doi:10.2533/chimia.2014.382 Chimia 68 (2014) 382–409

Unique Reactivity of Fluorinated Molecules with Transition Metals

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Abstract: Organofluorine and organometallic chemistry by themselves constitute two potent areas in organic synthesis. Thus, the combination of both offers many chemical possibilities and represents a powerful tool for the design and development of new synthetic methodologies leading to diverse molecular structures in an efficient manner. Given the importance of the selective introduction of fluorine atoms into organic molecules and the effectiveness of transition metals in C–C and C–heteroatom bond formation, this review represents an interesting read for this aim.

Keywords: Catalysis · Copper · Cross coupling · Fluorine · Gold · Metathesis · Pauson–Khand reaction · Silver · Transition metal

1. Introduction

The use of transition metals in organic synthesis has been immense throughout history and it is experiencing continuous development and increasing application. Over the past decades, transition metal-catalyzed/mediated reactions have become one of the most efficient methods for C–C and C–heteroatom bond formation, in particular for the construction of heterocyclic molecules. Indeed, the most important organic reactions, such as Suzuki, Sonogashira, Heck, olefin and alkyne metathesis and so forth, are catalyzed by transition metal complexes. Owing to the ongoing innovation in this area, transition metals have been successfully incorporated in the ever-growing field of organofluorine chemistry with remarkable and often unexpected results.

It is well-known that the selective introduction of fluorine atoms into organic molecules has become one of the most efficient methods for modulation of their biological properties[1] and a common strategy in new drug discovery processes,[2] either by modifying known natural products or by searching for more active drug-like molecules. In this way, the presence of fluorine in drugs has an extraordinary impact on a variety of medical applications, including anti-inflammatory, antibacterial, antitumor and antiviral agents, CNS-modulator compounds, or drugs for lowering blood cholesterol levels such as atorvastatin (Lipitor®), developed by Pfizer and one of the best selling drugs in the world. Furthermore, the use of ^{18}F-radiolabelled compounds employed in Positron Emission Tomography (PET) experiments has exponentially grown in the last few years. Therefore, the important role of the fluorine atom in medicinal chemistry is obvious,[1b,3] and it can be affirmed that fluorine chemistry will contribute significantly to the future progress in medicine.[4]

In this review, we provide an overview of recent advances in the field of fluorine chemistry combined with transition metal catalysis that have been reported in the last five years (Fig. 1). Given the significant number of reviews, which have appeared over the last few years about transition metal-mediated fluorination, difluoromethylation, and trifluoromethylation methods,[1d,5] we have also sought to compile some examples which display a significantly different reactivity of fluorinated molecules than their non-fluorinated analogs.

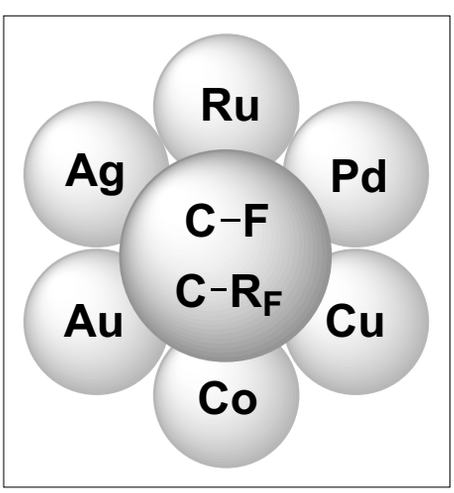

Fig. 1. Fluorine and transition metals.

2. Transition Metal-mediated Reactions

2.1 *Cobalt-mediated Pauson–Khand Reaction*

The Pauson-Khand reaction (PKR) is one of the key methods for the construction of cyclopentenone derivatives, which can in turn undergo diverse chemical transformations.[6] Nevertheless, the control of the regiochemical outcome of the PKR is an important setback. Whereas the intermolecular PKR of terminal alkynes is completely regioselective, always providing α-substituted cyclopentenones, the less frequently used internal nonsymmetric alkynes can afford two regioisomers. That is not the case for fluorinated alkynes, in which the electron-withdrawing effect of the fluorinated substituents determines the regioselectivity (Scheme 1).

In contrast to the intramolecular version, no report on intermolecular PKR of fluorinated alkynes had been described until Riera, Fustero and coworkers reported the first example with norbornadiene in the presence of a stoichiometric amount of dicobalt hexacarbonyl complex [$Co_2(CO)_8$] under standard thermal conditions (Scheme 2).[7]

Surprisingly, in all examples, the fluorinated moiety was α to the carbonyl group, as opposed to the standard selectivity. The authors suggested that the regioselectivity

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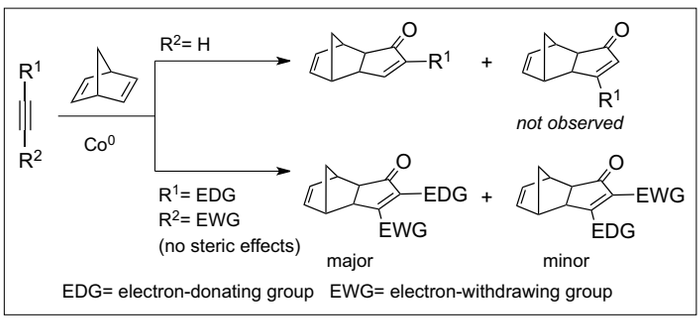
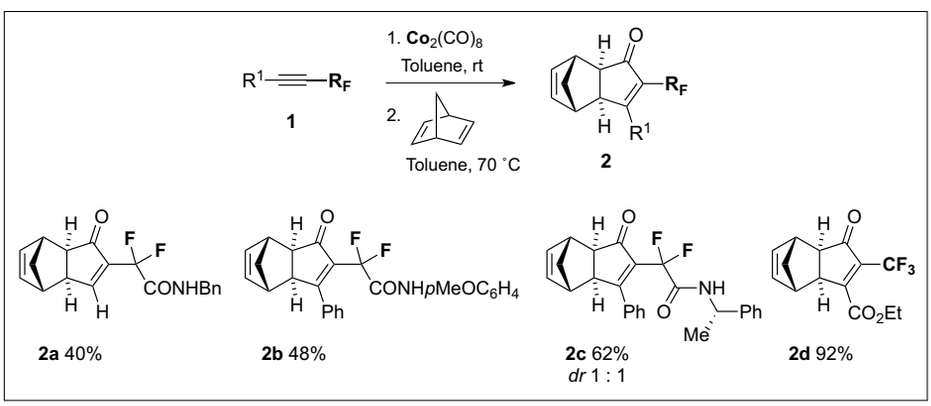
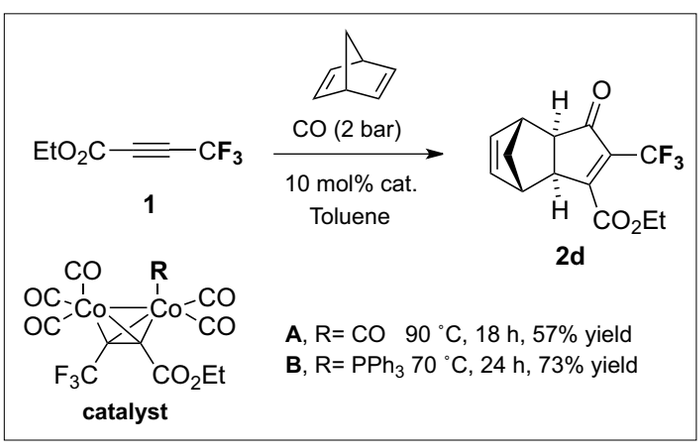


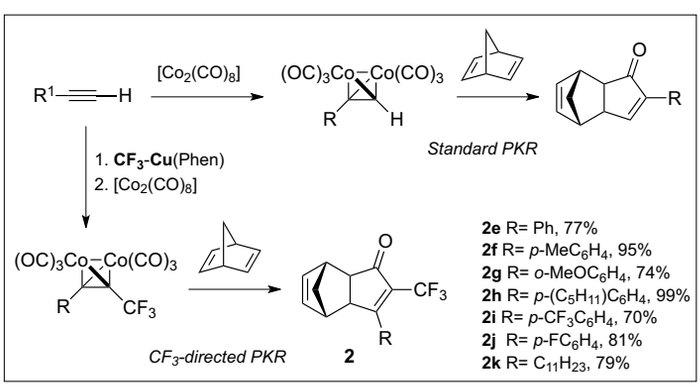
Scheme 1. General trends of the regioselectivity of intermolecular PKR.



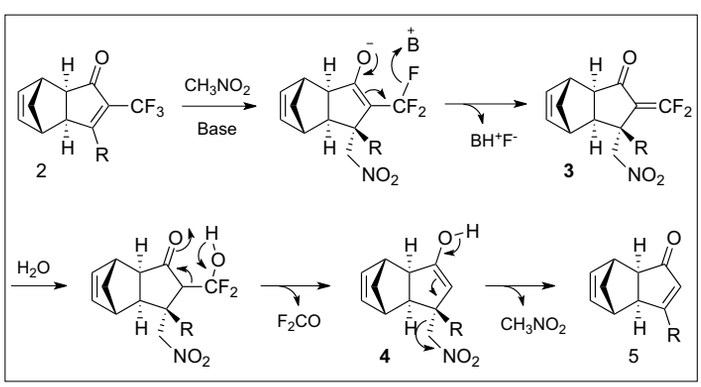
Scheme 2. Intermolecular PKR of fluorinated alkynes.



Scheme 3. Catalytic PKR of **1** with norbornadiene.



Scheme 4. Standard intermolecular PKR for internal alkynes and the sequence for internal CF_3-substituted alkynes.



Scheme 5. Postulated mechanism for the CF_3 elimination.

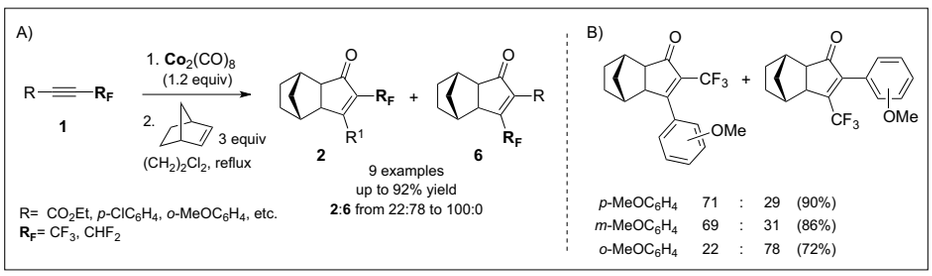
of PK adducts was not determined by electronic but by steric effects mainly. In addition, a catalytic version of this process was also developed successfully by Riera and coworkers, using 10 mol% of the cobalt-alkyne complex formed *in situ* (Scheme 3).

Subsequently, the scope of this process was studied employing a wide variety of internal CF_3-substituted alkynes containing aromatic, aliphatic, and olefinic substituents (Scheme 4). In all cases, the formation of a single regioisomer was observed, bearing a CF_3 group at the α position to the enone.[8]

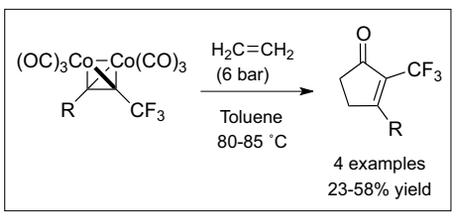
Furthermore, this methodology was extended to the removal of the trifluoromethyl group by treatment with DBU in nitromethane/water, affording the unexpected β-substituted PK adducts (Scheme 5). The mechanism proposed consisted of a Michael addition of nitromethane which would entail a loss of fluoride giving *gem*-difluoroenone **3**. Then, a conjugative addition of water would take place, followed by a retro-aldol reaction, which would afford intermediate **4**. The final cyclopentenone **5** would be formed by retro-Michael reaction on enol **4** (Scheme 5). This method constituted a novel procedure to obtain PK substrates from terminal alkynes with *inverse* regiochemistry employing the trifluoromethyl group as a steering group.

In contrast, Konno *et al*. reported the synthesis of 2-fluoralkyl-2-cyclopentenones *via* Co-mediated PKR of several trifluoromethyl alkynes with 2-norbornene instead of norbornadiene (Scheme 6, part A).[9]

In this process, the regioselectivity was not complete and the PK adducts were obtained as isomeric mixtures, despite applying the same strategy but different reaction conditions. Additionally, the influence of alkyne substitution was studied, supporting the idea that the steric hindrance is a determining factor in the regiochemical outcome of the reaction (Scheme 6, part B). Recently, Riera and coworkers have confirmed these results by expanding their previous work to norbornene and also ethylene (Scheme 7).[10] As Konno *et al*., they obtained mixtures of regioisomers with norbornene under established reaction conditions, identifying α-fluorinated cyclopentenone as the major isomer, whereas the minor one was the regioisomer with the CF_3 at the β-position. Nevertheless, only one PK adduct, α-trifluoromethyl cyclopentenone, was observed when using ethylene as the alkene, although the chemical yields were moderate.

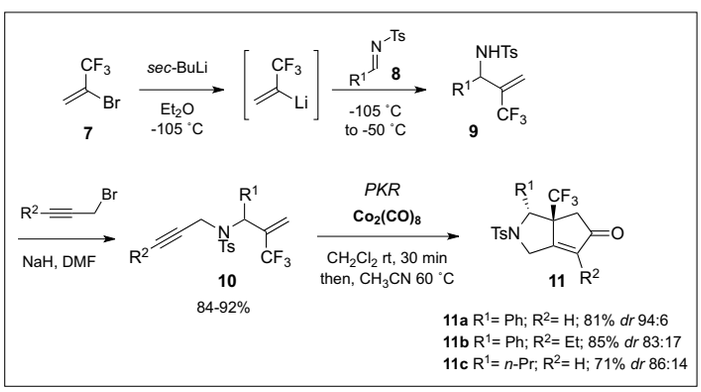


Scheme 6. PKR of CF_3-substituted alkynes **1** with 2-norbornene and influence of alkyne substitution in the regiochemical outcome.

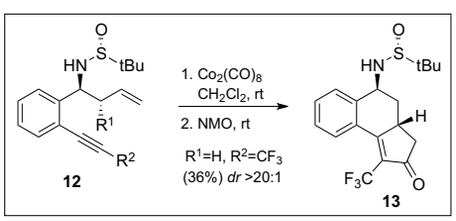


Scheme 7. Intermolecular PKR of **1** with ethylene.

Likewise, only a few examples of the intramolecular PKR of fluorinated enynes have been reported thus far. In this context, Ichikawa and Nadano described an attractive route to synthesize steroid and alkaloid analogs containing fluorine groupings in their structures.[11] In particular, pyrrolidine ring-fused fluorinated cyclopentenone derivatives **11** were synthesized through a



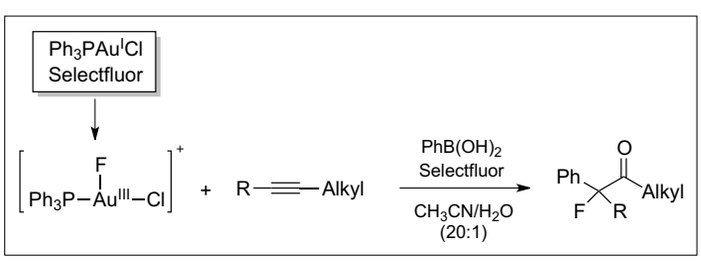
Scheme 8. Co-mediated intramolecular PKR in the synthesis of **11**.



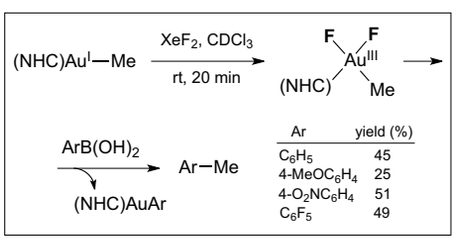
Scheme 9. Intramolecular PKR in the synthesis of tricyclic amines **13**.

Co-mediated intramolecular PKR from *N*-propargyl-*N*-[2-(trifluoromethyl)allyl] amides **10**, which were in turn prepared by a sequence of (trifluoromethyl)vinylation of imines **8**, followed by propargylation of amides **9** (Scheme 8).

More recently, Fustero *et al*. described, for the first time, an intramolecular PKR



Scheme 10. Gold-catalyzed one-pot cascade reaction.



Scheme 11. Au(III)-catalyzed cross-coupling with arylboronic acids.

of a CF_3-alkyne tethered to a chiral aryl-homoallylic sulfonamide skeleton in the asymmetric synthesis of tricyclic amines **13** (Scheme 9).[12] Building on the principles of *diversity-oriented synthesis*, different aryl, alkyl or terminal alkyne derivatives were subjected to this protocol with CF_3-alkyne being of particular interest. Although the isolated yield of the resulting CF_3-PK adduct was moderate (36% yield), diastereoselectivity was excellent (*dr* >20:1).

2.2 *Gold-catalyzed Reactions*

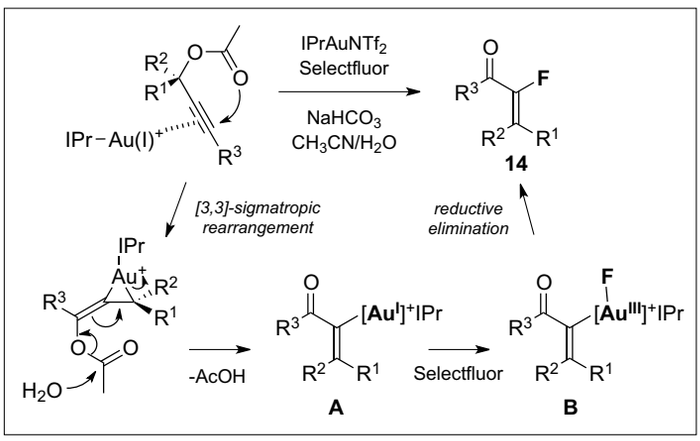
Arguably, gold chemistry attracts sufficient attention by itself owing to the exceptional properties of gold complexes to activate multiple bonds such as alkenes, alkynes, allenes or enynes, and promote surprising transformations in a single synthetic operation. By adding the unique reactivity of fluorinated substrates to this, an Au–F bond results in a great combination which offers many chemical possibilities.

In the last few years, important advances in this chemistry have been made and many reports have appeared in the literature involving the study of the influence of fluorine in gold-catalyzed processes. Based upon the pioneering studies reported by Zhang and others[13] about the evidence for the existence of an Au(I)/Au(III) catalytic cycle, Hammond and coworkers developed a direct route to α-substituted α-fluoroketones from alkynes by a gold-catalyzed one-pot cascade reaction (Scheme 10).[14] Only the combination of the pre-catalyst Ph_3PAuCl and Selectfluor as an external oxidant promoted the formation of the catalytically active gold(III) complex, which was able to trigger a hydration/oxidative arylation/electrophilic fluorination sequence under mild conditions in good yields and moderate regioselectivities.

Thus, Hammond proposed that Selectfluor was in fact the activator of the cationic gold complex. This hypothesis of an oxidation of gold(I) to gold(III) by 'F$^+$' was also supported by the studies of Toste and coworkers.[15] They isolated, for first time, a gold(III) fluoride complex as a dimer which was successfully characterized by X-ray crystallography. The gold(III) fluoride species showed a unique reactivity in cross-coupling reactions with arylboronic acids (Scheme 11).

In this context, a tandem gold-catalyzed process starting from propargyl acetates was reported by Nevado and de Haro.[16] Selectfluor was used again as an oxidant for the synthesis of α-fluoroenones **14** through a tandem [3,3]-sigmatropic rearrangement-fluorination process (Scheme 12). In contrast to previous statements, the cationic gold(I) complex was the catalytically active species which promoted a 1,3-migration of the acyloxy moiety by activation of the alkyne. The resulting vinyl-Au(I) intermediate **A** was then oxidized to gold(III) (**B**) by Selectfluor. Reductive elimination was considered the last step to transform the Csp^2–Au(III) bond into the Csp^2–F bond, giving rise to α-fluoroenone derivatives **14** in good yields.

Nevertheless, Gouverneur and coworkers reported a similar methodology



Scheme 12. Tandem gold-catalyzed [3,3]-sigmatropic rearrangement-fluorination process.

to obtain α-fluoroenones.[17] In this case, the proposed mechanism did not involve a gold-catalyzed electrophilic fluorination step but gold promoted the isomerization of the propargylic ester to give allenyl acetate, which then reacted with Selectfluor (Scheme 13).

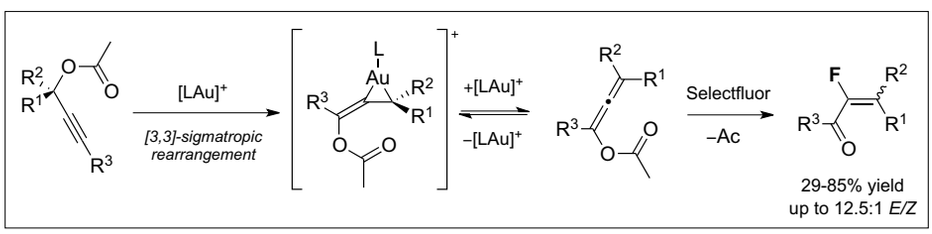
Based upon these observations, Hammond and coworkers employed allenyl carbinol esters **15** in the stereoselective synthesis of fluoroalkyl α,β-unsaturated ketones **17** (Scheme 14).[18] First, isomerization of the allene substrate in the presence of gold produced a diene intermediate (**16**), which quickly reacted with Selectfluor to exclusively give the *E* isomer of the corresponding fluorinated ketone **17** in high yield.

More recently, a gold-catalyzed tandem aminocyclization/electrophilic fluorination sequence has been reported by Arcadi *et al*. for the synthesis of 3,3-difluoro- and 3-fluoroindole derivatives **19** and **20** (Scheme 15).[19] Starting from *o*-alkynyl anilines (**18**) and by using an excess of Selectfluor in EtOH at room temperature, necessarily in the presence of a gold(I) or gold(III) catalyst (*e.g.* $Ph_3PAuNTf_2$, AuCl, $AuCl_3$ or $NaAuCl_4{\cdot}2H_2O$), an assorted library of C(3) difluorinated indoles **19** was prepared in good yields (Scheme 15).

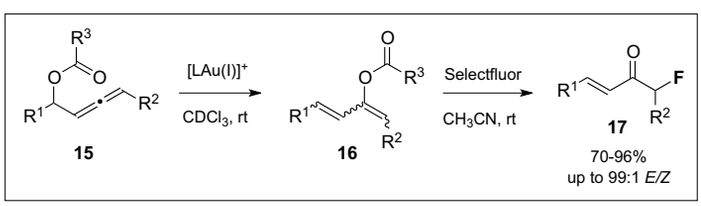
By slightly modifying the reaction conditions, the selective formation of C(3) monofluorinated derivatives **20** was feasible (Scheme 15 and 16). Considering that Selectfluor is able to oxidize gold(I) to gold(III) and the latter also catalyzed the cyclization/fluorination process, two possible mechanism pathways were proposed: the one (a) involving an Au(I)/Au(III) catalytic cycle and a second (b) involving a protodeauration followed by a non-catalyzed fluorination step on the indole intermediate (Scheme 16).

