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Trifluoromethylthiolation | *Very Important Paper* |

Trifluoromethylthiolation of α-Chloroaldehydes: Access to Quaternary SCF_3-Containing Centers

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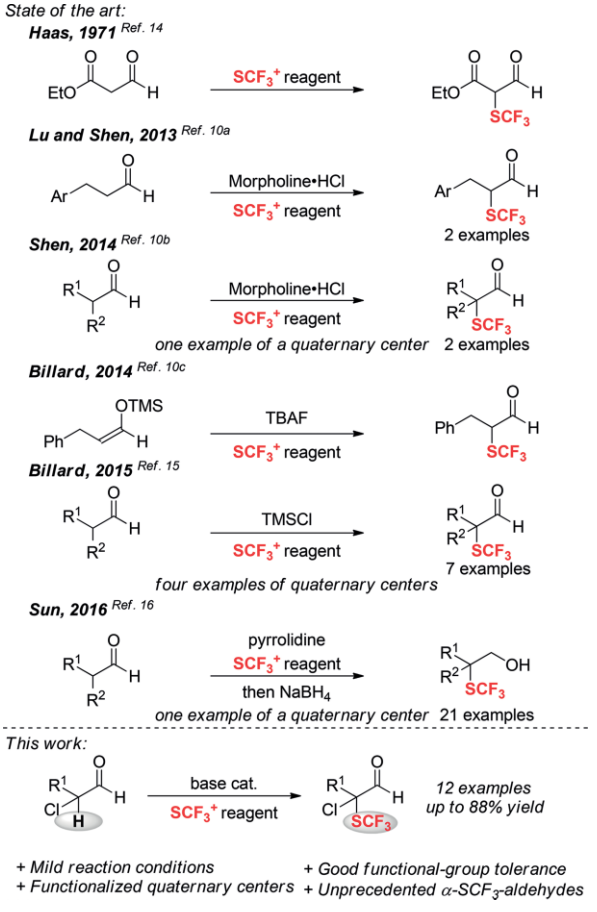
Abstract: In this study, a straightforward methodology was developed to access quaternary α-trifluoromethylthiolated chloroaldehydes. Using the Munavalli reagent as the electrophilic SCF_3 source, a base-catalyzed trifluoromethylthiolation reaction with a panel of α-chloroaldehydes was successfully achieved under mild reaction conditions. The α-trifluoromethylthiolated chloroaldehydes were obtained in moderate to high yields (up to 88 %). This approach demonstrated a good functional-group tolerance and offered access to highly functionalized quaternary trifluoromethylthiolated aldehydes, inaccessible so far. The development of an enantioselective version was investigated by using a chiral phase-transfer catalyst, giving the enantioenriched product in moderate enantiomeric excess.

Introduction

Molecules containing a fluorine atom and a fluorinated group are ubiquitous in our daily life and more particularly in agrochemicals and medicinal chemistry[1] due to their unique features.[2] Therefore, organofluorine chemistry is nowadays considered as a key research field and considerable advances are continuously made by the organic chemistry community to provide powerful synthetic tools as original transformations and newly-designed emergent fluorinated groups.[3] Among these emergent groups, the SCF_3 group[4] features attractive physicochemical properties like its high lipophilicity (Hansch hydrophobic parameter, $\pi = 1.44$)[5] and its electron-withdrawing character.[6] Moreover, its potential has already been demonstrated in molecules of interest such as the insecticide Fipronil or the Toltrazuril, a coccidiostatic drug, commercialized by BASF and Bayer, respectively.

Therefore, the quest for the introduction of this fluorinated residue onto molecules inspired the scientific community to develop new strategies, offering a large tool box for the incorporation of this fluorinated group onto various scaffolds.[7] To date, the formation of a $C(sp^2)$–SCF_3 bond has been intensively studied involving transition-metal-promoted transformations, organocatalyzed reactions or radical pathways. Conversely, the functionalization of $C(sp^3)$ centers remains underdeveloped and further progress has to be made to broaden the access to this class of compounds. So far, most of the strategies relied on the use of SCF_3-containing building blocks to construct more complex molecules[8] or the direct introduction of the SCF_3 resi-



Scheme 1. Trifluoromethylthiolation of aldehydes: state of the art and proposed strategy.

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due onto aliphatic compounds.[9] In the last case, the α-functionalization of a carbonyl group appeared as a privileged and efficient approach to provide the targeted C–SCF_3 bond (Scheme 1).

