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Ammonium bromides/KF catalyzed trifluoromethylation of carbonyl compounds with (trifluoromethyl)trimethylsilane and its application in the enantioselective trifluoromethylation reaction

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Abstract—The trifluoromethylation of aldehydes and ketones is a potentially powerful method to introduce the CF_3 moiety into organic molecules. In general, the trifluoromethylation reaction has been performed by treatment of Me_3SiCF_3 under initiation by TBAF, TBAT, TMAF as well as CsF. However, these commercially available fluorides are rather expensive and moisture sensitive. Potassium fluoride (KF) is an inexpensive and commonly used fluoride source and can be also used as an initiator for the trifluoromethylation, but the method suffers from the significant limitation that only DMF is available as a solvent. Therefore, novel methods are highly desirable for laboratory-scale as well as large-scale preparations. Here we wish to report a convenient procedure where a KF/TBAB combination acts as a catalyst for trifluoromethylation of aldehydes, ketones, and imides in a variety of organic solvents to provide trimethylsilyl-protected α-trifluoromethyl alcohols in good to high yields. Application of the method in the enantioselective trifluoromethylation is also discussed.

1. Introduction

The synthesis of trifluoromethyl-containing organic compounds has attracted significant interest in the fields of pharmaceuticals, agrochemical chemistry, and material science since these compounds possess unique properties.[1] The construction of α-trifluoromethyl alcohol units exemplified by $CF_3C(OH)RR'$ is particularly important as they frequently are a constituent of biologically active molecules.[2] Among various methodologies available for the preparation of α-trifluoromethyl alcohols, the nucleophilic trifluoromethylation reaction using Ruppert's reagent ((trifluoromethyl)-trimethylsilane, Me_3SiCF_3) is the most direct method for introducing a CF_3 unit in synthetically useful carbonyl compounds.[3] The Me_3SiCF_3 was first prepared by Ruppert et al.,[4] and in 1989, Prakash et al. found tetrabutylammonium fluoride (TBAF) to be an effective catalyst for the trifluoromethylation reaction of carbonyl compounds with Me_3SiCF_3.[5] The Me_3SiCF_3 is now becoming popular as the Ruppert–Prakash reagent[6] and considerable efforts have been devoted to the development of efficient catalytic systems for this process. Following the initial report, a number of fluoride reagents[5–9] such as tetrabutylammonium triphenyldifluorosilicate (TBAT),[5,7] tetramethylammonium fluoride (TMAF),[5,7] tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[7] as well as cesium fluoride (CsF)[8] have been successively reported to catalyze the trifluoromethylation with Me_3SiCF_3. On the other hand, trifluoromethylation catalyzed by other nucleophilic catalysts[9a,10c] including Lewis bases[10a,b] such as trimethylamine *N*-oxide,[10d] *N*-heterocyclic carbene,[10e] molecular sieves,[10f] LiOAc,[10g–i] $AcONBu_4$,[10g–i] phosphate salts,[10j] and K_2CO_3[10j] has made significant progress in recent years. Our group has recently begun a program with the nucleophilic trifluoromethylation reaction. Tri-*tert*-butyl phosphine, as well as triphenylphosphine oxide catalyzed trifluoromethylation of a variety of carbonyls with Me_3SiCF_3,[11a] and remote sulfinyl group-induced diastereoselective trifluoromethylation of aldehydes catalyzed by TMAF[11b] have been reported. Lewis acids such as TiF_4, $Ti(O\text{-}i\text{-}Pr)_4$, and $Cu(OAc)_2$/1,2-bis(diphenylphosphino)-ethane were also found to be able to promote the catalytic trifluoromethylation of aldehydes.[11c] Although the catalytic systems mentioned above for trifluoromethylation were examined by many research groups including us, the early fluoride anion catalysis, especially TBAF, is still very important because of its ability to promote transformations over a wide

