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Radical-Promoted Distal C–H Functionalization of C(sp³) Centers with Fluorinated Moieties

Enzo Nobile,^[a] Thomas Castanheiro,^[a] and Tatiana Besset*^[a]

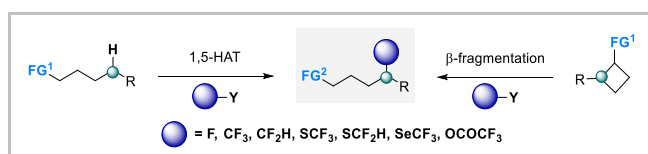
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Abstract: Due to their unique properties, fluorinated scaffolds are pivotal compounds in pharmaceuticals, agrochemicals and materials science. Over the last years, the development of versatile strategies for the selective synthesis of fluorinated molecules by direct C–H bond functionalization has attracted a lot of attention. In particular, the design of novel transformations based on a radical process was a bottleneck for the distal C–H functionalization reactions, offering synthetic solutions for the selective introduction of a fluorinated group. This Minireview highlights the major contributions that have been made in this blossoming field. The development of new methodologies for the remote functionalization of aliphatic derivatives with various fluorinated groups based on a 1,5-HAT process and a β -fragmentation reaction will be mainly showcased and discussed.

1. Introduction

Due to the ubiquity of fluorinated scaffolds in pharmaceuticals, agrochemicals and materials science,^[1] the quest for new transformations^[2] allowing the incorporation of a fluorine atom or a fluorinated moiety^[3] on compounds is of paramount importance. In that purpose, major advances were made over the years. Among them, the combination of organofluorine chemistry and transition metal C–H bond activation^{[2b],[4]} turned out to be an efficient and eco-friendlier strategy,^[5] offering an access to a large variety of fluorinated scaffolds in a step- and atom-economical way. Despite these important advances, some limitations remain. In particular, the functionalization of a C(sp³)–H bond with a fluorinated residue by transition metal catalysis is still a challenging task both in term of reactivity and selectivity. An ideal scenario will be a synthetic strategy for the efficient incorporation of a fluorinated group at the desired non-activated C–H bond with a total control of the regioselectivity, which to date remains an almost unmet goal. Therefore, a lot of attention was paid by the scientific community to the development of innovative and selective approaches for the challenging C–H functionalization of aliphatic derivatives at unactivated positions. In particular, the design of novel transformations based on a radical process was a bottleneck for the distal C–H functionalization reactions, offering synthetic solutions for the selective introduction of a fluorinated group at a remote position to a functional group.^[6] The goal of this Minireview is to showcase and discuss the different approaches for the synthesis of fluorinated aliphatic derivatives by the direct and distal incorporation of a fluorinated group (F, CF₃, CF₂H, SCF₃, SeCF₃...) by functionalization of a C–H bond. Hence, the distal functionalization involving a 1,5-Hydrogen Atom Transfer (HAT) process will be first highlighted. Then, a second section will be dedicated to transformations based on the β -fragmentation reactivity of constrained cyclic compounds. Finally, other tools allowing the fluorination of enone derivatives at a distal position will be depicted.

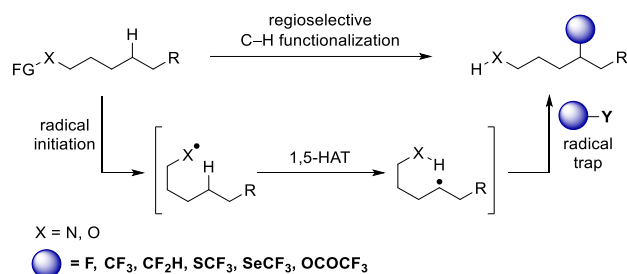


Scheme 1. Main synthetic strategies for the distal C–H functionalization of C(sp³) centers with fluorinated moieties.

2. Distal functionalization via a 1,5-Hydrogen Atom Transfer process

Hydrogen-Atom Transfer (HAT) serves as a straightforward strategy to functionalize non-activated C(sp³)–H bonds by generating alkyl radical intermediates. Typically, the 1,5-Hydrogen-Atom Transfer (1,5-HAT) process, the key step of the Hofmann-Löffler-Freytag (HLF) reaction,^[7] is a useful and powerful method to regioselectively functionalize an unactivated C(sp³)–H bond located at a remote position to a functional group under mild reaction conditions. This process can be described into three main steps (Scheme 2): (1) *Radical initiation* enabling to generate a radical as the first key open-shell intermediate. (2) Regioselective *Hydrogen Atom Transfer*. This exergonic step is driven by a higher bond dissociation energy (BDE) of the X–H bond compared to the targeted C–H one and the high site selectivity of this step is controlled by

the formation of a favored pseudo six-membered cyclic transition state leading to the formation of a more stable radical. (3) *The radical trap*. This last step is the reaction between the alkyl radical intermediate and a specific reagent, to furnish the expected product. This robust strategy gave birth to a wide range of new efficient transformations offering the possibility to functionalize C(sp³)-H bonds with various functional groups at a distal position.^{[8],[9]} Recently, major advances were made for the incorporation of fluorinated groups (Scheme 2). Furthermore, the high regioselectivity of the process makes it very attractive for the late-stage derivatization of pharmaceuticals and natural compounds, for instance. In this section will be highlighted a selected collection of the main advances based on a 1,5-HAT process for the selective incorporation of a fluorinated group at a remote position.

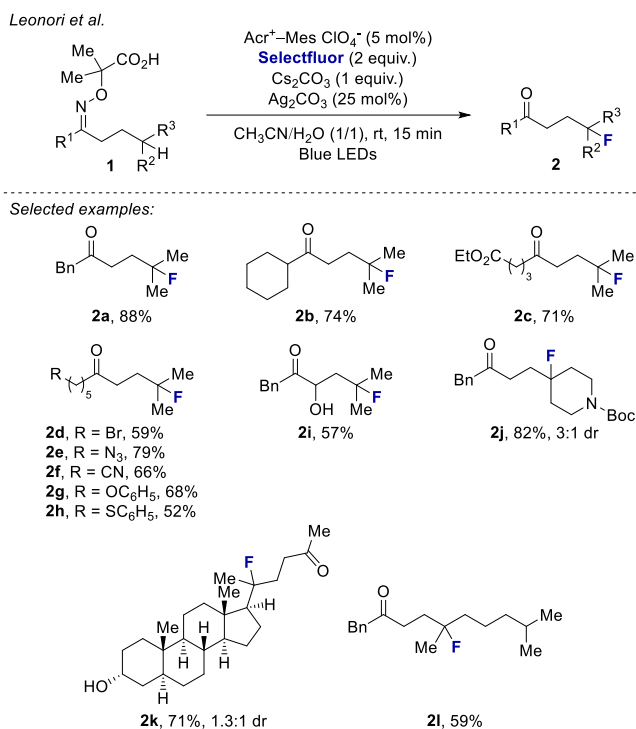


Scheme 2. C(sp³)-H functionalization with a fluorinated moiety at a remote position through a 1,5-HAT process.

2.1. Fluorination reactions

2.1.a. Intermolecular remote fluorination reactions

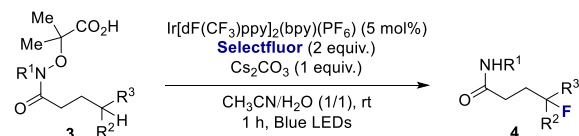
The distal introduction of a fluorine atom by means of a 1,5-HAT process was well-studied and several major contributions were reported over the years. In 2016, the group of Leonori developed an elegant strategy to synthesize γ -fluorinated aliphatic ketones through the formation of an iminyl radical intermediate. Indeed, a visible light-mediated fluorination of the oxime derivatives **1** was reported in the presence of Selectfluor, the Fukuzumi's acridinium salt (Acr⁺-Mes ClO₄⁻) as the photoredox catalyst and silver carbonate as the co-catalyst (Scheme 3, 14 examples, up to 88% yield).^[10] Under these basic conditions, the fluorination reaction of tertiary C(sp³) centers was possible. Aliphatic ketones bearing a benzyl (**2a**) and a cycloalkyl (**2b**) groups were successfully synthesized. Several functional groups were tolerated in that transformation such as an ester (**2c**), a halide (**2d**), an azide (**2e**), a nitrile (**2f**), an ether (**2g**), a thioether (**2h**), an alcohol (**2i**) and a *N*-Boc-protected amine (**2j**). The selective functionalization of a complex bioactive molecule containing multiple C(sp³)-H bonds was reported as illustrated by the fluorination of the lithocholic acid derivative (**1k**) at the γ -position leading to the corresponding compound (**2k**) in a good yield as a mixture of diastereoisomers in a 1.3:1 ratio. Moreover, when a substrate having several competitive positions was reacted (**1l**), only the product resulting from the γ -fluorination (**2l**) was obtained, showcasing the high regioselectivity of the reaction.



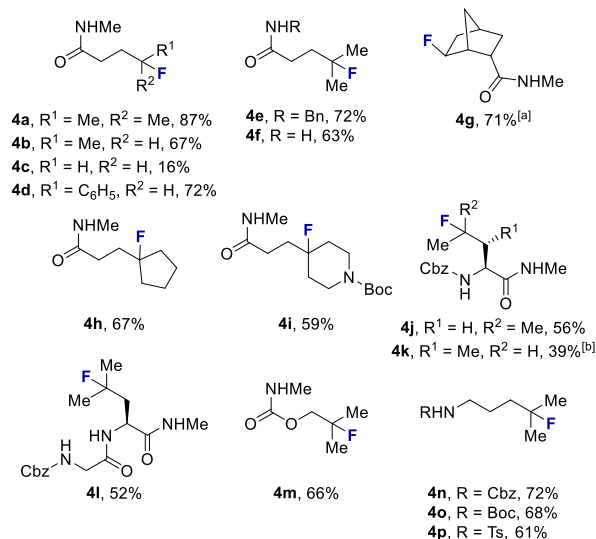
Scheme 3. Synthesis of γ -fluorinated ketone derivatives *via* an iminyl radical generated by a photoredox process. $\text{Acr}^+-\text{Mes ClO}_4^-$ = 9-mesityl-10-methylacridinium perchlorate. Boc = *tert*-butoxycarbonyl.

Aiming at developing a general approach, the same group showed that changing the nature of the nitrogen radical, from iminyl radicals to amidyl ones, the fluorination of remote tertiary, secondary and primary C–H bonds was possible (Scheme 4, 31 examples, up to 89% yield).^[11] Using an Ir^(III) catalyst, in the presence of Selectfluor along with cesium carbonate, an access to fluorinated amide derivatives at the γ -position was developed starting from the corresponding carboxylic acid precursors **3**. The reaction proved to be efficient for the remote fluorination of tertiary (**3a**), secondary (**3b**), and primary (**3c**) C(sp³) centers leading to the corresponding fluorinated *N*-methyl amides (**4a-c**). Note that the fluorination of a benzylic position was possible and the compound **4d** was synthesized in a good yield. The transformation was not limited to the functionalization of *N*-methyl amides as the γ -fluorinated *N*-benzyl amide (**4e**) or the primary amide (**4f**) were successfully obtained. This distal fluorination was efficient on amides containing cycloalkyls (**3g-i**), offering an access to potentially interesting bioactive building blocks such as a *N*-Boc-piperidine (**4i**). The methodology was extended to the selective late-stage remote fluorination of protected-amino acid derivatives (**3j** and **3k**) and the dipeptide building block **3l**. Furthermore, the transformation was not restricted to amide derivatives as the synthesis of fluorinated carbamate (**4m**) and *N*-protected amines (**4n-p**) at the γ - and δ -positions, respectively, was also possible. When the amide (**3q**) or the carbamate (**3r**) bearing a competitive tertiary center at the δ -position was used, the fluorination at this position was preferentially achieved *via* a 1,6-HAT process.^[12] However, in case of the *N*-Boc-protected amine **3s**, a mixture of fluorinated products (**4s** and **4s'**) at the δ - and ϵ -positions was obtained in a 1:1 ratio, presumably due to a higher chain flexibility. The following mechanism was suggested: under basic conditions, the deprotonated carboxylic acid precursor **I** would undergo an oxidative SET with the photocatalyst in its excited state to afford the corresponding amidyl radical **II** after CO₂ and acetone exclusion. Then, generation of the alkyl radical **III** after a 1,5-HAT followed by a reaction with Selectfluor would furnish the desired product **4** and an electron-poor radical **Y**, which would regenerate the photoredox catalyst (**PC**) through a reductive SET.

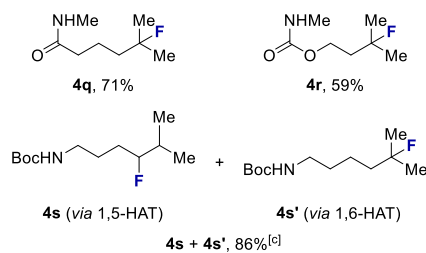
Leonori *et al.*



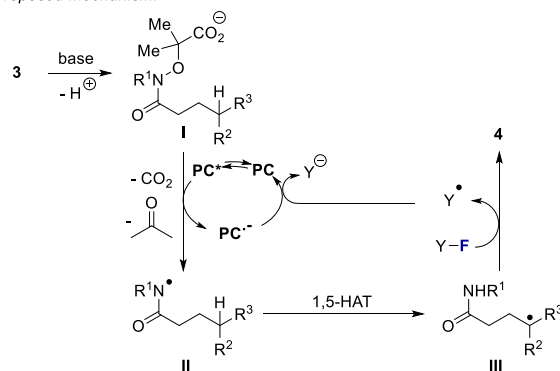
Selected examples:



Modification of the HAT regioselectivity:



Proposed mechanism:

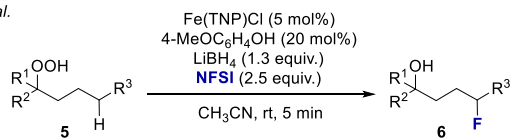


Scheme 4. Photoredox synthesis of γ -fluorinated amides and amines at a distal position via an amidyl radical. [a] 10:1 dr. [b] 3:2 dr. [c] A 1:1 mixture of both products was obtained resulting from a 1,5-HAT vs a 1,6-HAT process. Y-F = used for Selectfluor. ppy = phenylpyridine. bpy = 2,2'-bipyridine. Cbz = benzyloxycarbonyl. Ts = tosyl.