On the other hand, one of the most commonly used methods to generate fluorinated compounds consists of using fluorinated building blocks for assembling the new molecule. The presence of fluorine in these small fragments confers a particular reactivity upon them. Therefore, transition metal-catalyzed reactions involving fluorinated building blocks have gained importance in the last decade, especially gold-catalyzed processes. Among them, gold-catalyzed stereoselective tandem hydroamination-formal aza-Diels-Alder reaction of fluorinated α-substituted propargylic amino esters is a representative example.[20]

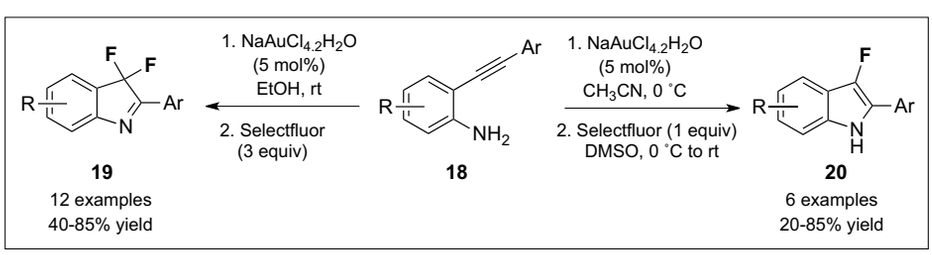
The starting α-amino esters **22** were synthesized by adding propargyl zinc to the corresponding fluorinated imino esters **21** in DMF as solvent under Barbier-type conditions (Scheme 17). The reactivity of **22** was then explored in the presence



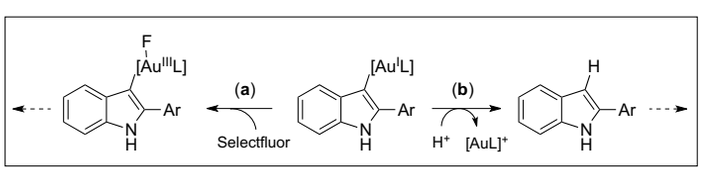
Scheme 13. Alternative proposal for the formation of α-fluoroenones catalyzed by gold.



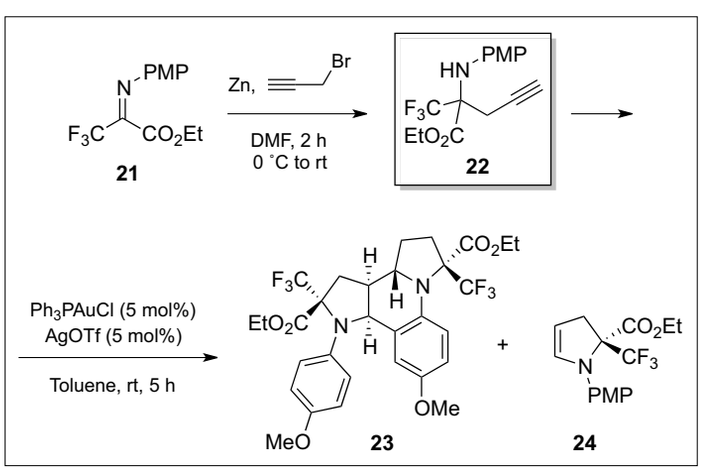
Scheme 14. Gold-catalyzed isomerization-fluorination of allenes **15**.



Scheme 15. Gold-catalyzed tandem aminocyclization/electrophilic fluorination of **18**.



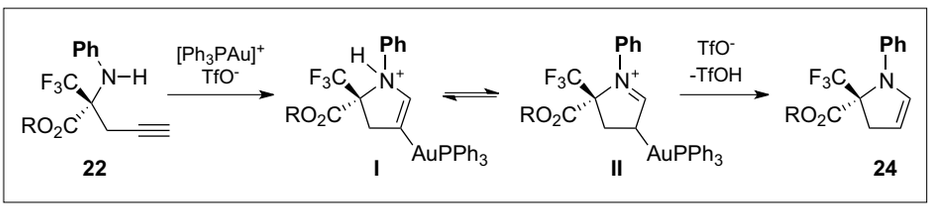
Scheme 16. Proposed mechanism pathways for Au-catalyzed cyclization-fluorination process.



Scheme 17. Gold-catalyzed stereoselective tandem hydroamination-formal aza-Diels-Alder reaction of fluorinated α-substituted propargylic amino esters **22**.

of gold salts. Unexpectedly, the isolated product was identified as a tetracycle **23** whose formation involved four new bonds and five stereocenters, as a single diastereoisomer. A gold(I)-catalyzed intramolecular hydroamination followed by a formal aza-Diels-Alder reaction was the sequence proposed for the final outcome, which was further extended to non-fluorinated substrates.

Moreover, when the aromatic group attached to the nitrogen atom was less activated, the process evolved to the hydroamination product, fluorinated pyrroline **24**, as a major product (Scheme 18).



Scheme 18. Proposed mechanistic explanation.

It is well known that the transition metal-catalyzed intramolecular hydroamination reaction has become one of the most significant methods to access nitrogen-containing heterocycles. In particular, gold complexes have emerged as powerful catalysts for this purpose. As a general rule, most gold-catalyzed hydroaminations lead to the formation of the isoquinoline framework *via* 6-*endo-dig* cyclization, the corresponding 5-*exo-dig* product being unstable.

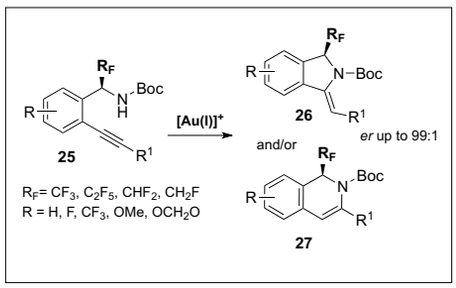
As reported by Fustero and coworkers, the hydroamination of fluorinated *o*-alkynylaryl carbamates **25** catalyzed by a cationic gold(I) complex evolved preferably to the isoindoline skeleton **26**,[21] as opposed to the standard statements (Scheme 19). Moreover, the regioselectivity could be controlled and directed toward one major product by tuning the electronic property of the alkyne moiety.

Also, an electronic effect of the fluorinated group was observed since the gradual introduction of fluorine atoms at the α-position A-F to the nitrogen promoted a 5-*exo-dig* mechanism, leading to isoindoline derivative **26** as the major product, in contrast to the published results with non-fluorinated substrates (Scheme 20). In some cases, 1,2-dihydroisoquinolines **27** arising from a 6-*endo-dig* mechanism were also detected.

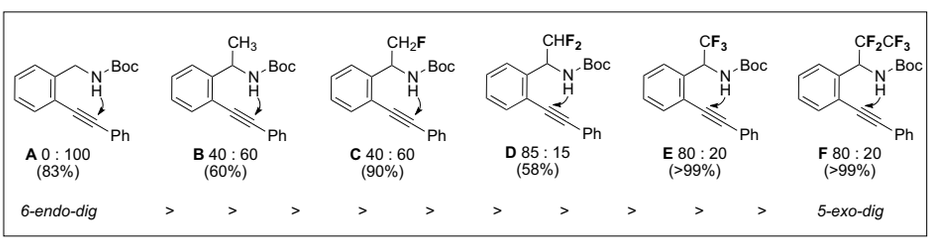
Gouverneur and coworkers reported a *de novo* synthesis of a variety of racemic fluorinated carbohydrates using *syn*-glycal (±)-*cis*-**29** as the key intermediate, which was in turn prepared by a gold-catalyzed cyclization as the key step (Scheme 21).[22] Difluorinated ynone **28** was used as building block for this purpose, which underwent a selective 6-*endo-dig* cyclization in the presence of Gagosz' catalyst ($Ph_3PAuNTf_2$), leading to the desired intermediate in good yield. An in-depth NMR investigation was carried out on the resulting *gem*-difluorinated hexose analogs to study the existence of intramolecular C–F···H–O hydrogen bonds.

2.3 *Palladium-catalyzed Reactions*

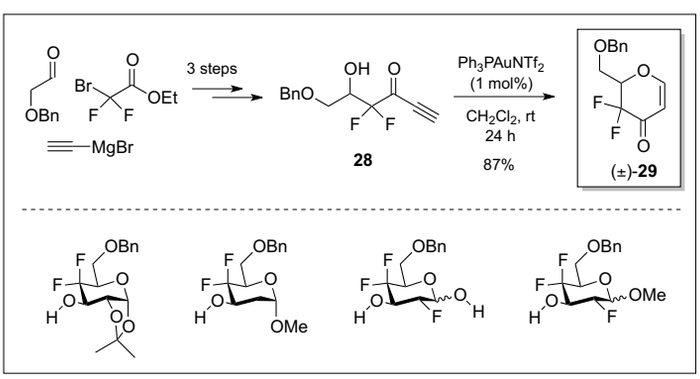
Despite widely-used fluorinated building blocks, new selective fluorination methods are continuously emerging in the literature. Herein, we focus on those catalyzed by palladium, among others. In this sense, the groups of Gouverneur and Brown described a palladium-catalyzed allylic fluorination reaction of properly functionalized substrates under mild conditions (Scheme 22).[23] The allylic leaving group resulted determining to yield 2-substituted propenyl fluorides **31** in high yields, as the traditionally used leaving groups in palla-



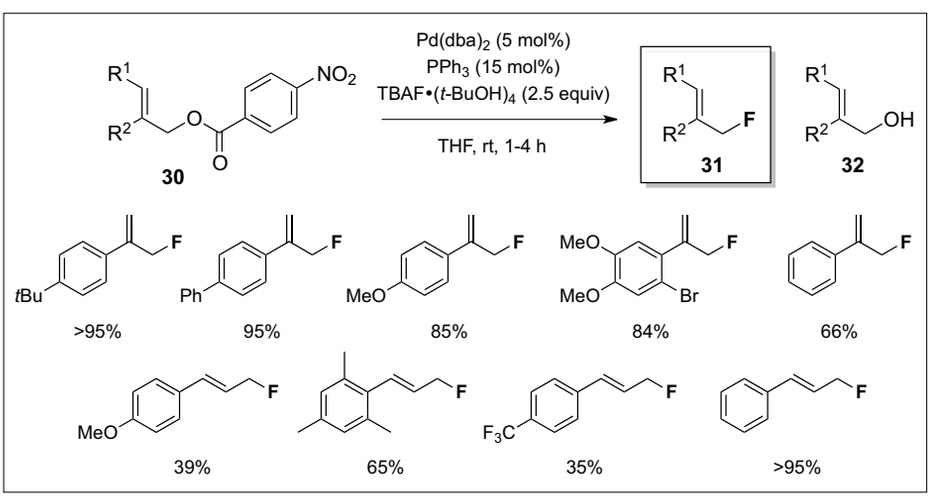
Scheme 19. Gold-catalyzed hydroamination of fluorinated *o*-alkynylaryl carbamates **25**.



Scheme 20. α-Substituent effect on the gold(I)-catalyzed cycloisomerization reaction.



Scheme 21. Preparation of the key intermediate **29** in the synthesis of racemic fluorinated carbohydrates.



Scheme 22. Pd-catalyzed allylic fluorination reaction of **30**.

dium-catalyzed allylic alkylations, such as carbonates or acetates, led to the recovery of the starting material or form the allylic alcohol **32** under the reaction conditions. Thus, *p*-nitrobenzoate was unexpectedly employed as the leaving group of choice. Fluorination was then carried out in the presence of 5 mol% of $Pd(dba)_2$ and 15 mol% of PPh_3 at room temperature, using tetra-*n*-butylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride [TBAF·(*t*-$BuOH)_4$] as a 'F-' source.

This methodology was also applied, for the first time, to the synthesis of [^{18}F]-radiolabeled compounds, which are widely employed in positron emission tomography (PET) experiments, and in oncology, despite their somewhat short half-life. Hence, as a first example of transition metal-mediated ^{18}F-fluorination, a palladium-catalyzed allylic fluorination reaction of propenyl esters **33** was carried out using, in this case, [^{18}F]TBAF as a fluorinating reagent in acetonitrile at room temperature (Scheme 23).

Also, Doyle and coworkers described an asymmetric version, the enantioselective synthesis of cyclic allylic fluorides **35** in just one step from the corresponding allylic chlorides **34** in the presence of a chiral biphosphine-ligated palladium(II) complex with AgF (Scheme 24).[24]

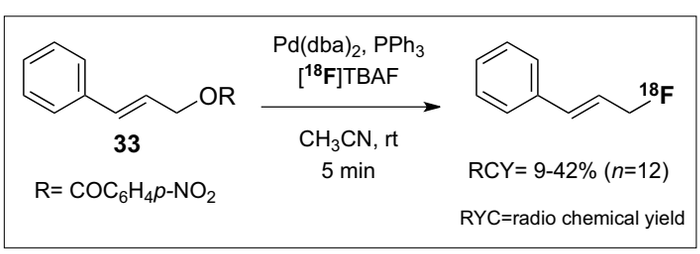
Experimental results supported a distinct mechanism for the C–F bond formation based on a S_N2-type nucleophilic attack of fluoride on a Pd(II) π-allyl intermediate with an overall retention of the configuration (Scheme 25).

Its wide substrate scope, including silyl ethers and alcohols, makes this method very useful to prepare allylic fluorides with excellent enantioselectivities, having become an essential alternative to the dehydroxyfluorination with (diethylamino) sulfur trifluoride (DAST).

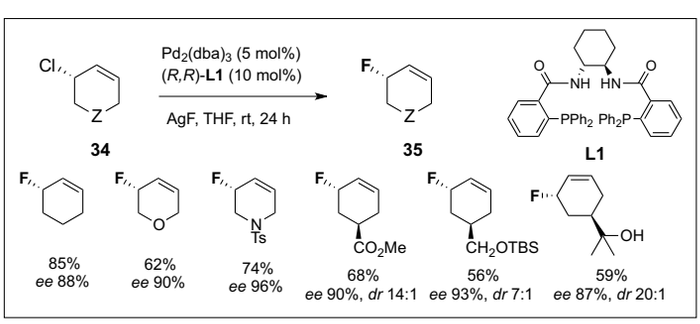
Later on, Doyle *et al*. extended this protocol to branched acyclic systems, developing a highly regio- and enantioselective synthesis of branched allylic fluorides **37** from allyl chlorides **36** and using **L2** as chiral ligand (Scheme 26).[25] As stated before, a Pd(II) π-allyl intermediate was involved in the catalytic cycle based on a nucleophilic attack of fluoride on this system.

Despite the tolerance with many functional groups, low enantioselectivities (*ee* 21–71%) were observed for those less sterically hindered and no fluorination reaction occurred with secondary alkyl amines. By contrast, α-branched allylic chlorides and bromides generated the corresponding fluorides with excellent regio- and enantioselectivity. Additionally, in the context of *diversity-oriented synthesis*, several transformations were carried out on the allylic fluoride **37** achieving access to a variety of optically pure fluorinated molecules whose synthesis would be unfeasible or comprise several steps (Scheme 27).

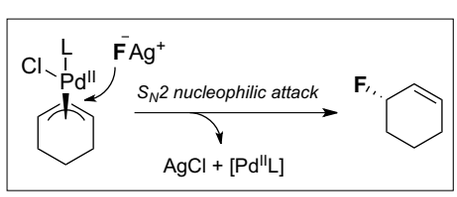
Thus far, several examples of fluorination reactions requiring a prefunctionalization of the substrate have been displayed. Nevertheless, the direct functionalization of C–H bonds has recently emerged as a powerful tool in organic synthesis.[26] Synthetic methods for assembling C–F bonds under mild conditions, even more so, at the final stage of the synthetic route, are of particular value. While C–H fluorinations using electrophilic fluorinating reagents have been slightly more explored, those using nucleophilic fluoride are scarce. In this sense, Sanford and coworkers described a palladium-catalyzed benzylic fluorination reaction by C–H bond activation of 8-methylquinoline derivatives **38** to obtain **39** in moderate to good yields (Scheme 28).[27]



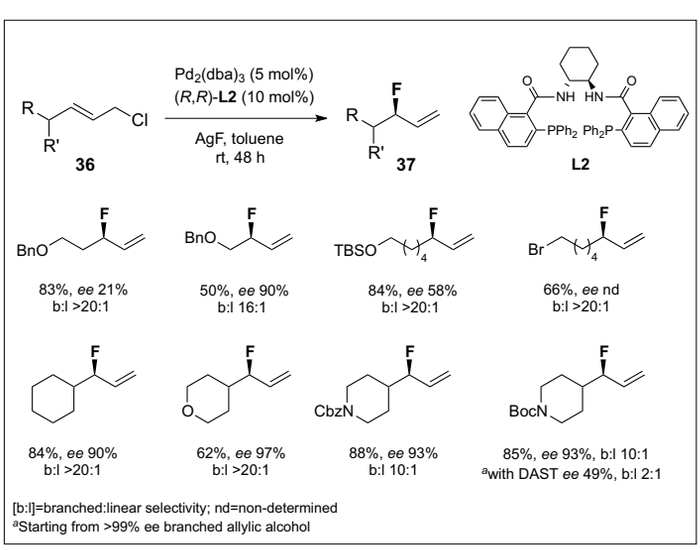
Scheme 23. Pd-catalyzed allylic fluorination reaction of **33** by using [^{18}F]TBAF.



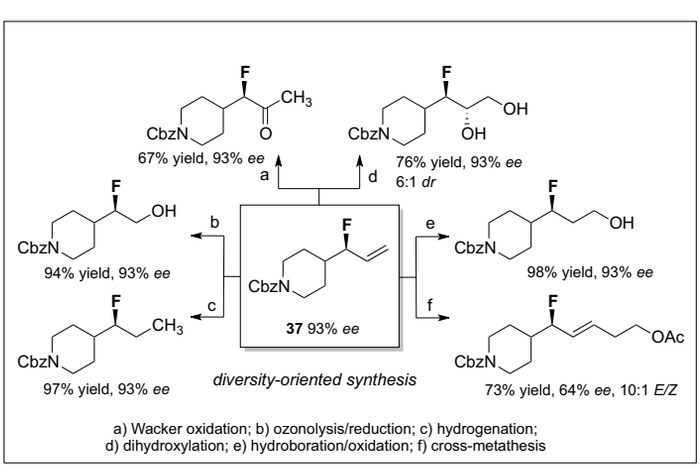
Scheme 24. Enantioselective synthesis of cyclic allylic fluorides **35**.



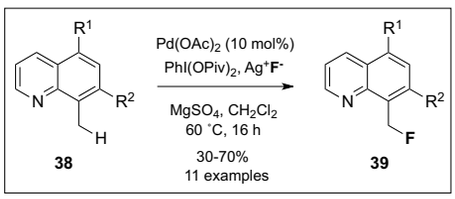
Scheme 25. Proposed mechanistic explanation.



Scheme 26. Selective synthesis of branched allylic fluorides **37**.



Scheme 27. Access to optically pure fluorinated molecules from allylic fluoride **37**.



Scheme 28. Pd-catalyzed benzylic fluorination by C–H bond activation of **38**.

In general, fluorination took place in the presence of different substituents including halogens (*e.g.* Br, F or I), although chemical yields were not as good as desirable owing to the C–H oxygenation side reaction. Sanford proposed an F–Pd(IV) complex as the key intermediate in the catalytic process but, neither the role of Ag^+ ion, whose presence was a requisite, nor the identity of the active fluorinating reagent could be elucidated.

In this context, Doyle *et al*. developed distinct reaction conditions for their palladium-catalyzed allylic C–H fluorination using a Pd(II)-sulfoxide complex as catalyst, $Et_3N{\cdot}3HF$ as fluoride source and benzoquinone (BQ) as an external oxidant.[28] The conversion of the allylic substrate **40** into **41** was markedly improved when a Cr(salen)Cl complex was used as catalytic additive. It should be noted that the addition of the fluorine atom was highly chemoselective for allylic position over other sensitive positions such as the propargylic or benzylic ones (Scheme 29).

Moreover, the authors applied this methodology to transform a polyfunctionalized steroid into its fluorinated analog, providing the desired molecule in good yield and regioselectivity (Scheme 30).

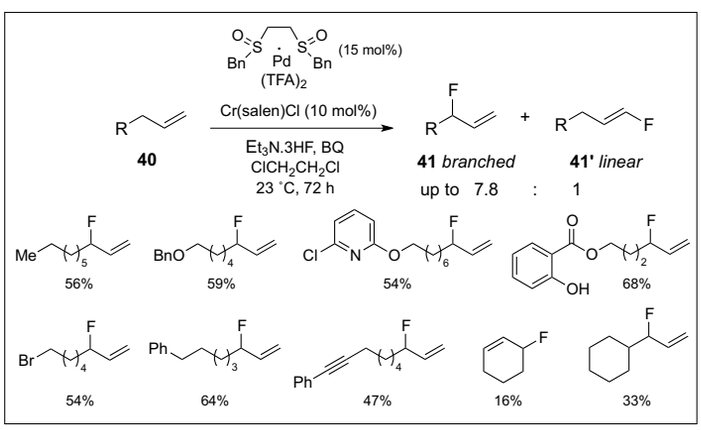
This process highlights the ready access to a wide range of fluorinated derivatives, for instance, from natural products, in a single operation under mild conditions without anhydrous requirements.

In the context of C–H activation, the recent work by Grushin and Takemoto on the selective H–CF_3 activation with palladium in the presence of a phosphine-based ligand should be mentioned (Scheme 31).[29] Apparently, the phosphine ligand played an important role in the process as a Lewis base promoter as it seems that it cleaved the H–CF_3 bond to provide the Pd–CF_3 complex **42** which could participate further in aromatic trifluoromethylations.

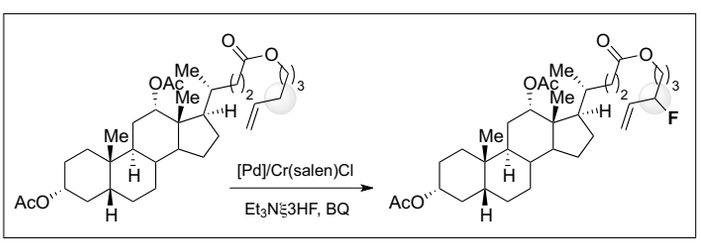
In the field of arene fluorination, Ritter and coworkers have recently reported a similar reaction with aryl trifluoroborates catalyzed by an air- and moisture-stable terpyridyl palladium(II) complex (Scheme 32).[30] This metal complex acted as a precatalyst since a rare palladium(III) species, which was further isolated and characterized by X-ray analysis, was in fact the catalyst in the fluorination reaction.

The trifluoroborates **43** could also be prepared *in situ* from arylboronic acid derivatives **43'** by treatment with NaF and KHF_2, giving the corresponding aryl fluorides **44** in excellent yields (Scheme 33). The mild reaction conditions used in this case were well tolerated by a wide range of functionalized aryl substrates apart from heterocycles. Furthermore, arene fluorination was highly regioselective, except for those compounds containing electron-withdrawing groups (*e.g.* amide), which gave constitutional isomers. The authors proposed a *single-electron-transfer* (SET) pathway as a plausible mechanism, involving a Pd(III) intermediate and radical species.