Keywords: Trifluoromethylation; Enantioselective; Ammonium bromide; Potassium fluoride; Cinchona alkaloid.
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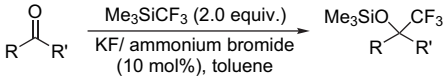
range of substrates with high chemical yields. Despite of its good solubility and reactivity, it is relatively expensive and very moisture sensitive. Potassium fluoride (KF) is an inexpensive and commonly used fluoride source and can also be used as an initiator for trifluoromethylation,[9] but the method suffers from the significant limitation that only DMF is available as a solvent. Although a KF/MeCN system with or without 18-crown-6 is reported to catalyze the trifluoromethylation of carbonyls, the method is limited to fluoro ketones and excess amount of KF is required.[9b] Therefore, novel methods are highly desirable for laboratory-scale as well as large-scale preparations. In the course of our research program for the development of novel methodologies in fluorine chemistry,[12] we wish to report a convenient procedure where a KF/TBAB combination (TBAB: tetrabutylammonium bromide) acts as a catalyst for trifluoromethylation of aldehydes, ketones, and imides in a variety of organic solvents to provide trimethylsilyl-protected α-trifluoromethyl alcohols in good to high yields (Scheme 1).[13] Application of this method to the enantioselective trifluoromethylation is also discussed.



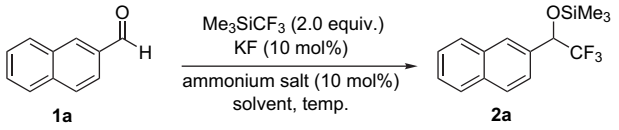
Scheme 1.

2. Results and discussion

2.1. Trifluoromethylation of aldehydes, ketones, and imides

As we mentioned in Section 1, a catalytic amount of KF acts a good trigger for the trifluoromethylation of aldehyde **1a** with Me_3SiCF_3 in DMF at −20 °C for 30 min (Table 1, run 1). However, the reaction of **1a** with Me_3SiCF_3 failed to provide the adduct **2a** in toluene, MeCN, or CH_2Cl_2 at room temperature (runs 2–4). When we attempted the same reaction in THF, the reaction was not complete at room temperature even after 12 h. Only **2a** was obtained in 12% yield (run 5). Incidentally, KF combined with quaternary ammonium salts have been shown as efficient fluorinating agents;[14] however, none have been reported to be used in the trifluoromethylation of carbonyls with Me_3SiCF_3. We therefore decided to add TBAB as a co-catalyst in all the cases. Reaction of **1a** with Me_3SiCF_3 in the presence of catalytic amounts of KF and TBAB in toluene, MeCN, CH_2Cl_2, or THF at −20 °C gave **2a** in high yields within 30 min, confirming our expectations. We next examined the effect of a variety of commercially available ammonium salts as additives for the KF-catalyzed trifluoromethylation reaction of **1a** with Me_3SiCF_3. The results collected in Table 1 refer to a representative variety of quaternary ammonium salts. Not surprisingly, the reaction is not limited to TBAB. Ammonium salts such as tetrabutylammonium chloride (TBAC), tetraethylammonium bromide (TEAB), tetraethylammonium chloride (TEAC), tetramethylammonium chloride (TMAC), and cetyl tetramethylammonium bromide (CTMAB) were equally effective as initiators when combined with KF, affording the CF_3 adduct **2a** in high yields (runs 10–21), except for the cases of tetramethylammonium bromide (TMAB, runs 16 and 17). The reaction did not proceed in the absence of KF (run 22).

