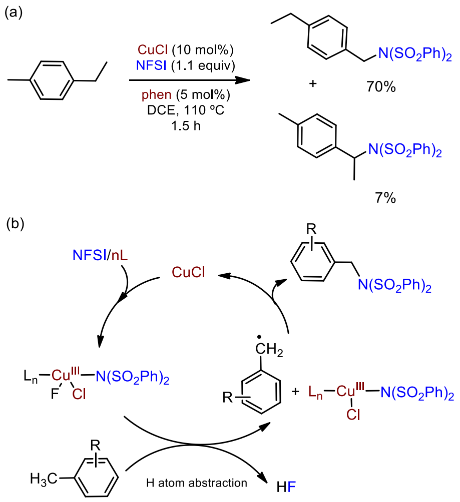


Scheme 3 Catalytic Csp^3–H fluorination of alkanes



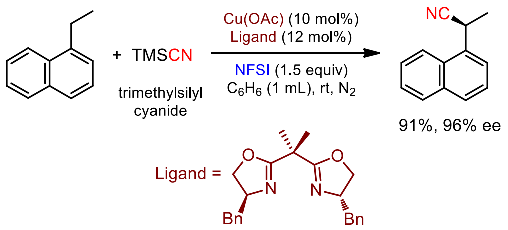
Scheme 4 Mechanism proposed by Lectka and co-workers for the Csp^3–H fluorination of alkane C-H bonds using copper(I) bisimine complexes and Selectfluor

Regarding to the amination processes, Liu and Zhang described a highly selective copper-catalyzed benzylic C-H amination reaction using NFSI as a non-nitrene nitrogen source.[13] The formation of a hindered Cu(III) complex, generated by the oxidation of CuCl with NFSI in the presence of 1,10-phenanthroline (phen), was proposed to explain the remarkable preference for primary over secondary C-H bonds (Scheme 5).



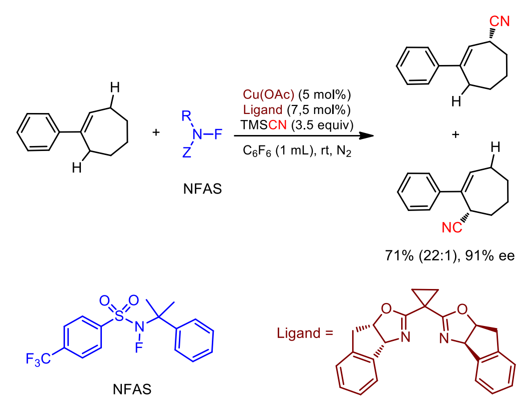
Scheme 5 Copper-catalyzed benzylic C-H amination reaction using NFSI (a). Mechanistic proposal (b)

At variance with the above transformations, the copper-catalyzed Csp^3-H bond activation processes, involving N-F reagents, frequently do not imply the incorporation of their fluorine or nitrogen atoms. Thus, in the field of the C-C bond formation, Liu reported the enantioselective conversion of benzylic C–H bonds into benzylic nitriles using a chiral copper catalyst, with NFSI as oxidant and trimethylsilyl cyanide (TMSCN) as cyanation agent, through a radical relay under mild conditions (Scheme 6).[14] It was proposed that the benzylic radical thus formed was selectively captured by a reactive metal center. The formation of a chiral Cu(II) cyanide was the key step to constructing a C–CN bond with excellent enantiomeric excess. Later, the same group found that the allylic radical could also be regioselectively and enantioselectively converted into the allylic cyanation products (Scheme 7).[15] The site selectivity is



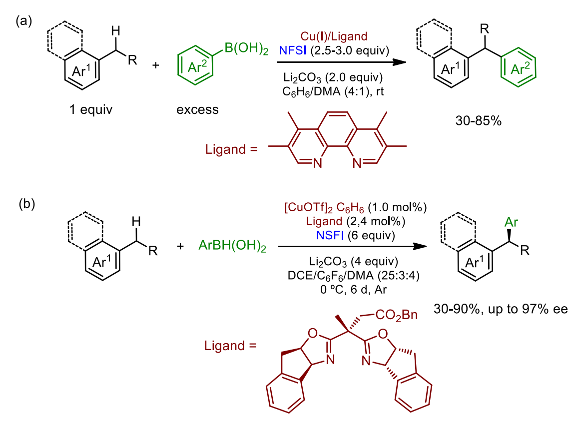
Scheme 6 Enantioselective Cu-catalyzed cyanation of benzylic C–H bonds

influenced, during the hydrogen atom transfer (HAT) step, by the reagent *N*-fluoroalkylsulfonamide (NFAS), which contained a bulky alkyl (R) and an electron-withdrawing aryl (Z) groups on the nitrogen atom. Subsequently, the allylic radical generated is trapped by the chiral Cu(II) cyanide in an enantioselective manner. Two gram-scale preparations were performed showing a practical application of the method in the laboratory.

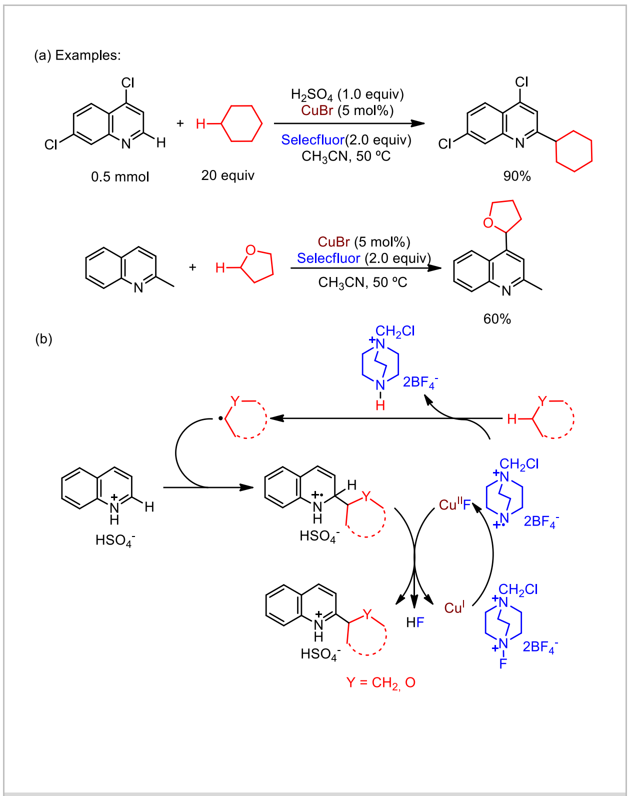


Scheme 7 Regio- and enantioselective Cu-catalyzed cyanation of allylic C–H bonds

The same group developed a copper-catalyzed arylation of benzylic C–H bonds protocol with nucleophilic arylboronic acids in which the alkylarenes act as limiting reagents and NFSI as the oxidant (Scheme 8a).[16] The catalytic system was suitable for a broad substrate scope and showed excellent functional group compatibility. Importantly, splitomycin (1H-benzo[f]chromen-3(2H)-one) was converted in its *m*-fluorophenyl derivative in 98% yield in gram scale. Liu and co-workers accomplished high enantioselective arylations using the bisoxazoline (Box) ligand bearing a benzyl ester moiety (Scheme 8b).[17] For two examples, the reaction was carried out in a gram scale to generate the products in high yield with enantiomeric excess.