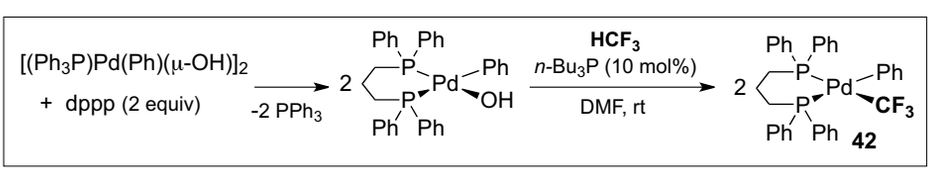
In line with this issue, a Pd-catalyzed difluoroalkylation of aryl boronic acids **45** has been reported very recently by Zhang and coworkers.[31] To attach the difluoromethylene group (CF_2) to the arene ring, they employed readily available bromodifluoromethylated phosphonate, acetate and amides as fluorinated building blocks (Scheme 34).



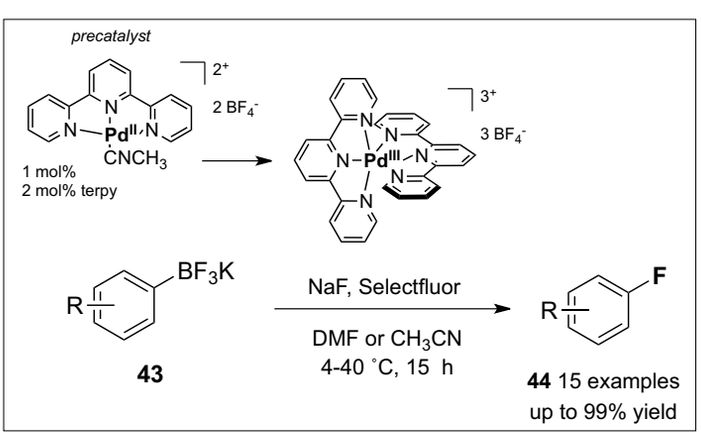
Scheme 29. Pd-catalyzed allylic C–H fluorination.



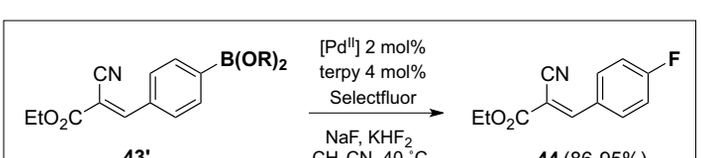
Scheme 30. Direct allylic fluorination of steroid derivatives.



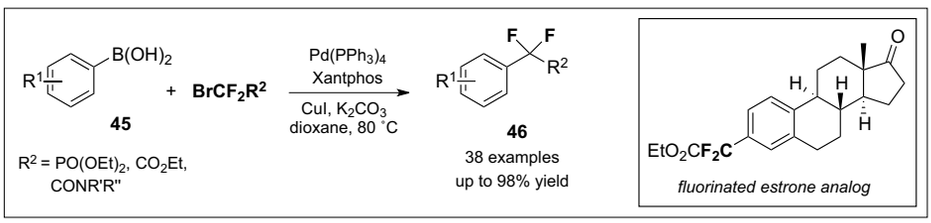
Scheme 31. Selective H–CF_3 activation by palladium.



Scheme 32. Catalytic fluorination of aryl trifluoroborates.

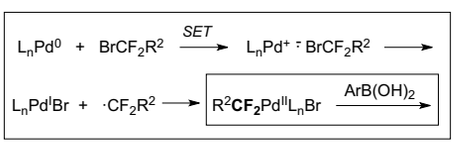


Scheme 33. Fluorination of trifluoroborates prepared *in situ* from arylboronic acid **43'**.



Scheme 34. Pd-catalyzed difluoroalkylation of aryl boronic acids **45**.

Interestingly, only the Xantphos-Pd complex formed in the reaction media catalyzed the process efficiently, providing aryldifluoromethyl derivatives **46** in good to excellent yields. Moreover, this approach has been successfully applied to the late-stage synthesis of interesting bioactive compounds for drug discovery (Scheme 34). Although the mechanism has not been elucidated so far, the authors proposed the formation of difluoromethylene radicals through a Pd-promoted SET pathway as the initial step. This radical species would react with $L_nPd(I)Br$ generated *in situ* to provide the active catalyst which would be involved in the subsequent cross-coupling reaction (Scheme 35).



Scheme 35. Proposed radical-based mechanism.

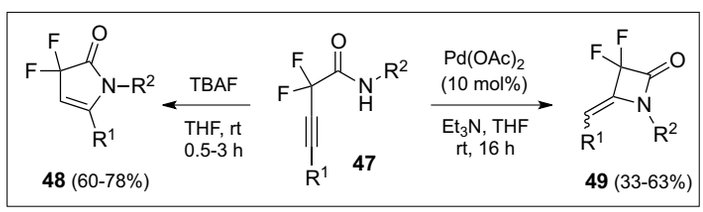
Leaving aside fluorination reactions, fluorine-containing compounds behave in a particular manner in the presence of palladium. That is the case of difluoropropargyl amides **47** synthesized for the first time by Hammond and coworkers[32] and further used in the synthesis of difluoro β- and γ-lactams by Fustero and coworkers.[33] These small heterocycles constitute attractive scaffolds in total synthesis as well as new molecular entities in drug discovery. As mentioned before, Fustero, Hammond *et al*. reported a regioselective synthesis of four- and five-membered ring lactams *via* an intramolecular hydroamination reaction of difluoroamides **47** (Scheme 36).

The formation of γ-lactam **48** could be explained by a base-promoted nucleophilic addition of the amidic nitrogen to the electron-deficient triple bond in the presence of TBAF. In contrast, the formation of β-lactam **49** was observed in the presence of palladium acetate and Et_3N favoring a 4-*exo-dig* over 5-*endo-dig* mechanism as a result of the *gem*-difluoro moiety (Scheme 37).

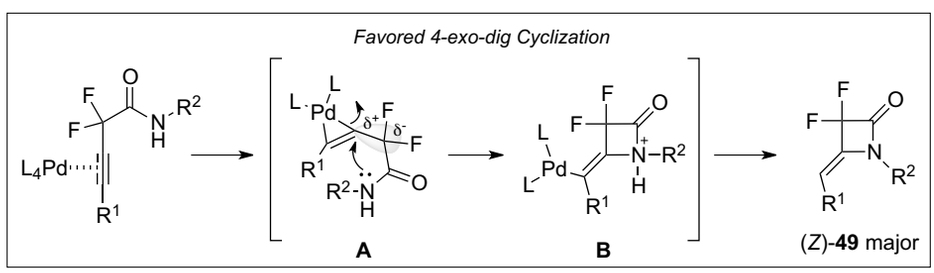
Given the high number of methods for selective fluorination recently reported in the literature,[5] the use of the resulting fluorides as appropriate substrates in subsequent transformations would be very interesting from a synthetic point of view. In this sense, Gouverneur and Brown explored the reactivity of benzylic fluorides **50** in palladium-catalyzed substitution and cross-coupling reactions in detail.[34] In that paper, the ability of fluoride as leaving group was disclosed even in the presence of other leaving groups such as acetate or carbonate. Based on their previous mechanistic experiments with allylic fluorides,[35] Gouverneur and coworkers established suitable conditions for a palladium(0)-catalyzed nucleophilic substitution of bicyclic and monocyclic fluorides **50**, compatible with different nucleophiles to obtain **51**. The selective benzylic fluoride displacement over other functional groups tethered to the molecule is particularly noteworthy (Scheme 38).

Furthermore, the authors adapted the previous reaction conditions to Suzuki–Miyaura cross-coupling of selected benzylic fluorides with phenylboronic acid. In that case, the regioselectivity of the process could be controlled by employing an appropriate phosphine ligand (Scheme 39).

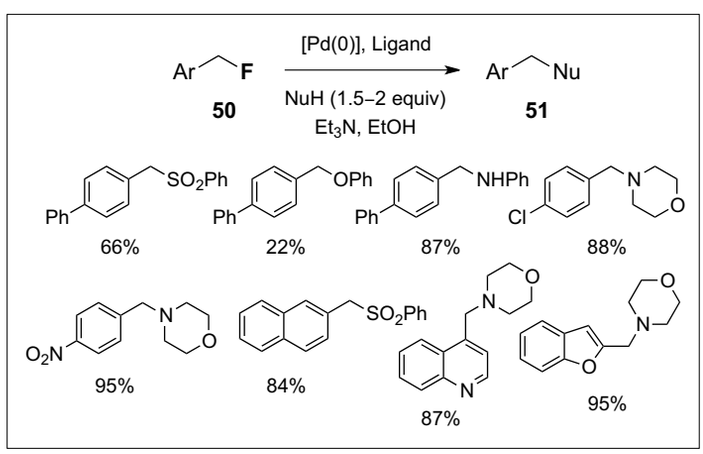
It is well-known that the inclusion of fluorinated fragments, such as the trifluoromethyl group, in organic molecules has contributed significantly to the development of new pharmaceuticals.[36] In this respect, the Ruppert–Prakash reagent ($TMSCF_3$) and its difluoromethyl variant ($TMSCF_2H$), as 'CF_3' and 'CF_2H' anion source respectively, have led to a substan-



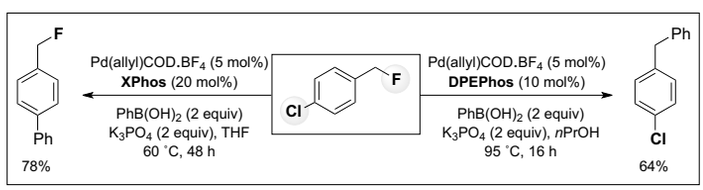
Scheme 36. Intramolecular hydroamination reaction of difluoroamides **47**.



Scheme 37. Formation of four-membered ring lactam **49**.

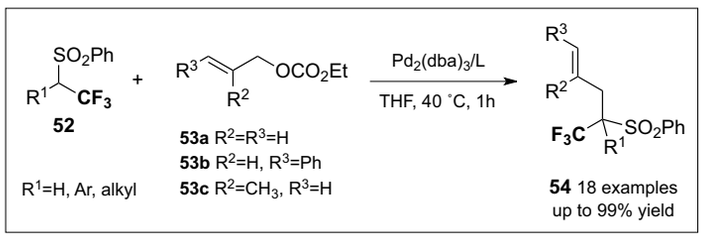


Scheme 38. Pd-catalyzed nucleophilic substitution of benzylic fluorides.



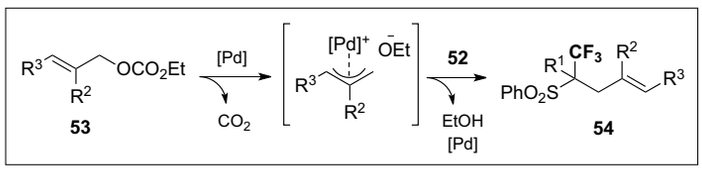
Scheme 39. Suzuki–Miyaura cross-coupling of benzylic fluorides with phenylboronic acid.

tial improvement in organic synthesis. However, the efficient incorporation of the trifluoroethyl moiety 'CF_3CH_2' had remained a challenge until recently. In 2012, Shibata and coworkers employed trifluoroethyl phenyl sulfones **52** and allyl carbonates **53** to provide trifluorohomoallylic sulfones **54** in excellent yields under mild conditions (Scheme 40).[37]



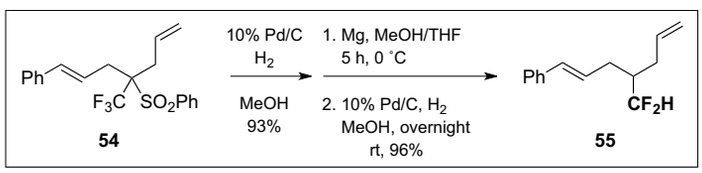
Scheme 40. Allylation of trifluoroethyl sulfones **52**.

This approach constitutes an advantage over typical base-mediated allylation and involved a Pd(0)-catalyzed decarboxylative allylation of **52** *via* a cationic π-allyl palladium complex intermediate. The ethoxy anion resulting from decarboxylation of allyl carbonate acts as a base deprotonating sulfone **52** and reacts further with the π-allyl palladium complex, regenerating the catalyst and leading to the desired product **54** (Scheme 41).



Scheme 41. Proposed mechanism of Pd-catalyzed decarboxylative allylation.

Furthermore, Shibata and coworkers explored the utility of these products which gave rise to the corresponding difluoromethyl derivatives **55** in high yields when they were subjected to reductive desulfonylation reaction (Scheme 42).



Scheme 42. Reductive desulfonylation reaction.

The difluoromethylene 'CF_2' grouping is also an interesting structural moiety as it confers particular biological properties to organic molecules.[38] Generally, the conversion of the carbonyl group with DAST or deoxofluor has been the method of choice to introduce the difluoromethylene group into organic molecules. However, a drawback of this method is its incompatibility with many functional groups. As an alternative, *gem*-difluoroallylation of boron-containing compounds **56** such as aryl and vinyl boronic acids, borates and trifluoroborates salts, has been described recently by Zhang and coworkers, involving a cross-coupling reaction catalyzed by palladium (Scheme 43).[39] A simple protocol, wide functional group compatibility, very low catalyst loading (0.4–0.01 mol%) and high regioselectivity (α/γ up to >37:1) are the advantages of this process.

2.4 *Silver-catalyzed Reactions*

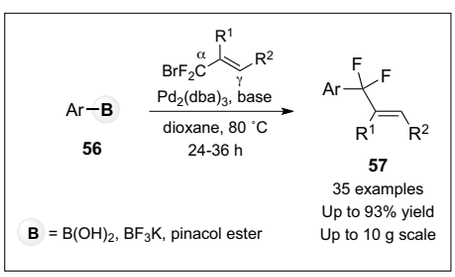
Although silver has been known since antiquity, its use had mainly been limited to ornament manufacture and minting, in spite of its outstanding electrical conductivity and unique redox chemistry. However, owing to its ability to act as both π and σ Lewis acid, as well as the availability of its f orbitals, utilization of silver(I) in organic synthesis has gained significant popularity in the past several years.[40a–e]

2.4.1 *Csp²–F Bonds*

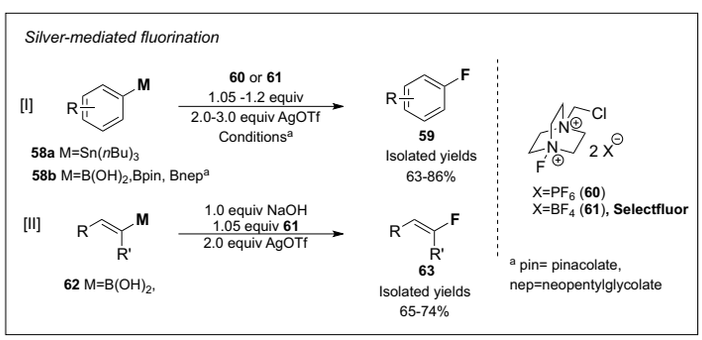
Due in part to their unique physicochemical and biological properties, aryl fluorides have found increased applications in fields of pharmaceutical, agrochemical and material sciences.[41] The direct formation of C(Ar)–F bonds has remained an important challenge for chemists and new and mild methods for direct incorporation of fluorine allowing a broader functional group tolerance are still ardently sought-after.

In recent years silver-mediated/catalyzed transformations have emerged as powerful tools for the construction of such an important functionality. As outlined by Ritter and coworkers,[42] aryl fluorides **59** can be prepared in good yields starting from functionalized aryl tri-*n*-butyl stannanes **58a** and the fluorinating reagent F-TEDA-PF_6 (**60**), a derivative of Selectfluor. The authors later expanded their methodology to the less toxic arylboronic acids **58b**[42b] with complete suppression of the difficult-to-separate proto-demetalated product obtained with the use of aryl stannanes. In the presence of a base, aryl boronic acids and esters were shown to transmetalate to silver in a methanolic solution; subsequent reaction with Selectfluor (**61**) in acetone afforded aryl fluorides **59** in a one-pot fashion in good yields (Scheme 44, part I). Unlike the metal-free fluorination of alkenylboronic acids and trifluoroborates,[43] which usually gives a 1:1 ratio of *E/Z* isomers,[44] transmetalation from boron **62** to silver occurs in a stereospecific way, thus providing complete control of the stereochemistry in the preparation of vinyl fluorides **63** (Scheme 44, part II).

Following the initial discovery of silver-mediated fluorinations, a catalytic fluorination of aryl stanannes **58a** was developed.[42c] Unproductive protodestannylation products were suppressed by addition of $NaHCO_3$ (2 equiv) and NaOTf (1 equiv), thereby making the use of 5 mol% of Ag_2O and 1.5 equiv of **60** possible (Scheme 45, part A). Mechanistic investigations suggested a Ag(I)-Ag(II) redox cycle. Oxidation of a species (ArAg)$^+$(AgOTf) with reagent **60** led to a bimetallic Ag(II) intermediate which is responsible for the carbon–fluorine bond formation,



Scheme 43. *gem*-Difluoroallylation of boron derivatives **56**.

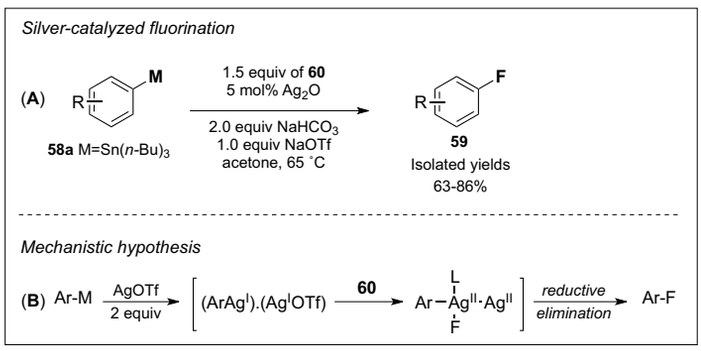


Scheme 44. Silver-mediated fluorination of aryl nucleophiles and vinylboronic acids.

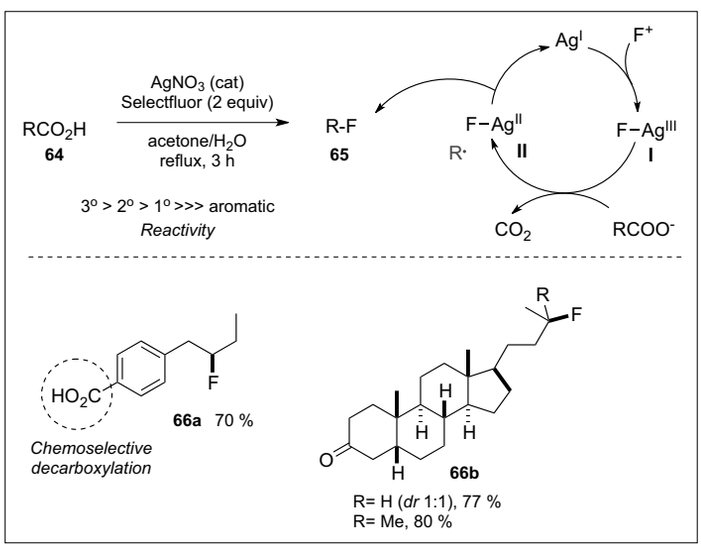
a mechanism that differs from traditional cross-coupling mechanisms with other transition metals (Scheme 45, part B). Hitherto, silver-catalyzed fluorinations of boron nucleophiles have not been reported.

2.4.2 *Csp³–F bonds*

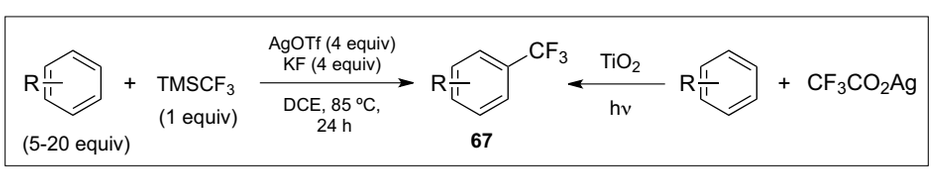
A substantial achievement in the construction of C*sp³*–F bonds not restricted to the synthesis of α-fluoro carbonyl compounds,[45] was reported by Li and coworkers in 2012.[46] Catalytic amounts of $AgNO_3$ were shown to promote decarboxylative fluorination of aliphatic carboxylic acids **64** by Selectfluor (Scheme 46). It was suggested, that an Ag(III)–F species I formed *in situ* from F^+ and the Ag(I) catalyst was reduced to an Ag(II)–F species II after a SET by a carboxylate anion, thus releasing CO_2 and the alkyl radical $R^{\cdot}$, which was later trapped by the Ag(II)–F species, regenerating the Ag(I) catalyst and forming the alkyl fluoride **65**, thus closing the catalytic cycle. A metal-free radical decarboxylative fluorination had been known from the corresponding *t*-Bu peresters by NFSI,[47] but the required extra step for their preparation was avoided in Li's protocol. Furthermore, the method made site-selective C*sp³*–F bond formation in aqueous media and with excellent chemoselectivity towards aliphatic carboxylic acids possible. Under these conditions, the reactivity of the substrates was in the order of 3°>2°>1°, while aromatic carboxylic acids were inert, thus, allowing the preparation of substrate **66a** in good yield. The authors demonstrated the scope of the process in the preparation of two biologically relevant fluorinated steroids **66b** (Scheme 46).



Scheme 45. Silver-catalyzed fluorination of aryl stannanes and mechanistic hypothesis.



Scheme 46. Decarboxylative fluorination of aliphatic carboxylic acids.



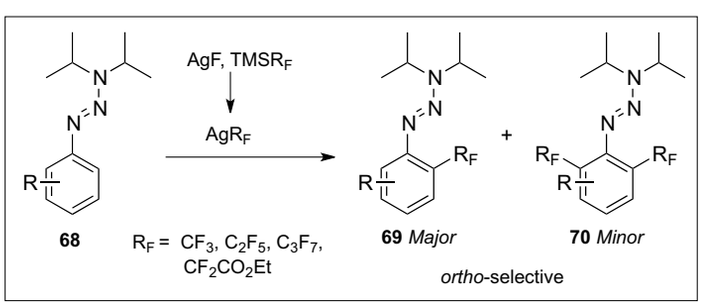
Scheme 47. C–H trifluoromethylation of arenes.

2.4.3 *Synthesis of CF_3-(Hetero)aromatic Compounds*

Direct C–H trifluoromethylation of aromatics can be achieved by means of a reaction of arenes and heteroarenes with silver trifluoroacetate[48] in the presence of TiO_2 as a photocatalyst. In this transformation, the photochemical decarboxylation of CF_3CO_2Ag on the surface of excited TiO_2 generated $^{\cdot}CF_3$ radicals, which underwent radical addition to the aromatic substrates, thus affording trifluoromethyl aromatics **67** as a mixture of regioisomers (Scheme 47).