The α-trifluoromethylthiolation of carbonyl compounds connected to a tertiary carbon center offers a straightforward access to SCF_3-substituted quaternary centers. The current methods relied on the functionalization of highly reactive carbonyl compounds such as oxindoles, benzofuranones, malonates and β-keto esters with electrophilic SCF_3 sources via 1) organocatalyzed,[10] 2) transition-metal-catalyzed[11] and 3) base-promoted[12] trifluoromethylthiolation reactions. Alternatively, the direct introduction of a SCF_3 group onto amides, *N*-acyl oxazolidinones and ketones was also studied, albeit restricted to a handful of examples.[10h,13]

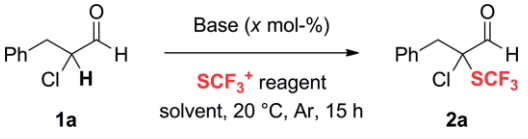
In sharp contrast, the construction of a quaternary SCF_3–C(sp^3) center on aldehyde derivatives at the α-position is scarce (Scheme 1). Since the pioneering work by Haas in 1971,[14] few reports dealt with the synthesis of α-trifluoromethylthiolated aldehydes. Lu and Shen reported the trifluoromethylthiolation of hydrocinnamaldehyde derivatives using enamine catalysis with the morpholine hydrochloride salt in the presence of an electrophilic SCF_3 source.[10a] A similar transformation was then reported by Shen using the *N*-trifluoromethylthiosaccharin reagent.[10b] In both cases, only two examples were depicted. Billard and co-workers reported the trifluoromethylthiolation of silyl enol ethers and described a single example with an aldehyde.[10c] The same group then developed a complementary approach to access α-trifluoromethylthiolated aldehydes under acid-catalysis.[15] The next year, Sun depicted the α-trifluoromethylthiolation of a wide range of aldehydes using enamine catalysis, although a single tertiary aldehyde was functionalized.[16] It is worth to mention that the methods for the α-trifluoromethylthiolation of aldehydes are restricted to very few examples. In addition, the access to α-SCF_3-containing quaternary centers is even more rare.

Therefore, the development of complementary and more general approaches to afford aldehydes bearing a α-trifluoromethylthiolated quaternary center is an appealing task. In that context, we turned our attention to the α-chloroaldehydes as a readily available starting material. Herein, we report the base-catalyzed trifluoromethylthiolation of α-chloroaldehydes, offering an original access to new and valuable SCF_3-containing fluorinated building blocks bearing a quaternary C–SCF_3 center.

Results and Discussion

At the outset of the study, α-chlorophenylpropanal **1a** was selected as the model substrate. When **1a** was reacted in the presence of the Munavalli reagent **I** and a stoichiometric amount of K_2CO_3 as a base at room temperature, the expected product **2a** was observed in 17 % yield (Table 1, entry 1). Using a catalytic amount of DABCO (15 mol-%), **2a** was still detected albeit in traces (entry 2). Then, other electrophilic sources were evaluated (entries 3–4), the Haas reagent **II** being the most efficient one. To further improve the yield, several solvents were tested, revealing that DMF provided the expected product **2a** in a higher 72 % yield (entries 5–9). Using the best reaction conditions and switching the electrophilic source from the Haas reagent **II** to the Munavalli one **I**, **2a** was obtained in a slightly better ^{19}F NMR yield (80 %) and was isolated in 78 % yield (entry 10).

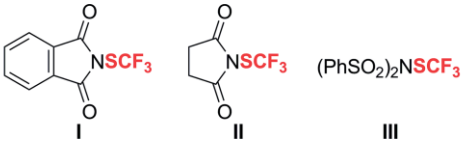
Table 1. Optimization of the base-catalyzed trifluoromethylthiolation of the α-chloroaldehyde **1a**.[a]



1a **2a**

Entry	Base (*x* mol-%)	SCF_3^+ reagent	Solvent	Yield **2a** [%][b]
1	K_2CO_3 (200)	I	CH_2Cl_2	17
2	DABCO (15)	I	CH_2Cl_2	3
3	DABCO (15)	II	CH_2Cl_2	22
4	DABCO (15)	III	CH_2Cl_2	NR
5	DABCO (15)	II	1,4-dioxane	9
6	DABCO (15)	II	THF	8
7	DABCO (15)	II	CH_3CN	35
8	DABCO (15)	II	toluene	4
9	DABCO (15)	II	DMF	72
10	DABCO (15)	I	DMF	80 (78)[c]

[a] Reaction conditions: **1a** (0.2 mmol), SCF_3^+ reagent (0.2 mmol), base (*x* mol-%), solvent (2 mL), 20 °C, 15 h, argon. [b] Yields determined by ^{19}F NMR analysis of the crude reaction mixture using α,α,α-trifluorotoluene as an internal standard. [c] Yield of isolated product. NR = no reaction.



