Asymmetric Trifluoromethylation of Ketones with (Trifluoromethyl)trimethylsilane Catalyzed by Chiral Quaternary Ammonium Phenoxides

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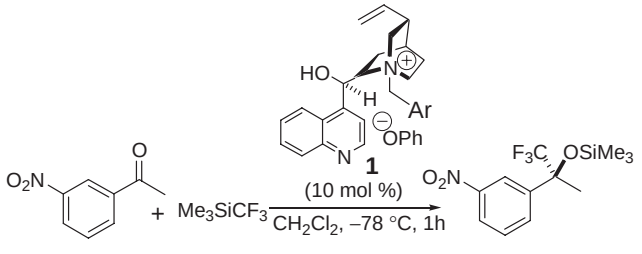
Asymmetric trifluoromethylation of ketones with (trifluoromethyl)trimethylsilane catalyzed by cinchonidine-derived quaternary ammonium phenoxides proceeded smoothly to afford the trifluoromethylated compounds in high yields with moderate to high enantioselectivities.

In recent years, trifluoromethylated compounds have attracted considerable interests in the fields of pharmacy and agrochemistry.[1] The introduction of a strong electron-withdrawing trifluoromethyl group has brought notable changes in physical, chemical, and biological properties of the compounds. Also, development of some useful medicines[2] that have trifluoromethyl moiety at the asymmetric center further emphasized the importance of the synthesis of chiral trifluoromethylated compounds. Although a few methods have been reported on the asymmetric introduction of a trifluoromethyl group into ketones,[3] the scope of these methods remained modest in enantiomeric excess or substrate specificity. Recently, it was reported from our laboratory that the novel types of cinchonidine-derived quaternary ammonium phenoxides were useful substances as new asymmetric catalysts.[4] In order to establish an efficient method for the preparation of chiral trifluoromethylated-alcohols, this chiral ammonium phenoxides were then applied to the Lewis base-catalyzed trifluoromethylation.[5] In this communication, we would like to report on enantioselective trifluoromethylation of ketones with (trifluoromethyl)trimethylsilane in the presence of a catalytic amount of cinchonidine-derived quaternary ammonium phenoxide.

In the first place, a reaction of 3-nitroacetophenone (**2a**) with (trifluoromethyl)trimethylsilane in the presence of 10 mol % of various cinchonidine-derived quaternary ammonium phenoxides **1a**–**1i**[6] in CH_2Cl_2 at −78 °C for 1 h was tried (Table 1). When the catalyst **1a** having a simple phenyl group was used, trifluoromethylation proceeded smoothly to afford (2*S*)-[1,1,1-trifluoro-2-(3-nitrophenyl)propan-2-yloxy]trimethylsilane (**3a**) in 93% yield with poor enantioselectivity (13% ee) (Entry 1). However, these enantioselectivities turned to increase up when substituents such as 2-naphthyl (**1d**), 3,5-bis(trifluoromethyl) phenyl (**1f**), and 3,5-diphenylphenyl (**1g**) groups were introduced (Entries 4, 6, and 7). It was shown next that the enantiomeric excess of **3a** increased up to 60% ee when catalysts having bulky substituents on the nitrogen atom of cinchonidine such as **1h** (Ar = 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl or **1i** (Ar = 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl) were used (Entries 8 and 9).

Next, the effect of solvents was examined (Table 2). When the catalyst **1i** was used in toluene at −78 °C, trifluoromethylation did not proceed because the catalyst scarcely dissolved in toluene (Entry 1). While the use of polar solvents such as THF or EtCN gave **3a** with low enantioselectivity (19% ee or 58% ee, Entries 3 and 4), the use of less-polar solvent as toluene increased the enantiomeric excess of **3a** up to 79% ee (Entry 2). In order to carry out the reaction at lower temperature

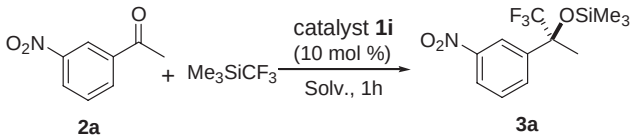
Table 1. Effect of catalysts



Entry	Catalyst	Yield[a]/%	% ee[b,c]
1	**1a**: Ar = Ph	93	13
2	**1b**: Ar = 2,6-$F_2C_6H_3$	98	8
3	**1c**: Ar = 1-Naphthyl	99	11
4	**1d**: Ar = 2-Naphthyl	97	26
5	**1e**: Ar = 3,5-(*t*-Bu)$_2C_6H_3$	96	17
6	**1f**: Ar = 3,5-$(CF_3)_2C_6H_3$	95	34
7	**1g**: Ar = 3,5-$(Ph)_2C_6H_3$	95	50
8	**1h**: Ar = 3,5-[3,5-(*t*-Bu)$_2C_6H_3$]$_2C_6H_3$	99	61
9	**1i**: Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$	99	62

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (volume ratio = 20:1) as a solvent. [c]Enantiomeric excess was measured after desilylation of **3a**.