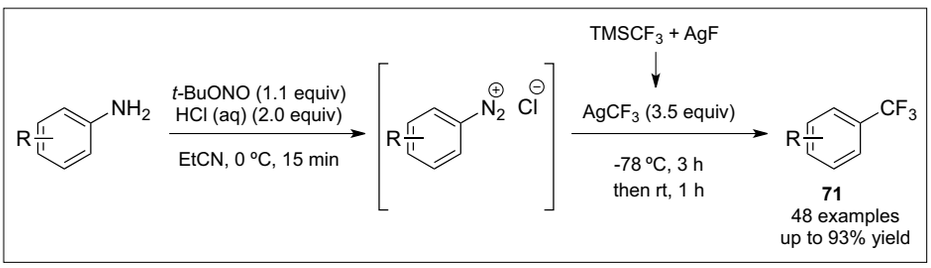
A silver-mediated direct C–H trifluoromethylation has also been accomplished by means of a AgOTf/$TMSCF_3$/KF system. In this fashion, Sandford and coworkers[49] were able to afford trifluoromethylated products by using an excess (20 equiv) of the arene, 4 equiv of AgOTf, 4 equiv of KF and $TMSCF_3$ (1 equiv) (Scheme 47). Noticeably, iodobenzene afforded a non-*ipso*-substituted product, thus contrasting with the Cu-catalyzed/mediated procedures (*vide infra*). Moreover, the fact that regioisomers were obtained and that the reaction was suppressed in the presence of TEMPO, lent further support to the intermediacy of a $^{\cdot}CF_3$ radical, possibly from $AgCF_3$.

Very recently, Bräse and coworkers[50] disclosed a procedure for the *ortho*-selective C–H functionalization of aromatics. By means of a triazene-directing group **68**, they were able to achieve direct trifluoromethylation, perfluoroethylations, heptafluoropropylation and ethoxycarbonyldifluoromethylation of aromatics **69**. In this transformation, the AgR_F species was generated *in situ* from TMS-R_F and AgF using perfluorohexane as solvent. Notably, other donor solvents commonly used in trifluoromethylations such as DMF led to a number of by-products and/or decreased yields. In some cases, the di-*ortho* R_F-substituted products **70** where observed, albeit in lower yields. Salient features of this process include: a remarkably high site-selectivity towards *ortho*-trifluoromethylated products as well as the possibility to further transform the triazene moiety, thus making this a highly attractive method for direct C–H trifluoromethylation (Scheme 48).

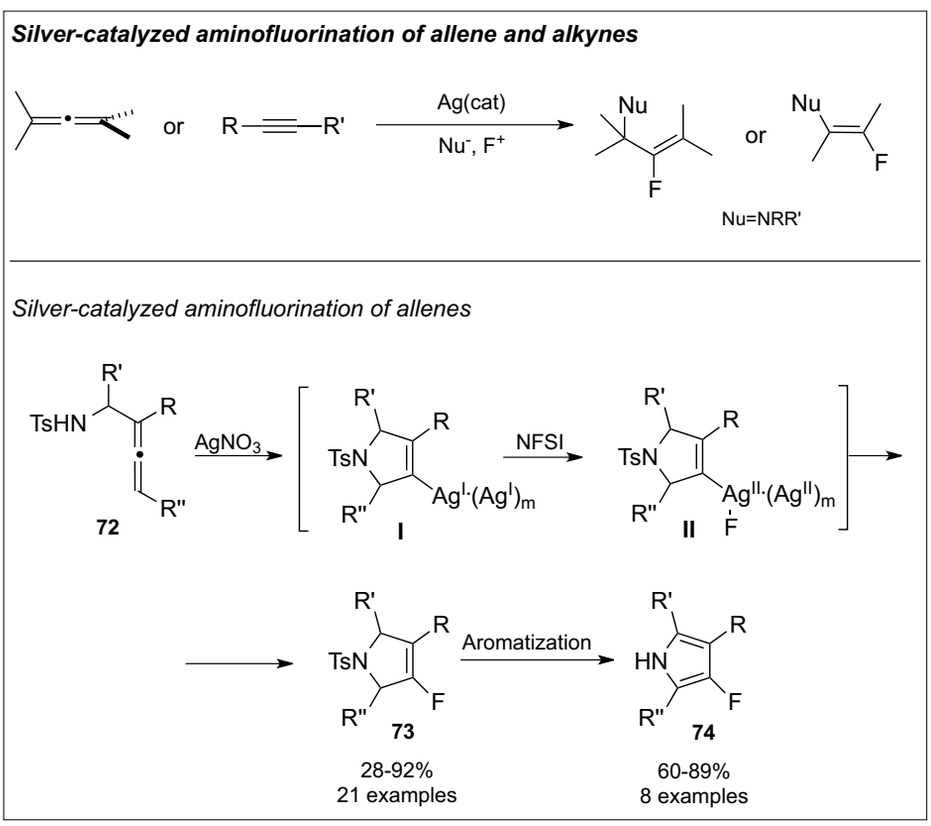


Scheme 48. Triazene-directed *ortho*-trifluoromethylation of aromatics.

A novel approach for the synthesis of benzotrifluorides **71** was recently introduced by Wang and coworkers.[51] Starting from $AgCF_3$ and readily available aromatic amines, trifluoromethyl arenes were obtained after the one-pot diazotization reaction with the *t*-BuONO/HCl(aq) system. After the generation of the corresponding diazonium chloride in an EtCN solution, 3.5 equiv of previously prepared $AgCF_3$ were added at low temperature (–78 ºC). Interestingly, the more stable and isolable tetrafluoroborate salts were less reactive under their optimized reaction conditions. This transformation tolerates a variety of functional groups, from electron-donor, electron-withdrawing, alkynyl, vinyl and even to boron pinacolates (Scheme 49). Furthermore, a number of benzofurans and indoles were smoothly converted into the corresponding CF_3-substituted products. However, 3-aminopyridine afforded only a 10% yield. Notably, *ortho*-substituted starting materials were also suitable substrates, thus, the corresponding products were obtained in high yields. Similar reports that use the $CuCF_3$ species have recently emerged (*vide infra*).



Scheme 49. Sandmeyer-type trifluoromethylation with $AgCF_3$.



Scheme 50. Silver-catalyzed synthesis of pyrrol derivatives.

2.4.4 *Electrophilic/Radical Fluorination/Fluoroalkylation of C–C Multiple Bonds*

2.4.4.1 *Reactions with Allenes and Alkynes*

In recent years, transition metal-catalyzed cyclization reactions have gained popularity for the fast and efficient synthesis of a number of biologically relevant heterocycles[40b] starting from readily available starting materials.[52]

In a series of reports, Liu's group[53] disclosed a novel tandem approach for the synthesis of fluorine-containing heterocycles. With the use of 20 mol% $AgNO_3$ and the electrophilic fluorinating reagent *N*-fluoro-bis(benzenesulfonyl) amine (NFSI), fluorinated dihydropyrroles **73** (Scheme 50), and isoquinolines **76** (Scheme 51) were assembled, starting from *N*-tosyl-protected allenes **72** and *N*-substituted-*o*-alkynyl benzaldimines **75**, respectively.

Intramolecular aminofluorination of the starting materials led to vinyl-Ag intermediate **I**, which was further oxidized by NFSI to afford the bimetallic Ag(II) fluoride intermediate **II** and a vinyl fluoride upon reductive elimination of the C–F fragment. The obtained dihydropyrroles **73** were successfully aromatized to afford the fluoro-pyrrol derivatives **74** in good yields (Scheme 50).

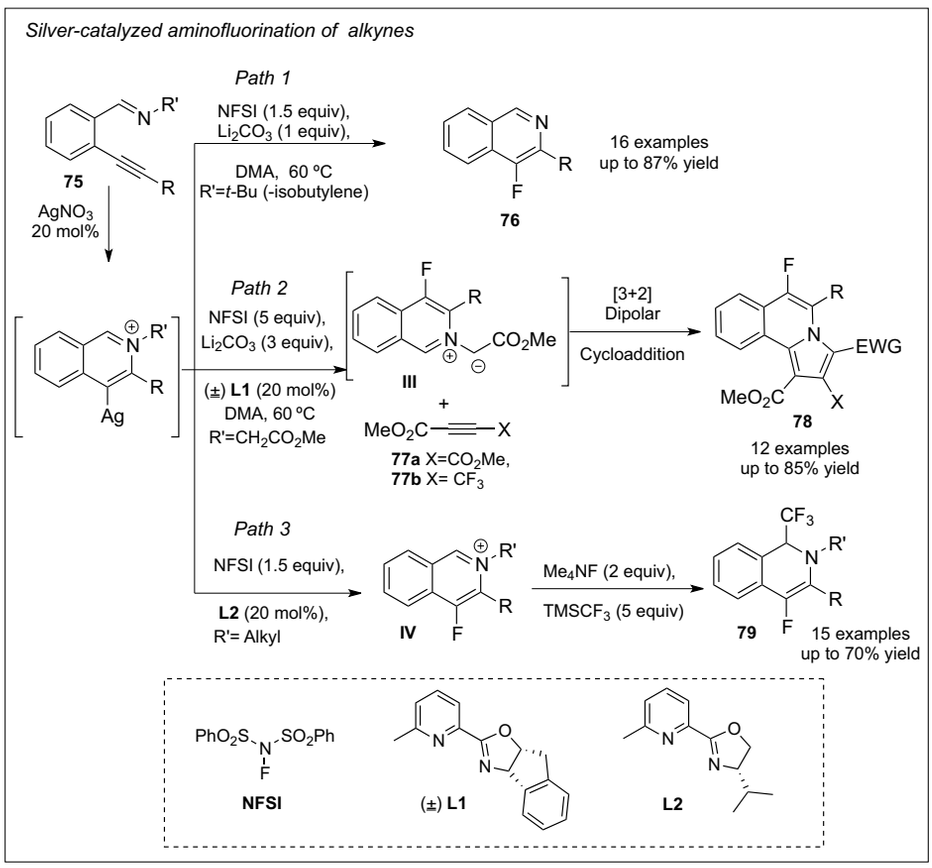
Fluorinated isoquinolines **76** were readily obtained from the aminofluorination of *N*-*t*-Bu-*o*-alkynyl benzaldimines **75** with 1.5 equiv of NFSI with concomitant elimination of isobutylene (Scheme 51, path 1). In the presence of 3 equiv of Li_2CO_3, 5 equiv of NFSI, suitably substituted *o*-alkynyl benzaldimines were shown to provide 1,3 dipolar intermediates of type **III**, which were later trapped with dimethyl acetylene dicarboxylate **77a** in a [3+2] dipolar cycloaddition reaction. In this transformation an oxazolidine-based bidentate ligand **L1** (Scheme 51) was proved to be essential to promote product formation. The pyrrolo(α)isoquinolines generated from this double tandem process were achieved in good yields. Furthermore, the presence of a CF_3 group in the dipolarophile **77b** afforded **78** in good yields and with excellent regioselectivity, thus demonstrating the usefulness of the CF_3 group as a tool to dictate the stereochemical outcome of these transformations (Scheme 51, path 2).

In a related report, the *N*-alkylated isoquinolinium species **IV** derived from the fluorination protocol was trifluoromethylated to afford 1-(trifluoromethyl)-4-fluoro-1,2-dihydroisoquinolines **79**. The success of the reaction with an *N*-alkyl substituent as opposed to the *t*-butyl substituent was explained in terms of the thermal stability of the resulting isoquinolinium species. In this report, a bidentate nitrogen ligand **L2** (Scheme 51) promoted the trifluoromethylation with the Ruppert-Prakash reagent $TMSCF_3$ to afford **79** in good yields (Scheme 51, path 3).

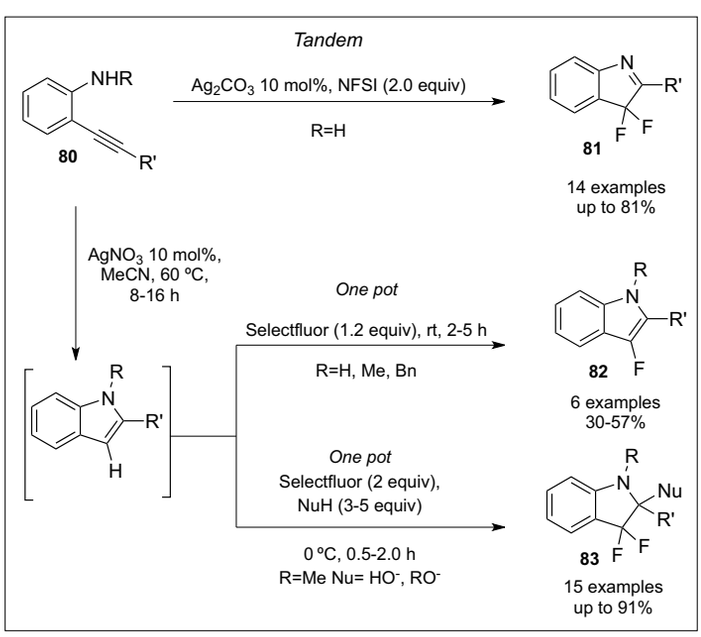
Recently, You and coworkers[54] combined a tandem cyclization approach and electrophilic fluorination for the synthesis of 3,3-difluoro-3*H*-indoles **81**, 3-fluoroindoles **82** and 2-subtituted-3,3-difluoroindolines **83** starting from readily available *o*-alkynylanilines. The combination of a silver-catalyzed cyclization and electrophilic fluorination with NFSI or Selectfluor provided fluorinated indole derivatives in a single operation efficiently and in good yields (Scheme 52). These tandem and one-pot procedures are regarded as highly efficient, avoiding the need for purification

of the corresponding intermediates. In this transformation, the 3-fluoro-indole derivatives **82** were isolated in modest yields, possibly due to the over-oxidation by the F^+ source.

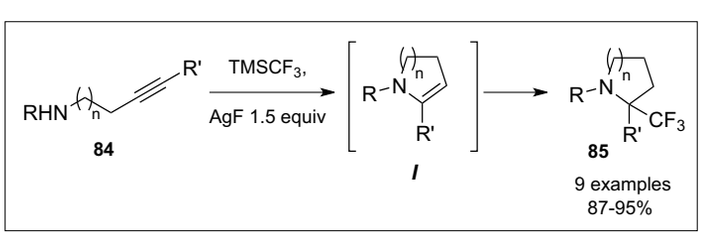
A related silver-mediated process disclosed by Hammond and coworkers[55] involves the cyclization-triggered addition of the Ruppert-Prakash reagent to aminoalkynes under microwave irradiation. The presence of 1.5 equiv of AgF enabled the one-pot preparation of α-trifluoromethyl amines **85** of varying ring sizes in short reaction times. Most likely, the real nucleophilic species is the *in situ* generated $AgCF_3$. Deuterium labeling experiments suggested that this species underwent nucleophilic addition to a reversibly formed enamine intermediate I. Accordingly, in the absence of a second nucleophile, intermediate **I**, generated after the initial alkyne hydroamination of **84**, was detected but could not be isolated. The role of silver in this transformation, apart from the generation of $AgCF_3$, was likely to be the alkyne activation for the intramolecular hydroamination step and the importance of a second nucleophilic species for the reaction was highlighted (Scheme 53). Noticeably, the reaction worked well not only with CF_3 as nucleophile, but excellent yields were also obtained when TMSCN was used under copper catalysis affording α-cyano-amines, thus, the broad nature of this alkyne double addition concept was showcased.



Scheme 51. Silver-catalyzed synthesis of isoquinolines, pyrrolo(α)isoquinolines and trifluoromethyl-substituted dihydroisoquinolines.



Scheme 52. Silver-catalyzed synthesis of fluoro-indol derivatives.



Scheme 53. Synthesis of α-trifluoromethyl amines.

2.4.4.2 *Reactions with Alkenes*

In recent years, radical fluoro-functionalization of alkenes has emerged as a powerful strategy for the efficient preparation of fluorine-containing molecules. Hydrofluorination, carbofluorination, oxyfluorination are among the methods of particular interest, and more recently, methods for the aminofluorination and phosphonofluorination have appeared in the literature (Schemes 54–58). Noteworthy, silver catalysis has been a crucial component in many of these transformations, in which other transition metals were unable to bring about product formation.

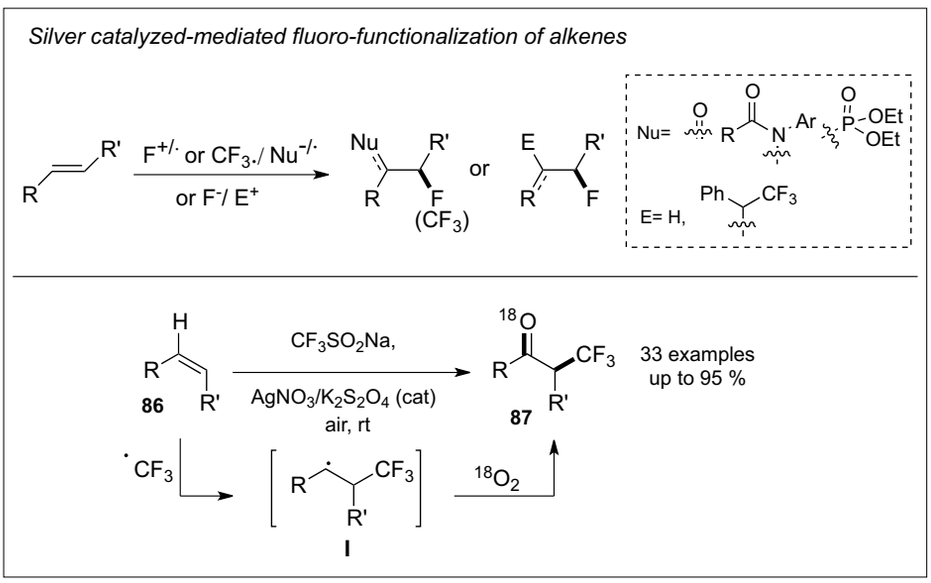
A significant achievement for the synthesis of α-CF_3-ketones from olefin starting materials and radical CF_3 sources was reported independently by Xiao[56] and Maiti.[57] In Xiao's report, styrene derivatives were transformed into the corresponding α-trifluoromethyl ketones **87** under metal-free conditions, albeit in low yields. In Maiti's methodology, yields and functional group tolerance were substantially improved with the aid of silver catalysis. Accordingly, α-trifluoromethyl ketones were obtained not only from styrenes but also from heteroaromatics, as well as vinyl cycloalkane starting materials. The use of the inexpensive Langlois reagent CF_3SO_2Na, room temperature and open-air conditions makes this method particularly attractive. Catalytic amounts of potassium persulfate $K_2S_2O_8$ as an external oxidant in conjunction with 20 mol% $AgNO_3$ under air

afforded the corresponding products **87** in excellent yields (Scheme 54). Mechanistic investigations suggested the involvement of an α-trifluoromethyl benzylic radical species **I**, generated by the reaction of a CF_3 radical with the olefin, which was later trapped by persulfate or dioxygen (as determined by ^{18}O-labeling experiments). Owing to the exceptionally mild reaction conditions, functional groups such as ester, keto, aldehyde, nitro and cyano were tolerated as well as the easily oxidized chloromethyl group (Scheme 54).

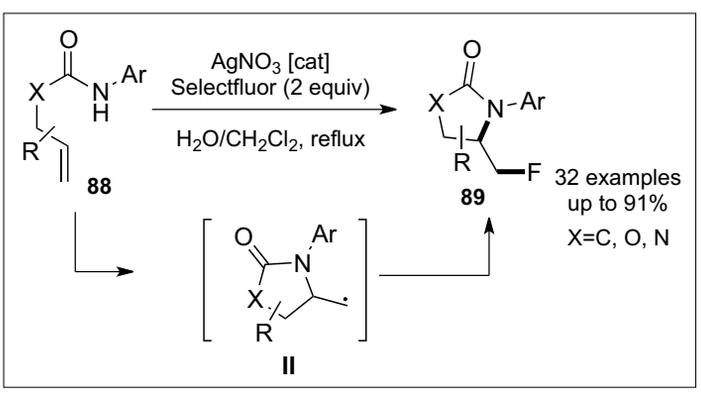
A similar fluoro-functionalization of olefins was reported in 2013 by Li and coworkers,[58] in which silver catalysis played an essential role in the radical aminofluorination of unactivated alkenes in aqueous media. Through the reaction of the corresponding substituted enamides **88** with 2 equiv of Selectfluor as the fluorine atom source and 10 mol% of Ag(I) salts, a range of fluorinated *N*-substituted pyrrolidin-2-ones, oxazolidin-2-ones and *N,N*-disubstituted imidazolidin-2-ones (**89**, X=C, O and N, respectively) was prepared (Scheme 55). The authors surmised that a radical intermediate **II** generated upon reaction of an amidyl radical and the double bond, was quenched by a fluorine atom from a Ag(II)–F generating the aminofluorination product **89** and regenerating the Ag(I) catalyst. A number of Ag(I) salts such as $AgNO_3$, AgOTf and AgOAc in a 10 mol% loading could efficiently catalyze this transformation and the best yields were observed with the use of a CH_2Cl_2/H_2O (2:1) biphasic solvent system. Noticeably, formation of the product was not observed when NFSI was used instead of Selectfluor, this observation being in accordance with the notion that Selectfluor is responsible for the oxidation of Ag(I) catalyst to Ag(III)–F, a transformation that would be less favorable with the less powerful oxidant NFSI (Scheme 55).

Expanding the above-mentioned methodology, the same team developed the analogous phosphonofluorination of alkenes.[59] In this instance, simple unactivated alkenes **90** were reacted with Selectfluor and catalytic amounts of $AgNO_3$ in the presence of a number of phosphites to give **91**. As in the radical aminofluorination, the presence of water was found to be crucial for product formation. While the presence of a base led to complete suppression of the reaction, a mixed solvent system consisting of CH_2Cl_2:H_2O:AcOH (1:2:1) was found to give the best results. The beneficial effect of such a particular system was rationalized on the basis that a biphasic system prevents the product from further oxidation. Even though the role of the acid remains to be clarified, the authors surmised that stability of Ag(III)–F and Ag(II)–F is enhanced under acidic conditions. This transformation was shown to exhibit a broad substrate scope. Additionally, stereoselective phosphonofluorination of a steroid derivative afforded **91a** in 89% yield with high diastereoselectivity. Nevertheless, electron-poor alkenes and easily oxidized functionalities were not tolerated under the optimized conditions (Scheme 56).

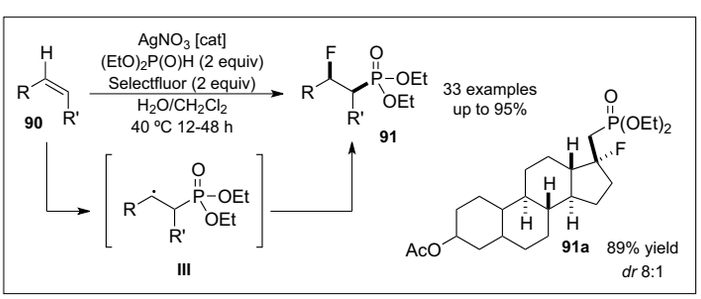
Recent efforts to prepare an elusive α-CF_3-benzyl silver species, from the reaction of AgF and *gem*-difluoroalkenes **92** led to the discovery by Hu and coworkers,[60] of a process for the preparation of symmetric 2,3-bis-(aryl)-1,1,1,4,4,4-hexafluorobutanes **93** that proceeds through a proposed CF_3-substituted benzyl radical species **IV**. These unanticipated results were explained by the thermal instability of *in situ* generated alkylsilver species, which are prone to dimerize to give alkyl dimers. This is in sharp contrast with the thermal stability exhibited by their perfluorinated counterparts, which are relatively stable at room temperature, thus, capable of engaging in various chemical transformations with other reactive species.[40e] In this transformation, only β,β-difluorostyrene derivatives were shown to homocouple, while other alkyl-substituted *gem*-difluoroalkenes afforded only the hydrofluorination products. The hexafluorobutanes **93** were generally obtained as a 1:1 mixture of *syn/anti* diastereoisomers. Notably, the products could also be obtained if a mixture of CsF and $AgBF_4$ was used instead of AgF (Scheme 57). Further applications of this novel α-CF_3-benzyl silver species remain to be developed and challenges as-



Scheme 54. Oxytrifluoromethylation of alkenes.



