An Efficient Method for the Preparation of Chiral Mosher's Acid Analogues

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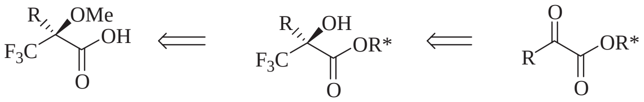
A diastereoselective trifluoromethylation of chiral α-keto esters derived from isosorbide with $TMSCF_3$ in the presence of a Lewis-base catalyst gave the corresponding trifluoromethylated α-hydroxy esters in good yields with moderate to high diastereomeric excesses.

Recently, organofluorine compounds have focused increased attention in the field of pharmaceutical and agricultural chemicals because of their unique physical and biological properties.[1] Out of many, a trifluoromethyl group of organofluorine compounds is one of the most important fluorine-containing functional groups that has the electronegativity similar to that of oxygen and also has a large hydrophobic nature. Mosher's acid (MTPA), for example, is a valuable reagent for determining enantiomeric excesses of alcohols or amines and examples for its preparation have therefore been reported ever since.[2] However, this convenient reagent is not fully used because the signals of certain diastereotopic groups from the MTPA overlap with another one. Then, some MTPA analogues that might solve this problem were developed, but yet there were only a few chiral ones.[3,4] Therefore, it remains to be an important topic to find more efficient and convenient procedure for the preparation of chiral MTPA analogues (Scheme 1).


MTPA

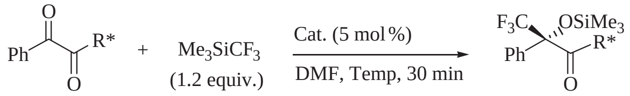
Scheme 1. Preparation of chiral MTPA derivatives.

In our previous communication, a catalytic trifluoromethylation of various carbonyl compounds or imines with $TMSCF_3$ in the presence of lithium acetate was reported.[5] This nucleophilic addition of a trifluoromethyl group to α-keto ester is one of the most facile and straightforward methods for the preparation of Mosher's acid analogues. In order to demonstrate the usefulness of this Lewis base-catalyzed reaction, the application of trifluoromethylation to the synthesis of chiral trifluoromethylated α-hydroxy acid, the immediate precursor of Mosher's acid, was then planned. In this communication, we would like to describe an efficient method for the preparation of MTPA derivatives by trifluoromethylation of chiral esters that are easily prepared from a commercially available chiral alcohol by using a Lewis-base catalyst.

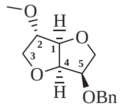
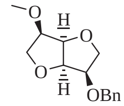
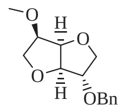
The starting chiral α-keto esters **1a**–**1c** were prepared from carbohydrate derivatives such as isomannide and isosorbide which were commercially available and could be used in large quantities at low cost.[6–8]

In the first place, trifluoromethylations of α-keto esters **1a**–**1c** with $TMSCF_3$ were tried in the presence of a catalytic amount of Lewis bases in DMF (Table 1). The reaction of **1a** was carried out in the presence of 5 mol % of lithium acetate at 0 °C to room temperature in DMF and the corresponding product was obtained in moderate yield with low diastereoselectivity (Entry 1). The effect of counter cations of the acetate was also examined so as to improve the diastereoselectivity of this reaction. However, there was no improvement observed (Entry 2). On the other hand, the desired products were obtained in good yields with moderate diastereoselectivities when chiral α-keto esters **1b** or **1c** derived from 2-endo-hydroxy carbohydrate were used as substrates (Entries 3 and 5). It was found that the substituents at C-2 position of carbohydrate played an important role in controlling the stereoselectivity in this reaction. Interestingly, it showed no selectivity when it was carried out in the presence of cesium fluoride as a Lewis base in DME (Entry 7).