Table 1. Trifluoromethylation of **1a** with Me_3SiCF_3



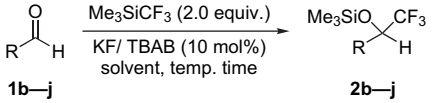
1a **2a**

Run	Solvent	Ammonium salt	Temp	Time (h)	Yield[a] (%)
1	DMF	—	−20 °C	0.5	82
2	Toluene	—	rt	12	Trace
3	CH_2Cl_2	—	rt	12	Trace
4	MeCN	—	rt	12	Trace
5	THF	—	rt	12	12
6	Toluene	TBAB	−20 °C	0.5	89
7	CH_2Cl_2	TBAB	−20 °C	0.5	89
8	MeCN	TBAB	−20 °C	0.5	87
9	THF	TBAB	−20 °C	0.5	82
10	Toluene	TBAC	−20 °C	2	80[b]
11	THF	TBAC	−20 °C	2	83[b]
12	Toluene	TEAB	0 °C	2	92
13	THF	TEAB	0 °C	2	82
14	Toluene	TEAC	−20 °C	1	87
15	THF	TEAC	0 °C	6	81
16	Toluene	TMAB	−20 °C	12	Trace
17	THF	TMAB	−20 °C	12	Trace
18	Toluene	TMAC	0 °C	0.5	77
19	THF	TMAC	−20 °C	1	63
20	Toluene	CTMAB	−20 °C	0.5	81
21	THF	CTMAB	−20 °C	0.5	90
22	Toluene	TBAB	rt	12	Trace[c]

[a] Determined by ^{19}F NMR with standard material, benzotrifluoride.
[b] A mixture of **2a** and its desilylated **2a** (OH form).
[c] The reaction was carried out in the absence of KF.

We next applied these conditions to the trifluoromethylation of a number of aldehydes (**1b–j**), ketones (**3a–c**), and imides (**3d**,**e**) to assess the potential scope and limitations of the method. The results are summarized in Tables 2 and 3. Aryl aldehydes such as benzaldehyde (entries 1 and 2), 1-naphthaldehyde (entries 3 and 4), and *p*- or *o*-methoxybenzaldehyde (entry 5–8) reacted in high yields (84–99%).

Table 2. KF/TBAB catalyzed trifluoromethylation of **1** with Me_3SiCF_3

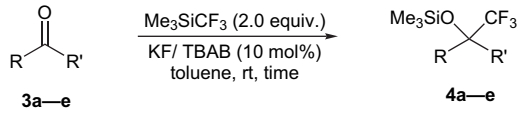


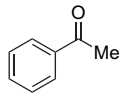
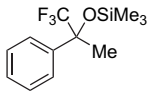
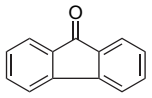
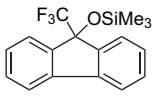
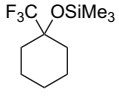
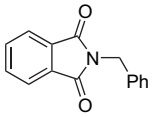
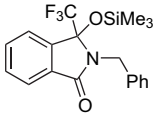
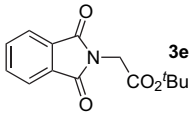
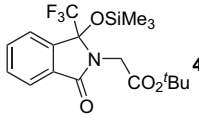
1b—j **2b—j**

Entry	1	R	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	**1b**	Ph	Toluene	rt	0.5	91
2	**1b**	Ph	THF	0	0.5	94
3	**1c**	1-Naphthyl	Toluene	0	1	99
4	**1c**	1-Naphthyl	THF	0	0.5	90
5	**1d**	*p*-$MeOC_6H_4$–	Toluene	−20	0.5	88
6	**1d**	*p*-$MeOC_6H_4$–	THF	0	0.5	92
7	**1e**	*o*-$MeOC_6H_4$–	Toluene	−20	0.5	84
8	**1e**	*o*-$MeOC_6H_4$–	THF	rt	1	85
9	**1f**	*p*-BrC_6H_4–	Toluene	−20	0.5	88
10	**1f**	*p*-BrC_6H_4–	THF	−20	1	99
11	**1g**	*p*-$NO_2C_6H_4$–	Toluene	−20	1	96
12	**1g**	*p*-$NO_2C_6H_4$–	THF	−20	0.5	88
13	**1h**	*o*-$NO_2C_6H_4$–	Toluene	−20	0.5	90
14	**1h**	*o*-$NO_2C_6H_4$–	THF	rt	6	94
15	**1i**	PhCH=CH-(*E*)	Toluene	0	0.5	94
16	**1j**	*n*-Heptyl	Toluene	rt	0.5	98
17	**1j**	*n*-Heptyl	THF	−20	0.5	79

[a] Isolated yield.

