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A Convergent, Unified Approach to Functionalized Fluoro- and Trifluoromethyl Alkenes

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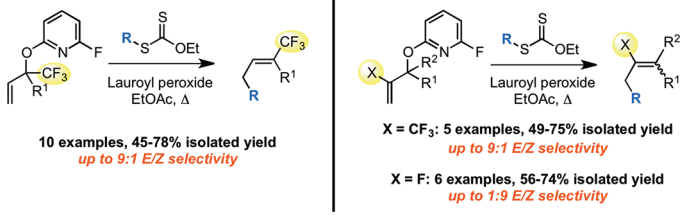
ABSTRACT



A modular, convergent, and operationally simple route to trifluoromethyl alkenes and vinyl fluorides involving a unique carbon−oxygen bond homolysis is reported. Highly functionalized trifluoromethyl alkenes and vinyl fluorides were obtained in good yields and good selectivity.

It is well established that the inclusion of fluorine atoms into a given molecule modifies profoundly and uniquely its chemical stability, bioavailability, and lipophilicity.[1] Not surprisingly, organofluorine derivatives are in increasing demand in the pharmaceutical, agrochemical, and material sciences areas.[2] Fluorinated molecules now account for a quarter to a third of all medicines and agrochemicals on the market.[3] Since fluorine-containing natural products are very rare, organofluorine compounds must be man-made, which nicely underlines the fundamental role of organic chemists in drug discovery and process development.[4] In this context, the introduction of the electron-withdrawing trifluoromethyl group has recently gained some importance. While a number of methods for the construction of sp^2 carbon−CF_3 bonds have been reported, processes allowing for the assembly of trifluoromethyl alkenes are still relatively scarce.[5,6] We now report a convergent and general method for the preparation of trifluoromethyl alkenes and vinyl fluorides.

As proposed by Baran et al.,[4] approaches to trifluoromethyl arenes and heteroarenes may be divided into two categories: those using a prefunctionalized substrate

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(programmed trifluoromethylations) and those exploiting the substrate's inherent reactivity (innate trifluoromethylations, Figure 1, eq 1). These two strategies have proven to be complementary and efficient for most purposes. Recent methods for the synthesis of trifluoromethyl alkenes are directly inspired from the programmed trifluoromethylation (Figure 1, eq 2). Despite recent progress, this particular strategy still faces a lack of generality with respect to the olefin substitution pattern and functional group tolerance.[6] Moreover, the preparation of trifluoromethyl alkenes from aldehydes and ketones developed by Hiyama's group enables the stereocontrolled assembly of elaborated structures but requires several synthetic steps and is rather incompatible with polar functions.[7]

Recent work from our laboratory has demonstrated that 2-fluoropyridyl derivatives of allylic alcohols are versatile intermediates for the synthesis of highly functionalized olefins.[8] We envisioned installing a CF_3 substituent directly on the double bond or alternatively on the carbon adjacent to the oxygen of the 2-fluoropyridyl moiety in order to generate the desired trifluoromethyl alkenes (Scheme 1). This dual approach would impart tremendous flexibility to this strategy. We were, however, concerned that the presence of the strong electron-withdrawing CF_3 group could dramatically affect both the first addition of the radical derived from the xanthate and, even more critically, the key β-fragmentation step because of a polarity mismatch between the adduct radical and the departing fluoropyridyloxyl radical, both of which are electrophilic in character. With these concerns in mind we evaluated the feasibility of both of these strategies.

Using dihydrocinnamaldehyde as a test starting aldehyde we could readily prepare the corresponding fluoropyridyl ether **1a** by the addition of the vinyl anion derived from commercially available 2-bromo-3,3,3-trifluoroprop-1-ene,[9] followed by aromatic nucleophilic substitution on 2,6-difluoropyridine.

