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Conversion of MT-sulfone to a trifluoromethyl group by IF_5: the application of an MT-sulfone anion as a trifluoromethyl anion equivalent†

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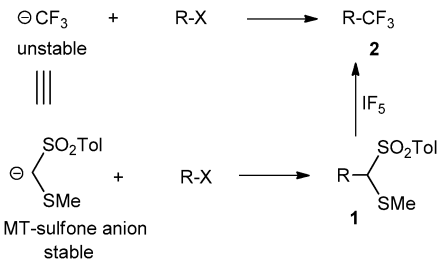
An MT-sulfone group was converted to a trifluoromethyl group by treatment with IF_5 after an alkylation reaction. Therefore, an MT-sulfone anion can be used as a trifluoromethyl anion equivalent. The formal asymmetric Michael-addition of a trifluoromethyl anion to crotonaldehyde was also performed.

The introduction of a trifluoromethyl group into a molecule is a challenging area of organic chemistry because both a trifluoromethyl anion and its cation are difficult to generate and use.[1] A carbon–carbon bond forming reaction between a trifluoromethyl anion and alkyl halides is the most fundamental method for introducing a trifluoromethyl group into the molecules, and a trifluoromethyl copper species was most successfully used, especially, for the introduction of a trifluoromethyl group into the aromatic ring or vinylic carbon.[2,3] However, a good yield cannot be expected from a reaction of the trifluoromethyl copper species with aliphatic alkyl halides.[4] Although trifluoromethyltrimethylsilane has been used as a trifluoromethyl anion equivalent,[5] it is rarely used in the S_N2 reaction with alkyl halides owing to the low yield of the expected products and the formation of inseparable by-products.[4c,6] On the other hand, MT-sulfone {(methylsulfanyl)methyl tolyl sulfone} is known to afford a stable anion species by treatment with a base under mild conditions, and its subsequent reaction with alkyl halides gives alkylated derivatives **1**.[7] We found that the MT-sulfone group in **1** can be converted to a trifluoromethyl group by the reaction with IF_5.[8] Therefore, the MT-sulfone can be used to introduce the trifluoromethyl group into the substrate (Scheme 1).

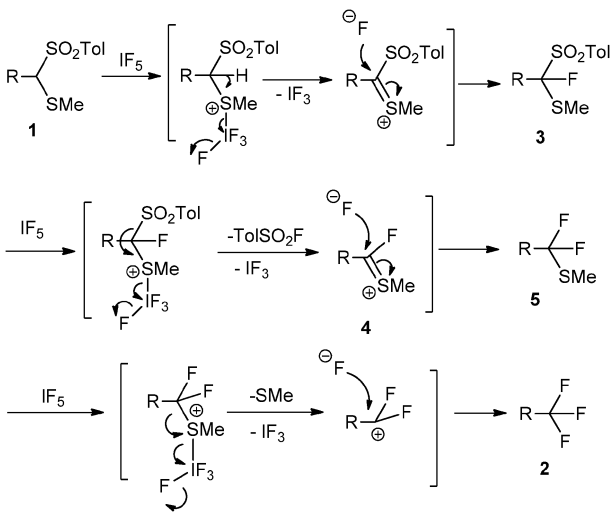
The reaction of **1** with IF_5 was performed under various conditions, and the best result was obtained by carrying out the reaction in Et_3N–5HF using 6 eq. of IF_5 at 60 °C for 48 h.[9] In this reaction, the presence of a methylsulfanyl group in **1** is critical, and the phenyl alkyl sulfone is inert to IF_5. During the reaction, the formation of tosyl fluoride was observed. From these observations, it can be assumed that the reaction



Scheme 1

proceeds as follows: the oxidative fluorination of **1** by IF_5 initially occurred to afford **3**.[10] In the second step, the tosyl group was eliminated as tosyl fluoride to afford a sulfonium salt **4**, which was converted to difluorosulfide **5** by the attack of a fluoride ion. Finally, the methylsulfanyl group in **5** was substituted by a fluoride ion to afford the trifluoromethylated product **2** (Scheme 2).

Under these conditions, an alkylated MT-sulfone **1a** was converted to 1,1,1-trifluoroalkane **2a** in good yield. Furthermore, a functional group such as an ester, an amide, and a chloride in **1** is tolerable under these conditions, and the functionalized trifluoromethyl compounds could be obtained as shown in Table 1.