Table 3. KF/TBAB catalyzed trifluoromethylation of **3** with Me_3SiCF_3



Entry	3	Time (h)	4	Yield[a] (%)
1	 **3a**	0.5	 **4a**	89
2	 **3b**	0.5	 **4b**	90
3	 **3c**	2	 **4c**	48
4	 **3d**	24	 **4d**	86
5	 **3e**	24[b]	 **4e**[c]	77[c]

[a] Isolated yield.
[b] Reaction was carried out at 40 °C.
[c] Mixture of **4e** and its OH form.

Entries 9–12 further demonstrated that the present conditions tolerated functional groups on the aromatics such as bromo and nitro groups. Selective 1,2-addition was observed in the reaction of cinnamyl aldehyde (**1i**) with Me_3SiCF_3 to furnish the trimethylsilyl ether of allyl alcohol **2i** in high yield (94%, entry 15). The reactions involving enolizable aldehydes posed some additional challenges due to the possibility of proton abstraction by the hard fluoride anion. As shown in entries 16 and 17, the enolizable *n*-octyl aldehyde (**1j**) was nicely converted to the corresponding α-trifluoromethyl alcohol **2j** in high yields under the KF/TBAB combination.

Ketones (**3a–c**) and imides (**3d**,**e**) also reacted nicely under the conditions described above in good to high yields (Table 3), but the trifluoromethylation of imides (**3d**,**e**) was relatively slow (entries 4 and 5), and the cyclohexanone (**3c**) shown in entry 3 afforded CF_3 adduct in moderate yield (48%, entry 3).

2.2. Reactive species

The KF/TBAB combination has proven effective for the trifluoromethylation of carbonyl compounds and the results are similar to those observed by TBAF catalyst. In order to discuss a reactive species in the reaction, we investigated the NMR study of the combination. The ^{19}F NMR gave the broad signal at −113 ppm (−105 ppm to −120 ppm) for TBAF monohydrate in toluene-d_8, whereas KF/TBAB in toluene-d_8 did not give any signal. These results show that in situ generation of TBAF from the KF/TBAB combination could be ruled out under this condition. Therefore, it appears that TBAB might be acting as some kind of phase transfer catalyst, which can help solubilize KF.[15] Although the reactive species has not been ascertained yet, the catalytic system using KF/ammonium bromide in toluene represents an attractive method for the trifluoromethylation of a range of carbonyl compounds. Compared to TBAF, the ammonium bromides and chlorides such as TBAB and TBAC are stable to moisture and are inexpensive.

2.3. Enantioselective trifluoromethylation

Asymmetric nucleophilic trifluoromethylation of carbonyl compounds represents an effective approach for the synthesis of optically active trifluoromethylated alcohols,[16] important synthons for the preparation of drugs such as Befloxatone[2a] and Efavirenz.[2b] Chiral trifluoromethylated alcohols are also attracting much attention in the field of material sciences, especially the development of novel liquid crystals[17] (Fig. 1).

Among the methods available to prepare these chiral synthons,[18] enantioselective catalysis is particularly important due to the accessibility of both enantiomers, and the ease with which small variations in the product can be introduced. However, chiral auxiliary-based stereoselective trifluoromethylation is still the most widely applied approach[19] and enantioselective catalysis is still a challenge.[20] Enantioselective trifluoromethylation using Me_3SiCF_3 was first examined by Iseki et al. in 1994.[20a] Chiral ammonium fluorides derived from cinchona alkaloids catalyzed the trifluoromethylation reaction of aldehydes to furnish the corresponding trifluoromethylated alcohols with low to moderate enantioselectivities up to 51% ee. After the initial report, considerable efforts were devoted to the development of an efficient catalytic system for the nucleophilic enantioselective trifluoromethylation reaction,[20] but the observed enantioselectivity has not improved except for one example reported by Pfizer research group.[20c] Their report suggests the enantioselectivity of the reaction is highly substrate dependent and the high enantioselectivity could be achieved by a thorough screening of chiral ammonium fluorides. However, this protocol is not an acceptable solution to this issue due to the troublesome preparation and purification of highly hygroscopic anhydrous ammonium fluorides from the corresponding chiral ammonium salts.[21] We therefore decided to extend our KF/ammonium bromide strategy to the enantioselective trifluoromethylation reaction.[22] Activation of KF with readily accessible chiral ammonium bromide derived from cinchona