With the best reaction conditions in hands, the scope of the transformation was studied (Scheme 2). First, the substitution on the aryl group of the α-chlorophenylpropanal backbone was studied. Aryls bearing an electron-donating group (OMe, **2b**) and an electron-withdrawing one (CF_3, **2c**) were efficiently functionalized; albeit with a somehow lower yield in the case of **2c**. The naphthyl derivative (**1d**) was also readily converted into **2d** in a decent 78 % yield. The transformation was not restricted to arylated propanal derivatives since α-chloro nonanal **1e** was trifluoromethylthiolated in a high 77 % yield. The reaction turned out to be compatible with a chlorine atom as a substituent, furnishing the expected compound **2f**. Various functional groups were suitable as demonstrated by the functionalization of benzyl-protected alcohol (**1g**) and phthalimide (**1h**) derivatives. Trifluoromethylthiolated aldehydes substituted with azide (**1i**) and cyano (**1j**) groups were efficiently obtained in 64 % and 63 % yields, respectively. From a synthetic point of view, this functional-group tolerance opened great perspectives in term of post-functionalization reactions and for the construction of more complex molecules using these fluorinated chemical platforms. The versatility of this transformation was further demonstrated by the trifluoromethylthiolation reaction of molecules of interest such as citronellal (**1k**) and oleic acid (**1l**), offering an access to the corresponding SCF_3-containing products in moderate yields (Scheme 2).

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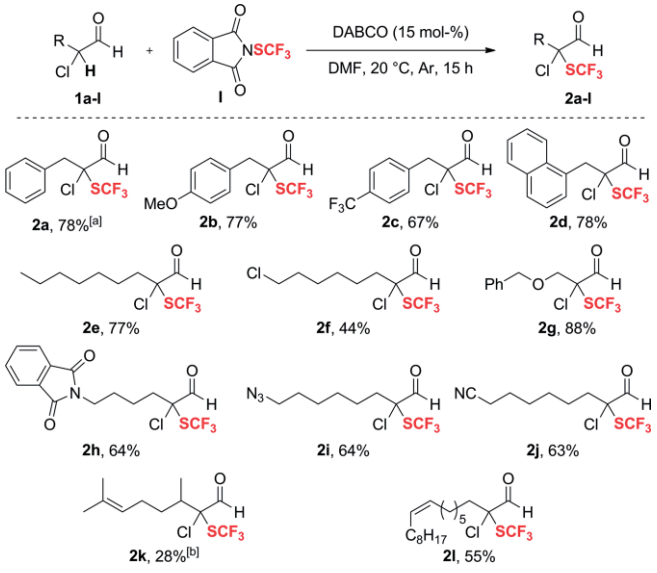
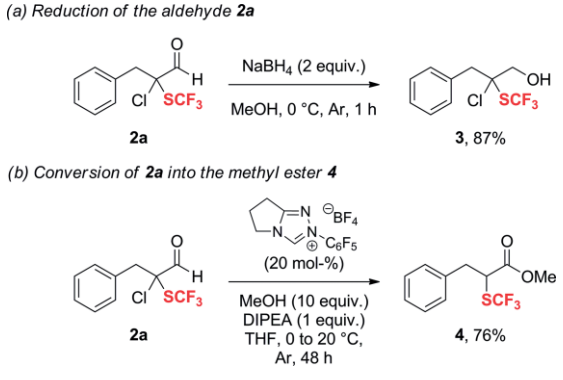


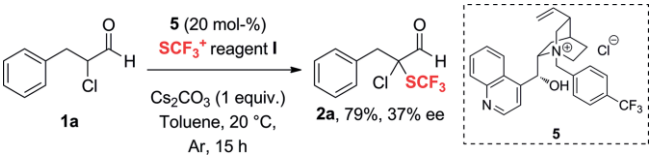
Scheme 2. Trifluoromethylthiolation of α-chloroaldehydes. Reaction conditions: **1** (0.5 mmol), electrophilic SCF_3 reagent **I** (1 equiv.), DABCO (15 mol-%), DMF (0.1 M), 20 °C, 15 h, argon. Yields of isolated products were reported. [a] Reaction performed on 0.2 mmol scale. [b] A diastereoisomeric ratio of 77:23 was obtained.