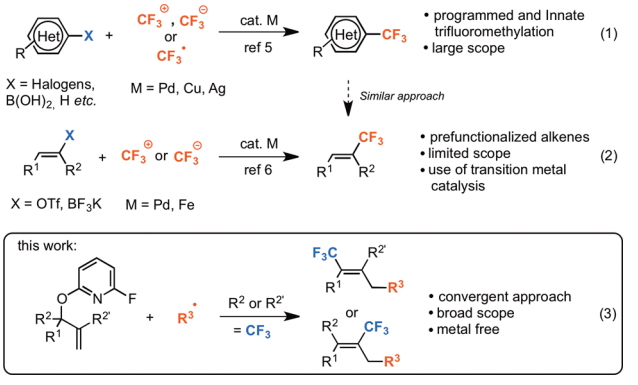
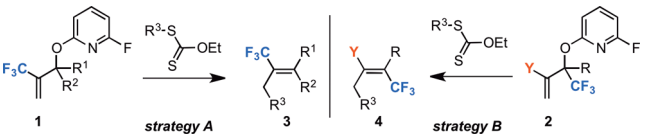


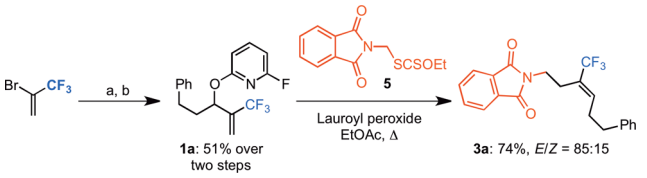
Figure 1. Synthetic approaches for the construction of $C(sp^2)-CF_3$ bonds.

To our delight, exposure of olefin **1a** and xanthate **5** to a stoichiometric amount of lauroyl peroxide in refluxing ethyl acetate furnished the corresponding trifluoromethyl alkene **3a** in good yield and good selectivity in favor of the most thermodynamically stable geometrical isomer (E/Z = 85:15, Scheme 2).

Scheme 1. Strategies for the Preparation of Trifluoromethyl Olefins

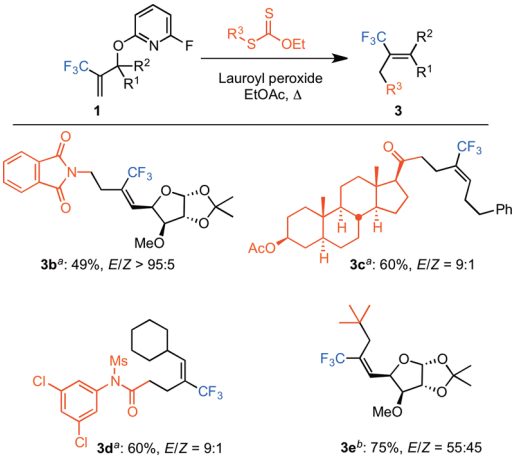


Scheme 2. Evaluation of Strategy A[a]



[a] Reaction conditions: (a) s-BuLi, Et_2O, −105 °C, 10 min then dihydrocinnamaldehyde, −105 °C to −50 °C; (b) 2,6-difluoropyridine, NaH, DMSO, 60 °C.

The formation of trifluoromethyl alkenes was extended to more elaborate derivatives (Figure 2). Both the xanthate and the olefin can be complex structures, as shown by adducts **3b**, stemming from a deoxyglucose derived olefin, or **3c**, arising from a steroid xanthate. Noteworthy, the xanthate technology allows electron-rich, electron-neutral, and even, gratifyingly, electron-deficient radicals to react with the electrophilic trifluoromethyl alkene.



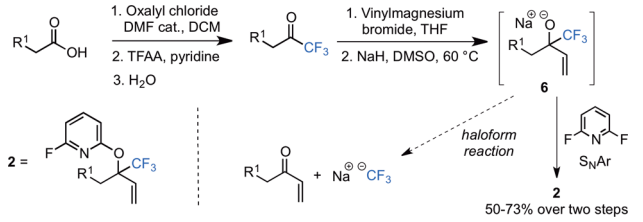
[a]Reaction conditions: olefin (2 equiv), xanthate (1 equiv), lauroyl peroxide was added in 30 mol % portions (with respect to the xanthate) every hour (5-8 h). [b]Reaction conditions: olefin (1 equiv), xanthate (2 equiv), lauroyl peroxide was added in 30 mol % portions (with respect to the olefin) every hour (5-8 h).