Table 1. Trifluoromethylation of chiral α-keto esters



1a–1c **2a–2c**

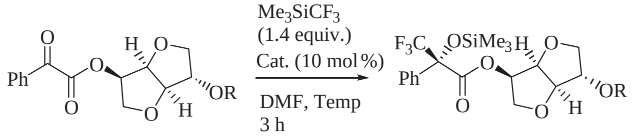
Entry	R*	Cat.	Temp/°C	Yield[a]/%	(*S*:*R*)[b]
1	 **1a**	AcOLi	0–rt	82	56:44
2		$AcONBu_4$	0	77	55:45
3	 **1b**	AcOLi	0–rt	88	79:21
4		$AcONBu_4$	0	75	79:21
5	 **1c**	AcOLi	0–rt	84	83:17
6		$AcONBu_4$	0	81	83:17
7		CsF	0	84	49:51[c]

[a]Yield was determined by ^{19}F NMR analysis (270 MHz) using $PhOCF_3$ as an internal standard. [b]Ratio was determined by ^{19}F NMR analysis. [c]DME was used as a solvent.

Next, the reaction was tried by using a phenoxide anion instead of an acetate one because Lewis-base catalyst could activate $TMSCF_3$ at low temperatures (Table 2). Consequently, the corresponding trifluoromethylated adducts were obtained in high yields with good diastereoselectivities when the reactions were carried out at −45 °C, and the diastereoselectivity increased at the lower temperature (Entry 3). The yields depended on the nature of a counter cation and the lithium was found most effective (Entries 3–5).

In order to monitor the influence of protecting groups of alcohols on the stereoselectivity, the reaction of chiral α-keto esters with various protecting groups were examined. The diastereoselectivities were not improved when several benzyl groups or

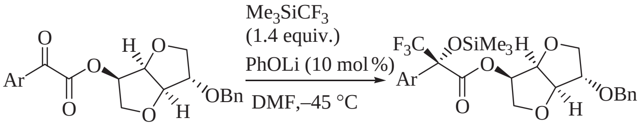
Table 2. Trifluoromethylation of chiral α-keto esters derived from isosorbide



Entry	R	Cat.	Temp/°C	Yield[a]/%	(*S*:*R*)[b]
1	$PhCH_2$	PhOLi	0	72	82:18
2		PhOLi	−20	83	85:15
3		PhOLi	−45	82	90:10
4		PhONa	−45	77	90:10
5		PhOK	−45	65	90:10
6	$4\text{-}ClPhCH_2$	PhOLi	−45	81	90:10
7	1-Naphthylmethyl	PhOLi	−45	82	90:10
8	*t*-Bu	PhOLi	−45	80	88:12
9	Me	PhOLi	−45	85	89:11

[a]Yield was determined by ^{19}F NMR analysis (270 MHz) using $PhOCF_3$ as an internal standard. [b]Ratio was determined by ^{19}F NMR analysis.

Table 3. Synthesis of Mosher's acid analogues



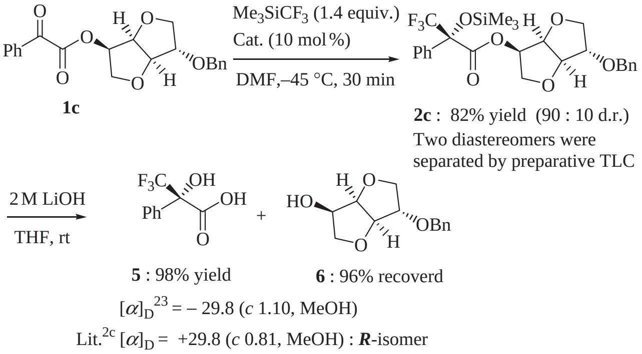
3a–3c **4a–4c**

Entry	Ar		Time/h	Yield[a]/%	(*S*:*R*)[b]
1	4-MeOPh	**3a**	5	81	92:8
2	4-ClPh	**3b**	3	80	88:12
3	2-Naphthyl	**3c**	3	73	89:11

[a]Yield was determined by ^{19}F NMR analysis (270 MHz) using $PhOCF_3$ as an internal standard. [b]Ratio was determined by ^{19}F NMR analysis.

alkyl groups such as *t*-butyl or methyl ones were used as hydroxy-protecting groups (Entries 6–9). It was also found that the stereoselectivity of this reaction was not influenced by the nature of the protecting groups.