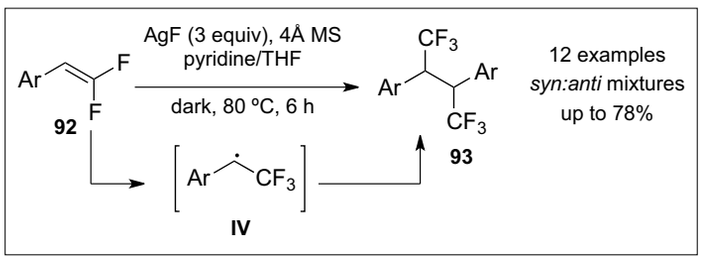
Scheme 55. Aminofluorination of alkenes.



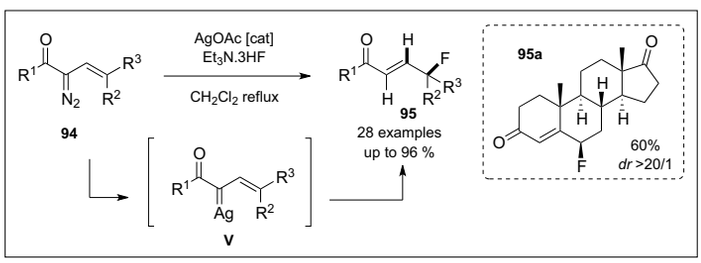
Scheme 56. Phosphonofluorination.

sociated with its thermal instability still need to be overcome.

In recent years, the reactivity of silver towards carbene and carbenoid species has been recognized as substantially different from other transition metals.[61] For instance, it has been shown that silver vinyl carbenes show electrophilic reactivity at the vinylogous position rather than the carbene site. Exploiting this property and as continuation of their work on silver vinyl carbene species, Davies and coworkers[62] reported a vinylogous fluorination of silver vinyl carbenes to afford γ-fluoro-α,β-unsaturated esters **95**. In this transformation, the silver carbene species **V** was suggested to form *in situ* from the corresponding vinyl diazoester compounds **94**. Nucleophilic fluorination by $Et_3N{\cdot}3HF$ led to the corresponding products in good yields. Using this methodology, the authors were able to prepare a fluorinated derivative of farnesol. Furthermore, in spite of the absence of a chiral ancillary ligand, the fluorinated steroid derivative **95a** was successfully synthesized with good diastereoselectivity. The origin of this diastereoselectivity was explained in terms of stereoelectronic effects arising from the conformation adopted by the substrate (Scheme 58).



Scheme 57. Fluorinative homocoupling of *gem*-difluorostyrenes.

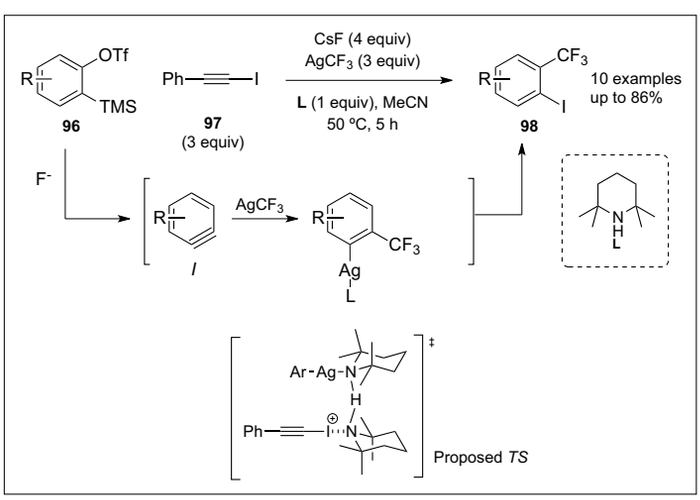


Scheme 58. Vinylogous fluorination of diazoesters.

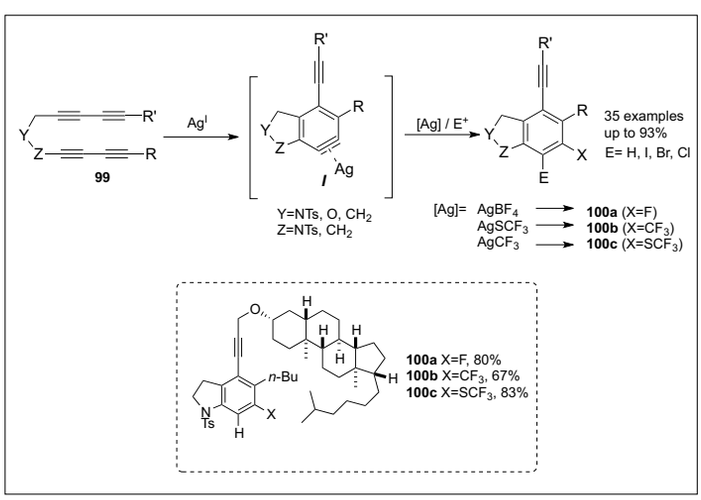
2.4.4.3 *Reactions with Arynes*

Arynes are widely recognized as an important class of reactive intermediates in synthetic organic chemistry.[63] Since their discovery, they have found numerous applications; however, it was only recently that they have successfully been used within the context of organofluorine chemistry. In an unprecedented transformation, Hu and coworkers[64] disclosed a protocol for the silver-mediated vicinal difunctionalization of *in situ*-generated benzyne intermediates **I**, obtained from *o*-trimethylsilyl aryl triflates **96**. In this fashion, the otherwise difficult to obtain *o*-iodo-trifluoromethyl arenes **98** were conveniently obtained in good yields with this trifluoromethylation-iodination protocol. The nucleophilic $AgCF_3$ species was generated *in situ* by the reaction of $TMSCF_3$ and AgF in a 1:1 ratio. In this transformation, the use of 1-iodophenylacetylene (**97**) was found crucial for the success of the difunctionalization, while other X^+ sources such as the *N*-halosuccinimides NCS, NBS and NIS mainly provided the trifluoromethyl arene arising from the protonolysis of the arylsilver species. Likewise, a sterically demanding secondary amine, 2,2,6,6-tetramethyl-piperidine (**L**, Scheme 59) was found to be of utmost importance to achieve best results. The role of the ligand was surmised to facilitate the trifluoromethylation step, as well as decreasing the barrier for the second iodination step by the formation of a 6-membered ring transition state (TS) assisted by hydrogen and halogen bonding (Scheme 59).

In a related report, Lee and coworkers,[65] as continuation of their work on aryne chemistry,[66] successfully prepared a series of fluorine-containing heterocycles (**100a–c**). A thermal hexadehydro-Diels-Alder reaction of a tetrayne scaffold **99** served as a novel access to benzyne intermediate **I**, which upon complexation with silver was functionalized by addition of fluoride (from $AgBF_4$), $AgCF_3$ (generated *in situ* from AgF and $TMSCF_3$) and $AgSCF_3$ nucleophiles. As in Hu's method, the authors were able to perform a double functionalization by trapping the arylsilver species with suitable electrophiles such as *N*-halosuccinimides. Although the strict necessity of a fourth alkyne moiety in order to promote the Diels-Alder reaction for aryne formation represents a drawback of this method, the mechanistic novelty and the possibility of assembling a number of biologically relevant fluorine-containing heterocycles such as indolines, isoindolines and dehydrobenzofurans in a single operational step, overrides such limitation. To illustrate its scope, the method was applied to substrates containing a dihydrocholesterol moiety, thus affording fluorinated, trifluoromethylated and trifluoromethylthiolated derivatives **100a–c**, respectively (Scheme 60).



Scheme 59. Iodo-trifluoromethylation of arynes.



Scheme 60. Fluorine-containing heterocycles.

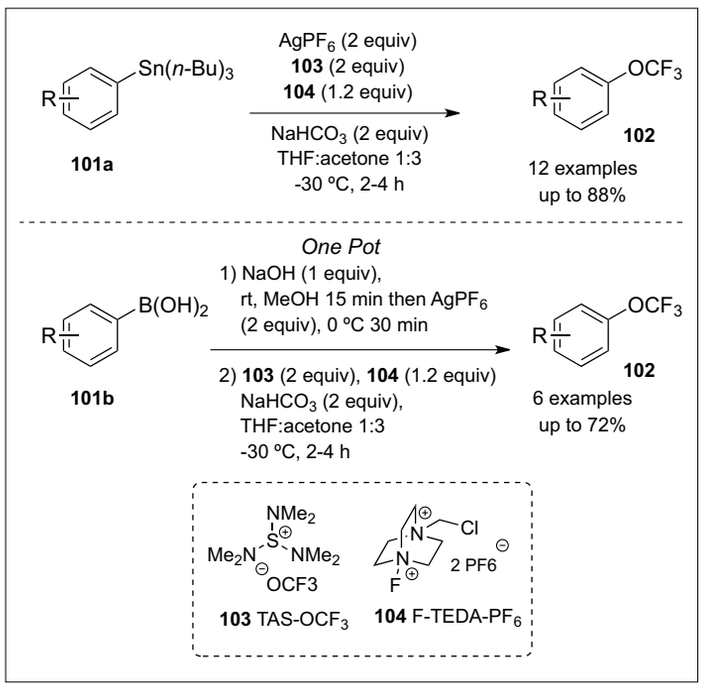
2.4.5 *Direct Functionalization with Trifluoromethyl-chalcogen (CF_3E) Fragments*

Due to their special properties, trifluoromethyl ethers, thioethers and selenoethers occupy a privileged position in the agrochemical and pharmaceutical fields. In recent years, the synthesis of $C sp^2$–ECF_3 compounds (E = group 6 element O, S or Se) has received considerable interest. Numerous methodologies[67,68] for the incorporation of CF_3E moieties based on halogen exchange, radical, electrophilic and nucleophilic approaches have been reported in the literature since the 1930s, however, they often rely on indirect approaches or require hazardous reagents/conditions. On the other hand, more efficient ways to introduce the CF_3E functionality, namely, the direct cross-coupling of a suitable coupling partner with a pregenerated or *in situ* formed CF_3E fragment have long been recognized as a superior strategy, mainly dominated by Cu- and Ag-mediated transformations. Accordingly, there has been a flurry of activity in the field and new reagents and methods have recently appeared in the chemical literature and previous methodologies have been improved. In this review, such advances will be briefly mentioned; comprehensive reviews are available elsewhere.[68]

Recently, a major breakthrough in the synthesis of trifluoromethyl ethers was achieved by Ritter and coworkers.[69] The team was able to perform, for the first time, a direct C(aryl)–OCF_3 bond formation *via* a silver-mediated oxidative coupling of aryl-stannanes **101a** and arylboronic acids **101b** with a trifluoromethoxide source TAS-OCF_3 (**103**). As originally reported by Kolomeitsev,[70] in Ritter's report, **103** was conveniently generated *in situ* from trifluoromethyltriflate ($CF_3SO_2OCF_3$) and tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TAS-F). Mediated by stoichiometric amounts of $AgPF_6$ in the presence of F-TEDA-PF_6 (**104**) as an oxidant, a series of aryl nucleophiles **101** afforded aryl trifluoromethyl ethers **102** in good yields (Scheme 61).

It is important to note that, due to the thermal instability of CF_3O^-, which decomposes to fluoride and difluorophosgene, to date, similar approaches for the direct construction of Ar–OCF_3 bonds with other transition metals remain unavailable, which is likely to be associated with the usually elevated temperatures that are generally employed to promote such a demanding reductive elimination. Furthermore, catalytic versions of this process are currently unavailable.

In contrast to their oxygen counterparts, direct incorporation of the SCF_3 functionality *via* organometallic species has long been known. Even though SCF_3 chemistry is highly restricted to the copper species $CuSCF_3$ (*vide infra*), a number of silver-mediated transformations have recently emerged. It is noteworthy that trifluoromethylthiosilver ($AgSCF_3$) was first reported by Emeleus[71] in the 1960s, while the more widely used $CuSCF_3$ species was prepared from the former *via* a metathetical reaction with copper(I) halides by Yagupolskii in 1975.[72]



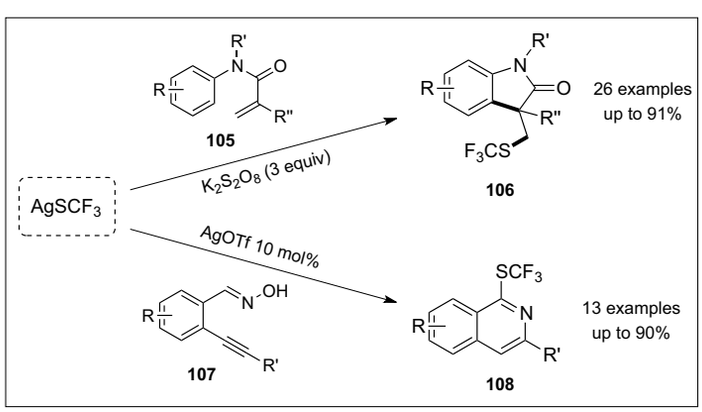
Scheme 61. Silver-mediated synthesis of trifluoromethyl ethers from aryl stannanes and boronic acids.

A recent development in the field of trifluoromethylthiolation chemistry was reported by Wang and coworkers.[73] In their report, a series of oxindoles **106** were prepared by the reaction of alkenes **105** and $AgSCF_3$ as a novel source of SCF_3 radicals under oxidative conditions. Noteworthy, radical SCF_3 chemistry was largely limited to the gaseous CF_3SH, CF_3SCl or CF_3S-SCF_3 developed 50 years ago.[67g,h] Noticeably, $CuSCF_3$ afforded no product under the optimized conditions, thus, highlighting the role of silver in the generation of $^{\bullet}SCF_3$ radicals (Scheme 62).

In a related report, SCF_3-containing heterocycles were successfully synthesized starting from $AgSCF_3$, *o*-alkynyl benzaldoximes **107** and catalytic amounts of AgOTf as a π-activator. In this fashion, trifluoromethylthiol-substituted isoquinolines **108** were obtained in good yields. The presence of 4-MeO-benzenesulfonyl chloride as activator for the *N*-oxide generated upon addition of $AgSCF_3$ was critical for the success of the process (Scheme 62).

2.5 *Copper-catalyzed Reactions*

Historically, fluoroalkyl and perfluoroalkyl compounds of copper have received more attention than perhaps any other metal. Since the pioneering work by McLoughling and Thrower[74] on the preparation of perfluoroalkylcoppers back in 1969, increasing attention has been paid to this species for the construction of biologically relevant molecules possessing the CF_3, CF_2H, SCF_3 and $SeCF_3$ functionalities and numerous copper-mediated as well as -catalyzed procedures have been reported in the literature. Although older works may be commented where necessary, this work focuses on the developments in the field since 2012. In cases for which some reviews on particular related

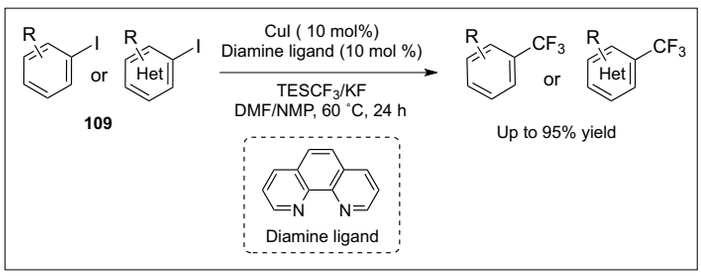


Scheme 62. Synthesis of SCF_3-substituted oxindoles and isoquinolines.

topics have been published more recently, only the literature published thereafter will be considered.

2.5.1 *Aromatic Trifluoromethylation*

Since the pioneering work by Kobayashi and coworkers,[75] who reported the first trifluoromethylation of aryl, vinyl, alkyl, and even heterocyclic halides with *in situ* generated $CuCF_3$ from CF_3I and copper powder, a number of other methodologies[76] employing stoichiometric amounts of Cu were reported. A catalytic transformation with fluorosulfonyl difluoroacetate was developed by Chen[77] and coworkers; however, a major step forward was reported by Amii's group.[78] Their protocol enabled the aromatic trifluoromethylation of (hetero)aryl iodides **109** with the use of $TESCF_3$/KF and 10 mol% CuI in the presence of a bidentate chelating ligand 1,10-phenantroline (Scheme 63).



Scheme 63. Aromatic trifluoromethylation catalytic using copper salts.

In recent years, there has been a flurry of activity in the field of copper-catalyzed or -mediated aromatic trifluoromethylations and a number of procedures have been developed which rely on an array of common CF_3 transfer reagents. Sources of CF_3 moiety can be categorized as nucleophilic, electrophilic and radical (Fig. 2).

Important developments in the area include the use of aryl bromides as electrophilic coupling partners,[79] arylboronic acids[79b,80] with CF_3^+ sources, as well as with nucleophilic CF_3 sources under oxidative conditions. Recently, a rapid synthesis of trifluoromethyl arenes was reported under flow chemistry conditions.[81] Furthermore, room temperature[80f] trifluoromethylations have also been enabled under ligand-free conditions[82] as well as by NHC ligand frameworks[83] (Scheme 64, part A and B).

Until recently, copper-catalyzed or -mediated aromatic trifluoromethylations had relied on aryl halides or arylboronic acids as starting materials for such transformations (Scheme 64, part A and B). However, a major development for the construction of Ar-CF_3 motifs, came independently from the groups of Fu[84] and Gooβen,[85] when they were able to prepare trifluoromethyl arenes starting from anilines *via* their aryldiazonium salts prepared *in situ* or separately (Scheme 64, part C).

Fu and coworkers utilized an electrophilic CF_3 reagent (**XV**, Fig. 2) for the synthesis of CF_3-substituted arenes. In their report, the aryl diazonium salts were prepared *in situ* by means of isoamyl nitrite, thus, avoiding the need for purification. These protocols tolerate functional groups such as ether, thioethers, amide, alkynyl and notably, bromide and hydroxyl. Heteroaromatic amines are also suitable substrates for this Sandmeyer trifluoromethylation reaction. Based on mechanistic studies, the authors surmised that this process involves a radical pathway. Thus, a series of trifluoromethylated bicyclic structures was accessed in this fashion.[84]

In a similar work, Gooβen's group achieved a copper-mediated trifluoromethylation of a series of aryldiazonium tetrafluoroborates prepared by a diazotization reaction of the corresponding anilines. The isolated salts were then reacted with $CuCF_3$ formed *in situ* from the Ruppert-Prakash reagent (**I**) and CuSCN to obtain Ar-CF_3 motifs in good yields. This transformation tolerated a range of electron-poor and electron-rich functional groups such as keto, cyano, ester and amino. Remarkably, iodo substituents were not affected under the reaction conditions, thus dramatically expanding the possibilities for further functionalization.[85]

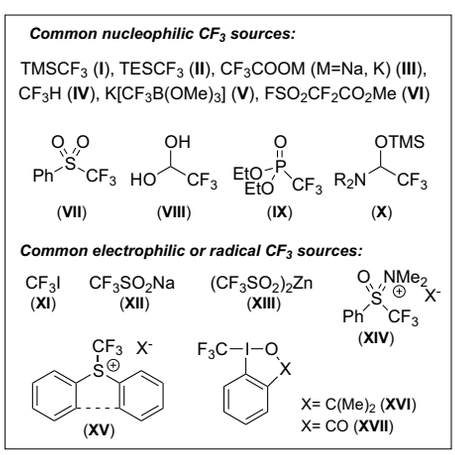
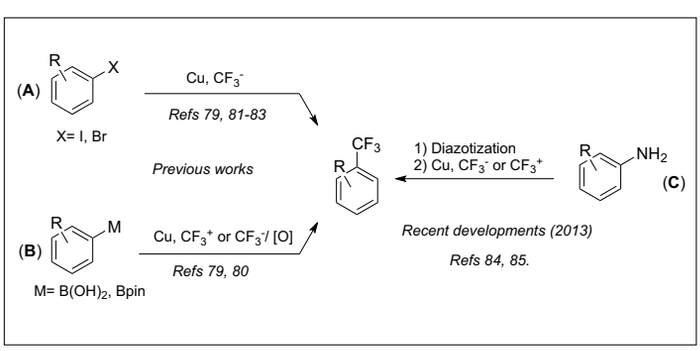


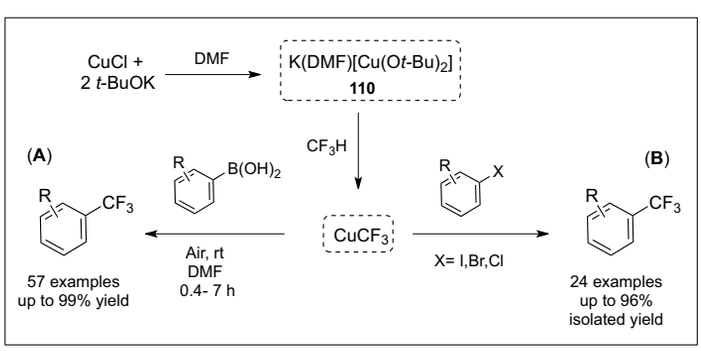
Fig. 2. Sources of CF_3 functionality.

Of particular significance is the successful utilization of fluoroform (CF_3H) as a direct source of the CF_3 motif. The importance is centered on the fact that fluoroform (a by-product of Teflon® manufacturing) is produced in amounts exceeding 20,000 tons annually. Furthermore, it is a potent green house gas with an estimated global warming potential 11,700 times greater than that of CO_2.[86] Thus, its efficient utilization for the synthesis of valuable chemicals and building blocks is of remarkable importance. Accordingly, the groups of Grushin[87] and Prakash[88] independently developed conditions for its direct utilization in several important chemical transformations (Scheme 65).

The direct cupration of fluoroform (**IV**) was first reported by Grushin and coworkers by means of a novel dialkoxycuprate **110**, obtained through the reaction of CuCl and 2 equiv of *t*-BuOK in DMF (Scheme 65). This process enabled the copper-mediated trifluoromethylation of arylboronic acids,[87b] aryl iodides, aryl bromides and even some aryl chlorides.[87d] In Grushin's report, arylboronic acids were smoothly trifluoromethylated at room temperature employing 2 equiv of fluoroform-derived



Scheme 64. Aromatic trifluoromethylation of aryl halides, arylboron species and anilines.



Scheme 65. Trifluoromethylation of aromatics by fluoroform-derived $CuCF_3$.