Figure 2. Synthesis of trifluoromethyl olefins via strategy A.

We next examined the second approach utilizing precursors **2** as the trifluoromethyl partner (Scheme 1). The requisite allylic alcohol precursors were synthesized in good yields by addition of vinyl magnesium bromide to various trifluoromethyl ketones. The latter were prepared from the corresponding carboxylic acids by a procedure we developed some time ago and which has since been used by industry to prepare trifluoromethyl ketones on the several hundred kilogram scale.[10] We were relieved to find that it was possible to substitute the 2,6-difluoropyridine by operating at 60 °C to overcome the poor nucleophilicity of alcoholate **6** (Scheme 3). Our concern was that the harsher conditions would cause elimination of a trifluoromethyl anion (the well-known haloform reaction which also operates in the fluorine series).[11]

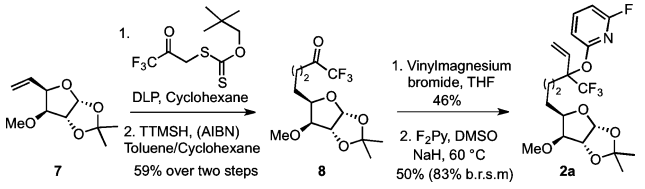
With the required substrates in hand, we explored the scope of the reaction with respect to the olefin and xanthate component (Figure 3). Generally, 2 equiv of the starting olefin were used to simplify the purification, but we found that performing the reactions with an excess of xanthate (2 equiv) does not impact the outcome (**4g** and **4h**) and can even be beneficial in some cases (**4a**).

Scheme 3. Synthesis of Precursors **2**



Enones (**4d**), α-chloro-ketones (**4j**), ketals (**4g** and **4h**), free alcohols (**4d**), amides (**4f**), ketones (**4a**, **4d**, **4i**, and **4j**), and oxazolidinones (**4g**) were well tolerated under the mild reaction conditions (Figure 3). Modifying steroid side chains by installing CF_3 moieties is a challenging problem of some interest for biological studies, in particular in the context of Vitamin D3 and sterols bearing a 24-methyl group in their side chain.[12] In this respect, the bile acid derived adducts **4a** and **4e** are particulary noteworthy. Even a xanthate derived from 9-fluorohydrocortisone could be readily converted into highly complex trifluoromethyl steroid **4d**. It is interesting to note that the glucose derived trifluoromethyl alkene partner **2a** used to make adducts **4h** and **4g** was itself obtained from trifluoromethyl ketone **8**, prepared by a xanthate addition, as shown in Scheme 4.[13,14]

Scheme 4. Exploitation of the Xanthate Radical Mediated Addition/Reduction for the Preparation of Trifluoromethyl Ketone **8**



Finally, the direct introduction of an α-chloro-ketone motif in **4j** is remarkable and offers numerous possibilities for further ionic or radical transformations.[15,8a]

Monofluoroalkenes may be accessed by a similar approach. Vinyl fluorides are known to be good bioisosteres of amides and have been used as metabolically stable and conformationally constrained peptide mimics in medicinal chemistry. Not surprisingly, this motif is found in a number of compounds covering a range of pharmacological activities.[16]

The precursor fluoroallylic alcohols were obtained according to literature procedures starting from dodecene[17a,b] and 3-aryl-1,2-allenes.[17c] The radical addition/elimination process was straightforward, and we could access various

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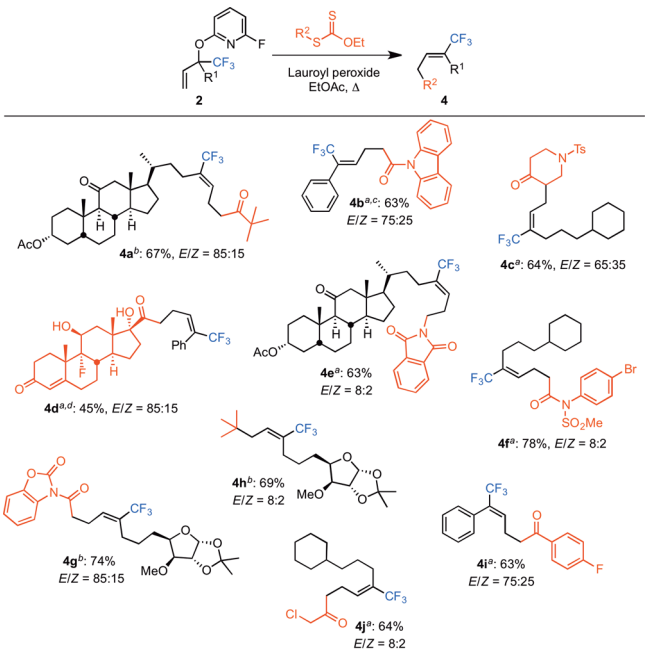