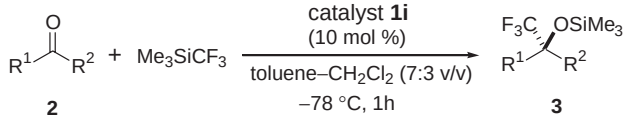
Table 2. Effect of solvents



Entry	Solv.	Temp/°C	Yield[a]/%	% ee[b,c]
1	Toluene	−78	N.R.	—
2	Toluene	−20	99	79
3	EtCN	−20	65	19
4	THF	−78	92	58
5	Toluene/CH_2Cl_2 = 7/3	−78	98	87

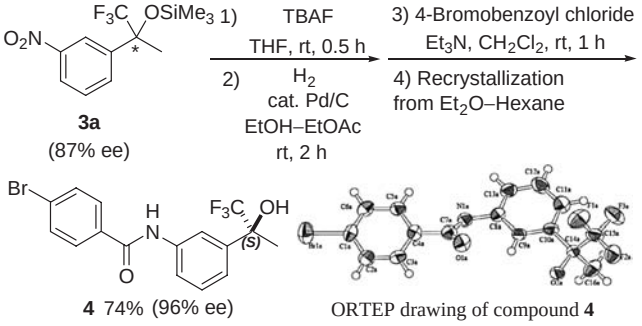
[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (volume ratio = 20:1) as a solvent. [c]Enantiomeric excess was measured after desilylation of **3a**.

Table 3. Enantioselective synthesis of trifluoromethylated silyl ethers by using catalyst **1i**



Entry	R^1	R^2	Product	Yield/%[a]	% ee[b]
1	2-$(NO_2)C_6H_4$	Me	**3b**	93	71[c]
2	4-$(NO_2)C_6H_4$	Me	**3c**	97	73[c]
3	3-$(CN)C_6H_4$	Me	**3d**	96	71[c]
4	3-BrC_6H_4	Me	**3e**	97	61[c]
5	3-$(MeO)C_6H_4$	Me	**3f**	90	59[c]
6	1-Naphthyl	Me	**3g**	91	51[c]
7	2-Naphthyl	Me	**3h**	95	77[c]
8	3-Pyridyl	Me	**3i**	90	46
9	4-Pyridyl	Me	**3j**	93	60
10	3-$(NO_2)C_6H_4$	Et	**3k**	99	64[c]

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or Chiralpak AD-H) with hexane/2-propanol (volume ratio = 20:1) as a solvent. [c]Enantiomeric excess was measured after desilylation of **3**.



Scheme 1. Conversion of **3a** to carboxamide **4** and determination of their absolute configurations.

(−78 °C), the use of a mixed-solvent was examined. Then, a 7:3 (v/v) mixture of toluene and CH_2Cl_2 was found most effective and gave the **3a** in 98% yield with high enantioselectivity (87% ee, Entry 5).[7]

Next, reactions of (trifluoromethyl)trimethylsilane with various ketones were tried in the presence of cinchonidine-derived quaternary ammonium phenoxide **1i** in toluene–CH_2Cl_2 at −78 °C for 1 h (Table 3). In most cases, the reactions proceeded smoothly to provide the corresponding trifluoromethylated silyl ethers in high yields with moderate to good enantioselectivities.

Absolute configuration of trifluoromethylated compound **3a** was determined to be S by X-ray crystallographic analysis after the conversion to the corresponding carboxamide 4 as shown in Scheme 1. Hydrogenation of the desilylated alcohol followed by N-acylation with 4-bromobenzoyl chloride gave the benzamide **4**, which was then recrystallized from Et_2O/hexane to afford the crystalline compound that was identified clearly by X-ray crystallographic analysis.[8]

Thus, successful asymmetric trifluoromethylation of various ketones was achieved in high yield with high stereochemical control in the presence of cinchonidine-derived chiral ammonium phenoxide **1i** as a Lewis base catalyst.

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7 Typical experimental procedure for the preparation of **3** is shown in the following (Table 2, Entry 5): To a stirred solution of **1i** (27 mg, 0.015 mmol) in toluene–CH_2Cl_2 (7:3, 0.6 mL) were successively added a solution of 3-nitroacetophenone (49.5 mg, 0.3 mmol) in toluene–CH_2Cl_2 (7:3, 0.8 mL) and a solution of (trifluoromethyl)trimethylsilane (59.7 mg, 0.42 mmol) in toluene–CH_2Cl_2 (7:3, 0.8 mL) at −78 °C. After the mixture was stirred for 1 h at the same temperature, it was quenched with sat. NH_4Cl (aq) and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC (hexane/EtOAc = 5/1) to give a (2*S*)-[1,1,1-trifluoro-2-(3-nitrophenyl)propan-2-yloxy]trimethylsilane (**3a**) (90.3 mg, 98%, 87% ee) as a coloress oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.26-8.20 (m, 1H), 7.90 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 1.88 (s, 3H), 0.2 (s, 9H). The enantiomeric excess was measured after desilylation of **3a** and determined by HPLC analysis using DAICEL Chiralcel OD-H, hexane/2-propanol = 20/1, λ = 254 nm, flow rate = 1.0 mL/min, retention time = 12.3 min (minor) and 15.2 min (major).

8 The product **4** was recrystallized from hexane/Et_2O. Crystal data: $C_{16}H_{13}BrF_3NO_2$ (FW 388.18), monoclinic, $P2_1$, a = 13.089(5) Å, b = 6.456(2) Å, c = 18.059(5) Å, β = 93.74(3) Å, V = 1522.7(9) Å^3, V = 2117(1) Å^3, Z = 4.0, D_{calcd} = 1.693 g cm^{-3}, T = 295 K. X-ray intensities were measured on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710690 Å). The final R factors was 0.043 (Rw = 0.130 for all data) for 3441 reflections with $I > 2\sigma(I)$.

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