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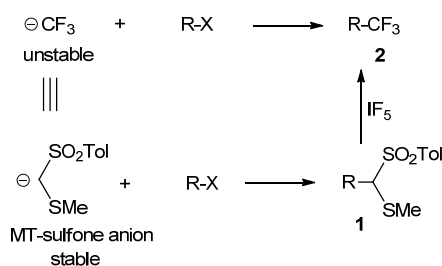
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# Conversion of MT-Sulfone to a Trifluoromethyl group by IF<sub>5</sub><sup>1</sup>: the Application of an MT-Sulfone Anion as a Trifluoromethyl Anion Equivalent

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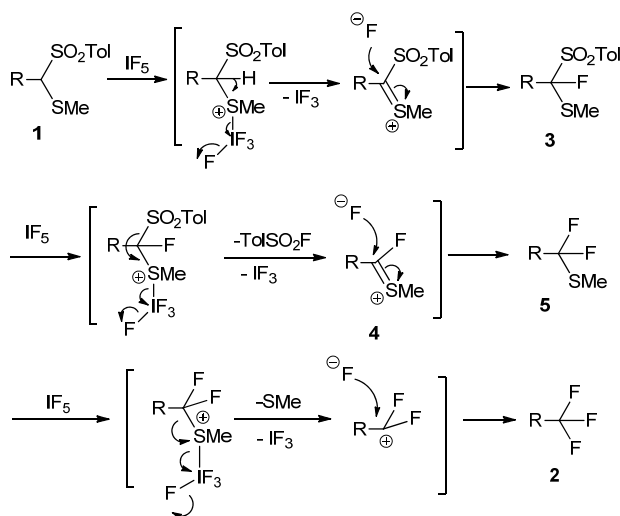
An MT-sulfone group was converted to a trifluoromethyl group by treatment with IF<sub>5</sub> after an alkylation reaction. Therefore, an MT-sulfone anion can be used as a trifluoromethyl anion equivalent. The formal asymmetric Michael-addition of a trifluoromethyl anion to crotonaldehyde was also performed.

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<sup>2</sup>. A carbon-carbon bond forming reaction between a trifluoromethyl anion and alkyl halides is the most fundamental method for introducing a trifluoromethyl group in 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<sup>3,4</sup>. However, a good yield cannot be expected from a reaction of the trifluoromethyl copper species with aliphatic alkyl halides<sup>5</sup>. Although trifluoromethyltrimethylsilane has been used as a trifluoromethyl anion equivalent<sup>6</sup>, it is rarely used in the S<sub>N</sub>2 reaction with alkyl halides owing to the low yield of the expected products and the formation of inseparable by-products<sup>5c,7</sup>. 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**<sup>8</sup>. We found that the MT-sulfone group in **1** can be converted to a trifluoromethyl group by the reaction with IF<sub>5</sub><sup>9</sup>. Therefore, the MT-sulfone can be used to introduce the trifluoromethyl group to the substrate (Scheme 1).



Scheme 1

The reaction of **1** with IF<sub>5</sub> was performed under various conditions, and the best result was obtained by carrying out the reaction in Et<sub>3</sub>N-5HF using 6 eq of IF<sub>5</sub> at 60 °C for 48 h. In this reaction, the presence of a methylsulfanyl group in **1** is critical, and the phenyl alkyl sulfone is inert to IF<sub>5</sub>. During the reaction, the formation of tosyl fluoride was observed. From these observations, it can be assumed that the reaction proceeds as follows: the oxidative fluorination of **1** by IF<sub>5</sub> initially occurred to afford **3**<sup>10</sup>. 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).



## Scheme 2

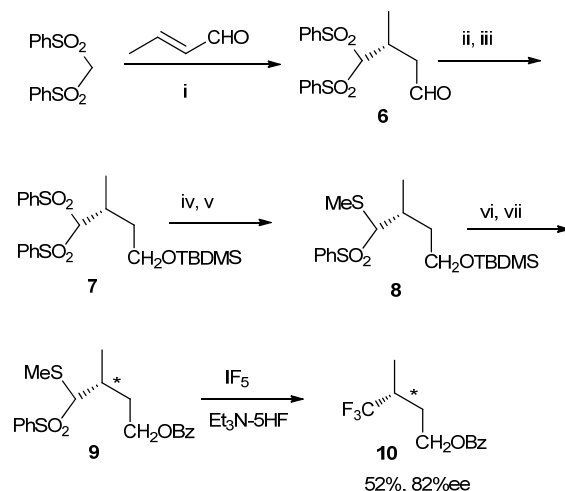
Under these conditions, an alkylated MT-sulfone **1a** was converted to 1,1,1-trifluoroalkane **2a** in good yield. Furthermore, a functional group such as an ester, an amide, and a chloride in **1** is tolerable under these conditions, and the functionalized trifluoromethyl compounds could be obtained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