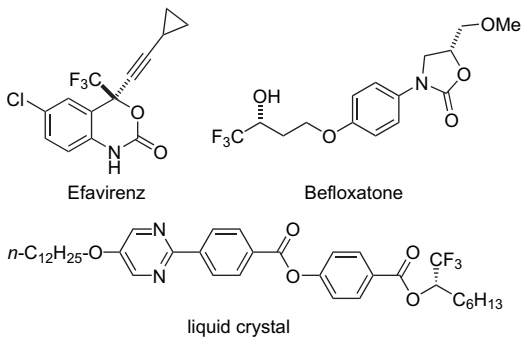
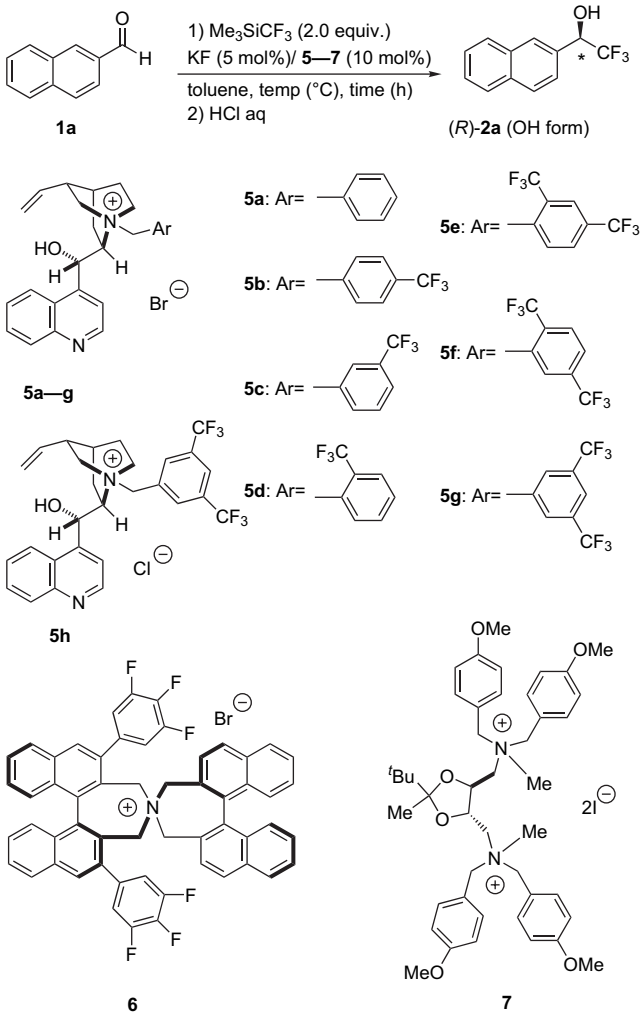


Figure 1.

alkaloids may allow for the rapid determination of suitable catalysts for a number of substrates in the enantioselective trifluoromethylation.