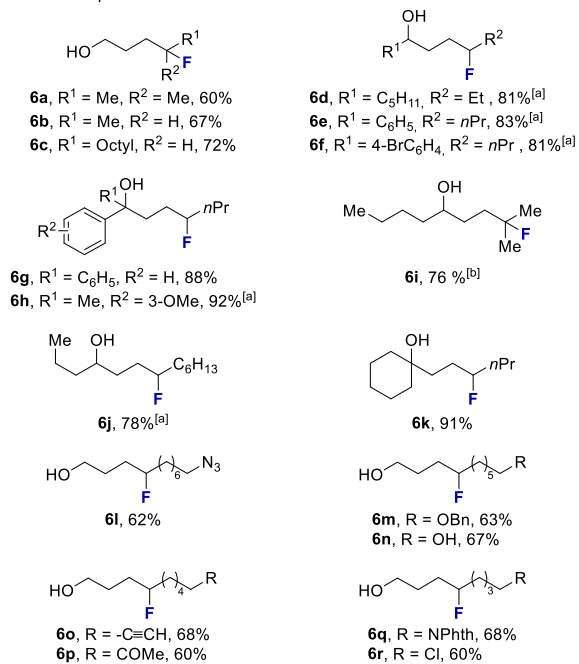
Due to the omnipresence of the hydroxyl moiety in natural and pharmaceutical products, Liu *et al.* depicted an iron-catalyzed selective remote fluorination of aliphatic peroxide derivatives to synthesize δ -fluorinated aliphatic alcohols via an alkoxy radical intermediate (Scheme 5, 38 examples, up to 94% yield).^[13] It turned out that the combination of the $\text{Fe}(\text{TNP})\text{Cl}$ complex (5,10,15,20-tetranaphthyl-21H,23H-porphyrin $\text{Fe}(\text{III})$ chloride), LiBH_4 as the reductant and *N*-fluorobenzenesulfonimide (NFSI) as the fluorine source was crucial. Note that the 4-methoxyphenol was needed as an

additive in the transformation to minimize the formation of the undesired non-fluorinated alcohols as by-products. Primary alcohols were efficiently functionalized at the δ -position on tertiary (**5a**) and secondary (**5b-c**) C(sp³) centers. The transformation also allowed the synthesis of δ -fluorinated secondary alcohol derivatives such as the undecan-6-ol (**6d**) and the fluorinated benzylic alcohols (**6e** and **6f**), as well as tertiary alcohols (**6g** and **6h**) with good yields. These alcohols (**6d-f, 6h**) were synthesized with a 1:1 diastereoisomeric ratio. Note that substrates possessing competitive C(sp³) centers were selectively fluorinated (**6i, 6j** and **6k**). This iron-catalyzed redox process displayed a good tolerance to various functional groups as an azide (**5l**), a Bn-protected alcohol (**5m**) or an alcohol (**5n**), an alkyne (**5o**), a ketone (**5p**), a phthalimide (**5q**) and a halogen atom (**5f** and **5r**) were smoothly fluorinated with a complete selectivity towards the δ -position. To further demonstrate the synthetic utility of the methodology, the late-stage functionalization of bioactive molecules was achieved, offering an access to a fluorinated analog of the estrone derivative (**6s**), for instance. Furthermore, an interesting one-pot procedure was also developed, providing an access to δ -fluorinated aliphatic alcohols (**6t-v**) starting from the corresponding alkanes (**7t-v**) *via* a two-step process (a C-H oxygenation at the benzylic position followed by a remote fluorination reaction, Scheme 5). A mechanism initiated by a reductive SET of the hydroperoxide catalyzed by Fe^(II)(TPP) was suggested. This first step would deliver the alkoxy radical **I** along with an oxo-bridged dimer (TPP)FeOFe(TPP), which would be reduced by LiBH₄ to regenerate the active catalyst. The intermediate **I** would provide an alkyl radical **II** at the δ -position through a 1,5-HAT process. The newly formed intermediate **II** would then react with NFSI furnishing the desired product **6** and a new (N(SO₂Ph)₂) nitrogen-radical. The latter would then react with the hydroperoxide **5** to generate a peroxide radical **III**, which would be reduced by Fe^(II)(TPP) resulting in the formation of the alkoxy radical **I**.

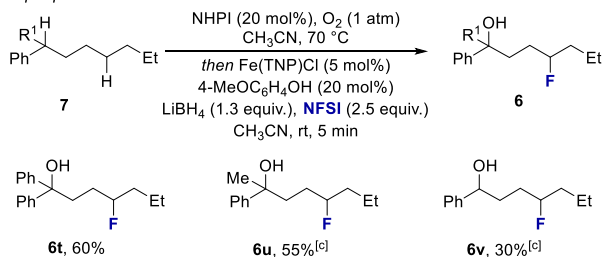
Liu et al.



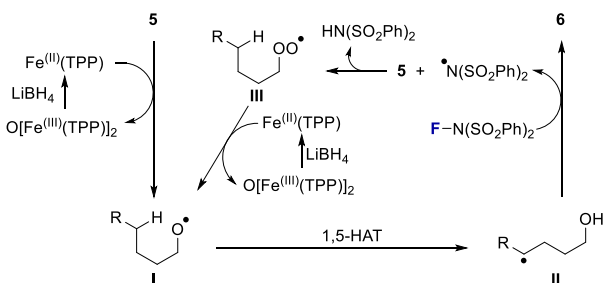
Selected examples:



One-pot procedure:

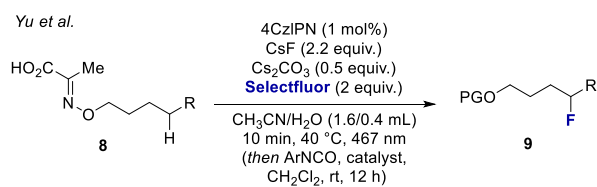


Proposed mechanism:

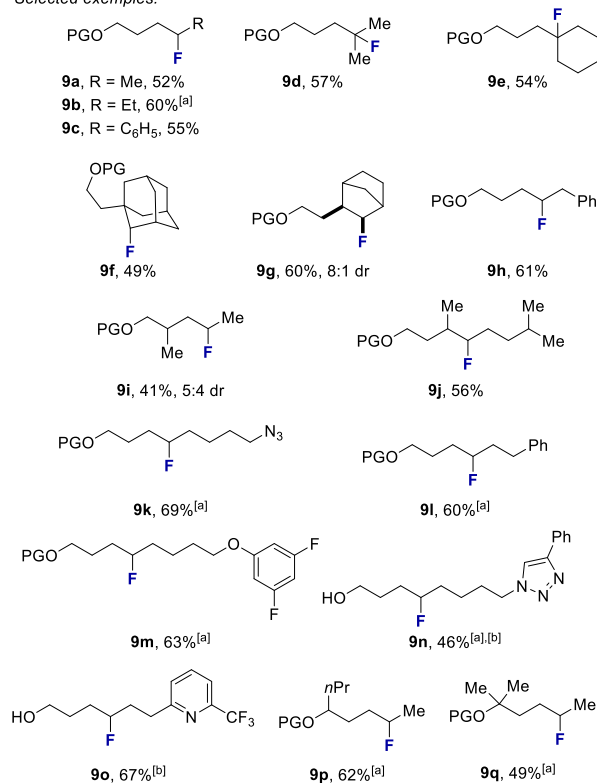


Scheme 5. Fe^{III} -catalyzed selective δ -fluorination of aliphatic peroxide derivatives. [a] 1:1 dr. [b] 4:1 dr. [c] 0.5 mol% AIBN was used for C–H oxygenation. NHPI = *N*-hydroxyphthalimide.

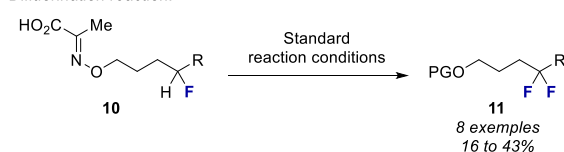
Nevertheless, methodologies allowing the remote fluorination of aliphatic alcohols through alkoxy radicals remain limited and the development of original approaches to synthesize remotely fluorinated alcohol derivatives is still highly desirable. In this context, Yu and co-workers recently reported the synthesis of δ -fluorinated aliphatic alcohols *via* the transient formation of an alkoxy radical.^[14] The latter would be generated from the stable and readily available alcohol-derived oximino acid precursors **8**,^[15] after an oxidative decarboxylation reaction. Using the organic photosensitizer (4*s*,6*s*)-2,4,5,6-tetra(9*H*-carbazol-9-yl)-isophthalonitrile (4CzIPN) in the presence of Selectfluor, the fluorination of **8** was selectively achieved at room temperature leading to the corresponding δ -fluorinated alcohols **9** in moderate to good yields (Scheme 6, 20 examples, up to 69% yield). Aliphatic protected-alcohols were functionalized on unactivated secondary C(sp³) centers (**8a** and **8b**) and on a benzylic one (**8c**). Moreover, the functionalization of tertiary positions of acyclic (**8d**) or cyclic (**8e**) oximino acid precursors provided the desired products (**9d** and **9e**) in 57% and 54% yields, respectively. Substrates bearing an adamantyl group (**8f**) or a norbornane moiety (**8g**) were also fluorinated. The transformation was highly selective to the δ -position. Indeed, when substrates bearing either a benzylic center at the ϵ -position (**8h**) or multiple tertiary centers (**8i** and **8j**), the fluorination occurred exclusively at the δ -position. Moreover, various functional groups and substituents on the alkyl chain like an azide (**8k**), an ether (**8m**) as well as a triazole (**8n**) and a pyridine (**8o**) were tolerated. The reaction was not restricted to the functionalization of primary alcohols, as the secondary and tertiary alcohols (**8p** and **8q**) were smoothly functionalized. However, some of these products (**9b** and **9k-n**, **9p-q**) were obtained as a mixture with an undetermined regioisomer. Finally, starting from mono- δ -fluorinated oximino acid derivatives (**10**), the corresponding δ -difluorinated protected-alcohols (**11**) were obtained in low to moderate yields (Scheme 6, 8 examples, up to 43% yield).



Selected examples:

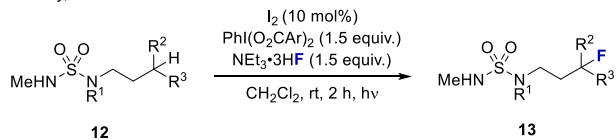


Difluorination reaction:

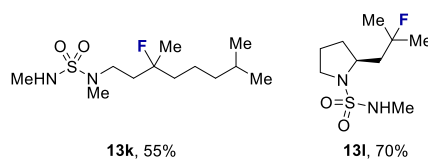
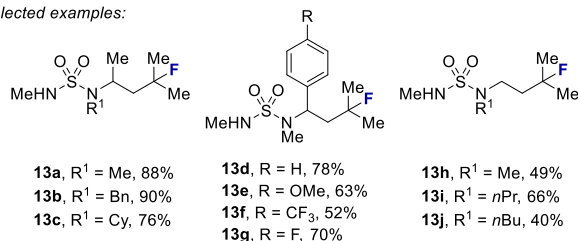


Scheme 6. Synthesis of δ -fluorinated aliphatic alcohols. 4CzIPN = (4s,6s)-2,4,5,6-tetra(9*H*-carbazol-9-yl)-isophthalonitrile. PG = CONH(4-NO₂)C₆H₄. [a] The products were isolated as a mixture with another undetermined regioisomer: **9b** (95:5), **9k** (95:5), **9l** (95:5), **9m** (95:5), **9n** (88:12), **9p** (97:3), **9q** (95:5). [b] Alcohols were not protected after the fluorination reaction. Catalyst = 1,8-Diazabicyclo[5.4.0]undec-7-ene or MoCl₂O₂(dmf)₂.

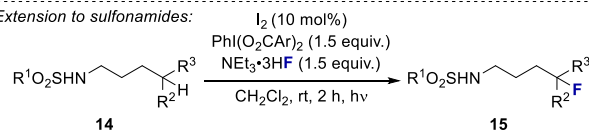
It is worth mentioning that the above-mentioned methods generally required the use of an electrophilic reagent as a fluorine source. Very recently, it was demonstrated that a fluoride might be used instead of an electrophilic reagent. In 2020, Bafaluy, Muñiz and co-workers developed an iodine-catalyzed fluorination of aliphatic sulfamides and sulfonamides with NEt₃-3HF under light irradiation.^[16] Kinetically favored by the particular geometry of sulfamides (elongated S–N bonds),^[17] the functionalization of these derivatives occurred at the γ -position through a 1,6-HAT process, while in case of sulfonamide derivatives, the distal fluorination was selective to the δ -position via a 1,5-HAT (Scheme 7). By using iodine as the catalyst in the presence of PhI(O₂CAr)₂ (Ar = 3-chlorobenzene) along with NEt₃-3HF under light irradiation, the aliphatic sulfamides were easily transformed into the corresponding γ -fluorinated products with moderate to good yields (Scheme 7, 15 examples, up to 90% yield). γ -Fluorinated secondary sulfamides bearing different substituents on the tertiary nitrogen of the sulfonamide such as a methyl (**13a**), a benzyl (**13b**) or a cyclohexyl (**13c**) were obtained in high yields. Sulfamide derivatives substituted at the α -position by an aryl group were suitable substrates as demonstrated by the functionalization of the compound **12d**. It turned out that the transformation was also efficient with compounds bearing an aryl moiety substituted by an electron-donating (**12e**) or an electron-withdrawing (**12f**) group as well as a fluorine atom (**12g**). The protocol was applied to the fluorination of primary sulfamides (**12h-j**) leading to the desired compounds (**13h-j**) in moderate to good yields. Regarding molecules having two competitive tertiary C(sp³) centers (**12k**), a total γ -selectivity was observed resulting from a 1,6-HAT. The proline derivative (**12l**) was transformed into the corresponding fluorinated derivative (**13l**) with a good yield. The methodology was successfully extended to the δ -fluorination of aliphatic sulfonamides via a 1,5-HAT process (Scheme 7, 10 examples, up to 98% yield). The functionalization of *N*-tosylated (**14a**) and *N*-nosylated (**14b**) sulfonamides gave the corresponding products (**15a-b**) in good yields. The fluorination of a cyclobutane derivative (**14c**) was also depicted leading to the desired product (**15c**) in a 50% yield. Secondary *N*-Ts and *N*-Ms sulfonamides led to the formation of the desired δ -fluorinated products (**15d-f**) in good to high yields. A comproportionation of molecular iodine and the hypervalent iodine reagent, which would generate the iodine active catalyst **I** was suggested to initiate the mechanism of the reaction. A *N*-iodination of the substrate **12** or **14** would generate a *N*-iodo intermediate **II** and a subsequent light induced homolysis of the N–I bond would form the key radical **III**. A 1,6-HAT process (in the case of the sulfamides) or a 1,5-HAT event (in the case of the sulfonamides) would result in the formation of the alkyl radical **IV**. Then, two alternative pathways were possible. Pathway **A**: the alkyl radical **IV** would undergo a radical recombination with an iodine radical (or a chain propagation with **II**) to form the intermediate **V**. Then, an oxidation of **V** would generate the alkyl iodine **VI**, which would afford the desired product **13** or **15** after a nucleophilic substitution with fluoride along with the regeneration of the species **I**. Pathway **B**: The alkyl radical **IV** would be oxidized to the corresponding carbocation **VII**, which would react directly with NEt₃-3HF to finally give the desired product **13** or **15** and regenerate the intermediate **I**.