Table 1. The reaction of MT-sulfone derivative with IF<sub>5</sub><sup>a</sup>

Substrate	Product	Yield (%) <sup>b</sup>
$\begin{array}{c} \text{SO}_2\text{Tol} \\   \\ \text{C}_{12}\text{H}_{25} \\   \\ \text{SMe} \\ \mathbf{1a} \end{array}$	$\begin{array}{c} \text{C}_{12}\text{H}_{25}\text{-CF}_3 \\ \mathbf{2a} \end{array}$	87
$\begin{array}{c} \text{SO}_2\text{Tol} \\   \\ \text{EtOOC-(CH}_2)_5 \\   \\ \text{SMe} \\ \mathbf{1b} \end{array}$	$\begin{array}{c} \text{EtOOC-(CH}_2)_5\text{-CF}_3 \\ \mathbf{2b} \end{array}$	75
$\begin{array}{c} \text{SO}_2\text{Tol} \\   \\ \text{Cl-(CH}_2)_{12} \\   \\ \text{SMe} \\ \mathbf{1c} \end{array}$	$\begin{array}{c} \text{Cl-(CH}_2)_{12}\text{-CF}_3 \\ \mathbf{2c} \end{array}$	81
$\begin{array}{c} \text{SO}_2\text{Tol} \\   \\ \text{MeS-(CH}_2)_{10}\text{-SO}_2\text{Tol} \\   \\ \text{SMe} \\ \mathbf{1d} \end{array}$	$\begin{array}{c} \text{CF}_3\text{-(CH}_2)_{10}\text{-CF}_3 \\ \mathbf{2d} \end{array}$	71
$\begin{array}{c} \text{SO}_2\text{Tol} \\   \\ \text{BzO-(CH}_2)_6 \\   \\ \text{SMe} \\ \mathbf{1e} \end{array}$	$\begin{array}{c} \text{BzO-(CH}_2)_6\text{-CF}_3 \\ \mathbf{2e} \end{array}$	73
$\begin{array}{c} \text{SO}_2\text{Tol} \\   \\ \text{Et}_2\text{N-C-(CH}_2)_5 \\    \\ \text{O} \\   \\ \text{SMe} \\ \mathbf{1f} \end{array}$	$\begin{array}{c} \text{Et}_2\text{N-C-(CH}_2)_5\text{-CF}_3 \\    \\ \text{O} \\ \mathbf{2f} \end{array}$	78 <sup>c</sup>

<sup>a</sup> If otherwise not mentioned, the reaction was carried out using 6 eq of IF<sub>5</sub>/Et<sub>3</sub>N-5HF at 60 °C for 48h. <sup>b</sup> Isolation yield based on substrate used. <sup>c</sup> 8 eq of IF<sub>5</sub>/Et<sub>3</sub>N-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<sup>11</sup>. However, the asymmetric Michael-addition of the trifluoromethyl anion to  $\alpha,\beta$ -unsaturated carbonyl compounds has not yet been reported. Therefore, we applied our method to introduce a trifluoromethyl group at the  $\beta$ -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 ( $pK_a = 23.4$ <sup>12</sup>). On the other hand, the organocatalyst-catalyzed asymmetric Michael-addition of bis(phenylsulfonyl)methane ( $pK_a = 12.5$ <sup>13</sup>) to  $\alpha,\beta$ -unsaturated aldehydes is known<sup>14</sup>. 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<sup>15</sup>. After the protection of alcohol with TBDMS, one sulfonyl group was removed by SmI<sub>2</sub><sup>16</sup> and a methylsulfonyl group was introduced to afford the (methylsulfonyl)methyl phenyl sulfoxide 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<sub>5</sub>/Et<sub>3</sub>N-5HF. Under the conditions described above, the (methylsulfonyl)methyl phenyl sulfoxide 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  $\beta$ -position of the carbonyl group enantioselectively (Scheme 3).



i, 20 mol% of (S)-2-(diphenyltrimethylsiloxy)methylpyrrole, toluene  
 ii, NaBH<sub>4</sub>, 78% from bis(phenylsulfonyl)methane, iii TBDMSCl, imidazole, 97%, iv Sml<sub>2</sub>, 93% v BuLi, MeSSO<sub>2</sub>Me, 79%  
 vi TBAF, vii BzCl, Et<sub>3</sub>N, 72% from 5

Scheme 3

## Conclusions

We found that the MT-sulfone group can be converted to a trifluoromethyl group by the reaction with IF<sub>5</sub>. 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 to β-position of crotonaldehyde enantioselectively.

## Notes and references

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- 15 1 IF<sub>5</sub> decomposes in air emitting hazardous HF fume, and, therefore, it should be carefully handled in a bench hood with rubber-gloved hands, and the reaction was carried out in a Teflon™ bottle (a glassware cannot be used).
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