Scheme 2

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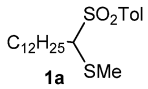
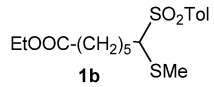
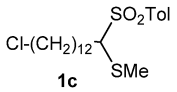
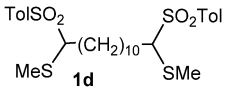
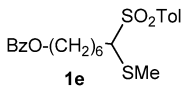
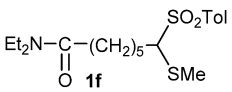
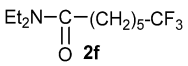
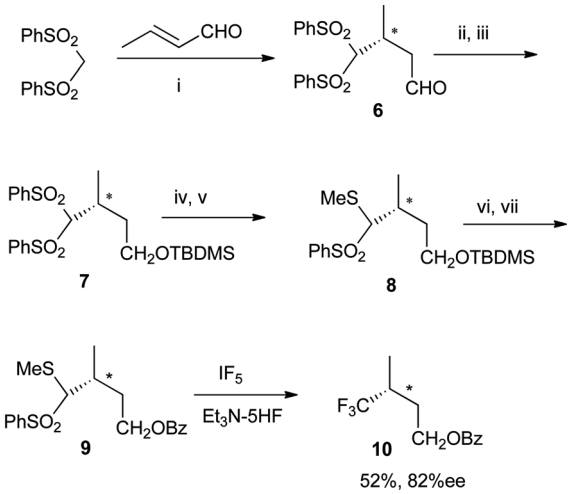
Table 1 The reaction of MT-sulfone derivative with IF_5[a]

Substrate	Product	Yield[b] (%)
 **1a**	$C_{12}H_{25}$–CF_3 **2a**	87
 **1b**	EtOOC–$(CH_2)_5$–CF_3 **2b**	75
 **1c**	Cl–$(CH_2)_{12}$–CF_3 **2c**	81
 **1d**	CF_3–$(CH_2)_{10}$–CF_3 **2d**	71
 **1e**	BzO–$(CH_2)_6$–CF_3 **2e**	73
 **1f**	 **2f**	78[c]

[a] If otherwise not mentioned, the reaction was carried out using 6 eq. of IF_5/Et_3N-5HF at 60 °C for 48 h. [b] Isolated yield based on the substrate used. [c] 8 eq. of IF_5/Et_3N-5HF was used.

Recently, the asymmetric trifluoromethylation reaction has received much attention and many elegant methods for producing a compound having a trifluoromethyl group at its asymmetric center have been reported.[11] However, the asymmetric Michael-addition of the trifluoromethyl anion to α,β-unsaturated carbonyl compounds has not yet been reported. Therefore, we applied our method to introduce a trifluoromethyl group at the β-position of the carbonyl group enantioselectively. The asymmetric Michael-addition of MT-sulfone catalyzed by an organocatalyst was unsuccessful owing to the low acidity of MT-sulfone (pK_a = 23.4).[12] On the other hand, the organocatalyst-catalyzed asymmetric Michael-addition of bis(phenylsulfonyl)methane (pK_a = 12.5)[13] to α,β-unsaturated aldehydes is known.[14] Therefore, the Michael-addition of bis(phenylsulfonyl)methane to crotonaldehyde was performed in the presence of (*S*)-2-(diphenyltrimethylsiloxy)methylpyrrolidine, and the resulting adduct **6** was reduced to an alcohol.[15] After the protection of alcohol with TBDMS, one sulfonyl group was removed by SmI_2[16] and a methylsulfanyl group was introduced to afford the (methylsulfanyl)methyl phenyl sulfone derivative **8**. Then, the protecting group of **8** was converted to a benzoyl group, and the resulting benzoate **9** was subjected to a reaction with IF_5/Et_3N-5HF. Under the conditions described above, the (methylsulfanyl)methyl phenyl sulfone group was converted to the trifluoromethyl group and 3-trifluoromethyl-1-butyl benzoate **10** was obtained in 52% yield with 85% ee. During the reactions, no racemization occurred, and the trifluoromethyl group could be introduced at the β-position of the carbonyl group enantioselectively (Scheme 3).



i, 20 mol% of (*S*)-2-(diphenyltrimethylsiloxy)methylpyrrolidine, toluene
ii, $NaBH_4$, 78% from bis(phenylsulfonyl)methane, iii TBDMSCl, imidazole, 97%, iv SmI_2, 93% v BuLi, $MeSSO_2Me$, 79%
vi TBAF, vii BzCl, Et_3N, 72% from **8**

Scheme 3

We found that the MT-sulfone group can be converted to a trifluoromethyl group by the reaction with IF_5. As the MT-sulfone affords a stable anion species by treatment with a base, and its subsequent reaction with alkyl halides gives alkylated derivatives, an MT-sulfone anion can be used as a trifluoromethyl anion equivalent. We also performed the formal asymmetric Michael-addition of a trifluoromethyl anion to crotonaldehyde, where the trifluoromethyl group was introduced at the β-position of crotonaldehyde enantioselectively.

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