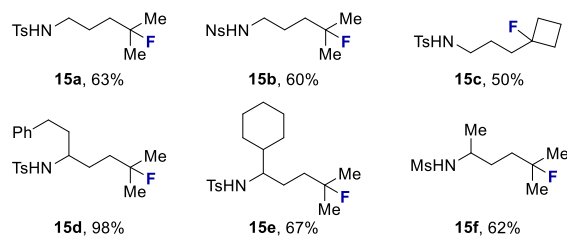
Selected examples:



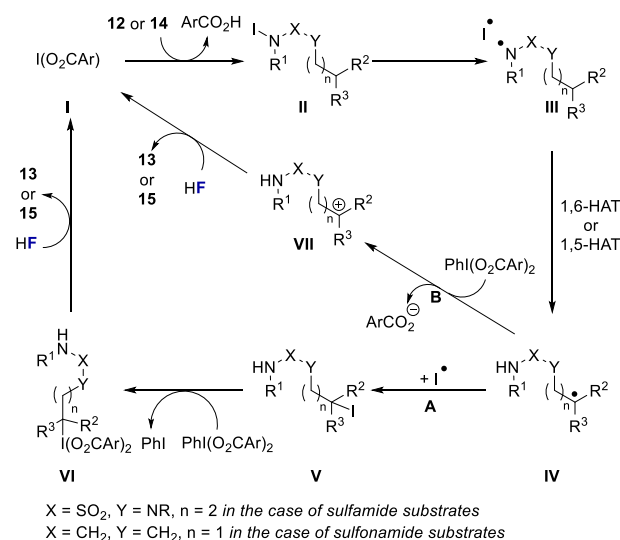
Extension to sulfonamides:



Selected examples:



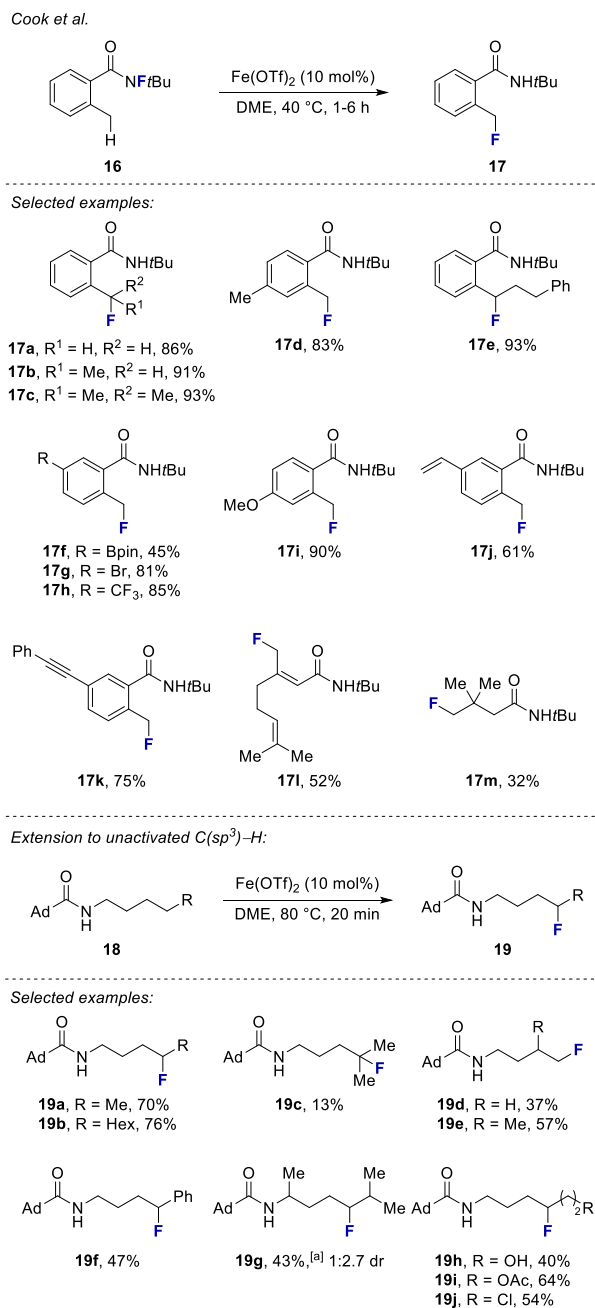
Proposed mechanism:

**Scheme 7.** Remote fluorination of C(sp³)–H centers with fluoride. Ar = 3-ClC₆H₄. Ms = mesyl. Ns = nosyl.

2.1.b. Intramolecular remote fluorination reactions

In 2016, Cook *et al.* reported the remote fluorination of amides.^[18] In this case, the *N-tert*-butyl-fluoroamide derivatives would direct the remote intramolecular hydrogen abstraction and act as the fluorine source. Under iron catalysis, the

formation of a benzylic C(sp³)-F selectively occurred at the γ -position with high yields (Scheme 8, 19 examples, up to 93% yield). The fluorination of primary (**16a**), secondary (**16b**) and tertiary benzylic C-H bonds (**16c**) was achieved. With substrates bearing multiple benzylic positions (**16d** and **16e**), the transformation proved to be highly selective towards the γ -position. Moreover, the transformation turned out to be tolerant to diverse functional groups such as a boronic pinacol ester (**16f**), a halogen (**16g**), an alkene (**16j**) and an alkyne (**16k**). γ -Allylic and γ -primary aliphatic positions were also functionalized under these conditions (**16l** and **16m**). This year, the same group showed that a slight modification of the reaction conditions allowed the fluorination of aliphatic adamantyl amides at the δ -position with moderate to good yields (Scheme 8, 19 examples, up to 76% yield).^[19] Indeed, the fluorination of a secondary C(sp³) center was smoothly achieved (**18a** and **18b**), as well as for tertiary (**18c**) and primary (**18d-e**) centers; the transformation being less efficient in these last cases. Additionally, a secondary benzylic δ -site (**18f**) was also fluorinated under these reaction conditions and a high δ -selectivity was also observed even in the presence of competitive tertiary positions (**18g**). Note that the reaction was tolerant to the presence of a free- or protected-alcohol (**18h-i**) and a chlorine atom (**18j**).

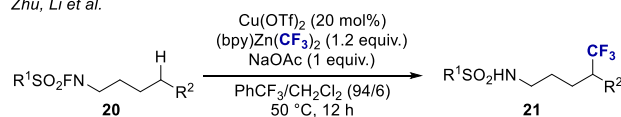


Scheme 8. Iron-catalyzed δ -fluorination of amide derivatives at aliphatic benzylic and unactivated positions. [a] 35 min reaction time. Ad = adamantyl. Bpin = pinacolborane. OTf = triflate. DME = 1,2-dimethoxyethane. Ac = acetyl.

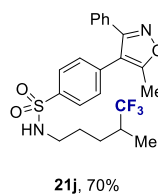
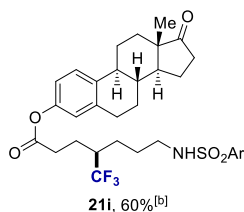
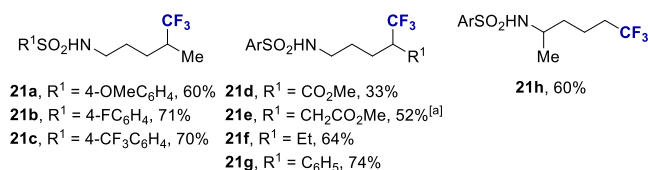
2.2. Trifluoromethylation and difluoromethylation reactions

Thanks to their unique features, fluoroalkyl groups such as the CF₃ or CF₂H residues play a crucial role in agrochemical and pharmaceutical derivatives.^{[2b,j],[20]} In 2019, Zhu, Li and co-workers designed a copper-catalyzed remote trifluoromethylation of sulfonamides and carboxamides.^[21] Exposing aliphatic *N*-fluorosulfonamides to a catalytic amount of Cu(OTf)₂ and (bpy)Zn(CF₃)₂ as the CF₃ source, allowed the synthesis of the desired δ -trifluoromethylated products (Scheme 9, 23 examples, up to 75% yield). Sodium acetate was a key additive to increase the reaction yield, probably by enhancing the rate of the transmetallation step of the CF₃ anion from the zinc species to the copper one. *N*-fluorobenzenesulfonamides either functionalized by electron-donating or electron-withdrawing groups (**20a-c**) on the phenyl moiety were fluorinated in good yields and the presence of an ester group on the alkyl chain (**20d-e**) was well tolerated under these reaction conditions. The δ -fluorination reaction was efficient on a secondary C(sp³) center (**21a-f**), in the particular case of a benzylic position (**21g**) and even on a primary C(sp³) center (**21h**). Complex bioactive molecules such as an estrone (**20i**) and the valdecoxib (**20j**) derivatives were efficiently transformed into the corresponding trifluoromethylated products (**21i-j**) in 60% and 70% yields, respectively, with a full δ -selectivity. Moreover, by using the sulfonamide (**20k**), the trifluoromethylation selectively occurred at the benzylic position *via* a 1,6-HAT event. Note that when substrates were bearing two competitive sites, a mixture of trifluoromethylated products at the ω - and δ -positions was obtained (**21l** and **21m**). The methodology was extended to the remote trifluoromethylation of *N*-fluorocarboxamides bearing a *gem*-dialkyl group at the α -position (**22**) with moderate to good yields with a full selectivity to the δ -position (Scheme 9, 19 examples, up to 84% yield).

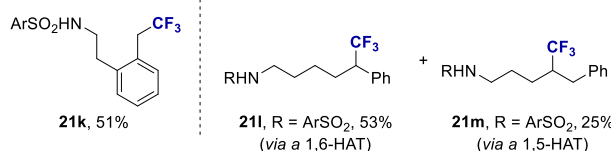
Zhu, Li et al.



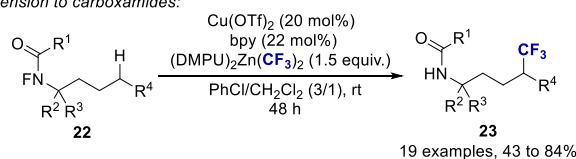
Selected examples:



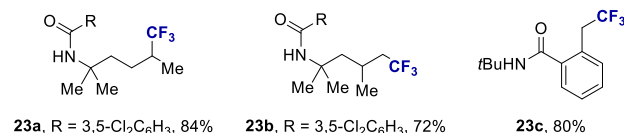
Modification of the HAT regioselectivity:



Extension to carboxamides:



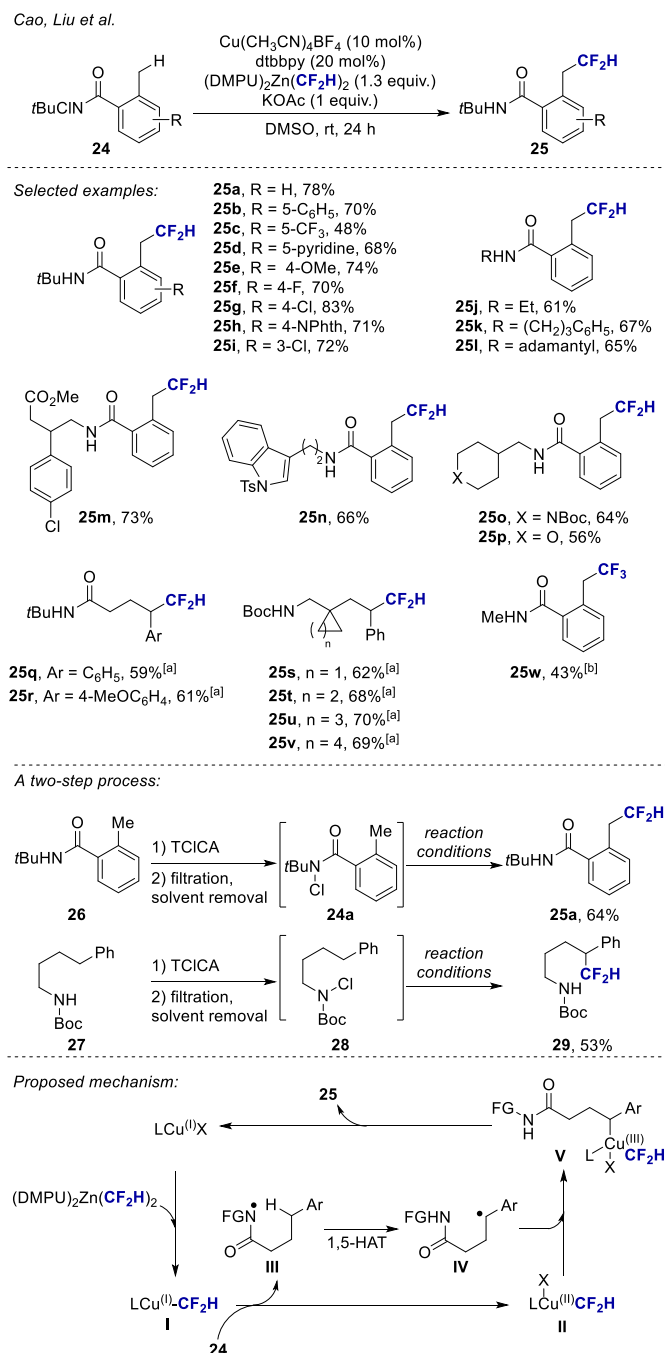
Selected examples:



Scheme 9. Distal copper-catalyzed trifluoromethylation of *N*-fluorosulfonamides and *N*-fluorocarboxamides via a nitrogen-centered radical. [a] without NaOAc. [b] 1:1 dr. Ar = 4-FC₆H₄. DMPU = *N,N'*-dimethylpropyleneurea.