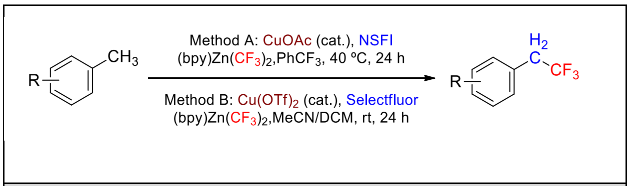


Scheme 8 Copper-catalyzed arylation of benzylic C-H bonds

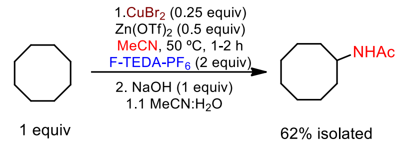


Scheme 9 CDC of heteroaromatics with simple alkanes and ethers

Recently, Chen and Li reported a mild and efficient method for the *N*-heteroarylation of the low reactive C-H bonds of alkanes as well as of ethers *via* an intermolecular cross-dehydrogenative coupling process (CDC) (Scheme 9a).[18] The catalytic cycle proposed was initiated with the oxidation of the copper(I) salt by Selectfluor. Subsequently, the R–H was oxidized to generate a radical R• which reacted with protonated nitrogen-containing heteroaromatics to form an intermediate adduct radical. This radical was finally oxidized by copper(II) to give the CDC product after deprotonation (Scheme 9b). Finally, Zhu and Li have reported the copper-catalyzed benzylic Csp^3–H trifluoromethylation using Cu(I) or Cu(II) complexes as the catalyst, with $(bpy)Zn(CF_3)_2$ (bpy = 2,20-bipyridine) as the CF_3 source, and NFSI (or Selectfluor) as the oxidant. The regioselective benzylic Csp^3–H trifluoromethylation was successfully implemented in high efficiency under mild conditions (Scheme 10).[19]

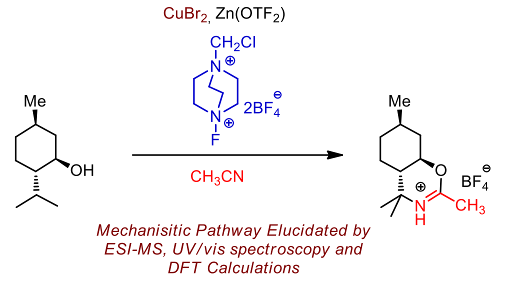


Scheme 10 Benzylic trifluoromethylation of primary Csp^3–H bonds



Scheme 11 Ritter-type C–H amination reaction

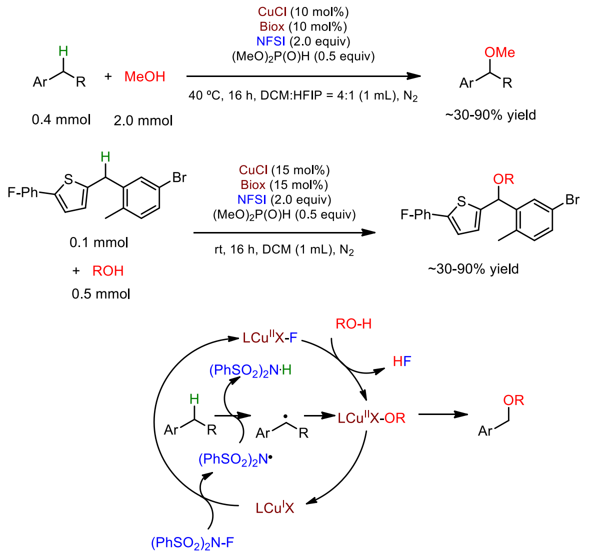
With respect to copper-catalyzed C-N bond formation, Baran and co-workers designed an intermolecular Ritter-type Csp^3-H bond amination under mild conditions using a derivative of Selectfluor, F-TEDA-PF$_6$, and acetonitrile as the source for nitrogen (Scheme 11).[20] Importantly, this reaction also allowed the C–H bond amination of a variety of hydrocarbons such as cyclohexane or cyclooctane without the need of installation of a directing group. In 2018, Zare used a variety of online ESI-MS experiments coupled with continuous UV/vis reaction monitoring to assess two pathways for the CuBr$_2$-mediated Ritter-type C–H bond amination reaction of menthol with Selectfluor (Scheme 12).[21] On the basis of those experiments the authors proposed the intermediacy of a transient highly reactive Cu(III) intermediate.



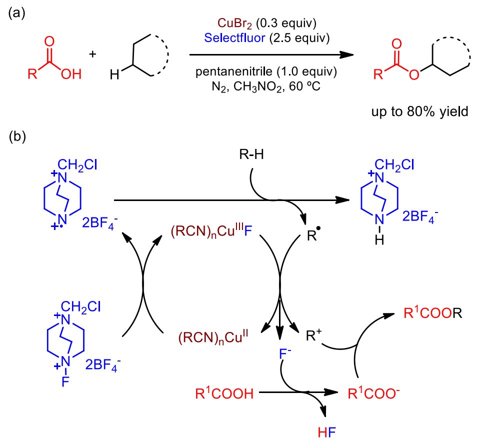
Scheme 12 Mechanistic studies of copper-catalyzed the Ritter-type C–H amination reaction of menthol

Similar strategies have been employed for the formation of C-O bonds of benzyl ethers. For instance, Stahl and co-workers have recently developed a copper-based catalytic system for the radical relay cross-coupling of benzylic C–H bonds with alcohols, enabled by a redox buffering that maintains the activity of the copper catalyst (Scheme 13). The reactions were carried out using the substrate containing the targeted C-H bond as the limiting reagent and NFSI as oxidant. The catalytic system was applied for a broad scope with respect to both alkylarenes and alcohols.[22]

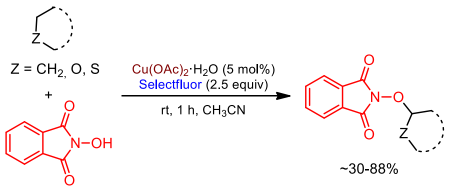
Previously, Su group described the esterification of non-activated (non-benzylic) and allylic Csp^3–H bonds of hydrocarbons catalyzed by copper and with Selectfluor as an oxidant (Scheme 14a). A catalytic cycle based on the oxidation of the copper(II) salt and generation of a fluorinated copper(III) species was proposed (Scheme 14b).[23] These authors extended their studies to the copper(II)-catalyzed cross dehydrogenative coupling reaction between *N*-hydroxyphthalimide (NHPI) and Csp^3–H bonds of alkanes and ethers using Selectfluor (Scheme 15).[24] By this methodology, the synthesis of *O*-substituted NHPI derivatives was achieved at room temperature. It should be pointed out that phthalimide N-oxyl (PINO) radical formed by the reaction of the copper catalyst and NHPI can perform HAT, in addition to the aminium radical (Scheme 14b).