[a]Reaction conditions: olefin (2 equiv), xanthate (1 equiv), lauroyl peroxide was added in 30 mol % portions (with respect to the xanthate) every hour (5-8 h). [b]Reaction conditions: olefin (1 equiv), xanthate (2 equiv), lauroyl peroxide was added in 30 mol % portions (with respect to the olefin) every hour (7-10 h). [c]The reaction was run in DCE. [d]The reaction was run in a 8:2 mixture of DCE/propanol.

Figure 3. Scope of the radical olefination process via strategy B.

functionalized vinyl fluorides in moderate to good yields using identical reaction conditions (Figure 4). The (*Z*)-isomer is obtained as the major product except when the double bond is substituted by an aryl group (**10b** and **10d**) as determined by nOeSY experiments. The same effect was observed for trifluoromethyl alkenes **4b**, **4d**, and **4i**, resulting in these cases in the preferential formation of the (*E*)-isomer. The causes underlying this difference are unclear at the moment.

The modularity and flexibility of the xanthate transfer technology is further illustrated by examples **10c** and **10d**, since the precursor xanthates **11** and **12** arise by a prior addition of xanthates **13** and **5** to vinyl acetate and *N*-phenyl maleimide respectively (Scheme 5).

In summary, we have developed a unified, convergent, and practical approach to trifluoromethyl alkenes and vinyl fluorides. Many of the products obtained in the present

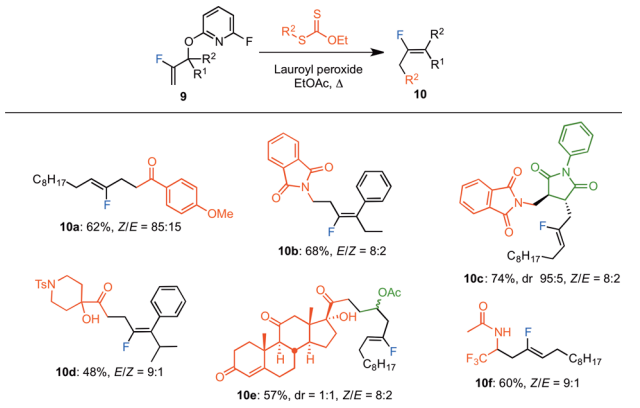
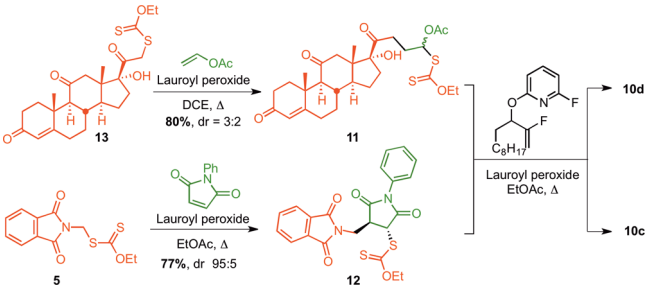


Figure 4. Scope of the radical olefination for vinyl fluorides. Reaction conditions: olefin (2 equiv), xanthate (1 equiv), lauroyl peroxide was added in 30 mol % portions (with respect to the xanthate) every hour (5−7 h). For **10c**, the reaction was run in refluxing DCE.

Scheme 5. Combination of the Xanthate Addition with the Allylation Reaction



work would be exceedingly tedious to produce by more conventional ionic or organometallic routes.

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Supporting Information Available. Experimental procedures and characterization spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.