Given the ability of the difluoromethyl group^[22] to act as a lipophilic hydrogen bond donor and as a metabolically stable bioisostere of a hydroxyl, or a thiol function, its incorporation to organic molecules received an ever-growing interest. The first copper-catalyzed remote benzylic C(sp³)–H difluoromethylation of amide derivatives has been reported recently by the group of Cao and Liu.^[23] A catalytic amount of Cu(CH₃CN)₄BF₄ and 4,4'-di-*tert*-butyl-2,2'-bipyridine along with (DMPU)₂Zn(CF₂H)₂ as the CF₂H source, allowed the remote difluoromethylation of *N*-chlorocarboxamide derivatives at the γ -benzylic position (Scheme 10, 52 examples, up to 92% yield). Under these reaction conditions, the desired difluoromethylated *N-tert*-butylcarboxamides (**25a** and **25b**) were synthesized with good yields. Electron-rich and electron-poor arenes were functionalized and the difluoromethylated products were obtained in good yields (**25c-i**). Moreover, various functional groups at different positions on the benzene ring were tolerated such as halogens (**25f-g**, **25i**) or a phthalimide (**25h**). Secondary amides were suitable substrates such as acyclic (**24j** and **24k**), and cyclic (**24l**) ones, as well as amides derived from baclofen (**24m**) and a tryptamine derivative (**24n**), giving the desired difluoromethylated products (**25j-n**) with good yields. Moreover, by using substrates having competitive δ -C(sp³) centers (vicinal to an amine (**24o**) or an ether (**24p**)), the remote difluoromethylation was fully selective towards the γ -benzylic positions. The reaction was then applied on amides bearing a secondary benzylic position and the γ -difluoromethylated *N-tert*-butyl amides (**25q** and **25r**) were synthesized with good yields under slightly modified reaction conditions. The difluoromethylation of aliphatic *N*-Boc-protected amines bearing a cyclopropane (**24s**), a cyclobutane (**24t**), a cyclopentane (**24u**) or a cyclohexane (**24v**) on the alkyl chain went smoothly. Note that with this methodology, a single example of a trifluoromethyl carboxamide (**25w**) was reported. It was also possible to perform the difluoromethylation reaction directly starting from the *N-tert*-

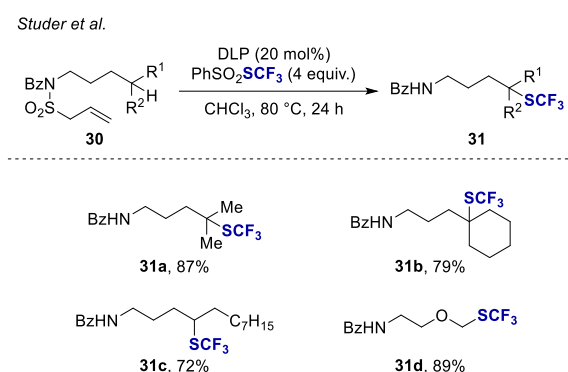
butylcarboxamide (**26**) or the carbamate (**27**) leading to the corresponding products **25a** and **29**, respectively, *via* a two-step process (chlorination/difluoromethylation) without purification of the *N*-chlorocarboxamide **24a** or the *N*-chlorocarbamate **28** intermediates (Scheme 10). A plausible mechanism was suggested starting with the formation of the $\text{Cu}^{\text{I}}\text{-CF}_2\text{H}$ complex **I** from a transmetalation reaction between $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ complex and $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$. The newly formed complex would undergo a SET with the starting *N*-chlorocarboxamide **24** to generate a $\text{Cu}^{\text{III}}\text{-CF}_2\text{H}$ intermediate **II** and the amidyl radical **III**, which after abstraction of the hydrogen at the γ -position would form the alkyl radical **IV**. This latter would recombine with the copper complex **II** to provide the intermediate **V**, which after a reductive elimination would provide the product **25** and regenerate the catalyst.



Scheme 10. Copper-catalyzed benzylic C–H difluoromethylation of *N*-chlorocarboxamide derivatives at the γ -benzylic position. [a] CuI was used instead of $\text{Cu}(\text{CH}_3\text{CN})_4$. [b] $\text{Cu}(\text{OTf})_2$ (20 mol%), 2,2'-bipyridine (22 mol%), KOAc (1 equiv.) and $(\text{DMPU})_2\text{Zn}(\text{CF}_3)_2$ in CH_2Cl_2 at rt. dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. TCICA = trichloroisocyanuric acid.

2.3. Trifluoromethylthiolation and trifluoromethylselenation reactions

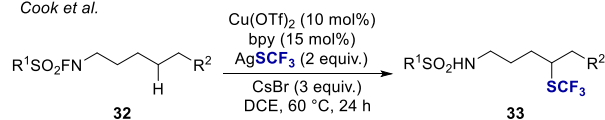
Since the SCF_3 group showed unique features such as a high electron-withdrawing character and a high lipophilicity (Hansch parameter = 1.44),^[24] the development of new methodologies for its incorporation into various classes of molecules has known a tremendous expansion.^{[25],[26]} Consequently, several research groups have been interested in the direct trifluoromethylthiolation of $\text{C}(\text{sp}^3)\text{-H}$ bonds, although the formation of a $\text{C}(\text{sp}^3)\text{-SCF}_3$ bond^[27] by C-H bond functionalization at a remote position is still highly challenging. Studer and co-workers developed a general strategy for the remote $\delta\text{-C}(\text{sp}^3)\text{-H}$ functionalization of aliphatic amides *via* an amidyl radical. In the course of their study, they reported the selective δ -trifluoromethylthiolation of *N*-alkylamide derivatives using *S*-(trifluoromethyl)benzenesulfonothioate ($\text{PhSO}_2\text{SCF}_3$) as the SCF_3 source (Scheme 11, 4 examples, up to 89% yield).^[28] The reaction was initiated by dilauroyl peroxide (DLP) to generate the key amidyl radical. Although the reaction was limited to few examples, the transformation was efficient for the trifluoromethylthiolation of tertiary (**30a-b**), secondary (**30c**) and primary (**30d**) $\text{C}(\text{sp}^3)$ centers.



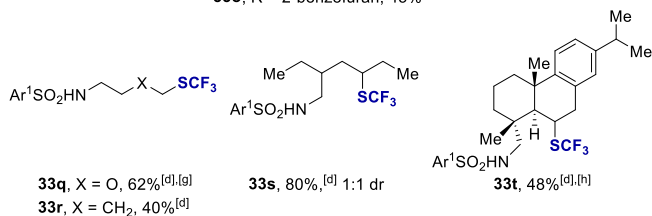
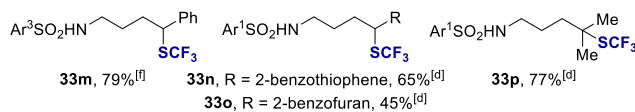
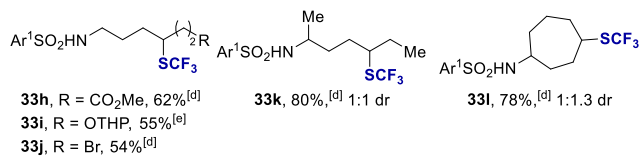
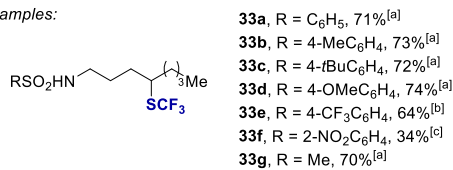
Scheme 11. Site selective δ -trifluoromethylthiolation of aliphatic amides. DLP = dilauroyl peroxide. Bz = benzyl.

In 2019, the group of Cook developed a methodology for the remote trifluoromethylthiolation of aliphatic sulfonamides.^[29] Starting from *N*-fluorosulfonamides, the key combination of $\text{Cu}(\text{OTf})_2$ and bipyridine as a ligand in the presence of AgSCF_3 as the SCF_3 source, yielded to the desired trifluoromethylthiolated products at the δ -position (Scheme 12, 35 examples, up to 87% yield). In this process, a sulfonamidyl radical intermediate was generated from a copper-catalyzed homolysis of the N-F bond from the substrate **32**. With this approach, both electron-neutral (**32a**) and electron-rich aryl (**32b-d**) *N*-fluorosulfonamides were efficiently trifluoromethylthiolated at the δ -position. Note that the presence of a trifluoromethyl group (**32e**) or a nitro group (**32f**) was well tolerated in this transformation. A *N*-mesyl-*N*-fluorosulfonamide (**32g**) was also used and furnished the desired trifluoromethylthiolated product (**33g**) with a good yield. *N*-fluoro-4-methoxybenzenesulfonamides substituted with an ester (**32h**), a protected-alcohol (**32i**) or a halide (**32j**) on the alkyl chain were smoothly functionalized. When non-cyclic or cyclic secondary *N*-fluoroarylsulfonamides (**32k** and **32l**) were used as substrates, the corresponding δ -trifluoromethylthiolated arylsulfonamides (**33k** and **33l**) were obtained in about a 1:1 mixture of diastereoisomers. Derivatives having a benzylic position (**32m**) or substituted with heterocycles such as a benzothiophene (**32n**) and a benzofuran (**32o**) were trifluoromethylthiolated with moderate to good yields. The methodology was also applied to the functionalization of tertiary (**32p**) and primary (**32q** and **32r**) $\text{C}(\text{sp}^3)$ centers at the δ -positions. The selectivity of the method was further illustrated with the functionalization of substrates having multiple $\delta\text{-C}(\text{sp}^3)$ positions. By using a substrate bearing a secondary $\text{C}(\text{sp}^3)$ center and a primary one at the δ -position (**32s**), a complete selectivity towards the trifluoromethylthiolation of the secondary center over the primary one was observed. The high selectivity of the transformation was further showcased with the functionalization of the lealamine derivative (**32t**). However, in the case of **32u**, the trifluoromethylthiolation occurred at the ϵ - and δ -positions leading to the corresponding products **33u** and **33u'** with a 3:2 ratio. Finally, the trifluoromethylthiolation of the *tert*-butyl sulfonic acid derivative (**32v**) and the adamantyl-derived amide (**32w**) was achieved. This method was successfully extended to the direct trifluoromethylselenation of unactivated remote C-H bonds by switching AgSCF_3 with AgSeCF_3 as demonstrated with the synthesis of compounds (**35a-c**) (Scheme 12, 5 examples, up to 71% yield). The authors suggested the following mechanism: first, a copper^(I) complex would be generated followed by a reaction with **32** or **34** to produce a $\text{Cu}(\text{II})\text{-F}$ complex **II** and the radical **A**. A transmetalation between **II** and the *in situ* generated $\text{Cs}(\text{AgXCF}_3)\text{Br}$ would lead to the formation of the $\text{Cu}(\text{II})\text{-XCF}_3$ complex **III** ($\text{X} = \text{S}, \text{Se}$). The key δ -alkyl radical **B** would be generated through a 1,5-HAT from **A**. After reaction between the radical **B** and the complex **III**, the intermediate **IV** would be obtained and this latter would undergo a reductive elimination to afford the desired products **33** or **35** and regenerate the active $\text{Cu}(\text{I})$ catalyst.

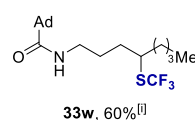
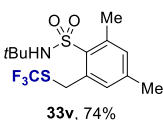
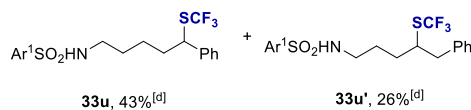
Cook et al.



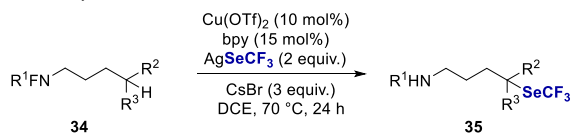
Selected examples:



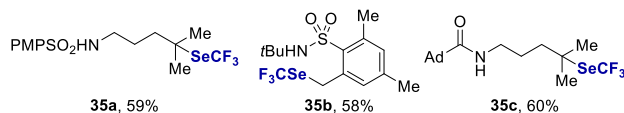
Modification of the HAT regioselectivity:



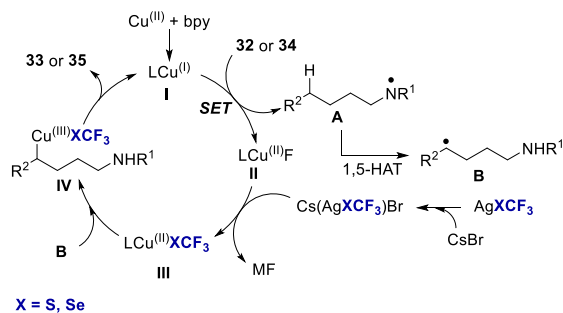
Trifluoromethylselenation:



Selected examples:



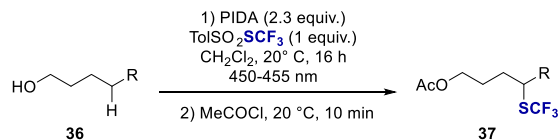
Proposed mechanism:



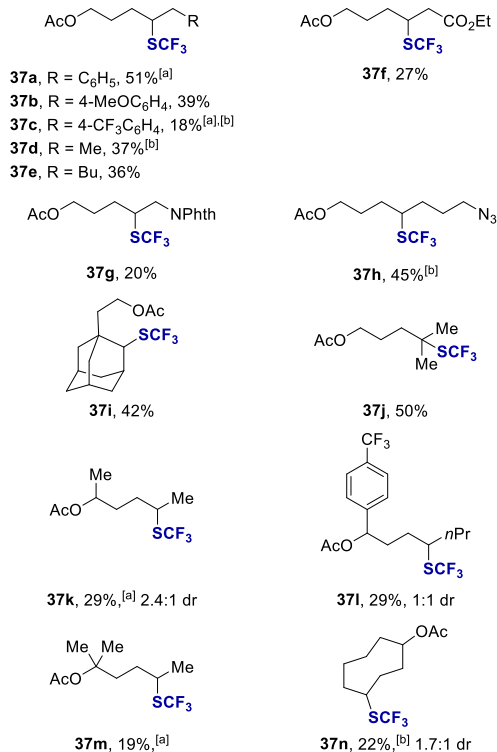
Scheme 12. Copper-catalyzed δ -trifluoromethylthiolation of **32** and δ -trifluoromethylselenation of **34**. [a] Regioisomer δ /all others: >40/1 except for **33g** (38/1). [b] Regioisomer δ /all others: 14/1. [c] Regioisomer δ /all others: 20/1. [d] Ar¹ = 4-OMeC₆H₄. [e] Ar² = 4-*t*BuC₆H₄. [f] Ar³ = 4-MeC₆H₄. [g] Cu(OTf)₂ (20 mol%), bpy (30 mol%), AgSCF₃ (3 equiv.). [h] 6% of other undetermined regioisomers were obtained in this case. [i] Use of 3 equivalents of AgSCF₃. bpy = 2,2'-bipyridine. Ad = adamantyl. PMP = 4-methoxyphenyl. DCE = 1,2-dichloroethane. THP = tetrahydropyran.