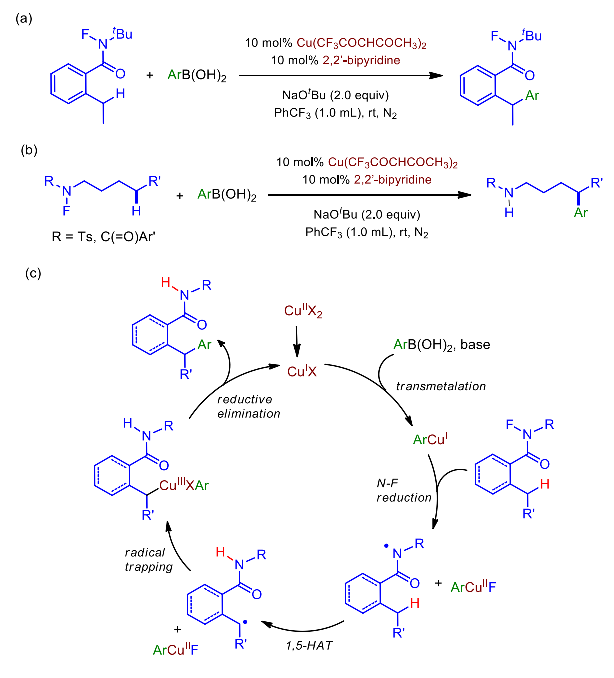
Scheme 13 Oxidative coupling of alkylarenes and alcohol



Scheme 14 Csp^3–H esterification catalyzed by copper with Selectfluor as oxidant



Scheme 15 Synthesis of *O*-substituted derivatives of N-hydroxyphthalimide

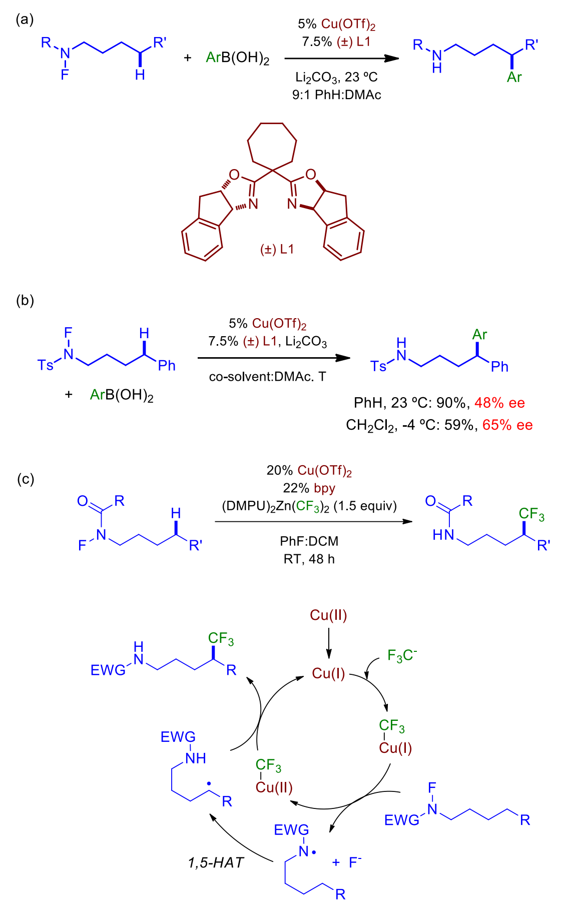


Scheme 16 γ-Arylation of carboxamides (a) δ-Csp^3-H bond functionalization of carboxamides and sulfonamides (b) Proposed mechanism (c)

3 Remote Csp^3-H Functionalization

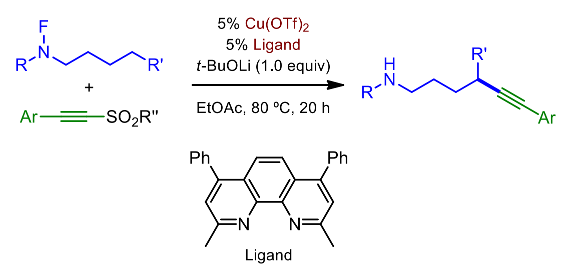
As mentioned in the Introduction, the commercially available N-F reagents are used to synthesize other N-F derivatives,[25] which have been employed to promote remote Csp^3-H activation reactions. Thus, in 2018 Zhu group described a variant of the Hofmann–Loffler–Freytag (HLF) reaction: the copper(II) trifluoroacetylacetonate catalyst induced the transformation of *N*-fluorocarboxamides or *N*-fluorosulfonamides and arylboronic acids, using sodium *tert*-butoxide as base, into the corresponding γ-and δ-Csp^3-H carboxamides and sulfonamides, in good to high yields (Scheme 16).[26] A possible mechanism based on a later contribution by Nagib and Zhang[27] is depicted in Scheme 16c. Thus, these authors reported the selective δ-Csp^3–H (hetero)arylation of sulfonamides (Scheme 17a). It is also worth to mention that the products obtained were subjected to HLF reaction to afford 2-aryl pyrrolidines. Importantly, in the same article the asymmetric variant was described (Scheme 17b).

The above system was also applied to the synthesis of 1,1-diaryl-pyrrolidines *via* iterative C–H bond functionalization (vide infra). Zhu and Li[28] used a similar methodology for the trifluoromethylation of unactivated aliphatic Csp^3-H bonds. Thus, the reaction of *N*-fluorocarboxamides (or sulfonamides) with Zn(CF$_3$)$_2$ complexes catalyzed by Cu(OTf)$_2$ provided the δ-trifluoromethylated carboxamides (or sulfonamides) under mild reaction conditions (Scheme 17c). In good accord with the arylation systems reported by Nagib and Zhou, the authors proposed that the CF$_3$ group was transferred from the Cu^{II}-CF$_3$ complexes to the alkyl radicals formed by 1,5-HAT of N-radicals (Scheme 17c), therefore the alkyl radicals do not coordinate to the copper(II) complexes to generate copper(III) intermediates.



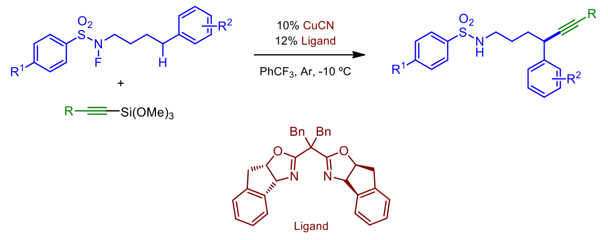
Scheme 17 δ C–H (hetero)arylation by Cu-catalyzed radical relay and coupling with aryl boronic acids. (a,b) Remote Csp^3-H trifluoromethylation of *N*- fluorocarboxamides and sulfonamides (c).