In screening the cinchona alkaloid, the reaction of 2-naphthaldehyde (**1a**) with Me_3SiCF_3 was examined as a model reaction (Table 4). First, commercially available cinchonium bromides, **5a** and **5b**, were used in this reaction under the optimized conditions described above. A better result was obtained when the **1a** was treated with Me_3SiCF_3 in the presence of the KF/**5b** combination. The optically active **2a** was produced in 81% yield with 26% ee (entry 2). The better selectivity of this catalyst might result from the CF_3 substituent on the aromatic ring. The cinchonium bromides, which have CF_3 groups on their aromatic moiety, were screened under the same conditions. The cinchonium bromides were easily prepared from cinchonine by quaternization using commercially available CF_3-substituted benzyl bromides in refluxing THF overnight. We found that the ee of **2a** was slightly improved to 40% ee when the reaction of **1a** with Me_3SiCF_3 was carried out using the KF/**5g** combination at room temperature for 18 h (entry 7). Interestingly, in the presence of KF/ammonium chloride **5h**, the trifluoromethylation of **1a** smoothly proceeded to completion in only 3.5 h to give **2a** in 90% yield, albeit at slightly lower enantioselectivity (entry 8, 36% ee). Finally, the enantioselective trifluoromethylation was also attempted using commercially available organocatalysts, *N*-spiro C_2-symmetric chiral ammonium bromide **6**[23] and TaDiAS diiodide **7**[24] in the presence of KF; however, the enantioselectivity was not improved and more through optimization of the conditions for each catalyst is required (runs 9–11).

Table 4. KF/chiral ammonium halides catalyzed enantioselective trifluoromethylation of **1a** with Me_3SiCF_3



Run	Ammonium salt	Temp	Time (h)	Yield[a] (%)	ee[b] (%)
1	**5a**	rt	10	67	10
2	**5b**	0 °C	2	81	26
3	**5c**	rt	24	67	19
4	**5d**	rt	24	44	19
5	**5e**	rt	16	58	31
6	**5f**	rt	48	34	28
7	**5g**	rt	18	54	40
8	**5h**	0 °C	3.5	90	36
9	**6**	rt	15	76	2[e]
10[c]	**6**	rt[d]	12	9	11[e]
11	**7**	rt	48	47	2

[a] Isolated yield.
[b] Determined by HPLC analysis using CHIRALCEL OJ-H.
[c] The reaction was carried out in THF.
[d] The reaction was started at −78 °C, then the reaction temperature was allowed to warm to rt over 2 h.
[e] (*S*)-**2a** was obtained.

3. Conclusion

In conclusion, we have developed a general synthetic strategy for the trifluoromethylation of carbonyl compounds based on the ammonium bromide/KF combination. Our approach does not require polar solvents especially DMF. This represents an advantage of ammonium bromide/KF combination because DMF solvent is often a major drawback when we attempt at extension of this chemistry to asymmetric transformations. Compared to TBAF, the ammonium bromides and chlorides are stable to moisture. The catalytic system using KF/TBAB in toluene is inexpensive and represents an attractive method for the trifluoromethylation of a range of carbonyl compounds. The usefulness of the methodology was demonstrated by enantioselective trifluoromethylation to provide the enantiomerically rich trifluoromethylated alcohols, which constitute key structural components of important drugs. Since chiral ammonium bromides can be easily prepared without the use of typical anion-exchange resins, highly hygroscopic anhydrous chiral ammonium fluorides, which require troublesome preparations and purifications would no longer be prerequisite. Utilizing the ubiquitous readily available chiral ammonium bromides,[25] this catalytic system offers a convenient straightforward route to various chiral CF_3-contaning organic molecules.

4. Experimental

4.1. General

All reactions were performed in oven- and flame-dried glassware under a positive pressure of nitrogen. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel plate (60F-254). The TLC plates were visualized with UV light and 7%

phosphomolybdic acid in ethanol/heat or *p*-anisaldehyde in ethanol/heat. Column chromatography was carried out on a column packed with silica gel 60N spherical neutral size 63–210 μm. ^{1}H NMR (200 MHz) and ^{19}F NMR (188 MHz) spectra for solutions in $CDCl_3$ were recorded on a Varian Gemini-200. Chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane for ^{1}H NMR and $CFCl_3$ for ^{19}F NMR. Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer. Mass spectra (EI) were taken on a SHIMADZU GC-MS-QP5050A. Mass spectra (ESI) were taken on a SHIMADZU LCMS-2010EV. HPLC analyses were performed on a JASCO PU-2080 Plus or SHIMADZU LC-2010A HT using 4.5×259 mm Daicel CHIRALCEL OJ-H. Optical rotations were measured on a HORIBA SEPA-300.