More recently, Besset and co-workers^[30] reported, for the first time, a selective remote δ -trifluoromethylthiolation of aliphatic alcohols^[31] mediated by an alkoxy radical. In the presence of (diacetoxyiodo)benzene (PIDA) and the TolSO₂SCF₃ reagent, a two-step process (trifluoromethylthiolation/acetoxylation) was developed under blue light irradiation affording the desired products with a full δ -selectivity (Scheme 13, 16 examples, up to 51% yield). Firstly, the trifluoromethylthiolation of primary alkyl alcohols bearing either an electron-rich or an electron-poor aryl as a substituent on the alkyl chain furnished the desired products (**37a-c**). It turned out that the modification of the alkyl chain length did not have any impact on the outcome of the transformation (**37d** and **37e**). An ester (**36f**), a phthalimide (**36g**) and an azide (**36h**) were also tolerated in that transformation. Worth mentioning that an alcohol substituted with an adamantyl group (**36i**) was a suitable substrate and an aliphatic alcohol bearing a tertiary C(sp³) center (**36j**) was also well trifluoromethylthiolated on that position. Finally, the depicted method was applied to the functionalization of more hindered substrates as secondary and tertiary alcohols (**36k-n**) were reacted with TolSO₂SCF₃ to give the expected products (**37k-n**). The authors suggested that first the synthesis of the dialkoxyiodobenzene intermediate **I** would occur. Then, under blue LEDs irradiation, this latter would lead to the key alkoxy radical **II**, which could undergo a 1,5-HAT to selectively furnish the δ -alkyl radical **III**. This newly formed intermediate would react with either the TolSO₂CF₃ reagent or the *in situ* generated CF₃SSCF₃ dimer to yield the product.

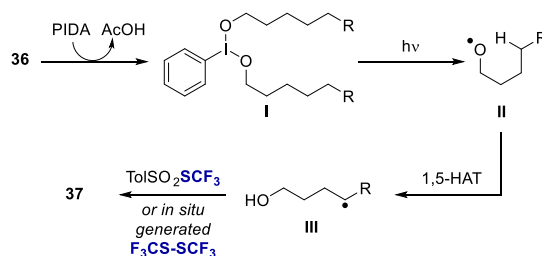
Besset *et al.*



Selected examples:



Postulated mechanism:

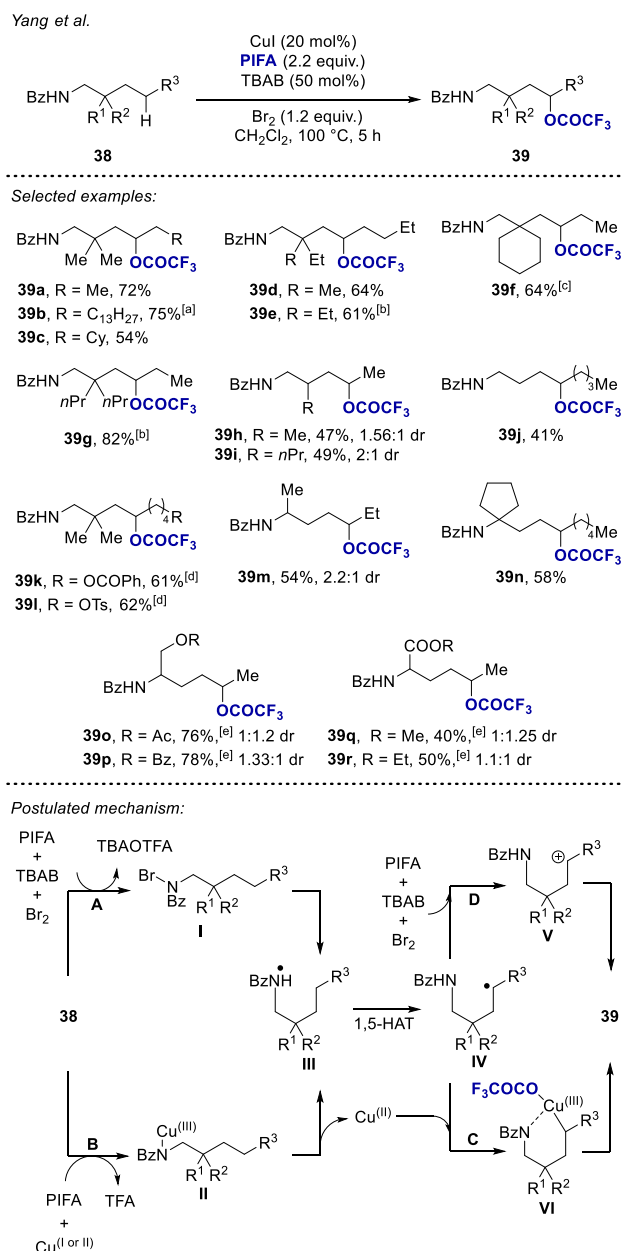


Scheme 13. Trifluoromethylthiolation of free-alcohols under visible light. [a] 1.2 equiv. of TolSO₂CF₃ was used. [b] The product was obtained with an inseparable impurity. PIDA = (diacetoxyiodo)benzene.

2.4. Trifluoroacetoxylation reactions

Due to the synthetic utility of the trifluoroacetoxy group,^[32] Yang *et al.* described the direct remote trifluoroacetoxylation reaction of aliphatic *N*-protected benzoyl amines at the δ -position mediated by an amidyl radical.^[33] The use of a catalytic amount of copper iodide and tetrabutylammonium bromide in presence of the bis((trifluoroacetoxy)iodo)benzene and bromine to form the intermediate radical, allowed the synthesis of the desired δ - trifluoroacetoxylation products (Scheme 14, 31 examples, up to 82% yield). Aliphatic benzoylamides having various carbon chain lengths (**38a-c**) were functionalized with a full selectivity towards the δ -position. Trifluoroacetoxylation products were generally obtained in good yields when the substrates were substituted with a *gem*-dialkyl group (**38a-g**) at the β -position (methyl, ethyl, cyclohexyl and *n*-propyl groups), while the transformation was less efficient in case of benzoylamides substituted with a methyl (**38h**), a *n*-propyl (**38i**) or unsubstituted one (**38j**). Protected-alcohols were well tolerated with this approach as demonstrated with compounds **39k** and **39l**. Note that the reaction was not restricted to primary amides, as secondary and tertiary benzoyl amides were efficiently functionalized leading to the corresponding products (**39m-n**) in 54% and 58% yields, respectively. Furthermore, both protected-amino alcohols (**38o** and **38p**) and ester derived from natural amino acids (**38q** and **38r**) were

suitable substrates in this transformation, providing the expected products (**39o-r**) in 40 to 78% yields with a high δ -selectivity. The authors suggested that the copper catalyst and PIFA would allow the generation of a N–Br intermediate **I** (Pathway **A**) or a N–Cu^(III) complex **II** (Pathway **B**). A homolysis of the N–Br or the N–Cu bond would furnish the key amidyl radical **III**. A subsequent 1,5-HAT would give the alkyl radical **IV**, which would react following two potential pathways. In pathway **C**, **IV** would recombine with Cu^(II) species to form a new Cu^(III) complex **VI** and a subsequent reductive elimination would furnish the desired product **38**. In pathway **D**, **IV** would be oxidized to form a carbocation **V**, which would react directly with the trifluoroacetate to give **38**. Alternatively, the generation of a δ -brominated intermediate, which would undergo a nucleophilic substitution reaction with the trifluoroacetate to afford **38** could not be ruled out.



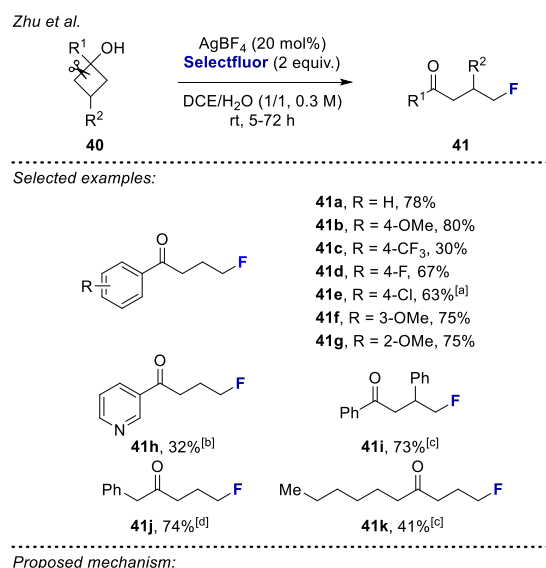
Scheme 14. Selective trifluoroacetylation of aliphatic *N*-protected benzoylamines via a 1,5-HAT. [a] 8 h of reaction. [b] PIFA (2.5 equiv.), 8 h. [c] PIFA (3 equiv.). [d] Ag(OAc) (20 mol%) was used instead of CuI with PIFA (2.5 equiv.) for 8 h. [e] 20 mol% of AgOAc instead of CuI. TBAB = tetrabutylammonium bromide. PIFA = bis((trifluoroacetoxy)iodo)benzene.

3. β -Fragmentation reactivity as an efficient tool for the remote functionalization

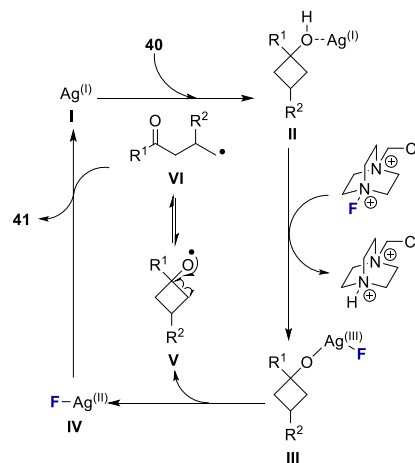
As a complementary strategy for the distal functionalization of molecules with fluorinated groups, the ring-opening functionalizations of various strained cyclic compounds (*ie.* cycloalkanols, cyclic oximes, cyclic amines) *via* a radical process were designed.^{[6b,c],[34]}

3.1. Fluorination reactions

In 2015, Zhu and co-workers reported the synthesis of γ -fluorinated ketones starting from cyclobutanols *via* a silver-catalyzed ring-opening reaction.^[35] A large panel of cyclobutanol derivatives was selectively fluorinated at the γ -position with an electrophilic fluorine source (Selectfluor) using a catalytic amount of AgBF_4 at room temperature (Scheme 15, 17 examples, up to 80% yield). Both substrates bearing a phenyl (**40a**) or an aryl substituted with an electron-donating group (OMe, **40b**) at the *ipso* position of the alcohol gave the corresponding fluorinated ketones in good yields (**41a** and **41b**). The transformation was also suitable with a cyclobutanol bearing an arene substituted with an electron-withdrawing group (**40c**). The reaction was tolerant to halogens (**41d** and **41e**). Note that the outcome of the reaction was similar whatever the substitution pattern of the aromatic ring at the *ipso* position (*eg.* **41b**, **41f**, and **41g**). Even a cyclobutanol substituted with a (hetero)arene (**40h**) was a suitable substrate in that reaction, albeit a lower yield was obtained (32%). Moreover, the substitution on the cyclobutanol ring was also tolerated and **40i** was smoothly functionalized leading to the corresponding product (**41i**) in a 73% yield. When cyclobutanols bearing an aliphatic chain at the *ipso* carbon were reacted, the fluorinated products (**41j** and **41k**) were obtained in 74% and 41% yields, respectively. It is worth noting that for the last two examples, the fluorine atom was introduced selectively on the carbon atom involved in the C–C bond cleavage. The following plausible mechanism was suggested for the depicted transformation. First, the coordination of a silver^(I) salt **I** with the cyclobutanol **40** would lead to the intermediate **II**, which would afford the species **III** after a reaction with Selectfluor. After the homolytic cleavage of the Ag–O bond, the silver^(II) species **IV** and the cyclobutyloxy radical **V** would be generated. This later would give the corresponding alkyl radical **VI**, which would react with the silver^(II) fluoride **IV** to furnish the expected product **41** and to regenerate the Ag catalyst **I**.

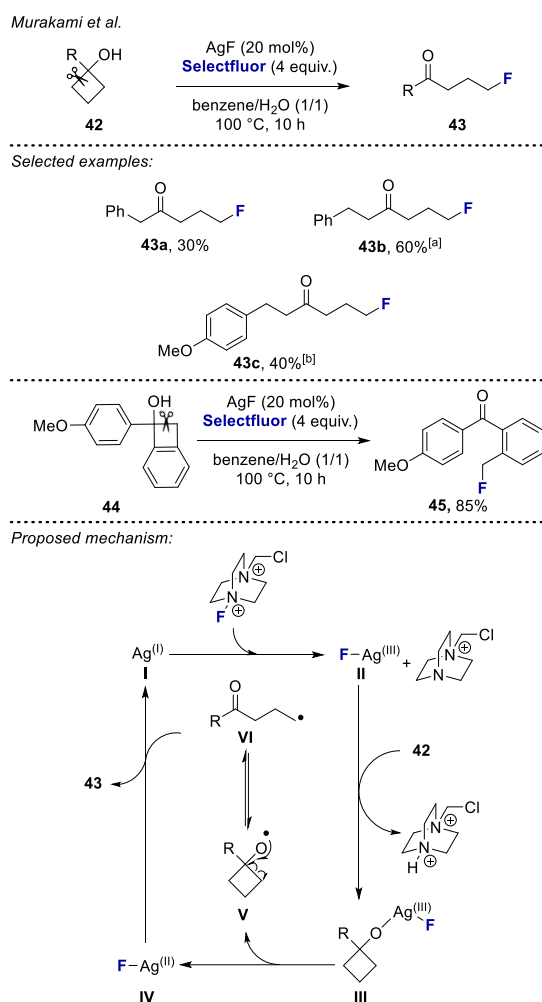


Proposed mechanism:



Scheme 15. β -scission strategy for the preparation of γ -fluorinated ketones starting from cyclobutanols. [a] 60 °C. [b] 2.5 equiv. of Selectfluor. [c] 50 mol% of AgBF₄ and 3 equiv. of Selectfluor. [d] 30 mol% of AgBF₄ and 3 equiv. of Selectfluor.