Based on those precedents, Wu has recently studied the reaction of *N*-fluorosulfonamides with acetylene sulfones. The alkyl radicals, generated from 1,5-HAT reactions of the amidyl radicals, undergo the alkynylation process, affording internal alkynes in high yield and regioselectivity (Scheme 18).[29]



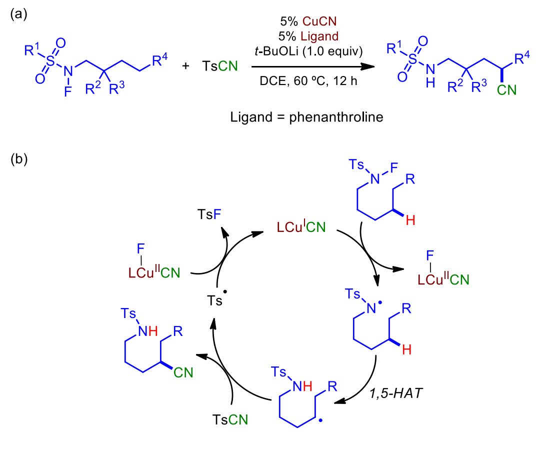
Scheme 18 Alkynylation of Csp^3-H bonds in *N*-fluorosulfonamides

Following this radical relay strategy, Wang,[30] has reported the highly enantioselective alkynylation of remote Csp^3–H bonds in linear primary sulfonamides catalyzed by chiral box–copper species (Scheme 19). For this system, a similar mechanism to that shown in Scheme 17c has been proposed, with an alkynyl ligand bonded to copper instead of CF_3. The chiral δ-alkynylated sulfonamides are enantioselectively formed by trapping of the benzyl radical with the L^*Cu^{II}–alkynyl species.

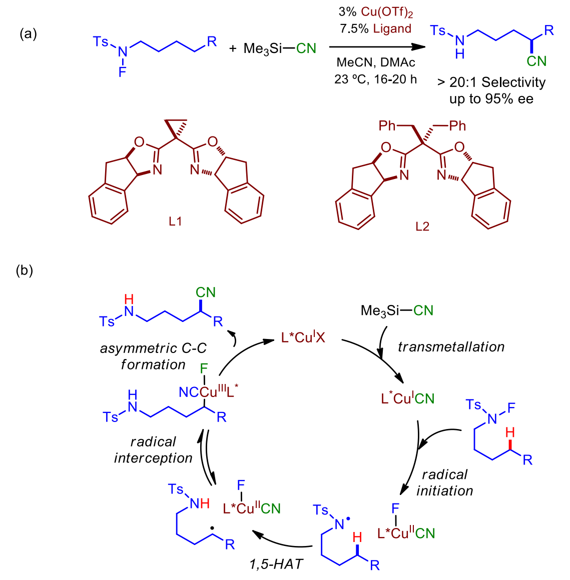


Scheme 19 Enantioselective alkynylation of remote Csp^3–H bond in linear primary sulfonamides.

On the other hand, Zhang and coworkers designed a protocol that allowed efficient remote Csp^3–H bond cyanation of aliphatic sulfonamides, using TsCN as the cyanating reagent and a Cu(I)/phenanthroline complex as catalyst (Scheme 20a).[31] The system showed good functional group tolerance and high regioselectivity. The authors proposed that the *N*-fluorotosylamide was reduced by Cu(I) by a single-electron-transfer (SET) mechanism to generate amidyl radical and a $(FCu^{II}CN)L_n$ complex (Scheme 20b). Subsequently, the alkyl radical formed by the 1,5-HAT reaction is trapped by TsCN providing the cyanation product. Importantly, in a previous contribution Nagib and co-workers[32] have developed an enantioselective δ Csp^3–H bond cyanation of *N*-fluorotosylamides, using trimethylcyanosilane (Me_3SiCN) and a chiral copper complex as the catalyst (Scheme 21a). This conversion of *N*-fluorotosylamides to enantioenriched δ-amino nitriles constituted the first example of a highly asymmetric variant of a HLF reaction. In this case it was proposed that the δ alkyl radical, generated from the 1,5-HAT reaction, was reversibly intercepted by the oxidized $L^*Cu^{II}(F)CN$ complex to generate an organocopper(III) species, which underwent stereoselective reductive elimination and provided the enantioselective formation of the δ C–H cyanation product, also regenerating the Cu(I) catalyst (Scheme 21b). Remarkably the authors showed the synthetic utility of this system by the sequential conversion of the products to piperidines.

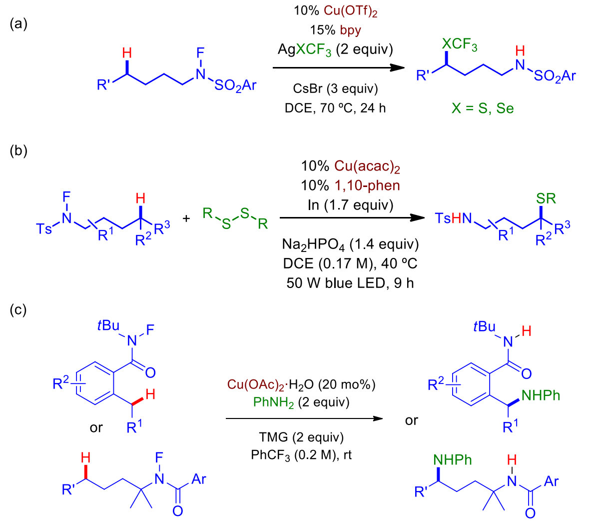


Scheme 20 Regioselective Csp^3–H cyanation of aliphatic sulfonamides



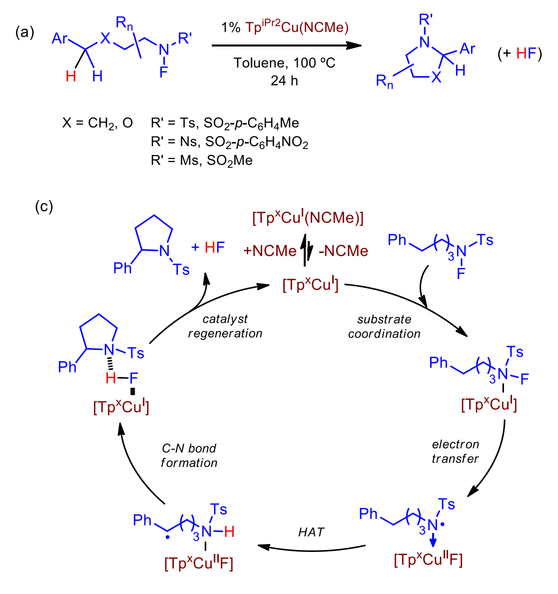
Scheme 21 Enantioselective copper-catalyzed δ Csp^3–H cyanation of *N*-fluorotosylamide via radical relay