4.1.1. Typical procedure for the trifluoromethylation: trimethyl[2,2,2-trifluoro-1-(2-naphthalenyl)ethoxy]-silane (2a).[10j] To a mixture of **1a** (50.0 mg, 0.32 mmol), TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1.0 mL) was added Me_3SiCF_3 (94.6 μL, 0.63 mmol) at −20 °C. After 30 min, the reaction was quenched with water, and the aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane). Product **2a** was obtained in 89% yield, as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 9H), 5.07 (q, J=6.4 Hz, 1H), 7.47–7.58 (m, 3H), 7.82–7.88 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −78.2 (d, J=6.0 Hz, 3F); IR (KBr) 3066, 2958, 2927, 2856, 1363, 1262, 1177, 1128, 969, 900, 853, 818, 748, 697, 575, 548 cm^{-1}; MS (EI, *m*/*z*) 298 (M$^+$). Although the reaction can also be performed using a catalytic amount of TBAC, a mixture of **2a** and desilylated **2a** was obtained.

4.1.2. Trimethyl(2,2,2-trifluoro-1-phenylethoxy)silane (2b).[10j] Using the typical procedure, reaction of **1b** (32.5 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in THF (1 mL) gave **2b** (113.4 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 9H), 4.90 (q, J=6.6 Hz, 1H), 7.34–7.50 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −78.5 (d, J=6.0 Hz, 3F); IR (neat) 3069, 3036, 2961, 2898, 1497, 1456, 1369, 1271, 1172, 1133, 1031, 882, 756, 701, 634, 552 cm^{-1}; MS (EI, *m*/*z*) 248 (M$^+$).

4.1.3. Trimethyl[2,2,2-trifluoro-1-(1-naphthalenyl)ethoxy]silane (2c).[10f] Using the typical procedure, reaction of **1c** (43.5 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **2c** (75.5 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H), 5.74 (q, J=6.2 Hz, 1H), 7.46–7.62 (m, 3H), 7.79–7.89 (m, 3H), 8.08 (d, J=8.0 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −77.4 (d, J=6.0 Hz, 3F); IR (KBr) 3066, 2962, 1599, 1514, 1354, 1272, 1172, 1131, 1008, 875, 850, 798, 776, 751, 696, 633, 536, 442 cm^{-1}; MS (EI, *m*/*z*) 298 (M$^+$).

4.1.4. Trimethyl[2,2,2-trifluoro-1-(4-methoxyphenyl)-ethoxy]silane (2d).[10j] Using the typical procedure, reaction of **1d** (38.9 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in THF (1 mL) gave **2d** (81.5 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 9H), 3.81 (s, 3H), 4.85 (q, J=6.6 Hz, 1H), 6.88 (dt, J=2.6, 9.0 Hz, 2H), 7.34 (d, J=8.2 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −78.8 (d, J=6.0 Hz, 3F); IR (neat) 2960, 2840, 1614, 1516, 1466, 1368, 1254, 1172, 1131, 1036, 882, 845, 754, 682, 623, 587, 527 cm^{-1}; MS (EI, *m*/*z*) 278 (M$^+$).