$CuCF_3$. In some cases, reactions were performed at 0 ºC in order to minimize the proto-deborylation by-product. This method is particularly attractive due to the low cost of CF_3H and the use of air as the oxidant. Furthermore, no ligand or external additive was necessary to promote the transformation. Arguably, the cost-effectiveness of this transformation overcomes the issue of using super-stoichiometric quantities of Cu (Scheme 65, part A).

For the case of aryl halides, most aryl and heteroaryl iodides were smoothly trifluoromethylated at temperatures from 25 ºC to 60 ºC with 1.2 to 2.0 equiv of $CuCF_3$. On the other hand, only electron-poor aryl bromides and 2-bromopyridines afforded the corresponding products in practical yields at elevated temperature (*ca.* 60 ºC) (Scheme 65, part B). The isomeric 3-bromopyridines are much less reactive and can only be obtained in yields of up to 17%. In this transformation, an interesting *ortho* effect was observed, *i.e.* substrates with electron-withdrawing substituents in the *ortho* position were particularly reactive, thus, providing high yielding products. As expected only highly electrophilic heteroaryl chlorides with *ortho* electron-withdrawing moieties were reactive enough to afford the corresponding products, albeit in lower ^{19}F NMR yields and requiring higher reaction temperature (80 ºC).

2.5.2 *Aromatic Difluoromethylation*

Amongst fluoroalkyl moieties, the difluoromethyl (CF_2H) group has attracted increasing attention due to its potential application in the pharmaceutical arena. The difluoromethyl group is bioisosteric with the carbinol (OH) group, yet reasonably lipophilic. Additionally, it can act as a hydrogen bond donor. For these properties, the CF_2H motif has been used in the preparation of numerous biologically active compounds such as sugars,[89] enzyme inhibitors and agrochemicals.[90] In sharp contrast to its perfluoro counterpart, direct incorporation of this functionality is extremely rare. Most of the methods available rely on indirect methods such as deoxofluorination of aromatic aldehydes.

Recently, a multistep procedure involving a copper-catalyzed cross-coupling of aryl iodides with $TMSCF_2CO_2Et$, hydrolysis and decarboxylation sequence was reported by Amii's group.[91] In this sequence, the last decarboxylation step was successful only for electron-poor substrates, thus limiting the reaction scope (Scheme 66, part A). To date, there are only two reports on the direct and regiospecific difluoromethylation of aromatics; both relying on copper-mediated transformations.

Fier and Hartwig[92] disclosed a method for the direct difluoromethylation of aryl and vinyl iodides with 5 equiv of a difluoromethyl analog of the Ruppert-Prakash reagent $TMSCF_2H$ and stoichiometric amounts of CuI. In this transformation electron-rich and electron-neutral iodoarenes are suitable substrates, however, electron-withdrawing functionalities afforded only the protodehalogenated products and a competitive difluoromethylation of carbonyl moieties was observed (Scheme 66, part B).

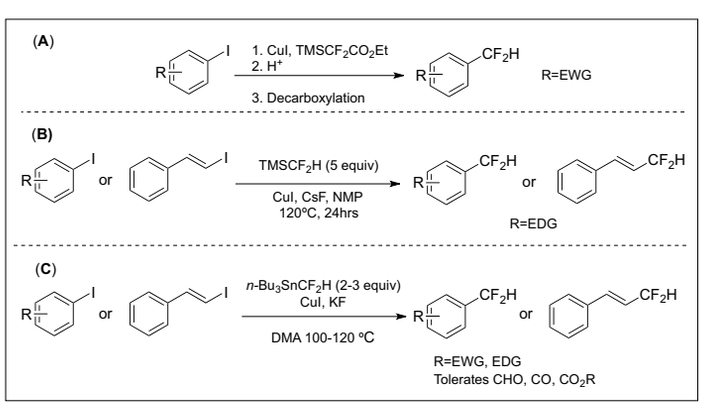
In a related report, Prakash and coworkers[93] introduced a novel reagent for the direct incorporation of the CF_2H functionality, namely, tributyl(difluoromethyl) stannane n-Bu_3SnCF_2H. This non-volatile reagent was conveniently accessed from the reaction of $TMSCF_3$ and n-Bu_3SnH *via* difluorocarbene insertion[94] into the Sn–H bond. In this fashion, difluoromethylations of aryl and heteroaryl iodides proceed smoothly with 2–3 equiv of n-Bu_3SnCF_2H in DMA at 100–120 ºC. Contrary to Hartwig's protocol, electron-withdrawing groups are tolerated affording the corresponding difluoromethyl arenes in good yields. Remarkably, owing to the reduced oxophilicity of tin *vs* silicon, aldehyde, keto and even ester moieties are unaffected, thus, carbonyl difluoromethylation was not observed (Scheme 66, part C).

2.5.3 *Ar–F Bond Formation*

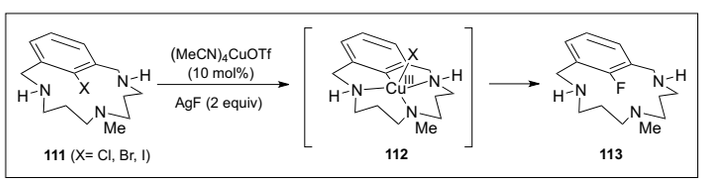
The generation of C(aryl)–F bonds catalyzed by copper was recently reported by Ribas and coworkers (Scheme 67).[95] A macrocyclic arylcopper(III) complex **112** generated after oxidative addition of an aryl halide **111** to a Cu(I) catalyst, was shown for the first time, to undergo facile C–F reductive elimination at room temperature in acetonitrile, a transformation previously limited to Pd species. Noteworthy, the same protocol could be used to perform the halogen exchange in any direction with the use of appropriate halide salts. Remarkably, even defluorination was possible at room temperature. These outstanding results however, are limited to the very specific macrocyclic ligand framework and their application to more general substrates was not reported. Nevertheless, Ribas' seminal work paved the way for the discovery and development of more general Cu mediated fluorination reactions.

Soon after Ribas' report, Hartwig and coworkers disclosed a Cu-mediated protocol for the fluorination of aryl iodides using AgF as the fluoride source. As noted by previous authors, the success in the transformation relies heavily on weakly coordinating counterions and ligands on Cu, thus, after screening a series of nitrile-ligated copper(I) species, it was found that the best results were obtained with the use of 3 equiv of $(t$-$BuCN)_2CuOTf$ in DMF at 140 ºC. In this manner, electron-poor as well as electron-rich iodoarenes were smoothly converted into the corresponding aryl fluorides (Scheme 68, part A).

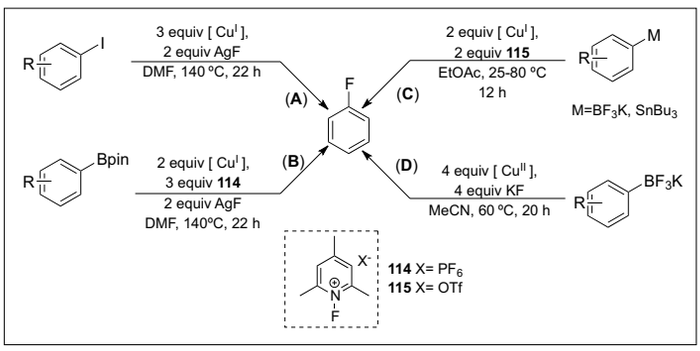
Next, the same group reported an alternative approach starting from arylboronate esters and the electrophilic fluoride reagent **114**. In this transformation, the choice of the base proved to be of critical importance. Not only transmetallation must be promoted, but also base-induced decomposition of the F^+ source must be avoided. To that end, only AgF successfully afforded the corresponding products in good yields, whereas other alkoxide bases were less effective. The authors surmised that the success of AgF as a base was due to its lower solubility and nucleophilicity, thus, preventing an unproductive transmetallation of the arylboronate to a Cu(I) species. Furthermore, ^{19}F NMR spectroscopy studies, made the identification of an Cu(III)-fluoride species, analogous to the



Scheme 66. Difluoromethyl arenes by three-step sequence (A), direct cross-coupling with $TMSCF_2H$ (B) and from n-Bu_3SnCF_2H (C).



Scheme 67. First copper-catalyzed C–F bond formation.



Scheme 68. Copper-mediated aromatic fluorination of aryl iodides (A), arylboron pinacolates (B), aryltrifluoroborates (C), stannanes and oxidative fluorination of aryltrifluoroborates (D).

one described by Ribas (*vide supra*), possible. Subsequent rate-limiting transmetalation afforded an arylcopper(III) fluoride which underwent rapid reductive elimination (Scheme 68, part B).

A very similar approach is the utilization of aryl trifluoroborates and aryl stannanes as nucleophilic coupling partners. As outlined by Sandford,[96] such arylboron and aryltin species can be fluorinated with the use of **115** as an electrophilic fluorine source and 2 equiv of (*t*-BuCN)$_2$CuOTf, under mild conditions. Interestingly, and contrasting with Hartwig's report, arylboron pinacolates afforded only traces of the desired product under these conditions. In the case of aryl stannanes, fluorinations occurred at room temperature, while aryltrifluoroborates required heating at 80 °C. Both electron-poor and electron-rich substrates were suitable substrates for this transformation, achieving the corresponding products in practical yields (Scheme 68, part C).

A considerable improvement was later disclosed by Sanford's group,[97] who published a procedure for the fluorination of aryltrifluoroborates from the inexpensive KF mediated by Cu(OTf)$_2$. The use of an inexpensive fluorine source, as well as the operational simplicity and mild reaction conditions, make this method particularly attractive for large-scale industrial applications. The role of Cu(OTf)$_2$ is believed to be twofold: as the promoter for the C–F bond formation and as an oxidant. This hypothesis is in agreement with the observation that >2 equiv of Cu(OTf)$_2$ are required in order to achieve good yields. In this fashion, substrates bearing electron-donor, electron-withdrawing, as well as carbonyl groups is successfully fluorinated. Heteroaromatic substrates are also fluorinated, albeit in a modest yield (20%). As in previous reports, a high valent Cu(III) intermediate is surmised to be responsible for the C–F bond formation event (Scheme 68, part D).

In spite of such developments, all these methods for the construction of C(aryl)–F bonds suffer several drawbacks that are mainly associated with the contamination by side products and product purification. In all of the above-mentioned reports (Scheme 68), products are often contaminated by the virtually inseparable arenes, originated from the protodehalogenation or protodeborylation side reactions. Furthermore, catalytic versions of such transformations are currently unavailable, the only examples being possible *via* Ag or Pd catalysis (*vide supra*).

2.5.4 *Trifluoromethylation of Olefinic C–H Bonds*

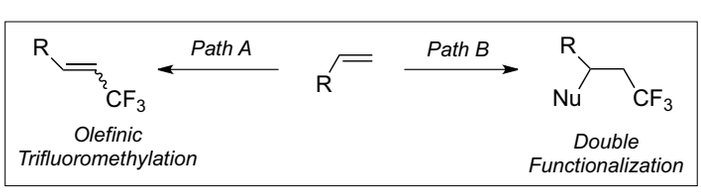
In recent years, a number of copper-catalyzed procedures that enable the direct trifluoromethylation of C–H bonds have been published. These protocols include: a) methods in which a C*sp*^{2}–CF$_3$ motif can be accessed and b) methods for the construction of C*sp*^{3}–CF$_3$ motifs *via* olefin difunctionalization reactions (Scheme 69). The most recent protocols are commented on below.

2.5.4.1 *Construction of Csp^2–CF$_3$ Bonds*

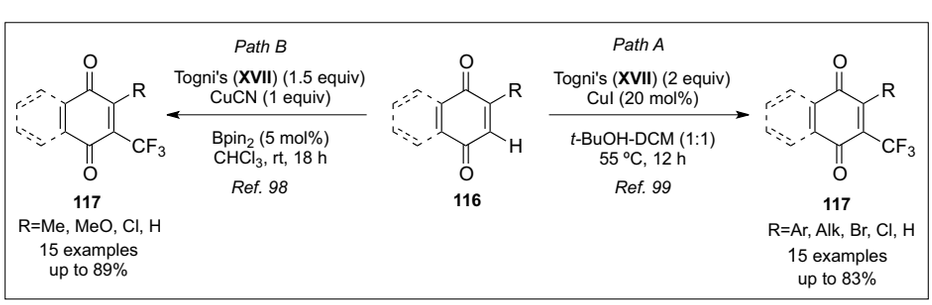
Recently, the groups of Szabo[98] and Wang[99] disclosed a protocol for the direct C–H trifluoromethylation of quinones **116**. In Wang's report, the transformation was performed with catalytic amounts of CuI (*ca.* 20 mol%). Owing to the dichotomous nature of the hypervalent iodine reagent **XVII** (Fig. 2), •CF$_3$ radicals can be generated *in situ* after an initial SET from the Cu(I) catalyst. The ensuing CF$_3$ addition to the olefinic double bond and subsequent deprotonation afforded the corresponding products in good yields. In this fashion, quinones and naphtoquinones possessing either electron-rich or -deficient aryl substituents **117** were successfully prepared. Notably, halogen substituents were unaffected under the reaction conditions, thus, enabling further chemical transformations (Scheme 70, path A).

Alternatively, Szabo's procedure employed 1.5 equiv of **XVII**, stoichiometric amounts of a Cu(I) salt as well as catalytic amounts of bis(pinacolato)diboron (5 mol%) as a radical activator. Nevertheless, contrasting with Wang's procedure, the stoichiometric version of this transformation enabled the bis(trifluoromethylation) of substrates by employing 2 equiv of Togni's reagent. In this fashion, a series of CF$_3$-functionalized quinones and naphtoquinones bearing Me, MeO and chloro substituents were prepared in good yields (Scheme 70, path B).

Copper catalysis has enabled olefinic trifluoromethylations of a series of enamides at room temperature to obtain **119**. As outlined by Feng and Loh,[100] *N*-vinyl acetamides **118** were reacted with 1.1 equiv of Togni's reagent **XVII** in THF at room temperature in the presence of 10 mol% of the cationic copper species (MeCN)$_4$CuPF$_6$. Interestingly, single crystal X-ray diffraction analysis of the product revealed a *trans* configuration with respect to the nitrogen atom. In this transformation, functionalities such as acetyl, cyano, sulfonyl and chloro were tolerated, thus enabling further functionalizations. A single heterocyclic enamide was also a suitable substrate albeit affording the desired product in only 50% yield even with a higher catalyst loading (*ca.* 20 mol%) (Scheme 71).



Scheme 69. Pathways for olefin trifluoromethylation.

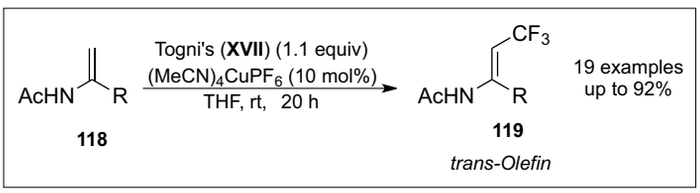


Scheme 70. Direct quinone C–H trifluoromethylation.

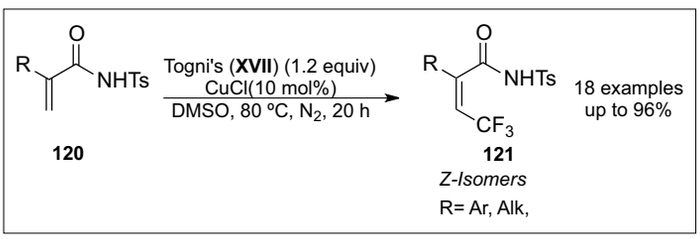
Building upon this transformation, the same team reported a procedure for an olefinic C–H trifluoromethylation of alkenes.[101] This time, by employing a series of *N*-tosyl-protected acrylamides **120**, 1.2 equiv of Togni's reagent and 10 mol% CuCl, the authors were able to obtain β-trifluoromethyl enamides **121** in good yields and with a *Z*-configuration exclusively. Importantly, the success of this transformation greatly relies on the presence of the *N*-tosyl group, since other directing groups such as NHBn, NHPh, OH and OMe all failed to afford the desired product. The authors surmised that the increased acidity of the NH moiety was likely to be associated with that observation. In this manner, electron-donating as well as electron-withdrawing α-aryl acrylamides were smoothly converted into products. Notably, the thioether moiety was compatible with this reaction and no catalyst poisoning was observed in that case. Furthermore, α-alkyl acrylamides were also suitable substrates. In that case, the products were obtained as mixtures of allylic-CF_3 and the desired olefinic-CF_3 products; nevertheless, the desired product was the major one in all cases (Scheme 72). A short time later, a very similar protocol employing Umemoto's reagent **XV** and *N,N*-diethyl acrylamides was also reported.[102]

Very recently, Bi and coworkers[103] disclosed a synthetic protocol for the α-trifluoromethylation of α,β-unsaturated carbonyl compounds. In their report, the olefinic trifluoromethylation was possible through the reaction of 1.5 equiv of Togni's reagent and a series of enones, enamides as well as α,β-unsaturated esters, thioesters and amides **122** in the presence of 10 mol% CuI. Mechanistic investigations suggest that a $^{\bullet}CF_3$ radical generated by a SET from CuI is likely to be involved. In this process, the products **123** were regioselectively trifluoromethylated at the α-position. Furthermore, the geometry around the double bond was determined to be of an *E* configuration. Although the authors did not comment on the origin of the regio- and stereoselectivity, this nonetheless, certainly represents an important synthetic procedure that complements the one previously described by Loh (*vide supra*). To further illustrate the synthetic applicability of their procedure, the team successfully prepared a series of biologically active trifluoromethylated compounds including the antiviral agent trifluridine with a 76% yield (Scheme 73).

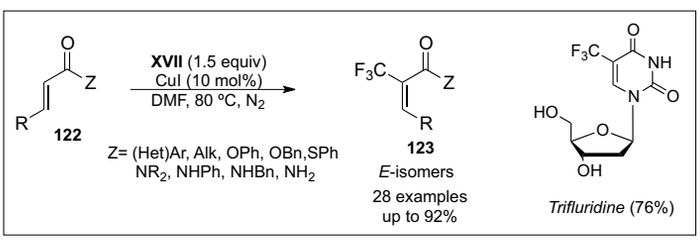
An alternative approach for the preparation of α-trifluoromethyl carbonyl compounds was reported by Yu's group.[104] In this process, the authors were able to perform a copper-catalyzed trifluoromethylation reaction of a series of cyclic and



Scheme 71. Room temperature preparation of (*E*)-β-trifluoromethyl enamides.



Scheme 72. Synthesis of (*Z*)-α,β-unsaturated trifluoromethyl amides.

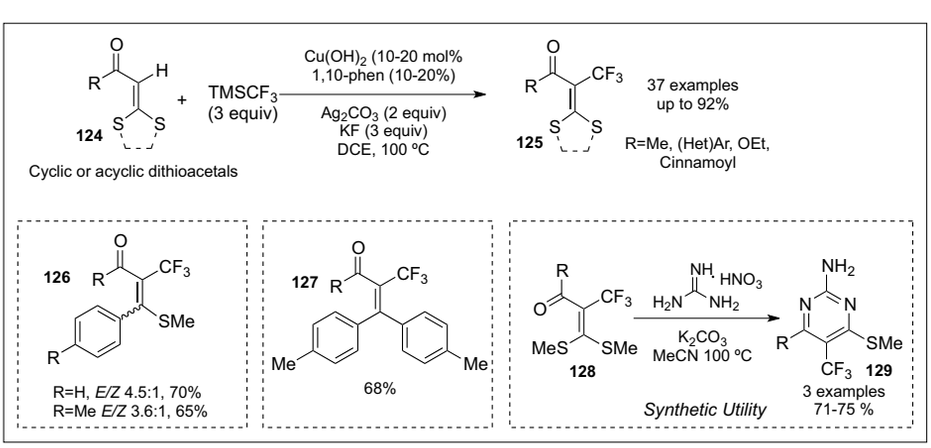


Scheme 73. Synthesis of α-trifluoromethyl α,β-unsaturated carbonyl compounds.

acyclic α-oxoketene dithioacetals **124** with the Ruppert-Prakash reagent under oxidative conditions in the presence of 10–20 mol% of a Cu(II) salt. Addition of the bidentate ligand 1,10-phenantroline, 3 equiv of KF as a base and 2 equiv Ag_2CO_3 as an external oxidant was found to be critical for achieving good yields, while oxidants such as $PhI(OAc)_2$ or ligand-free conditions failed to provide the desired products **125**. In this transformation, benzoyl substrates bearing methyl, methoxy, chloro and fluoro substituents were tolerated. Additionally, cinnamoyl ketene dithioacetals were also trifluoromethylated, albeit in a substantially lower yield. Notably, heteroaroyl (furoyl and thienoyl) as well as an ester ketene dithioacetal were found to be suitable substrates, affording the corresponding products in good yields. Furthermore, not only dithioacetals **124**, but also monomethylthio acetals **126** were found to be suitable substrates. However, the latter afforded products as a mixture of *E/Z* isomers. In that work, one example of trifluoromethylation of an internal olefin was reported in 68% yield (**127**). Although an isolated case, this result clearly demonstrates the possibility to circumvent the limitations involved with the incorporation of dithioacetal activating groups. To further illustrate the synthetic applicability of the method, the authors prepared a series of trifluoromethyl-pyrimidines **129** *via* a condensation of **128** with guanidine (Scheme 74).

2.5.4.2 *Alkene Double Functionalization: Construction of Csp^3–CF_3 Bonds*

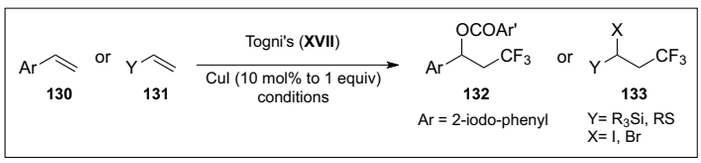
As previously mentioned, electrophilic CF_3 sources can also enable the double functionalization of olefins if coupled with external nucleophiles. Alternatively, the nucleophilic fragment can arise from the



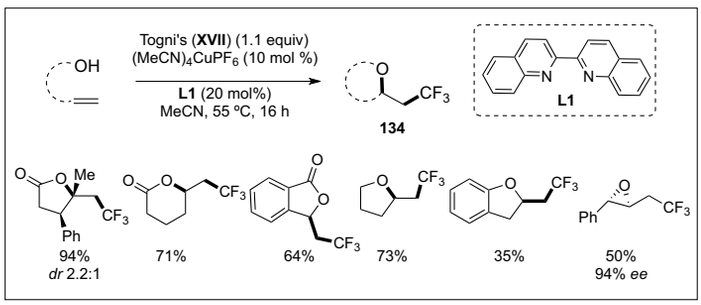
Scheme 74. Trifluoromethylation of α-oxoketene dithioacetals.

same electrophilic reagent, as in the case of the carboxylate fragment from Togni's reagent (*vide infra*).