Other groups have also accomplished the formation of C-X bonds (X = heteroatom) by these types of HLF variants. For instance, Cook and coworkers[33] reported the copper-catalyzed trifluoromethylthiolation and trifluoromethylselenation of primary, secondary, and tertiary aliphatic C–H bonds of *N*-sulfonamides with a good functional group tolerance (Scheme 22a). Yang group[34] developed a site-selective thiolation of Csp^3–H bonds of *N*-fluorosulfonamides using aryl disulfide (Scheme 22b), whereas Ao and Liu[35] described the regio- and chemoselective intermolecular Csp^3–H amination by the copper-



Scheme 22 δ-C–H Trifluoromethylthiolation of amine derivatives (a), Selective thiolation of aliphatic *N*-fluorosulfonamides (b) and Synthesis of aminated carboxamides (c)

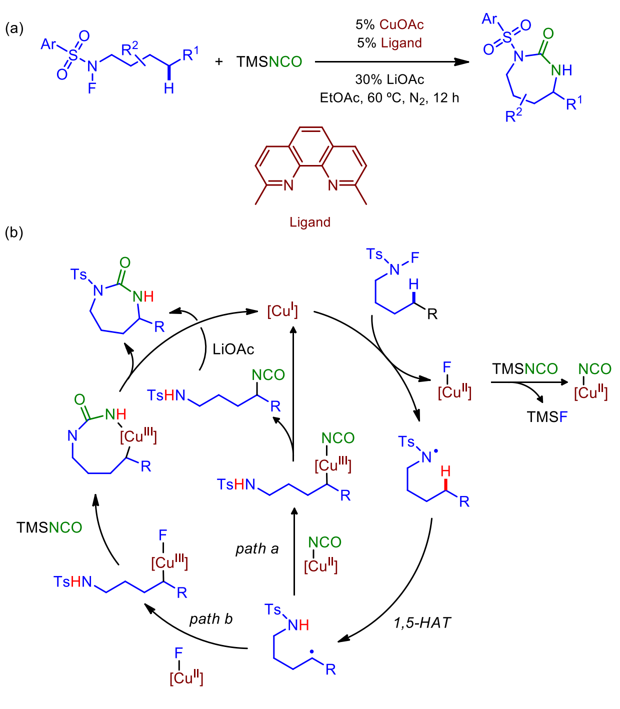
catalyzed reaction of *N*-fluorocarboxamide and amines (Scheme 22c). In all cases the mechanistic explanations were similar to those commented in this section, with particularities derived from the reactants employed as the heteroatom sources.



Scheme 23 Tp^{x}Cu-catalyzed pyrrolidine (a) and piperidine (b) synthesis. Mechanistic Proposal (c)

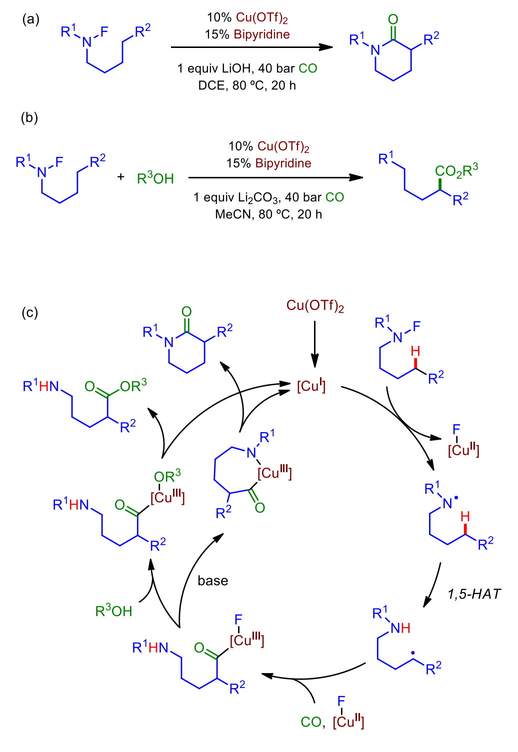
Pérez and Muñiz showed that these HLF variants may induce a cyclization process. They reported the first example of a well-defined trispyrazolylborate-copper precatalyst, Tp^{x}Cu^I, that enables uniquely uniform conditions for the formation of both pyrrolidine and piperidine products (Scheme 23a).[25b] The applicability of the system was demonstrated by the 1 gram scale reaction (2.95 mmol) of *N*-fluoro-4-methyl-*N*-(4-phenylbutyl)benzenesulfonamide to provide the corresponding pyrrolidine in 79% isolated yield. The authors proposed a copper(I/II) catalytic cycle based on the experimental data and theoretical calculations (Scheme 23b). The alternative oxidative addition pathway through a Cu(III) intermediate, postulated for some of the systems previously described, could be discarded. It was proposed the coordination of the substrate *via* the nitrogen before single electron transfer from the Cu(I) center to the N-F leading to the cleavage of the N-F bond and formation of a new Cu-F bond. The intermediate formed contains a nitrogen centered radical that remains coordinated to a Cu(II) center. Fluorine-assisted hydrogen atom transfer (HAT) leads to the Csp^3-H functionalization step and the formation of the alkyl radical. Finally, the cyclic product and HF, as byproduct, are generated by a second N-H-F shuttled SET from the benzylic radical to the copper center. It has to point out that Nagib and Zhang[27] also observed the formation of pyrrolidine by a similar transformation.

Recently, Zhang and coworkers[36] have described the synthesis of seven membered N-heterocycles by a copper-catalyzed regioselective δ-Csp^3–H bonds activation of aliphatic *N*-fluorosulfonamides, using (trimethylsilyl)isocyanate, TMSNCO, as a coupling reagent (Scheme 24a). The authors postulated that both a F-Cu^{II} complex and an amidyl radical are formed by oxidation of the Cu(I) catalytic species by *N*-fluorotosylamide (SET step) (Scheme 24b). The amidyl radical undergoes intramolecular 1,5-HAT to afford the alkyl radical. The strong affinity of F and Si would promote ligand transfer of F-Cu^{II} with TMSNCO, leading to the cyanate-copper(II) intermediate, F-Cu^{II}-NCO. Two possible pathways may then occur. By one of them, the F-Cu^{II}-NCO complex undergoes a radical rebound with the alkyl radical, the cyanate-alkylcopper(III) intermediate is thus formed. Reductive elimination would lead to the formation of an alkyl which in presence of base would generate the cyclic urea. In the other possible pathway, the alkyl radical might be also trapped by the F-Cu^{II} complex to form a F-Cu^{II}-alkyl intermediate which could react with TMSNCO to generate a copper(III) metallacycle. The final reductive elimination gives the cyclic urea, also regenerating the Cu(I) catalytic species.