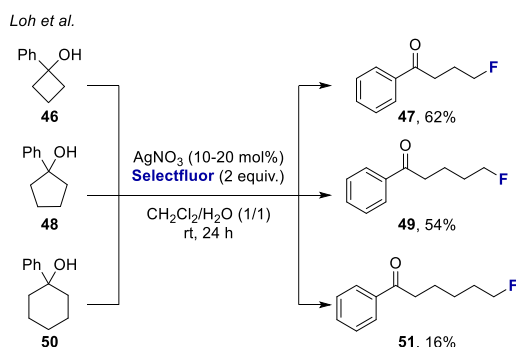
The same year, Murakami and co-workers reported a complementary approach for the synthesis of γ -fluorinated ketones starting from various cyclobutanols.^[36] A handful of molecules were selectively fluorinated at the γ -position using Selectfluor and a catalytic amount of AgF at 100 °C (Scheme 16, 6 examples, up to 85% yield). The transformation turned out to be very sensitive to the nature of the substituent at the *ipso* position of the alcohol. Indeed, starting from the 1-benzylcyclobutanol (**42a**), the corresponding product (**43a**) was obtained in a 30% yield. A higher yield was observed when switching the benzyl group by a phenylethyl one, leading to the fluorinated product (**43b**) in a 60% yield under milder reaction conditions. When the 1-(2-(4-methoxyphenyl)ethyl)cyclobutanol (**42c**) was used as a substrate, the fluorinated product (**43c**) was obtained in a 40% yield. The reaction was also tolerant to the benzocyclobutenol (**44**) and the γ -fluorinated ketone (**45**) was selectively obtained in an efficient manner (85% yield). The authors suggested a radical-type mechanism for the synthesis of **43**. Initially, a silver^(I) salt I would be oxidized by Selectfluor to provide the silver^(III) fluoride II. After coordination with the cyclobutanol **42**, the intermediate III would be obtained, which would undergo a single-electron transfer (SET) to afford the species IV and the alkoxy radical V. This latter would lead to the more stable radical VI. Then, a reaction between the F-Ag^(III) IV and the intermediate VI would provide the γ -fluoroketone **43** and regenerate the Ag^(I) catalyst.



Scheme 16. Preparation of fluorinated ketones at the γ -position starting from cyclobutanols. [a] 60° C, 5 h. [b] 1.2 equiv. of Selectfluor.

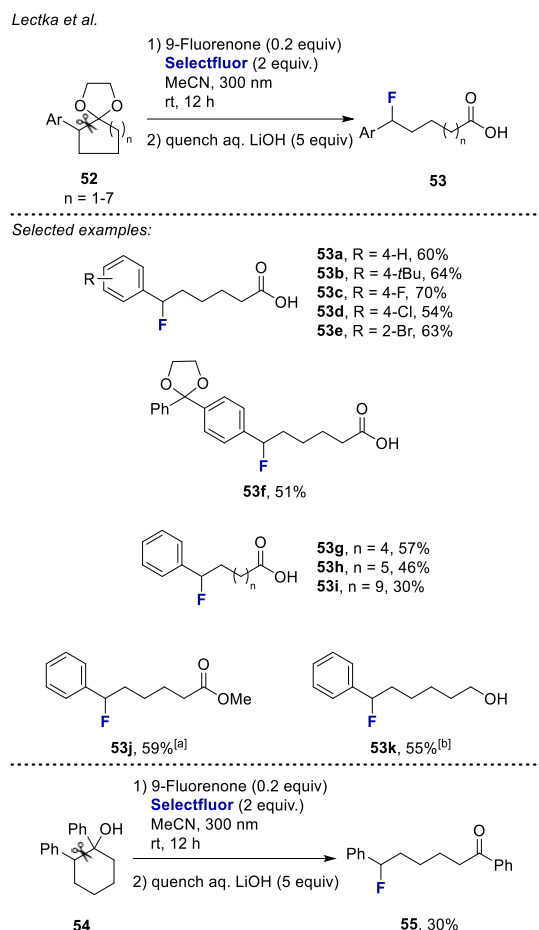
In the course of their investigation regarding the synthesis of β -fluoroketones by means of a silver- or iron-catalyzed oxidative functionalization of cyclopropanol derivatives, the group of Loh reported the synthesis of fluorinated ketones at different remote positions *via* an oxidative ring opening fluorination process.^[37] Using Selectfluor and a catalytic amount of AgNO₃ at room temperature, the cyclobutanol, the cyclopentanol and the cyclohexanol derivatives substituted by a phenyl group at the *ipso* position were fluorinated leading to the corresponding γ -, δ - and ϵ -fluoroketones with moderate

to good yields (Scheme 17, 3 examples, up to 62% yield). Note that when the ring size increased, the expected products were obtained in somehow lower yields (eg. comparison between **47**, **49** and **51**).



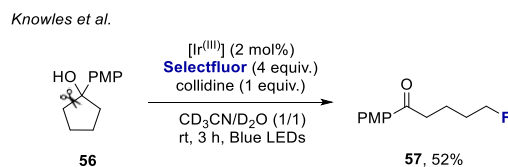
Scheme 17. Preparation of γ -, δ - and ϵ -fluoroketones starting from cyclic alcohols.

The same year, Lectka and co-workers reported the fluorination of less strained ring systems, offering an access to remote fluorinated aliphatic carboxylic acids (Scheme 18, 20 examples, up to 70% yield).^[38] A photocatalytic approach using an organic photosensitizer catalyst was developed to perform the selective monofluorination on 1-acetal-2-aryl-containing cycloalkyls (up to 12-membered rings) with Selectfluor under UV irradiation (300 nm). It turned out that the presence of an arene at the α -position of the acetal group was crucial for this reaction, leading to the corresponding products with a complete selectivity for the fluorination at the benzylic position. Good yields were obtained with substrates bearing a phenyl (**52a**) or an aryl substituted with either an electron-donating group (**52b**) or halogens (**52c-e**). The presence of another acetal at the *para* position of the phenyl substituent did not impact the outcome of the reaction (**53f**). Higher-membered cyclic substrates, from 7 to 12-membered rings, provided the corresponding fluorinated carboxylic acids (**53g-i**) in 30 to 57% yields. Note that the fluorinated ester (**53j**) or alcohol (**53k**) were obtained by changing the quenching conditions. The methodology was extended to the synthesis of distal fluorinated ketones. Indeed, starting from the 1,2-diphenylcyclohexanol (**54**), gave selectively the fluorinated ketone (**55**).



Scheme 18. Monofluorination of 1-acetal-2-aryl-cycloalkyls. [a] The reaction was quenched with LiOMe (5 equiv.) [b] Instead of the quenching step, the reaction was concentrated and treated with LiAlH₄ (6 equiv.) in anhydrous THF for 1 h.

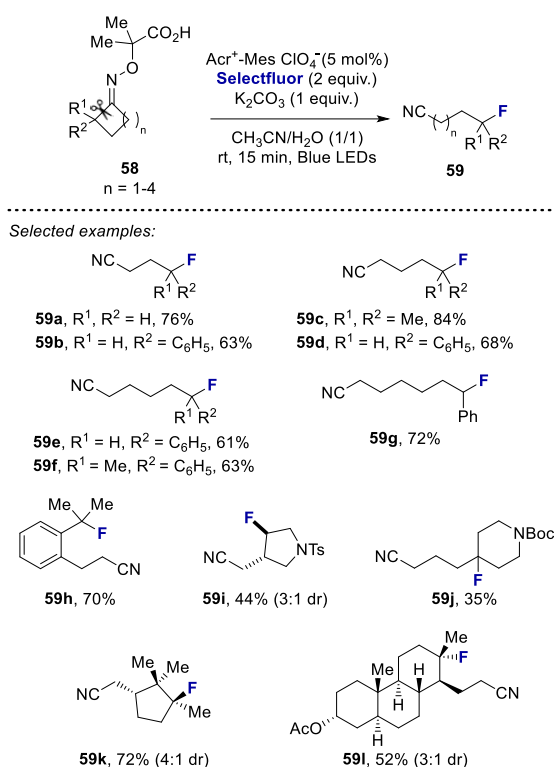
In 2016, Knowles *et al.* studied the isomerization of cyclic alkanols to the corresponding linear ketones *via* a Proton-Coupled Electron Transfer (PCET) strategy.^[39] A unique example leading to a fluorinated molecule was depicted. Indeed, they reported the synthesis of the 5-fluoro-1-(4-methoxyphenyl)pentan-1-one (**57**) *via* a C–C bond β -scission starting from the cyclopentanol substituted with the 4-methoxyphenyl group (PMP) at the *ipso* position (**56**) in a 52% yield (Scheme 19).



Scheme 19. Synthesis of the 5-fluoro-1-(4-methoxyphenyl)pentan-1-one **57** starting from the 1-(4-methoxyphenyl)cyclopentanol **56**. PMP = 4-MeOC₆H₄. $[\text{Ir}^{\text{III}}] = [\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})(5,5'\text{-dCF}_3\text{bpy})](\text{PF}_6)$.

In 2018, the group of Leonori reported the synthesis of remotely fluorinated nitrile compounds *via* a Fukuzumi's acridinium salt-catalyzed ring opening/fluorination process involving iminyl radicals.^[10] A panel of cycloalkanone oxime esters was selectively functionalized at a remote position with Selectfluor as the fluorine source under blue light irradiation (Scheme 20, 19 examples, up to 84% yield). The reaction was effective on cyclobutanone, cyclopentanone, cyclohexanone, and even cycloheptanone derivatives to give the corresponding fluorinated nitriles at different remote positions in moderate to good yields (**59a-g**). Furthermore, for higher-membered rings, the transformation only occurred in good yields on substrates substituted by an aromatic group at the α -position (**59e-h**). Note that this transformation was compatible with the presence of functional groups like tosyl, carbamate or acetoxy (eg. **58i**, **58j** and **58l**). This strategy was applied to the synthesis of complex fluorinated molecules resulting from the deconstruction/fluorination of natural products as for example the δ -fluorinated nitriles **59k** and **59l**.

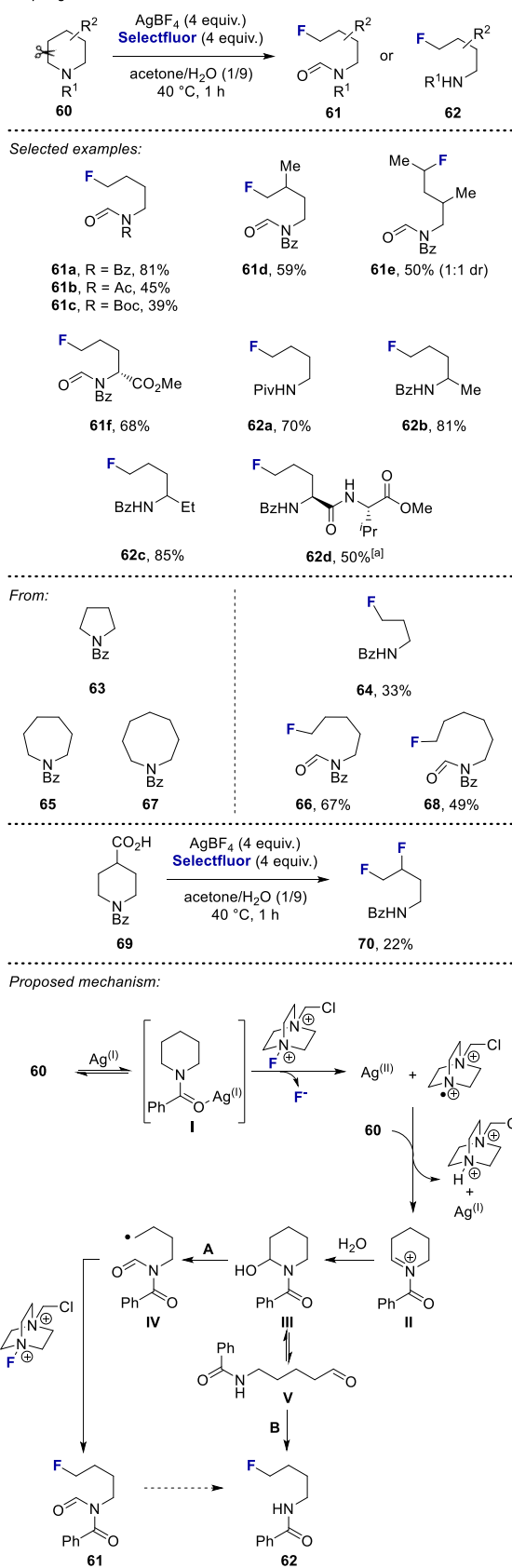
Leonori et al.



Scheme 20. Synthesis of fluorinated nitriles starting from cycloalkanone oxime esters. Acr⁺-Mes ClO₄⁻ = 9-mesityl-10-methylacridinium perchlorate.

In 2018, a method for the monofluorination of cyclic amines was developed by Sarpong and co-workers to access new acyclic amine derivatives via a “deconstructive fluorination” strategy.^[40] In that process, the cyclic amines were considered as an amino alkyl radical synthons by means of an oxidative and radical ring-opening sequence. Using a stoichiometric amount of AgBF₄ and Selectfluor at 40 °C, various *N*-protected cyclic amines were selectively fluorinated affording the corresponding acyclic distal fluorinated amines in moderate to good yields (Scheme 21, 20 examples, up to 85% yield). First, several *N*-protected piperidines were fluorinated (**60a-c**). Moreover, *N*-benzoylated piperidine substituted by a methyl group provided the corresponding fluorine-containing acyclic amine (**61d**) at the δ -position in a 59% yield. The fluorination of a secondary C(sp³) center was possible like in the case of the compound (**61e**) starting from the (3,5-dimethyl)piperidine. The reaction was also tolerant to the presence of an ester (**61f**). It is worth mentioning that in some cases, this transformation led to the deformylated product (eg. **62a**). In addition, 2-substituted *N*-benzoylated piperidines with a methyl or an ethyl group gave a selective access to the products **62b** and **62c** in high yields. The synthetic utility of this approach was further demonstrated with the functionalization of more complex molecules such as peptides, and for instance the deformylated product **62d** was obtained in a 50% yield. The reaction was not limited to piperidine derivatives as other *N*-containing heterocycles, from five to eight-membered ring, were suitable for the deconstructive fluorination providing the corresponding fluorinated compounds at the γ -, ϵ - and ζ -positions, respectively, in moderate to good yields (**64**, **66** and **68**). In addition, the difluorination of cyclic amines was achieved starting from piperidines substituted with a carboxylic group. Indeed, the difluorination reaction of **69** occurred through a deconstructive and decarboxylative fluorination process^[41] leading to the corresponding product **70** in a 22% yield. The following mechanism was proposed to explain the outcome of the reaction. First, the coordination of a silver salt with the amide **60** would result in the intermediate **I**, which would be oxidized by Selectfluor via a single-electron transfer to form Ag^(II) and the radical cation derived from the fluorine source. Then, an iminium species **II** would be generated after a single-electron transfer between Ag^(II) and **60**, followed by a hydrogen abstraction by the radical cation. The iminium species **II** would be subsequently trapped by H₂O to deliver the hemiaminal **III**. From here, two pathways were suggested: 1) cleavage of the C(sp³)–C(sp³) bond of the hemiaminal **III** would allow the formation of alkyl radical **IV**, which would react with Selectfluor to furnish the desired product **61** (Pathway **A**). 2) The hemiaminal **III**, in equilibrium with the linear aldehyde **V**, would afford the deformylated product **62** after an oxidation into the corresponding carboxylic acid followed by a decarboxylative fluorination (Pathway **B**). Mechanistic studies showed that the deformylation process could also occur from the product **61**. In consequence, for cases where deformylated products were obtained exclusively, the pathway **B** could not be excluded.