To showcase the synthetic utility of these functionalized scaffolds, post-functionalization reactions were conducted. The aldehyde **2a** was smoothly reduced with $NaBH_4$ into the corresponding alcohol **3** in 87 % yield. Then, the aldehyde **2a** was efficiently converted in one-step into the corresponding methyl ester **4** in 76 % yield via NHC catalysis (Scheme 3).[17] This method afforded a straightforward and functional-group tolerant access to α-SCF_3 ester derivatives under mild conditions, which are usually synthesized using a stoichiometric amount of a strong base (LDA) from the corresponding esters.[10c]



Scheme 3. Post-functionalization reactions. DIPEA = *N*,*N*-diisopropylethylamine.

Finally, the catalytic asymmetric trifluoromethylthiolation of α-chloroaldehydes was studied using **1a** and a phase-transfer catalyst. After extensive investigations, we found that 1-{[4-(trifluoromethyl)phenyl]methyl}cinchonidinium chloride **5** was the best catalyst. Using **5** (20 mol-%), Cs_2CO_3 as a base in toluene, the enantioenriched aldehyde **2a** was isolated in good yield and moderate enantiomeric excess (79 %, 37 % *ee*, Scheme 4).



Scheme 4. Catalytic enantioselective trifluoromethylthiolation of the α-chloroaldehyde **1a** under phase-transfer catalysis.

Conclusions

In summary, a novel synthetic approach was developed for the synthesis of the highly functionalized quaternary α-trifluoromethylthiolated aldehydes. Using a catalytic amount of DABCO, various aldehydes were functionalized in moderate to good yields under mild conditions. The transformation showed a good functional-group tolerance. The enantioselective trifluoromethylthiolation reaction was studied by means of phase-transfer catalysis affording the expected aldehyde in good yield and moderate enantiomeric excess. These original fluorinated building blocks are of particular interest due to the presence of various functional groups (CHO, Cl and SCF_3) and would be very useful to access new value-added SCF_3-containing molecules that have been inaccessible so far.

Experimental Section

In an oven-dried tube equipped with a magnetic stirrer, DABCO (0.075 mmol, 15 mol-%) was added to a solution of the α-chloroaldehyde derivative **1** (0.5 mmol, 1 equiv.) and phthalimide-SCF_3 reagent **I** (0.5 mmol, 1 equiv.) in DMF (5 mL) under argon. The reaction mixture was stirred at 20 °C for 15 h. Then, brine (15 mL) was added and the aqueous layer was extracted with Et_2O (3 × 15 mL). Organic layers were combined and washed with brine (2 × 15 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure at 20 °C under 100 mbar. The residue was purified by flash column chromatography on silica gel (petroleum ether/dichloromethane) to afford the desired trifluoromethylthiolated ester derivative **2**.

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Keywords: Fluorinated compounds · Trifluoromethylthiolation · Quaternary centers · Building blocks · Phase-transfer catalysis · Aldehydes

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Trifluoromethylthiolation

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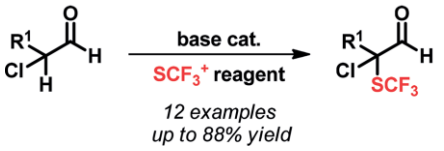
Trifluoromethylthiolation of α-Chloroaldehydes: Access to Quaternary SCF_3-Containing Centers



- *Mild reaction conditions*
- *Functionalized quaternary centers*
- *Good functional-group tolerance*
- *Unprecedented α-SCF_3-aldehydes*

A new access to highly functionalized quaternary α-trifluoromethylthiolated aldehydes was developed. Using the electrophilic Munavalli reagent, the direct introduction of a SCF_3 group onto a panel of α-chloroaldehydes was successfully achieved under mild reaction conditions via a base-catalyzed trifluoromethylthiolation reaction.

Base-catalyzed trifluoromethylthiolation of alpha-chloroaldehydes #OutstandingOrganics

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