Scheme 24 The Csp^3–H activation for the synthesis seven-membered cyclic urea

Wu group[37] developed a copper-based catalytic system for the synthesis of δ-lactams and esters in high yields and regioselectivity by intra- and intermolecular carbonylative functionalization of the remote Csp^3-H bonds of *N*-fluoro-sulfonamide (Scheme 25a and 25b). The reaction pathway involves the alkyl radical generation by 1,5-HAT and its interaction with the F-Cu^{II} to afford a copper(III) complex, which undergoes a carbonylation reactions leading to a F-Cu^{III}-acyl complex (Scheme 25c). The reaction of this latter species with alcohol can conduct to the formation of an alkoxo-copper(III)-acyl complex that by reductive elimination gives an ester and the regeneration of the Cu(I) catalytic species. Alternatively, the reaction of the F-Cu^{III}-acyl complex can react with base to lead to the formation of a metallacyclic compound, which generates the δ lactam by reductive elimination.

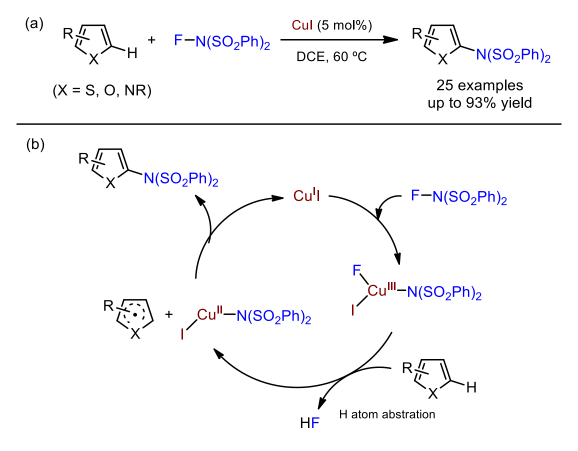


Scheme 25 Carbonylative synthesis of δ-lactams (a) and esters (b). Proposed mechanism (c)

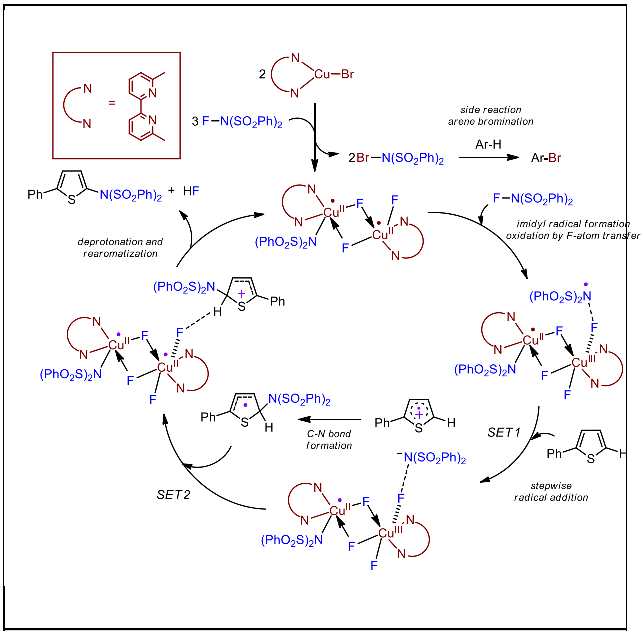
4 Csp²-H Functionalization

Csp²-N bond formation is commonly achieved by transition-metal-catalyzed/mediated coupling reaction of aryl halides with amines such as palladium-mediated Buchwald-Hartwig amination/amidation[38] and copper-catalyzed Ullmann and Goldberg type C-N formation.[39] Transition-metal-catalyzed radical C-H bond amination of arenes has become an atom economical alternative to those processes. Among them, the interest in the use of N-F reagents for the direct amination of C_{aryl}–H bonds has increased in recent years.[10,40]

In 2014, Pan and coworkers[41] described the efficient amidation of heterocycles with cuprous iodide as the catalyst and NFSI as the N-F reagent (Scheme 26). The authors postulated a mechanism which involved the formation of Cu(I), Cu(II), and Cu(III) complexes. This seminal contribution opened this field in the area of Csp²-H bonds amination. Itami and Musaev[42] carried out a mixed computational and experimental study to understand the mechanism and governing factors of Cu-catalyzed aromatic (i.e. thiophene) C–H bond imidation with NFSI. They proposed a dinuclear mechanism (Scheme 27), where the reaction of two molecules of $LCu^{I}Br$ (L = 6,6'-dimethyl-2,2'-bipyridine) and NFSI generate a dinuclear Cu^{II}–Cu^{II} complex $[LCu^{II}F(NSI)/LCu^{II}Br_2]$. Subsequently, two molecules of NFSI react with the dinuclear Cu^{II}–Cu^{II} complex producing two molecules of NBrSI and the catalytically active dinuclear complex $[LCu^{II}F(NSI)/LCu^{II}F_2]$. From this species, the catalytic cycle initiates by the reaction with NFSI, as a one-electron oxidant, forming the reactive imidyl radical and a Cu^{II}–Cu^{III} dinuclear intermediate. The turnover-limiting single-electron-transfer (SET) from the substrate to the imidyl radical and the coupling of the imidyl anion with the aryl radical-cation produces an aryl radical intermediate, which reduces the Cu^{II}–Cu^{III} dinuclear species regenerating the active catalyst, aryl cation and fluoride anion. Finally, deprotonation and rearomatization of the arene ring by the fluoride anion afford the imidated product and HF.

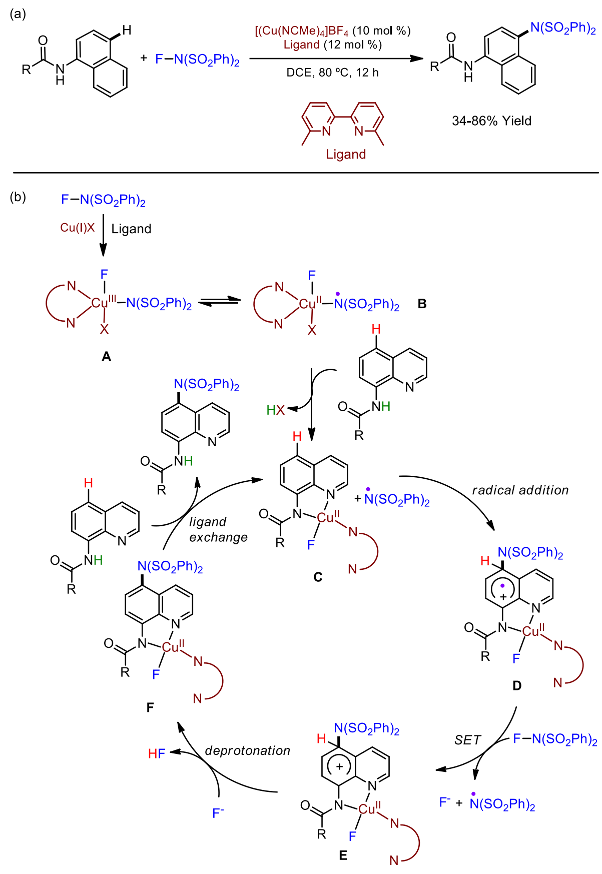


Scheme 26 Copper-catalyzed direct amination of thiophene, furane and pyrrole with NFSI

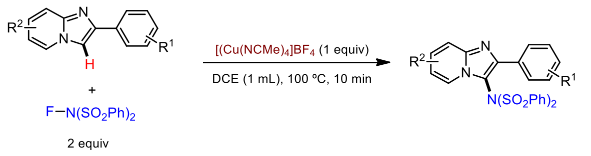


Scheme 27 Proposed mechanism for Cu-catalyzed aromatic C–H imidation by NFSI.