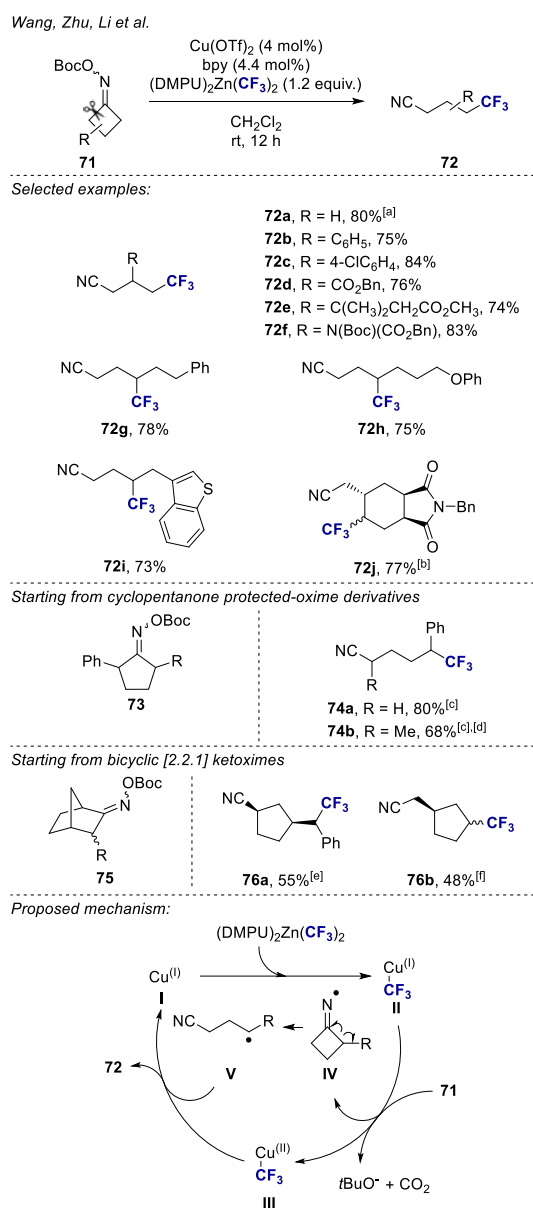
Sarpong et al.



Scheme 21. Fluorination of cyclic amines via deconstructive fluorination. Bz = benzoyl, Ac = acetyl, Boc = *tert*-butoxycarbonyl, Piv = pivaloyl. [a] rt for 15 h; recovering of the starting material = 25%.

3.2. Trifluoromethylation reactions

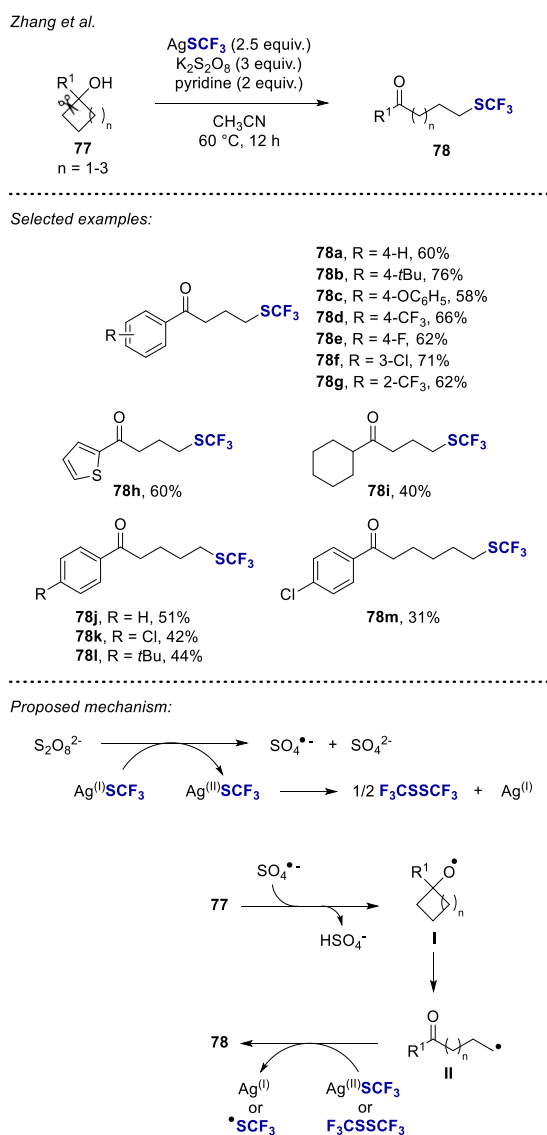
In 2019, Wang, Zhu, Li and co-workers reported the synthesis of γ - and δ -trifluoromethylated nitriles starting from cycloalkanone protected-oximes.^[42] A copper-catalyzed ring opening of cyclobutanone oxime esters was developed using $(\text{DMPU})_2\text{Zn}(\text{CF}_3)_2$ as the trifluoromethylating reagent (Scheme 22, 27 examples, up to 92% yield). Good yields were obtained on cyclobutanone oximes substituted at the 3-position (**71a-f**), at the 2-position (**71g-i**) or both (**71j**). Several functional groups were tolerated such as esters (**71d-e**), a carbamate (**71f**), an ether (**71h**), a benzothiophene (**71i**) and an imide (**71j**). The methodology was easily extended to the functionalization of cyclopentanone oxime derivatives (**73**) (4 examples, up to 88% yield) and bicyclic[2.2.1]ketoximes (**75**) (2 examples, up to 55% yield) leading to the δ -trifluoromethylated compounds. A plausible mechanism was suggested to explain the reaction (Scheme 22). First, the $\text{Cu}^{\text{II}}-\text{CF}_3$ intermediate **II** would be generated after transmetalation between the trifluoromethylzinc complex and the copper species **I**. Then, **II** would reduce the cyclobutanone oxime **71** leading to the formation of a $\text{Cu}^{\text{I}}-\text{CF}_3$ **III** intermediate and the iminyl radical **IV**. The ring-opening β -scission of the latter gave the corresponding alkyl radical **V**, which would react with the trifluoromethylated copper species **III** to furnish the desired trifluoromethylated nitrile **72** and regenerate the catalyst.



Scheme 22. Trifluoromethylation of cycloalkanone oxime esters. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone. [a] Yields were determined by ^{19}F NMR analysis by using 1-chloro-4-fluorobenzene as an internal standard. [b] *trans:cis* = 77:23. [c] 50 °C in DCE. [d] dr = 50:50. [e] $\text{Cu}(\text{OTf})_2$ (20 mol%), bpy (22 mol%) and $(\text{DMPU})_2\text{Zn}(\text{CF}_3)_2$ (1.2 equiv.) in DCE at 50 °C for 12 h; dr = 50:50. [f] $\text{Cu}(\text{OTf})_2$ (5 mol%) and $(\text{bpy})\text{Zn}(\text{CF}_3)_2$ (1.2 equiv.) in DCE at 70 °C for 12 h; dr = 50:50. bpy = 2,2'-bipyridine. DCE = 1,2-dichloroethane.

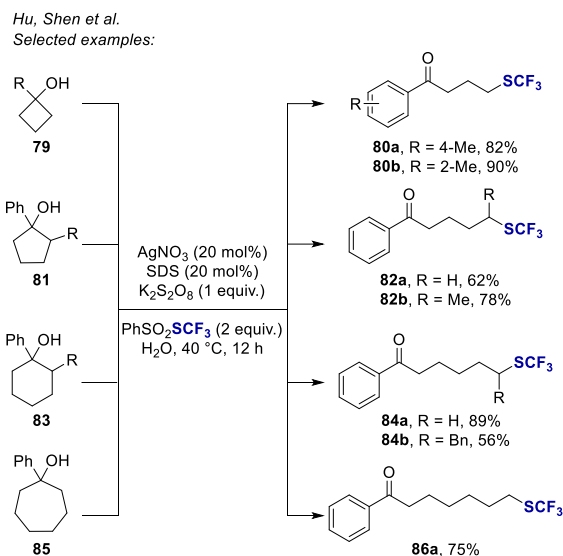
3.3. Trifluoromethylthiolation reactions

Due to the importance of the SCF_3 residue, Zhang and co-workers reported in 2016 a silver-mediated trifluoromethylthiolation of cyclic alcohols offering an access to the corresponding β -, γ -, δ - and ε -trifluoromethylthiolated ketones *via* a ring-opening process.^[43] Using a nucleophilic SCF_3 source (AgSCF_3) under oxidative conditions, an array of cyclic alcohols was functionalized in moderate to good yields (Scheme 23, 20 examples, up to 76% yield). Cyclobutanols bearing a phenyl (**77a**), an aryl substituted with an electron-donating (**77b-c**) or an electron-withdrawing (**77d**) group at the *ipso* position of the alcohol provided the corresponding γ -trifluoromethylthiolated ketones (**78a-d**). The reaction was tolerant to halogens (**78e-f**) and the substitution pattern on the aromatic ring did not have any impact on the outcome of the reaction (*ie.* **78d** vs **78g**). When cyclobutanols substituted with an heteroaryl (**77h**) or a cyclohexyl ring (**77i**) were used as substrates, the expected ketones (**78h** and **78i**) were obtained in 60% and 40% yields, respectively. The methodology was smoothly applied to the trifluoromethylthiolation of cyclopentanol and cyclohexanol derivatives resulting into an access to δ - and ε -trifluoromethylthiolated ketones (**78j-m**). The authors suggested the following mechanism to explain the reaction. Initially, $\text{K}_2\text{S}_2\text{O}_8$ would be reduced by $\text{Ag}^{\text{I}}\text{SCF}_3$ to produce the radical anion $\text{SO}_4^{\bullet-}$ and generate $\text{Ag}^{\text{III}}\text{SCF}_3$ or the disulfide F_3CSSCF_3 from the latter. Then, a proton would be abstracted from the starting alcohol **77** by the radical anion $\text{SO}_4^{\bullet-}$ to form the alkoxy radical **I**, which would lead to the corresponding alkyl radical **II** after a subsequent β -scission. The final trifluoromethylthiolated product **78** would be obtained after reaction between **II** and either $\text{Ag}^{\text{III}}\text{SCF}_3$ or F_3CSSCF_3 as the SCF_3 source.



Scheme 23. Preparation of trifluoromethylthiolated ketones starting from cyclic alcohols.

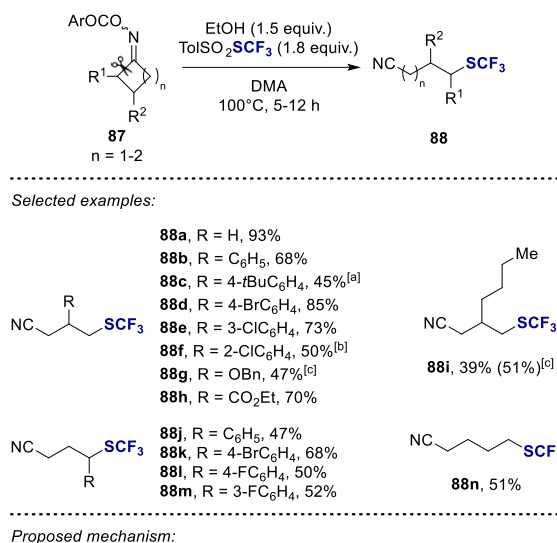
In the course of their investigation for the difluoromethylthiolation of cycloalkanols via a Ag-catalyzed ring opening, the group of Hu and Shen further demonstrated the potential of their methodology based on the use of the PhSO_2SR_f reagents by extending it to the trifluoromethylthiolation of various cycloalkanols.^[44] Indeed, the synthesis of distal trifluoromethylthiolated ketones by the silver-catalyzed ring opening of 4-, 5-, 6- and even 7-membered ring cycloalcohols was successfully achieved in water under oxidative conditions in the presence of sodium dodecyl sulfate (SDS) as a surfactant and $\text{PhSO}_2\text{SCF}_3$ (Scheme 24, 9 examples, up to 90% yield).



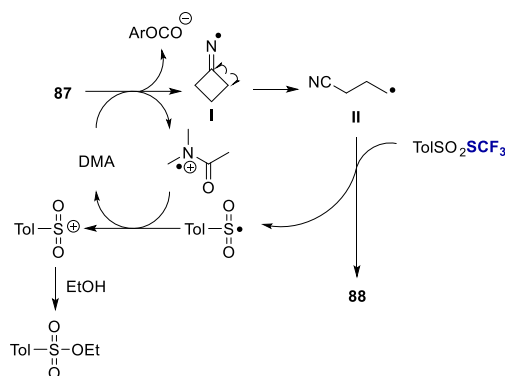
Scheme 24. Trifluoromethylthiolation of cycloalkanol derivatives by silver catalysis. SDS = sodium dodecyl sulfate.

In 2020, Zhao and co-workers reported the synthesis of trifluoromethylthiolated nitriles at the γ - and δ -positions.^[45] Taking benefit from β -fragmentation reactivity of constrained cyclic compounds, a metal-free process based on the trifluoromethylthiolation of cycloalkanone oxime esters was developed. Similarly to the work of Hu and Shen, the *S*-(trifluoromethyl)-4-methylbenzenesulfonothioate ($\text{ToI}(\text{SO}_2\text{SCF}_3)$) was used as the SCF_3 source. The reaction was efficient as a broad panel of derivatives was remotely functionalized at the γ - and δ -positions (Scheme 25, 17 examples, up to 93% yield). Starting from a non-substituted cyclobutanone oxime ester gave an access to the corresponding γ -trifluoromethylthiolated nitrile derivative (**88a**) in a 93% yield. The synthesis of nitriles substituted at the β -position with a phenyl (**88b**), an aryl substituted with an electron-donating group (**88c**) or with halogens at different positions (**88d-f**) was achieved. With this transformation, an access to γ -trifluoromethylthiolated nitriles substituted at the β -position with a benzyloxy group, an ester or an alkyl chain (**88g-i**) was possible. Moreover, this transformation was efficient with 2-aryl-substituted cyclobutanone oxime esters (**87j-m**). Starting from cyclopentanone *O*-(4-(trifluoromethyl)benzoyl) oxime (**87n**) resulted in the synthesis of the δ -trifluoromethylthiolated nitrile (**88n**) in a 51% yield. A plausible mechanism was proposed (Scheme 25). First, generation of the iminyl radical **I** after a SET between **87** and DMA, followed by a β -scission would afford the corresponding alkyl radical **II**. This latter would react with the electrophilic SCF_3 source to furnish the expected product **88** and a sulfone radical, which would be further oxidized and trapped by ethanol.