Next, the reaction of various chiral α-keto esters with $TMSCF_3$ was tried by using a catalytic amount of PhOLi in DMF (Table 3). Chiral α-keto esters having electron-donating or -withdrawing groups on their benzene rings reacted smoothly to afford the trifluoromethylated adducts in high yields with good diastereosectivities (Entries 1–3). These trifluoromethylated adducts were easily purified by column chromatography and optically pure major diastereomers were isolated. The absolute configuration of newly formed chiral center was assigned to be the *S* configuration, which was determined by the optical rotation of the corresponding α-hydroxy acid **5** after the complete hydrolysis of the α-hydroxy-α-trifluoromethylated ester **2c** (Scheme 2).[9] The chiral auxiliary, the monobenzylated isosorbide **6**, was recovered in quantitative yield.



Scheme 2. Determination of absolute configuration.

It is noted that the chiral α-keto esters, prepared by introducing chiral auxiliary derived from isosorbide to benzoylformic acids, were successfully applied to the asymmetric reaction and enantiomerically pure α-hydroxy-α-trifluoromethylated esters were obtained in high yields with good diastereoselectivities. Further investigation on this reaction is now in progress.

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References and Notes

1 For a review on trifluoromethylation, see: a) R. P. Singh, J. M. Shreeve, *Tetrahedron* **2000**, *56*, 7613. b) G. K. S. Prakash, M. Mandal, *J. Fluorine Chem.* **2001**, *112*, 123. c) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119.

2 a) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543. b) W. E. Hull, K. Seeholzer, M. Baumeister, I. Ugi, *Tetrahedron* **1986**, *42*, 547. c) Y. L. Bennani, K. P. M. Vanhessche, K. B. Sharpless, *Tetrahedron: Asymmetry* **1994**, *5*, 1473. d) C. Pareja, E. Martin-Zamora, R. Fernandez, J. M. Lassaletta, *J. Org. Chem.* **1999**, *64*, 8846.

3 a) G. Blay, I. Fernandez, A. Marco-Aleixandre, B. Monje, J. R. Pedro, R. Ruiz, *Tetrahedron* **2002**, *58*, 8565. b) G. K. S. Prakash, P. Y. B. Török, G. A. Olah, *Synlett* **2003**, 527.

4 a) W. Zhuang, N. Gathergood, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **2001**, *66*, 1009.

5 a) T. Mukaiyama, Y. Kawano, H. Fujisawa, *Chem. Lett.* **2005**, *34*, 88. b) Y. Kawano, H. Fujisawa, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 422. c) Y. Kawano, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 894.

6 Isosorbide and isomannide are easily obtained by dehydration of sorbitol and mannitol, respectively. a) L. F. Wiggins, R. Montgomery, *J. Chem. Soc.* **1945**, 4. b) R. Montgomery, L. F. Wiggins, *J. Chem. Soc.* **1946**, 390.

7 For the reactions using isosorbide or isomannide, see: a) O. Sageot, D. Monteux, Y. Langlois, C. Riche, A. Chiaroni, *Tetrahedron Lett.* **1996**, *37*, 7019. b) A. Loupy, D. Monteux, *Tetrahedron Lett.* **1996**, *37*, 7023. c) A. Loupy, D. A. Monteux, *Tetrahedron* **2002**, *58*, 1541. d) M.-H. Xu, W. Wang, L.-J. Xia, G.-Q. Lin, *J. Org. Chem.* **2001**, *66*, 3953. e) L.-L. Huang, M.-H. Xu, G.-Q. Lin, *J. Org. Chem.* **2005**, *70*, 529.

8 For the preparation of isosorbide or isomannide derivatives, see: D. Abenhaim, A. Loupy, L. Munnier, R. Tamion, F. Marsais, G. Queguiner, *Carbohydr. Res.* **1994**, *261*, 255.

9 The configurations of **4a**–**4c** were assigned by comparing ^{19}F NMR chemical shifts of **2c** with that of **4a**–**4c**.

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