Using a similar procedure, Qi and Zhang[43] developed the copper-catalyzed synthesis of 5-aminated quinolines, in moderate to excellent yields, by the remote C-H amination of 8-aminoquinoline (Scheme 28a). The authors postulated that oxidation of Cu(I) with NFSI provides a Cu(III) species **A**, which could be in equilibrium with a Cu(II) complex **B** bearing the bis-sulfonylamidyl radical as ligand. This latter species undergoes the coordination of the deprotonated 8-aminoquinoline and decoordination of the bis-sulfonylamidyl radical affording **C,** which, subsequently, suffers the regiospecific addition of the bis-sulfonylamidyl to the C5 position of the aminoquinoline en route to a new radical intermediate **D**. This complex is oxidized by NFSI to give a Cu(II) species **E** and bis-sulfonylamidyl radical through a SET process. **E** deprotonated by fluorine anion to produce **F**, which finally leads the formation of the product and the regeneration of the initial copper complex by ligand exchange (Scheme 28b). Inspired by this methodology, Song and coworkers[44] reported a copper-mediated direct C–H amination of imidazopyridines using NFSI (Scheme 29), although the reaction was stoichiometric (1 equiv of the copper source was used). A gram-scale production of amination of 2-phenylimidazo[1,2-a]pyridine was conducted to demonstrate the synthetic application, providing the amination product in 79% yield.

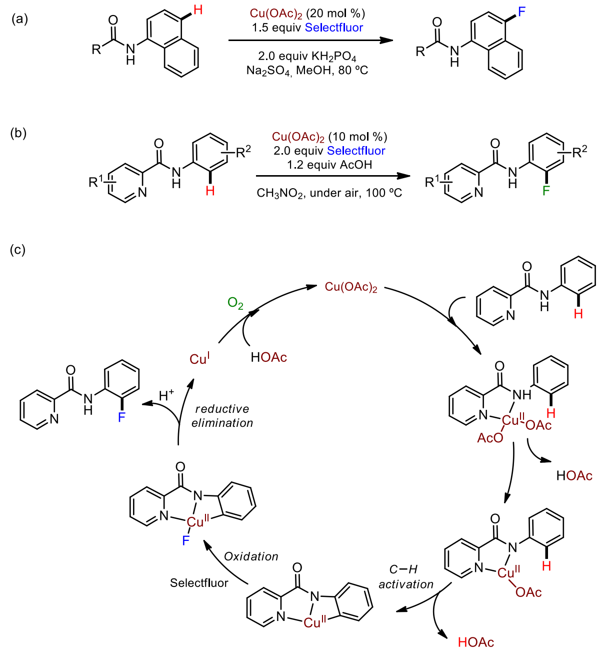


Scheme 28 Synthesis of 5-aminated quinolines using NFSI as amination agent



Scheme 29 Copper-mediated amination of imidazopyridines with NFSI

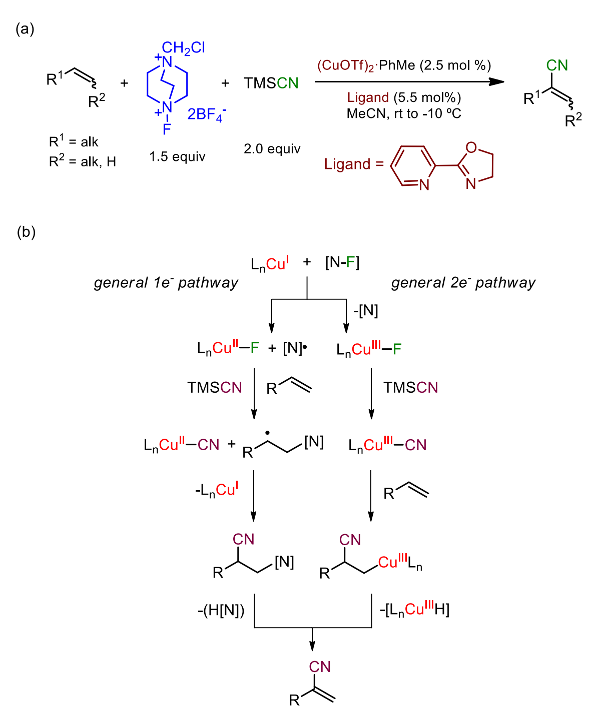
In contrast to the studies carried out by Qi and Zhang with NFSI,[43] Sun and Liu reported the direct regioselective fluorination at the C-5 position of 8-aminoquinoline when Selectfluor was employed as the N-F reagent (Scheme 30a).[45] They proposed a mechanism analogous to the Qi-Zhang system[43] for the amination with NFSI Similarly to this methodology, Li group[46] reported *ortho*-monofluorination of aniline derivatives directed by picolinic acid amides using Selectfluor, $Cu(OAc)_2$ and acetic acid (Scheme 30b). The authors studied the applicability of this fluorination methodology by performing a two grams scale reaction under standard conditions. The proposed mechanism involved a Cu(II/III/I) catalytic cycle (Scheme 30c), which initiated by the coordination of the substrate to the $Cu(OAc)_2$. Then, deprotonation of NH of the ligand occurred, releasing one molecule of AcOH. The resulting copper(II) species underwent *ortho*-C–H activation on the benzene ring to generate the aryl-copper(II) complex. The oxidation of this complex by Selectfluor leads to the formation of F-Cu^{III}-aryl, which suffered reductive elimination to give the fluorinated aniline derivative. Finally, Cu(I) was oxidized to Cu(II) completing the catalytic cycle.



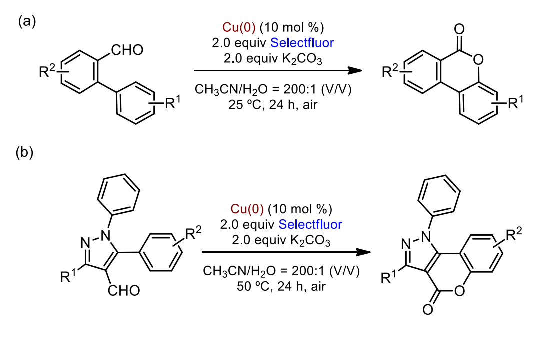
Scheme 30 Fluorination of quinolines at C-5 position (a). *ortho*-C—H Fluorination of anilines derivatives (b). Proposed mechanism (c)

As already described for the Csp^3-H activation, in the case of Csp^2-H bonds the N-F reagents can be involved in other copper catalyzed transformations. For instance, Engle and coworkers[47] developed a catalytic method for oxidative cyanation of terminal and internal (Scheme 31a) alkenes using Selectfluor as oxidant and TMSCN as cyanation agent. Two possible pathways were postulated for this cyanation process: i) 2e$^-$ pathway, which implied the formation of several Cu(III) species, such as Cu^{III}-F, Cu^{III}-CN and Cu^{III}-H; ii) 1e$^-$ pathway that involved single-electron transfer (SET) steps (Scheme 31b).