Along these lines, Szabo[105] and Sodeoka[106] independently disclosed a method for the trifluoromethyl-benzoyloxylation of alkenes by means of Togni's reagent **XVII** and olefin derivatives **130**, in the presence of catalytic or stoichiometric Cu(I) salts. In this fashion, a series of styrene derivatives were trifluoromethylated at the β position with subsequent addition of the carboxylate moiety at the α position of **132**. Intriguingly, when performed in the presence of stoichiometric amounts of CuX (X = I, Br) and vinyl silanes or sulfides **131** as substrates, an α-addition of halide ion was observed instead of the expected carboxylate fragment **133**. Although these methods are limited to the incorporation of halide or carboxylate as nucleophiles, they certainly showcase the possibilities of Cu catalyzed/mediated alkene double functionalization chemistry and in some ways, complement the silver chemistry reported in this area (*vide supra*) (Scheme 75).



Scheme 75. Trifluoromethyl-benzoyloxylation and trifluoromethyl-halogenation of alkenes.



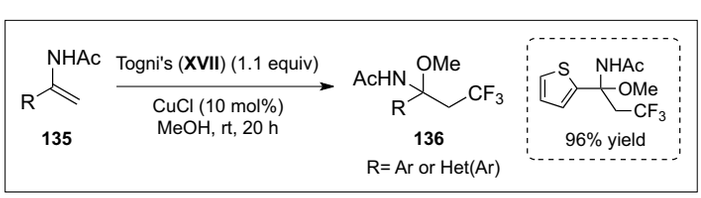
Scheme 76. Oxytrifluoromethylation of unactivated alkenes.

Recently, a significant improvement in terms of the scope of O-nucleophiles that can be employed in oxytrifluoromethylation reactions was disclosed by Buchwald's group.[107] In their report, the team was able to employ a series of nucleophiles other than the 2-iodo-phenyl carboxylate fragment using Togni's reagent. In this fashion, upon addition of the CF_3 motif from the electrophilic Togni's reagent, simple carboxylates, primary alcohols, phenols and even allylic alcohols were able to trap the thus-generated intermediate in an intramolecular fashion. Consequently, by varying the chain size, a series of trifluoromethyl substituted lactones and various heterocycles were accessed (Scheme 76). Remarkably, enantiopure allylic alcohols gave rise to the corresponding trifluoromethyl epoxides without a drop in enantiomeric excess. Keys to the success of this protocol include the use of the cationic copper complex $(MeCN)_4CuPF_6$ as well as a quinoline-based bidentate ligand **L1** (Scheme 76).

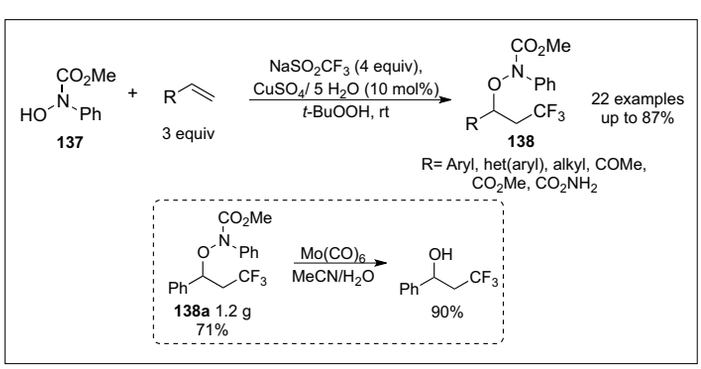
A similar approach for the oxytrifluoromethylation of enamides **135** was reported by Loh.[100] In that work, quantitative yields of a series of trifluoromethyl aminals **136** were obtained simply by the reaction of a series of enamides with Togni II reagent (**XVII**) in the presence of 10 mol% CuCl in methanol at room temperature (Scheme 77). In this fashion, substrates possessing electron-withdrawing as well as electron-releasing substituents in the aromatic ring were smoothly transformed. Furthermore, substrates bearing heteroaromatic substituents were also efficiently transformed into products in excellent yields. It must be further emphasized that this transformation was shown to be very clean, thus products were obtained in pure form simply by a $NaHCO_3$ wash, thus avoiding column chromatography (Scheme 77).

Very recently, Qing[108] reported a variant of the above mentioned reaction. In that work, the team was able to utilize an alternative CF_3 source, namely, the Langlois reagent $NaSO_2CF_3$ as a source of $^{\bullet}CF_3$ radicals. Additionally, with the use of N-hydroxy-carbamate **137** as the O-nucleophile, they were able to perform a copper-catalyzed oxytrifluoromethylation of alkenes in a three-component fashion. Styrene derivatives bearing electron-donating and electron-withdrawing groups were suitable substrates. Noticeably, even unactivated alkenes were shown to undergo double functionalization under the reaction conditions. Furthermore, α,β-unsaturated esters, ketones and amides were also efficiently transformed. In order to illustrate the scalability of the process, the authors prepared 1.2 g of substrate **138a** in 71% yield. In addition, this product was efficiently reduced to the corresponding β-trifluoromethyl alcohol in 90% yield. However, it is noteworthy that a current limitation of this protocol is that an excess of alkene was necessary in order to achieve good yields (Scheme 78).

Building upon the above methodologies, efforts have focused on the development of double functionalization of alkenes in which nucleophiles other than O-nucleophiles could be employed. Accordingly, owing to the important properties of organoazides in pharmaceutical and agricultural sectors, Liu and coworkers[109] recently disclosed an efficient copper-catalyzed trifluoromethylazidation of alkenes. In that work, a series of olefin derivatives **139** were trifluoromethylazidated with the aid of Togni II reagent (**XVII**) and catalytic amounts of Cu(I) salt at room temperature. In this transformation, 2 equiv of $TMSN_3$ served as the source of the N_3 motif. The substrate scope of the present transformation is remarkably broad. For example, not only styrene derivatives were transformed but also cyclic and acyclic internal olefins delivered the corresponding trifluoromethyl azides in good yields. Moreover, monosubstituted

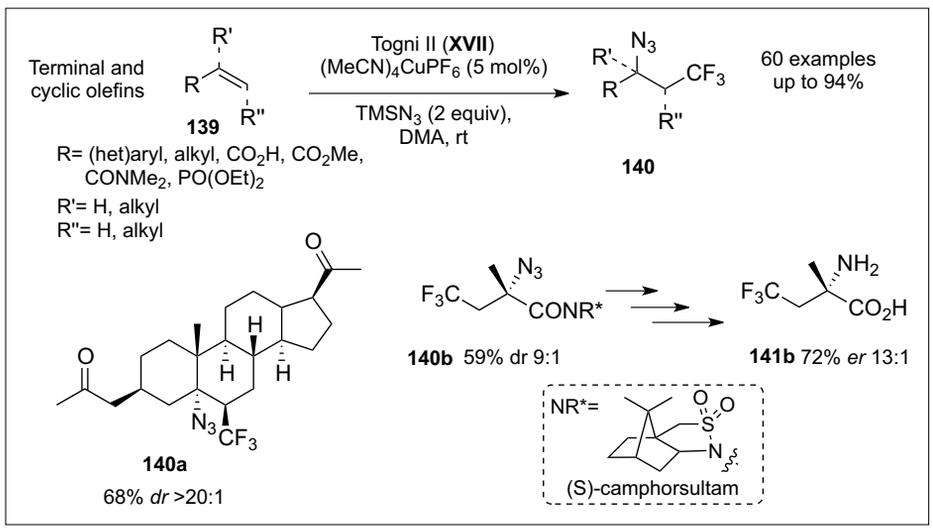


Scheme 77. Oxytrifluoromethylation of enamides.



Scheme 78. Oxytrifluoromethylation of alkenes with N-hydroxy-carbamate.

and 1,1-disubstituted alkenes were also smoothly transformed. Of particular significance is the fact that α,β-unsaturated carbonyl compounds were also suitable substrates. In this fashion, with the aid of a chiral auxiliary, they were able to synthesize precursors of type **140b**, which could be further transformed into the corresponding β-CF_3-α-amino acids **141b**. To further illustrate the synthetic applicability, the same group synthesized a series of complex olefins including a steroidal derivative, which successfully delivered compound **140a** in good yield and good diastereoselectivity (Scheme 79).



Scheme 79. Trifluoromethylazidation of alkenes.

2.5.5 *Trifluoromethylthiolation Reactions: Direct Introduction of SCF_3 Fragments*

As previously mentioned, the SCF_3 motifs have attracted a great deal of attention for a very long time. Since the preparation of $CuSCF_3$ by Yagupolskii,[72] a great amount of work has been focused on the field. Recently, milder and more efficient methods and reagents that allow the direct trifluoromethyl-chalcogenation have been reported.[67,68] The current methods for such transformation could be categorized in: a) nucleophilic, where a CF_3S^- anion is the putative active species and b) electrophilic, in which a 'SCF_3^+' source is involved in the bond formation. Some common sources of SCF_3 moiety are shown in Fig. 3.

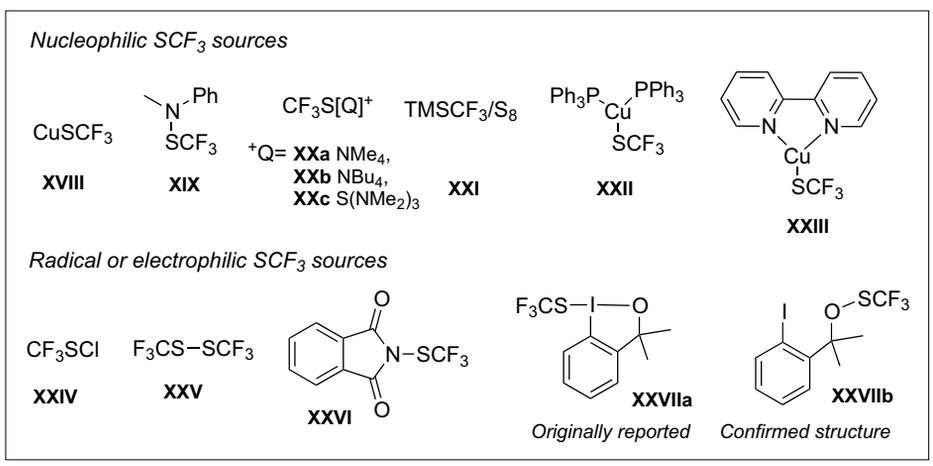
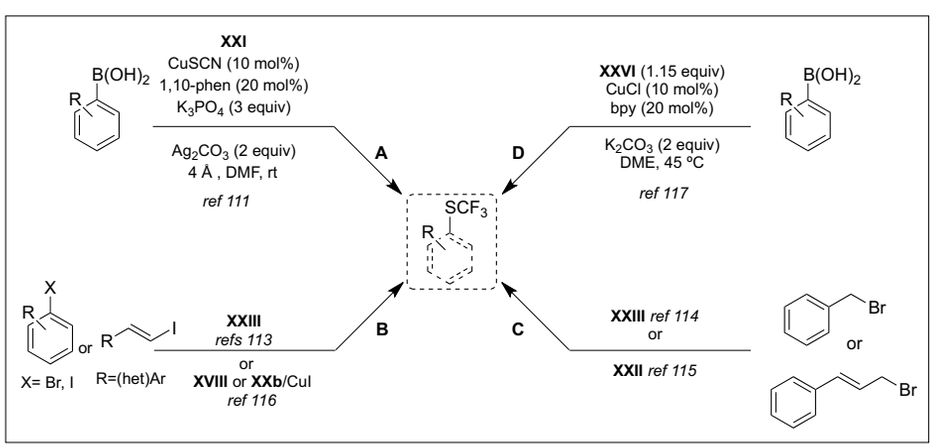


Fig. 3. Nucleophilic, radical or electrophilic SCF_3 sources.

2.5.5.1 *Nucleophilic Trifluoromethylthiolation*

The most recent advances in nucleophilic trifluoromethylthiolation are based in transition metal-catalyzed cross-coupling protocols, in which copper-catalyzed/mediated protocols represent the vast majority of available methods. Nevertheless, reports utilizing other transition metals such as Pd[110] and Ag have also been published (*vide supra*). Only the most recent works will be discussed here. For a more comprehensive treatment, the reader is encouraged to consult other specialized reviews.[67,68]

Recently Qing and coworkers[111] utilized a strategy previously reported by Y. L. Yagupolskii,[112] in which the $^-SCF_3$ anion is prepared *in situ* from elemental sulfur and $TMSCF_3$. In his report, a series of arylboronic acids were converted into the corresponding trifluoromethylthioethers in good to excellent yields. A current limitation of such method is the employment of expensive Ag_2CO_3 as an oxidant (Scheme 80, path A).



Scheme 80. Some nucleophilic and electrophilic trifluoromethylthiolation reactions.

An alternative approach was reported by Weng and Huang.[113] Recently the team developed an air-stable $CuSCF_3$ reagent **XXIII** possessing a bidentate chelating nitrogen ligand which was efficiently used to perform trifluoromethylthiolation of aryl electrophiles. In such transformation aryl iodides as well as aryl bromides were successfully transformed (Scheme 80, path B). Remarkably, benzyl bromides[114] were also suitable substrates and the corresponding products were delivered in good to excellent yields. Furthermore, expanding upon the above methodology, the same team prepared a complex bearing triphenyl phosphine as ligand and efficiently utilized it to effect trifluoromethylthiolation of allylic bromides[115] (Scheme 80, path C). Although the main drawback of such a method involves the use of stoichiometric amounts of copper, the enhanced reactivity and such well-defined systems is greatly showcased by their ability to transform such challenging substrates.

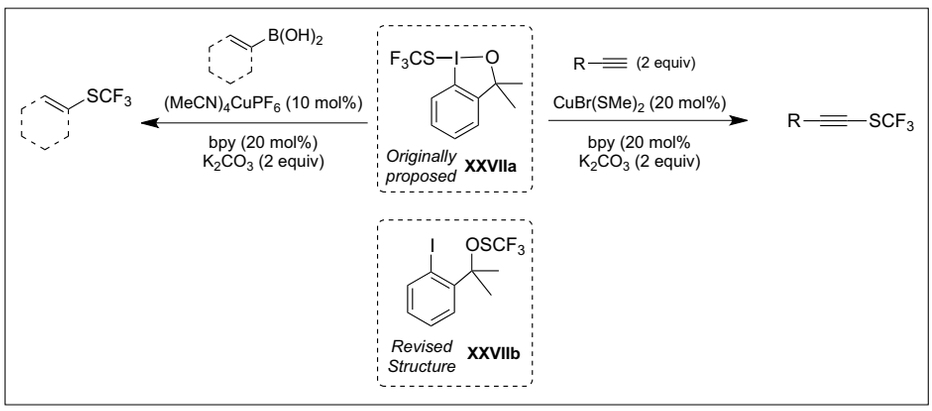
Alternatively, Rueping and coworkers[116] disclosed a procedure for the synthesis of vinyl-trifluoromethylthioethers

through the reaction of **XVIII** and the corresponding vinyl iodides as the electrophilic coupling partner in pyridine as solvent. In this report, the team also applied catalytic quantities of CuI (*ca.* 10 mol%) and reagent **XXb**, albeit with longer reaction times (Scheme 80, path B).

Very recently, the same team[117] disclosed a new synthetic procedure to access the previously reported reagent **XXVI**, which avoids the use of the gaseous and toxic **XXIV**. In this report, **XXVI** was conveniently prepared by a metathetical reaction of *N*-chlorophtalimide and $CuSCF_3$. Next, reagent **XXVI** was successfully employed to perform a copper-catalyzed trifluoromethylthiolation of arylboronic acids in good yields (Scheme 80, path D). It should be mentioned that the team also utilized **XXVI** to perform the same transformation to alkynes.

In recent years, owing to their synthetic potential, several benziodioxole and benziodioxolone-based hypervalent iodine compounds have received great attention from the research community.[118,119] Along these lines, the group of Shen[120] recently disclosed a protocol in which an electrophilic SCF_3 transfer reagent was successfully utilized to perform trifluoromethylthiolations of several nucleophiles. In this fashion, several enolates, alkynes and arylboronic acids were successfully transformed into the corresponding trifluoromethyl thioethers in good yields (Scheme 81).

Originally, the electrophilic reagent used in this work was proposed to consist of a sulfur-bound hypervalent iodine motif, such as the one depicted in **XXVIIa** (Fig. 3). However, as outlined by Buchwald and coworkers,[121] thanks to a recently introduced crystalline sponge method for X-ray diffraction analysis,[122] the structure of **XXVIIa** was unambiguously determined. The analysis demonstrated that the reagent possesses a thioperoxy framework such as the one depicted in **XXVIIb**, rather than the previously reported benziodoxole unit. In this report, the authors provide significant evidence by NMR analysis, which suggests that such a structure is still the prevalent one not only in the solid state, but also in solution. However, it must be further emphasized, that such findings do not in any form, affect the previously reported reactivity of the reagent (Scheme 81).



Scheme 81. Electrophilic trifluoromethylthiolation and revised structure of reagents.

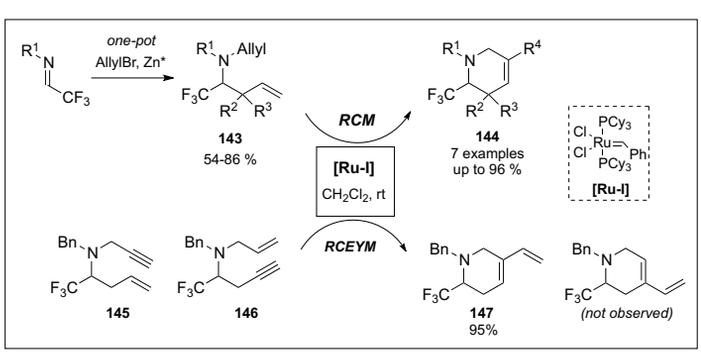
2.6 *Ruthenium-catalyzed Reactions*

Among the different processes catalyzed by ruthenium, metathesis reactions surely belong to the most important ones. Particularly, cross (CM) and ring-closing metathesis (RCM) have turned into some of the most efficient tools for the creation of C–C bonds.[123] As a result, Ru-based metathesis catalysts have widely been used to prepare a range of interesting synthetic and natural products including amino acids, carbo- and heterocycles, *etc*. Moreover, it is common to find in the literature many examples of metathesis, in particular enyne metathesis (EYM), in combination with Diels-Alder or Pauson-Khand reactions, for instance. However, examples that involve fluorinated substrates are lacking.

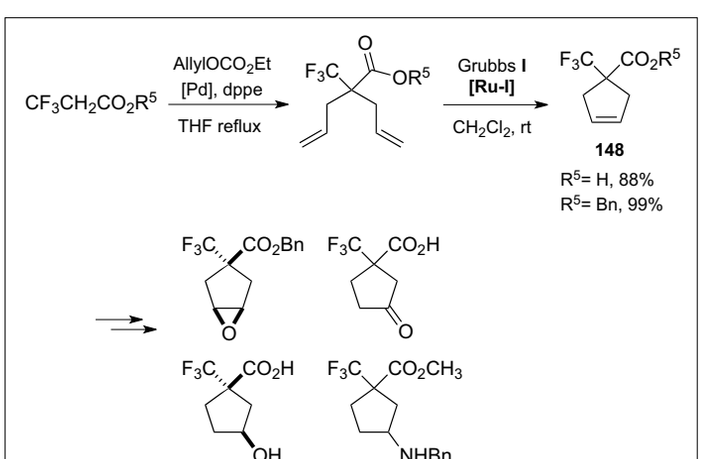
On these premises, Bonnet-Delpon and coworkers reported the synthesis of CF_3-substituted piperidine derivatives **144** by Ru-catalyzed RCM from doubly unsaturated trifluoromethylated amines **143** (Scheme 82).[124] The starting fluorinated amines **143** were readily prepared through a one-pot, Zn-mediated *C*-allylation/*N*-allylation sequence in moderate to good yields.

Then, RCM in the presence of Grubbs catalyst [**Ru-I**] was carried out under mild conditions leading to fluorinated piperidines **144** in excellent yields. Interestingly, when two enyne isomers, homopropargyl allyl amine **146** and homoallyl propargyl amine **145**, were subjected to the optimized reaction conditions, only the latter underwent cyclization, providing the corresponding 1,3-diene **147** (Scheme 82). In 2012, Portella and coworkers developed a similar strategy for the synthesis of CF_3-containing cyclopentenecarboxylic acid derivatives **148** as promising building blocks.[125] The derivatization of the final products would be a special feature of this work (Scheme 83).

On the other hand, Osipov and Dixneuf described the behavior of *N*-tethered

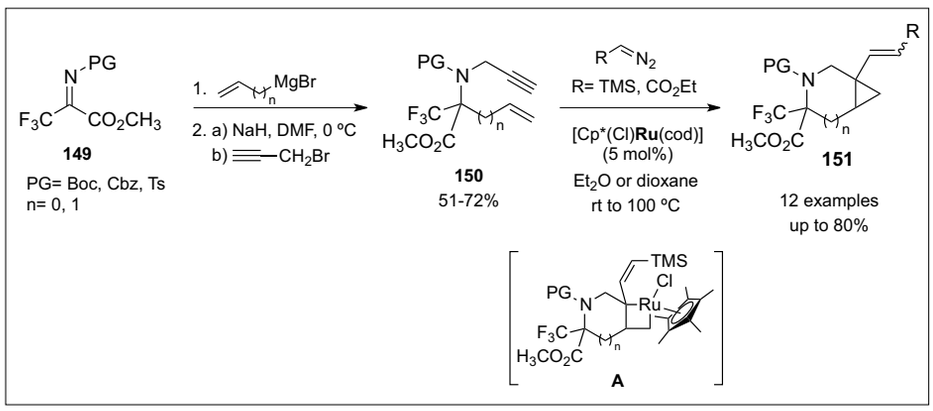


Scheme 82. Ru-catalyzed RCM of doubly unsaturated trifluoromethylated amines **143**.

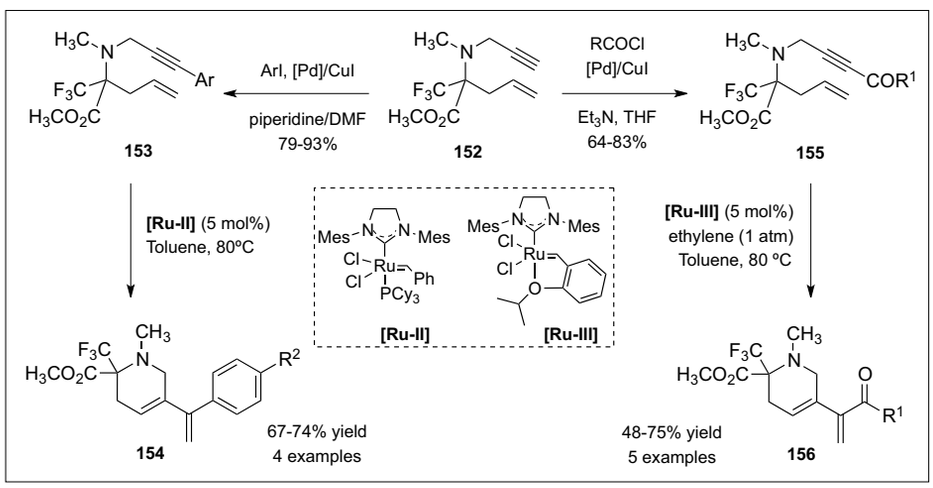


Scheme 83. Synthesis and derivatization of cyclopentenecarboxylic acid derivatives **148**.

trifluoromethyl enynes towards ruthenium-based metathesis catalysts.[126] The addition of vinyl- or allylmagnesium bromide to imines **149** followed by *N*-propargylation afforded closely related 1,6- and 1,7-enynes **150** (Scheme 84).[126b,c] However, these intermediates were not used in 'normal' RCEYM. Instead, they were treated with the ruthenium pre-catalyst [Cp*(Cl)Ru(cod)], in the presence of a diazocompound, affording the first trifluoromethylated bicyclic proline and pipecolic acid derivatives **151**, respectively. The only difference between this tandem carbene addition–cyclopropanation reaction and an RCEYM, besides the initial carbene insertion step, was the last step of the catalytic cycle based on intermediate A (Scheme 84). The authors suggested that the Cp*(Cl)Ru moiety favors reductive elimination with respect to the $(IMes)Cl_2Ru$ moiety, finally leading to metathesis.