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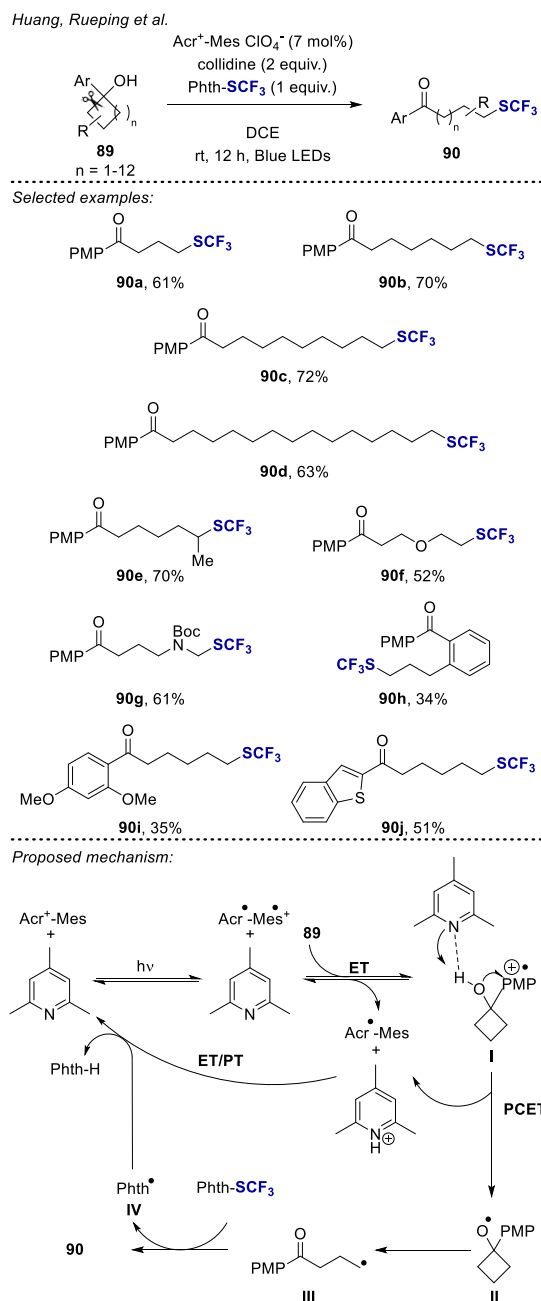


Proposed mechanism:



Scheme 25. Trifluoromethylthiolation of cycloalkanone oxime esters. Ar = 4-CF₃C₆H₄. [a] 2 equiv. of TolSO₂SCF₃, Ar = C₆F₅. [b] 2 equiv. of TolSO₂SCF₃. [c] Using Ar = 3,5-CF₃C₆H₃.

The same year, the group of Huang and Rueping depicted the metal-free photocatalyzed remote trifluoromethylthiolation of cycloalkanols offering an access to trifluoromethylthiolated ketones at a remote position.^[46] Using a Proton-Coupled Electron Transfer strategy (PCET), they were able to functionalize cycloalkanols with an aryl group at the *ipso* position of the alcohol in presence of 9-mesityl-10-methylacridinium perchlorate (Acr⁺-Mes ClO₄⁻), collidine and *N*-trifluoromethylthiophthalimide (Phth-SCF₃) at room temperature under blue light irradiation (Scheme 26, 24 examples, up to 83% yield). The scope of the reaction was first studied starting with cycloalkanols bearing 4-methoxyphenyl as the aryl group. Similar yields were obtained whatever the ring size of the cycloalkanols (up to 12-membered rings), and various distal trifluoromethylthiolated ketones were synthesized (**90a-d**). Substitution of the starting cyclohexanol by a methyl group gave selectively the more substituted trifluoromethylthiolated ketone (**90e**) in a 70% yield. Moreover, this reaction was suitable using tetrahydropyranol (**89f**), unsymmetrical cycloalkanols (eg. the protected-piperidine (**89g**)) and even the 1,2,3,4-tetrahydro-1-naphthol derivative (**89h**), as substrates. In addition, when the 4-methoxyphenyl was replaced by a disubstituted anisole (**89i**) or a benzothiophene (**89j**), the expected products were obtained in somehow lower yields (**90i-j**, 35% and 51% yields, respectively). The following mechanism was suggested to explain this transformation (Scheme 26). The excited photocatalyst oxidized the 4-methoxyphenyl group to produce a transient radical cation **I**, which would then lead to the formation of the alkoxy radical **II** after an intramolecular Proton-Coupled Electron Transfer (PCET). This latter would undergo a C-C bond cleavage (*via* a β -scission) leading to the corresponding alkyl radical **III**, which would then react with the electrophilic SCF₃ source to furnish the expected product **90**. A final reduction of the radical phthalimide **IV** by the Acr⁺-Mes species would regenerate the organophotocatalyst and the phthalimide would be released after a protonation step.

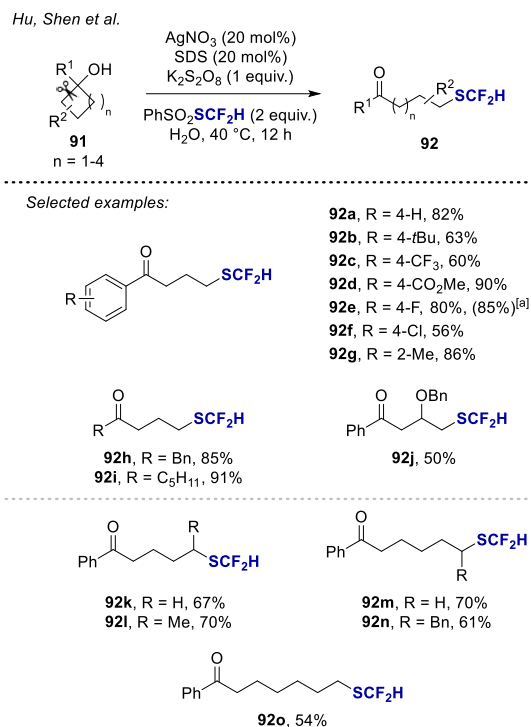


Scheme 26. Preparation of trifluoromethylthiolated ketones starting from cycloalkanols using Proton-Coupled Electron Transfer strategy (PCET). PMP = 4-methoxyphenyl. Acr⁺-Mes ClO₄⁻ = 9-mesityl-10-methylacridinium perchlorate. ET = Electron Transfer. PT = Proton Transfer.

3.4. Difluoromethylthiolation reactions

Due to the unique properties of the SCF₂H group (a Hansch parameter of 0.68 and known as a good hydrogen bond donor),^{[22e],[47]} the development of original methodologies is of prime importance.^{[25f],[48]} In that context, Hu, Shen and co-workers reported in 2018 the synthesis of distal difluoromethylthiolated ketones starting from the corresponding cycloalkanols.^[44] Indeed, in the presence of the PhSO₂SCF₂H reagent, potassium persulfate and sodium dodecyl sulfate (SDS), the silver-catalyzed difluoromethylthiolation reaction of a variety of cycloalkanols offered an efficient access to the remote difluoromethylthiolated alkyl ketones (Scheme 27, 22 examples, up to 95% yield). Good to excellent yields were obtained with cyclobutanol derivatives bearing a phenyl, an electron-rich or electron-poor arenes at the *ipso* position (**91a-d**). The reaction was tolerant to the presence of an ester (**92d**) and halogens (**92e-f**) on the aromatic part and in the case of **92e**, the reaction was smoothly scaled up to 6 mmol scale. When the cyclobutanol **91g** having an *ortho* tolyl group at the *ipso* position was used as a substrate, the expected ketone **92g** was isolated in a 86% yield. Cyclobutanols substituted with a benzyl group (**91h**) or an aliphatic chain (**91i**) were suitable substrates leading to the corresponding difluoromethylthiolated ketones (**92h** and **92i**) in high yields. In addition, substitution on the cyclobutanol ring was well

tolerated as demonstrated with the synthesis of the ketone (**92j**) bearing a benzyloxy group at the β -position. Furthermore, higher-membered cycloalkanols such as cyclopentanol (3 examples, up to 70% yield), cyclohexanol (3 examples, up to 70%) and cycloheptanol were also efficiently difluoromethylthiolated, and ketones substituted at various distal positions were obtained (**92k-o**). Preliminary mechanistic studies suggested that the reaction occurred *via* the formation of a cycloalkoxy radical, which would afford an alkyl radical after a ring-opening β -scission. The latter reacted with the electrophilic reagent to furnish the desired compounds **92**.

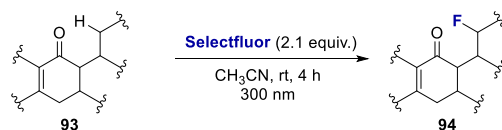


Scheme 27. Silver-catalyzed difluoromethylthiolation of cycloalkanol derivatives. SDS = sodium dodecyl sulfate. [a] Gram scale.

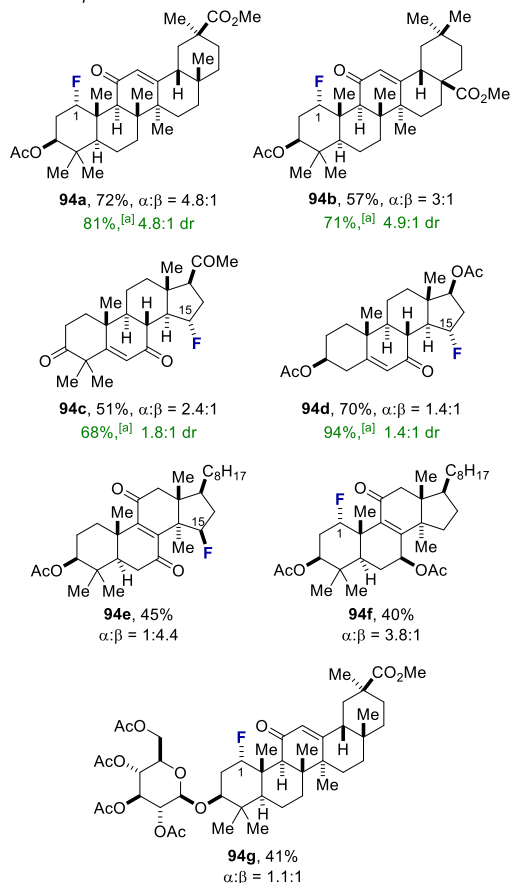
4. Miscellaneous

This section is dedicated to the remote and regioselective photochemical fluorination of complex polycyclic molecules on unactivated C(sp³) centers via the astutely use of an enone or a ketone to control the regioselectivity of the reaction. Recently, Lectka *et al.* depicted how upon photoexcitation, an enone directed the selective C(sp³)-H fluorination of polycyclic terpenoid structures at a γ -position. Indeed, under mild reaction conditions, the fluorination of diverse bioactive polycyclic terpenoid compounds (**93a-g**) was achieved using Selectfluor as a fluorine source in moderate to good yields (Scheme 28, 11 examples, up to 72% yield).^[49] The fluorinated steroid derivatives were generally obtained as a mixture of α - and β -isomers. Moreover, the high selectivity of the transformation was further demonstrated by the selective fluorination of the triterpenoid saponin derivative (**93g**), which contains 65 C(sp³)-H bonds. The following mechanism was suggested by the authors: a photoexcitation of the substrate **93** would lead to the formation of the enone triplet state **I**. Then, an intramolecular hydrogen abstraction would allow the generation of the alkyl radical **II**, which would recombine with Selectfluor *via* an intermolecular fluorine atom transfer to form the desired C-F bond (intermediate **III**) along with a N-centered radical. The latter would finally abstract the hydrogen atom from the hydroxyl group of **III** affording the expected product **94**. However, this method was limited to polycyclic terpenoid enone derivatives that can be excited at 300 nm. To tackle this issue, a benzil-catalyzed fluorination of C(sp³) centers was developed using ketones to direct the reaction. In the presence of Selectfluor under visible light irradiation, the fluorination was achieved at the β - and γ -positions. Different polycyclic ketone derivatives were fluorinated with good yields, and a high γ -selectivity (Scheme 29, 5 examples, up to 85% yield).^[50] Interestingly, this new protocol was then applied to a selection of enone terpenoid derivatives (**93a-d**) previously used by the authors. These new conditions improved the efficiency of the γ -fluorination (Scheme 28, yields are depicted in green, 10 examples, up to 94% yield).^[51]

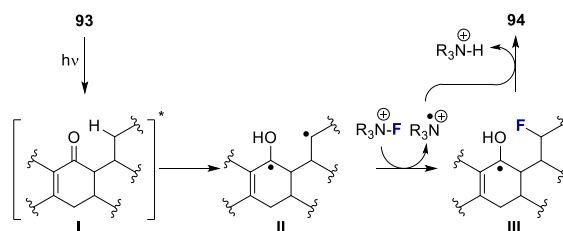
Lectka et al.



Selected examples:

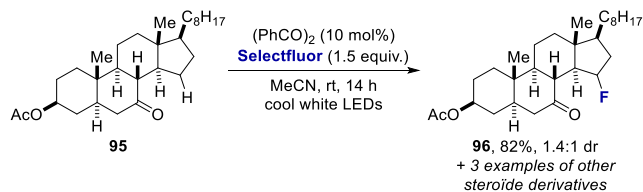


Postulated mechanism:



Scheme 28. Photochemical γ -fluorination of terpenoid derivatives. [a] Reaction conditions: $(\text{PhCO})_2$ (10 mol%), Selectfluor (1.5 equiv.), MeCN, rt, 14 h, cool white LEDs (see reference [51]).

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Scheme 29. Photoredox benzil-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ γ -fluorination of steroidal ketones. $(\text{PhCO})_2 = \text{Benzil}$.

5. Conclusion

In summary, recent advances were made over the last years to address the challenging functionalization of aliphatic derivatives with a fluorinated group at a distal position. Straightforward and original strategies based on a 1,5-HAT or the β -fragmentation of constrained rings were developed with a large panel of fluorinated moieties. The newly-designed tools will definitely have a strong impact on the way to synthesize fluorinated molecules. These recent advances will be inspiring to the scientific community to further develop key synthetic transformations and to reach unprecedented molecular complexity. We do believe that groundbreaking milestones are expected in the up-coming years.

Acknowledgements

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Keywords: radical process • C-H functionalization • remote positions • fluorinated moieties • C(sp³) centers

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