In terms of C-O bond formation and cyclization, Jin and Liu reported a method for the synthesis of dibenzopyranones and pyrazolobenzopyranones from 2- arylbenzaldehydes and 5-arylpyrazole-4-carbaldehydes, catalyzed by the Cu(0)/Selectfluor system (Scheme 32).[48] The authors showed the synthetic potential of the method by the intramolecular lactonization of 2-biphenylcarboxaldehyde at the gram scale: 1.8 g of the aldehyde (10 mmol) gave 1.49 g of dibenzopyranone (76% yield).

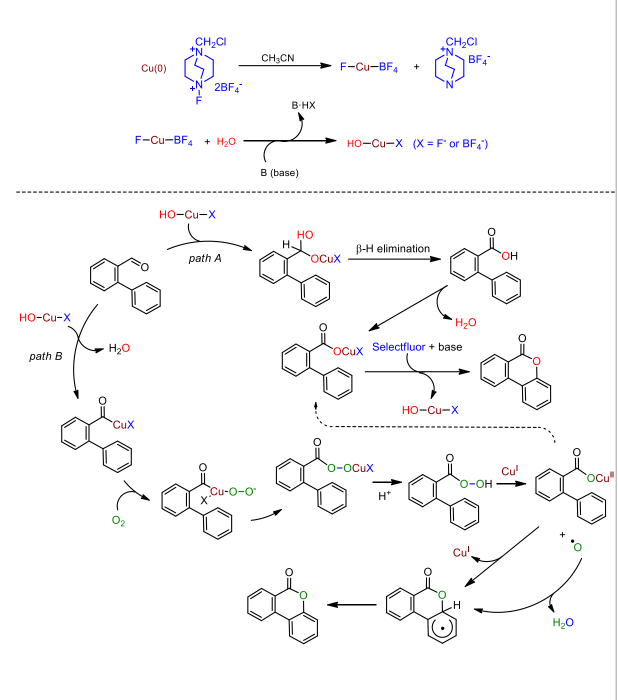


Scheme 31 Cyanation of alkenes (a) and the two possible pathways proposed (b).



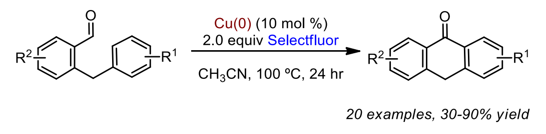
Scheme 32 Cu(0)/Selectfluor system-catalyzed double C-H activation/oxygen insertion of 2-arylbenzaldehydes (a) and 5-arylpyrazole-4-carbaldehydes (b)

On the basis of the mechanistic studies the catalytic cycle depicted in Scheme 33 was proposed. Firstly, the oxidation of the Cu(0) powder by Selectfluor could generate an intermediate F-Cu^{II}-BF_4, which could be converted into X-Cu-OH (X = F or BF_4) by reaction with base. After the formation of the active X-Cu-OH species, the reaction may occur *via* two possible pathways. One route (path A) involved an oxycupration of the arylbenzaldehyde followed by a fast β-H elimination of the resulting intermediate to give a carboxylic acid ArCOOH. The latter compound reacted with the X-Cu-OH species to afford ArCOO-Cu-X. This intermediate underwent intramolecular cross- dehydrogenative C=O coupling reaction to give dibenzo-pyranone and regenerate intermediate X-Cu-OH in the presence of Selectfluor and base. The second possible pathway B started with the direct proton abstraction from the formyl group of arylbenzaldehyde by X-Cu-OH to lead to acyl-Cu-X complex. That species suffered oxidation by dioxygen. Then a rearrangement of the resulting peroxo complex would lead to the formation of the perbenzoate-copper intermediate, which evolved to a perbenzoic derivative. The latter compound decomposed in the presence of Cu(I) to generate a copper-benzoate intermediate and hydroxy radical. Annulation of the copper-benzoate gave a radical species, which finally afforded dibenzopyranone by the abstraction of a proton by the hydroxy radical previously formed.



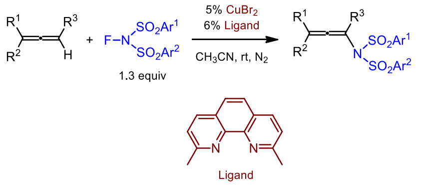
Scheme 33 Proposed mechanism for Cu(0)/Selectfluor system-catalyzed double C-H activation/oxygen insertion of 2-arylbenzaldehydes

Liu and coworkers[49] applied this methodology for synthesis of xanthones from 2- aryloxybenzaldehydes (Scheme 34). A gram-scale (5 mmol) of 2-phenoxybenzaldehyde was used to synthesize the desired xanthone in 80% yield.



Scheme 34 Cu(0)/Selectfluor system-catalyzed cross-dehydrogenative coupling of 2-aryloxybenzaldehydes for the synthesis of xanthones

The radical amination of Csp^2-H bonds of allenes has been achieved even though these transformations are challenging in terms of regioselectivity and the competing formation of aminodifunctionalization products. The modification of allenes has attracted great interest in the context of synthetic protocols for bioactive molecules within the pharmaceutical field. In 2015, Zhang and coworkers described the first example of a highly regioselective oxidative amination of allenes with NFSI catalyzed by a copper complex (Scheme 35).[50] A variety of allenamides can be accessed from both terminal and internal allenes using a catalytic system which operates under mild conditions with good functional group tolerance.



Scheme 35 Direct oxidative coupling of the C(sp2)-H bond of allenes with *N*-fluoroarylsulfonimides

5 Conclusion

Copper-mediated transformations involving N-F reagents has been described for inter- and intramolecular Csp^3–H and Csp^2–H bond activation, either promoting the formation of C-F or C-N bonds or the oxidation and subsequent alkylation, arylation, borylation, or alkynylation, among others, reactions at those sites. Most of those processes involve the use of commercially available NFSI and Selectfluor, or any related derivatives. Importantly, most of the reactions known to date show a high degree of chemo- and regioselectivity and functional groups compatibility. In some cases, the enantioselective versions have also been reported. The practical applicability of some systems has been shown by gram scale reactions. Despite such progress, there are still some limitations that need to be overcome. That is the case of a number of systems which only operate for benzyl Csp^3–H bonds or with aid of directing groups. High catalyst loading is also a drawback in many examples, for which the development of more active catalysts is mandatory within this field.

Funding Information

We thank MINECO for Grants CTQ2017-82893-C2-1-R and PO FEDER 2014-2020, UHU-1254043.

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Biosketches

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