Scheme 84. Carbene insertion/cyclopropanation tandem reaction.



Scheme 85. RCEYM on substituted fluorinated 1,7-enynes.

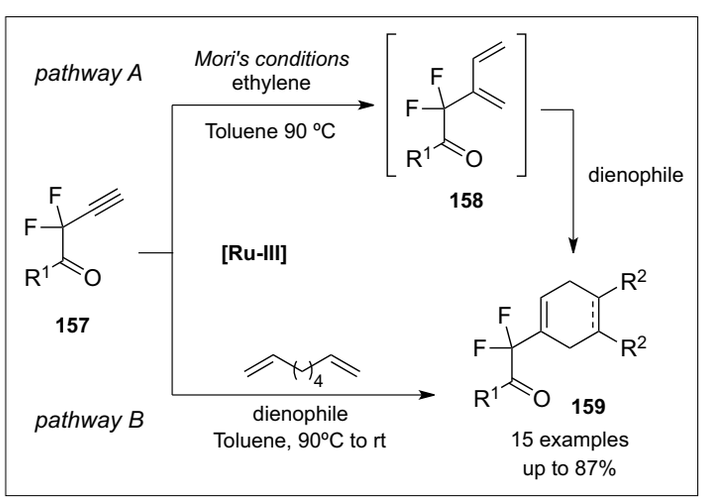
Interestingly, enynes derived from *ortho*-substituted aryl iodides were completely inert to RCEYM under different reaction conditions. The authors attributed this observation to a steric effect that would shield the triple bond, thus preventing coordination to the ruthenium center. Furthermore, terminal enyne **152** was cross-coupled with different acid chlorides affording enynones **155**, which were in turn cyclized using Hoveyda-Grubbs catalyst **[Ru-III]**, under an ethylene atmosphere to obtain **156** (Scheme 85).

In contrast to RCEYM, the intermolecular version, *i.e.* the cross-enyne metathesis (CEYM) reaction, has been much less applied in synthesis probably due to the difficulty of controlling *E/Z* selectivity in its final products. Nevertheless, the beneficial effect of ethylene gas discovered by Mori *et al*.[127] revolutionized this issue, providing 1,3-dienes efficiently. To the best of our knowledge, only a few examples of CEYM involving fluorinated alkynes have been reported so far.[128]

Fustero *et al*. disclosed a tandem one-pot CEYM/Diels-Alder reaction of difluoropropargylic alkynes with different dienophiles under Mori's conditions, giving rise to fluorinated carbo- and heterocyclic derivatives in moderate to good yields (Scheme 86, pathway A).[128b] The one-pot protocol began with the ethylene-mediated CEYM on alkynes **157** in the presence of Hoveyda-Grubbs catalyst **[Ru-III]** leading to a full conversion into the diene intermediate **158**. Then, dienophile was added at room temperature to initiate the subsequent Diels-Alder reaction.

As an alternative to Mori's conditions, the same authors reported a complementary methodology based on a tandem multicomponent protocol in which 1,7-octadiene was used as an *in situ* source of ethylene gas (Scheme 86, pathway B).[128c] In this case, the ethylene released from the RCM of 1,7-octadiene activated the ruthenium precatalyst, which in turn reacted with the alkyne **157** triggering the tandem CEYM/Diels-Alder reaction sequence.

A different tandem process involving cross metathesis but, this time, in combination with aza-Michael addition, was reported by Fustero *et al*. Based upon previous work using carbamates[129a] or



Scheme 86. Sequential CEYM/Diels-Alder reaction.

N-sulfinyl amines[129b] as nucleophilic nitrogen sources, a tandem CM/intramolecular aza-Michael reaction (IMAMR) was performed on α,α-difluorinated amides **160**, leading to interesting scaffolds such as fluorinated γ- and δ-lactams **162** (Scheme 87).[130]

In a tandem fashion, fluorinated amides **160** reacted with methyl vinyl ketone **161a** in the presence of Hoveyda-Grubbs catalyst **[Ru-III]** and titanium(IV) tetraisopropoxide as a co-catalyst, leading to the corresponding lactams **162** by IMAMR in good yields. In contrast to ketones, esters derived from ethyl acrylate **161b** stopped at the CM step (**163**) and the addition of potassium *tert*-butoxide was required to promote cyclization (Scheme 87).

One of the best ways of revealing the distinct reactivity of fluorine-containing molecules is to compare them with their non-fluorinated analogs. Thus, Hoff and coworkers exposed these differences between aryl fluorinated and non-fluorinated ketones in Ru-catalyzed asymmetric transfer hydrogenation (ATH).[131] A range of aryl fluoromethyl ketones **164** were subjected to reduction with complex **I**, observing that the gradual introduction of fluorine atoms into the α-methyl substituent of the ketone accelerated the reaction significantly and improved conversion into **165** (>99%) in most cases. However, a sharp decrease of enantioselectivity was observed for trifluoroketones (Scheme 88).

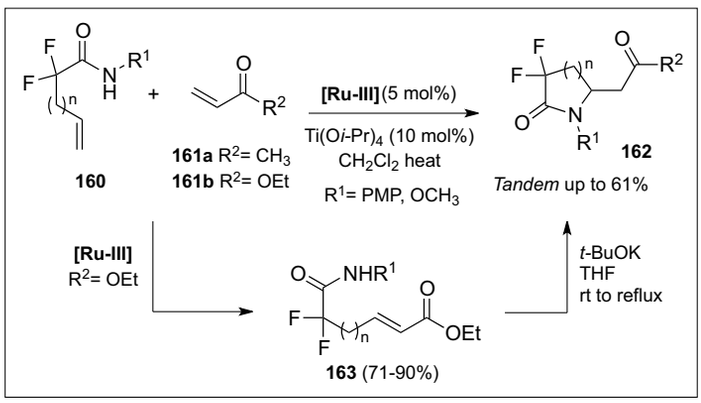
The authors attributed the lower selectivity mainly to a size effect, *i.e.* an increase in the size of the fluoroalkyl group. Also, an additional electronic effect caused by the aromatic group was suggested by calculations; this effect would play an important role in the π–π interaction between the catalyst and the substrate.

Another example was recently reported by Ikariya and coworkers in the synthesis of α-fluorinated alcohols **167** and hemiacetals **168** from fluorinated esters **166** *via* ruthenium-catalyzed selective hydrogenation (Scheme 89).[132] It is noteworthy that the hydrogenation of β-fluorinated esters or non-fluorinated methyl acetate were unsuccessful. Moreover, aliphatic α-monofluoro esters were hydrogenated in good yields but decreasing selectivity probably due to the epoxidation of the resulting monofluorinated alcohol. Although the reaction proceeded under mild conditions, the process exhibited a strong dependence on the reaction conditions as any change in temperature, amount of base, catalyst or hydrogen pressure modified the product ratio of **167/168**.

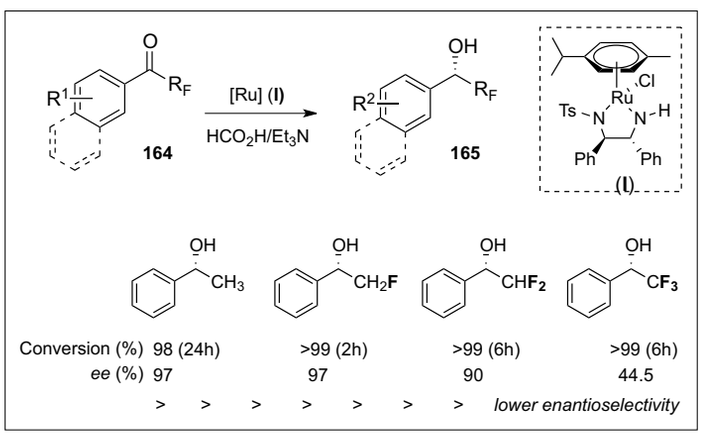
The behavior of CF_3-substituted allenes in the presence of a ruthenium complex were studied by Krische and coworkers.[133] Furthermore, an effective synthesis of 1-aryl-1-trifluoromethylallenes **174** was performed starting from trifluoromethyl ketones **170** (Scheme 90), which underwent olefination to give the corresponding methylene dibromides **171**. Through two equivalent pathways, the latter was transformed into the allylic bromide **172** and/or **173** and subsequent treatment with zinc dust led to the expected allenes **174**.

The optimized combination of $RuHCl(CO)(PPh_3)_3$ as a precatalyst and DPPM as a ligand catalyzed efficiently the reductive coupling of 1-aryl-1-trifluoromethylallenes **174** with paraformaldehyde to give CF_3-containing homoallylic alcohols **175** (Scheme 91), involving the formation of a new quaternary stereocenter. The authors proposed a mechanism based on allylruthenium species **Ia**-**Ib** as the key intermediates in the catalytic cycle. To complement this study, the final synthon **175** was employed as building block for the synthesis of different substrates such as the fluorinated nitrile **176** and the methyl ester **177** (Scheme 91).

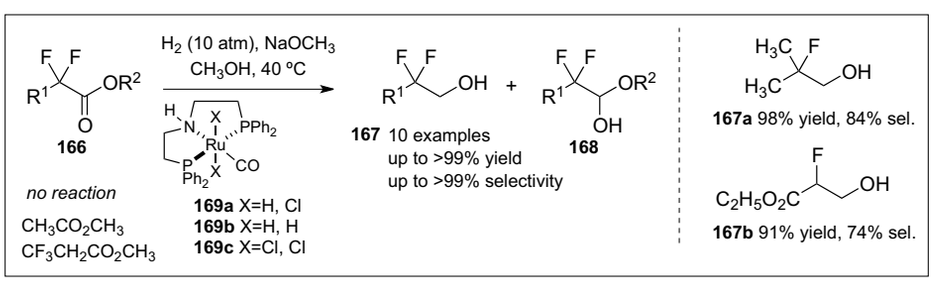
On the other hand, an efficient, regioselective cyclotrimerization of trifluoromethylated internal alkynes **178** catalyzed



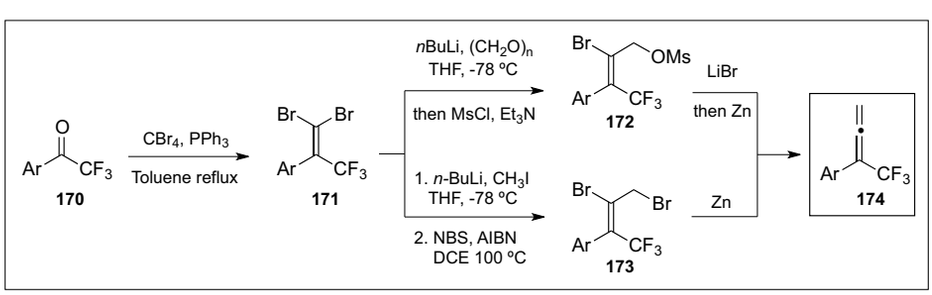
Scheme 87. Tandem CM-IMAMR sequence.



Scheme 88. Asymmetric reduction of fluorinated ketones using Ru-based catalysts.



Scheme 89. Selective hydrogenation of α-fluorinated esters catalyzed by Ru(II) catalysts **169**.



Scheme 90. Synthesis of CF_3-substituted allenes **174**.

by a $Ru_3(CO)_{12}$/2-DPPBN [2-(diphenyl phosphine)benzonitrile] catalytic system was described by Kawatsura *et al.* (Scheme 92). Although this reaction had already been reported previously using nickel[134a] and rhodium[134b] catalysis, this example was the first one catalyzed by a ruthenium complex.

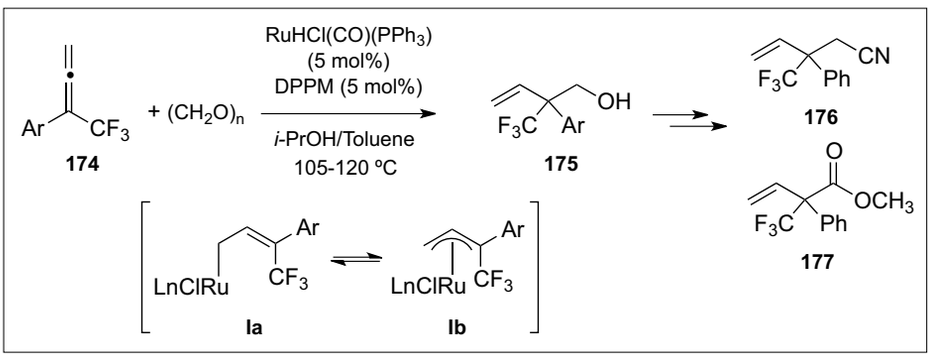
Optimization revealed that $Ru_3(CO)_{12}$ as a precatalyst with 2-DPPBN phosphine in a 2:1 specific ratio was the perfect combination for providing unsymmetrical fluorinated benzene derivatives **179** in high yields and excellent regioselectivities. The ruthenacyclopentadiene species **A** was identified as the active catalyst-intermediate (Scheme 92). In general, this method tolerated different substituents at the aromatic moiety of the alkyne; however, electron-withdrawing groups slightly favored the formation of symmetrical products **180**. A steric effect of an *ortho*-substituted aromatic group was also observed, inhibiting the process.

Up to now, we have reviewed the most recent advances in transition metal-catalyzed trifluoromethylations. Besides palladium, silver or copper, ruthenium is also able to participate in such a reaction. In general, the ruthenium complex catalyzes the redox formation of the electrophilic trifluoromethyl radical ($^{\bullet}CF_3$), which is indeed the active species in the addition to the substrate.

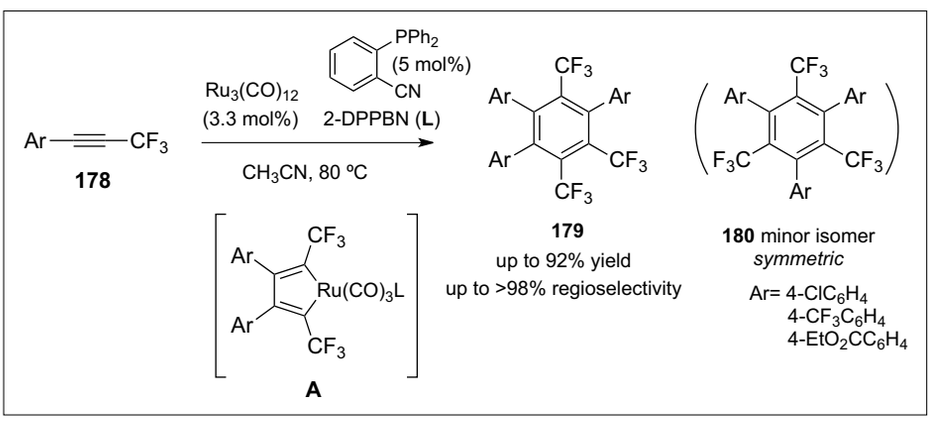
In this context, Zakarian and coworkers described the diastereoselective addition of $^{\bullet}CF_3$ to *N*-acyl oxazolidinones **181** *via in situ* generated zirconium enolates.[135] In contrast to previously reported α-trichloromethylation of titanium enolates,[136] $TiCl_4$ was not effective for fluoroalkylation and other metal halides were screened. The optimized reaction conditions established $ZrCl_4$ and $HfCl_4$ as the metal halides of choice for enolization of **181**, $Ru(PPh_3)_3Cl_2$ as the best catalyst and trifluoromethyl or perfluoroalkyl/benzyl iodides (R_FI) **182** as the fluoroalkyl radical source (Scheme 93).

Additionally, Zakarian and coworkers demonstrated by NMR experiments the formation *in situ* of zirconium enolates **184** by reaction of **181** with $ZrCl_4$ and Et_3N at room temperature. The freshly formed enolate was then trapped by $^{\bullet}CF_3$ species, which were in turn generated from iodotrifluoromethane **182** by a Ru(II)-catalyzed redox process (Scheme 93). A final single electron transfer from intermediate **II**, in equilibrium with **I**, to Ru(III) complex led to the final CF_3-substituted oxazolidinone **183**, initiating a new catalytic cycle.

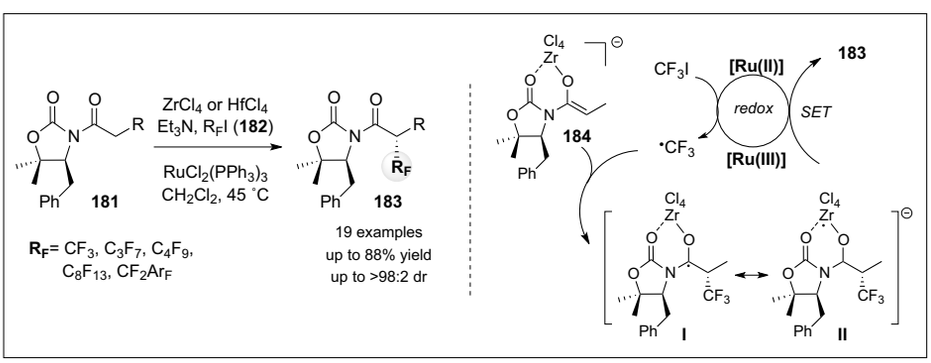
The group of Gouverneur have perfectly combined this kind of process with the effect of visible-light on ruthenium catalysts, *i.e.* photoredox catalysis.[137] Thus, the photoredox-based trifluoromethylation of allylsilanes **185** was developed under mild conditions, employing Togni reagent **XVII** or Umemoto reagent **XV** (Fig. 2) as CF_3 radical source.[137a] The photoredox catalyst of choice was $Ru(bpy)_3Cl_2{\cdot}6H_2O$ which, under visible-light irradiation, re-



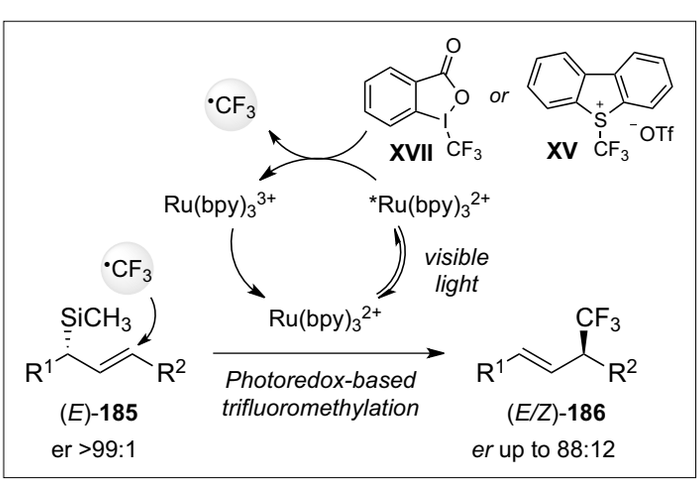
Scheme 91. Ru-catalyzed reductive coupling of CF_3-containing allenes to paraformaldehyde.



Scheme 92. Ru-catalyzed regioselective cyclotrimerization of trifluoromethylated alkynes.



Scheme 93. Asymmetric trifluoromethylation of *N*-acyl oxazolidinones.



Scheme 94. Photoredox-based trifluoromethylation of allylsilanes **185**.

sulted in excited-state [Ru*]-species involved in $^{\bullet}CF_3$ generation (Scheme 94).

Arguably, the silyl group in the starting substrate would be the steering group since it was crucial to get good regio- and stereoselectivity. Additionally to this effect, the CF_3 source was found to be determining on reactivity as well as stereoselectivity. In general, this method allowed the synthesis of allylic CF_3 products **186** as the *E* isomer as the major product by using Togni reagent **XVII** (Fig. 2). However, Umemoto reagent **XV** provided higher *E*-selectivity to the detriment of the chemical yield. Furthermore, trifluoromethylation as well as addition of other fluorine grouping (*e.g.* CF_2CF_3 group) were successfully performed on enantioenriched substrates, although a loss of the optical purity was observed for the *E*-isomer.

The same authors also worked on the *net* fluoroform (CF_3H) addition to alkenes and alkynes employing separately CF_3 radical and hydrogen atom sources, *i.e.* Umemoto reagent **XV** and methanol respectively.[137b] Besides being the solvent of the reaction, the role of methanol as a hydrogen donor should be particularly highlighted since an external hydrogen source such as Hantzsch ester was not required. Thus, the hydrotrifluoromethylation would be based on a similar mechanism to the aforementioned (Scheme 95) in which a Ru-based photoredox process generated $^{\bullet}CF_3$ species to be added regioselectively to the alkene/alkyne **187/188**. Final oxidation of methanol by the strong oxidant $Ru(bpy)_3^{3+}$ regenerated the catalyst on one hand and, on the other hand, it transferred a hydrogen atom to the radical intermediate **189** leading to the expected terminal CF_3-substituted compounds **190** and/or **191**.

3. Conclusions

This review aims to give a systematic overview of the most relevant aspects of organofluorine chemistry and some of the most representative transition metals such as Co, Au, Pd, Ru, and in greater detail, Ag and Cu. More specifically, the unique, differential reactivity of these transition metals towards organofluorine compounds have received the most attention. Because of the tremendous advances achieved in this field over the last few years, this review may provide valuable complementary information on this issue, including preferably those examples reported in the last three years. Indeed, this promising field is significantly growing, as much in academy as in industry and, as a result, a future review about the further developments in this area should be considered in a short time.

Acknowledgments

We thank the Spanish Ministerio de Ciencia e Innovación (CTQ2010-19774-C02-01) and the Generalitat Valenciana (PROMETEO/2010/061) for their financial support. S.C. thanks the Spanish government for a Juan de la Cierva contract.

Received: March 27, 2014

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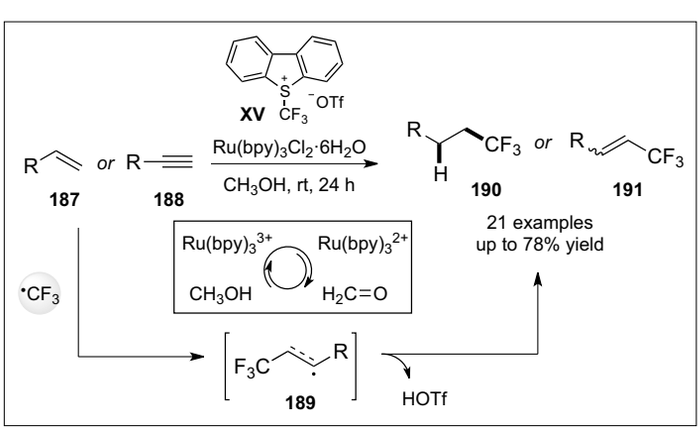

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