4.1.5. Trimethyl[2,2,2-trifluoro-1-(2-methoxyphenyl)-ethoxy]silane (2e).[20c] Using the typical procedure, reaction of **1e** (38.9 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in THF (1 mL) gave **2e** (75.7 mg, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 3.84 (s, 3H), 5.53 (q, J=6.6 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 6.98 (dt, J=1.8, 7.4 Hz, 1H), 7.31 (dt, J=1.8, 8.4 Hz, 1H), 7.56 (d, J=7.6 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −78.3 (d, J=6.6 Hz, 3F); IR (neat) 2961, 2843, 1605, 1592, 1494, 1467, 1442, 1378, 1250, 1173, 1134, 1090, 1050, 1030, 885, 847, 756, 685, 628 cm^{-1}; MS (ESI, *m*/*z*) 301.0 (M+Na$^+$).

4.1.6. [1-(4-Bromophenyl)-2,2,2-trifluoroethoxy]trimethylsilane (2f).[10j] Using the typical procedure, reaction of **1f** (59.2 mg, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in THF (1 mL) gave **2f** (112.5 mg, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 9H), 4.86 (q, J=6.6 Hz, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −78.8 (d, J=6.0 Hz, 3F); IR (neat) 2960, 2900, 1594, 1489, 1407, 1367, 1257, 1173, 1135, 1012, 880, 846, 755, 725, 667, 622 cm^{-1}; MS (EI, *m*/*z*) 328 (M$^+$+1), 326 (M$^+$−1).

4.1.7. Trimethyl[2,2,2-trifluoro-1-(4-nitrophenyl)ethoxy]silane (2g).[10j] Using the typical procedure, reaction of **1g** (48.4 mg, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **2g** (89.7 mg, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 9H), 5.01 (q, J=6.4 Hz, 1H), 7.64 (d, J=9.0 Hz, 2H), 8.24 (dt, J=2.4, 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −78.2 (d, J=6.0 Hz, 3F); IR (neat) 2961, 2900, 1528, 1351, 1269, 1176, 1138, 1016, 879, 848, 753, 710, 623, 554, 533 cm^{-1}; MS (EI, *m*/*z*) 293 (M$^+$).

4.1.8. Trimethyl[2,2,2-trifluoro-1-(2-nitrophenyl)ethoxy]silane (2h).[11a] Using the typical procedure, reaction of **1h** (48.4 mg, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in THF (1 mL) gave **2h** (88.2 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 6.12 (q, J=6.0 Hz, 1H), 7.53 (dt, J=1.4, 8.8 Hz, 1H), 7.68 (dt, J=1.4, 7.8 Hz, 1H), 7.93 (d, J=1.2 Hz, 2H), 7.97 (d, J=1.2 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −78.2 (d, J=5.0 Hz, 3F); IR (neat) 2962, 1682, 1536, 1353, 1258, 1176, 1137, 884, 849, 788, 748, 714, 673, 627 cm^{-1}; MS (EI, *m*/*z*) 293 (M$^+$).

4.1.9. Trimethyl[[(2E)-3-phenyl-1-(trifluoromethyl)-2-propenyl]oxy]silane (2i).[10j] Using the typical procedure, reaction of **1i** (40.3 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and

KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **2i** (124.3 mg, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H), 4.55 (quint, J=6.4 Hz, 1H), 6.17 (dd, J=6.4, 16.0 Hz, 1H), 6.74 (d, J=16.0 Hz, 1H) 7.24–7.50 (m, 5H); ^{19}F NMR ($CDCl_3$) δ −78.7 (d, J=7.0 Hz, 3F); IR (neat) 3030, 2961, 1373, 1271, 1132, 970, 893, 847, 749, 694 cm^{-1}; MS (EI, m/z) 274 (M^+).

4.1.10. Trimethyl(1-trifluoromethyloctyloxy)silane (2j).[11a] Using the typical procedure, reaction of **1j** (51.8 μL, 0.33 mmol) with Me_3SiCF_3 (97.8 μL, 0.66 mmol), catalyzed TBAB (10.7 mg, 0.033 mmol), and KF (1.9 mg, 0.033 mmol) in toluene (1 mL) gave **2j** (88.3 mg, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 9H), 0.89 (t, J=6.8 Hz, 3H), 1.28 (br s, 9H), 1.54–1.70 (m, 2H), 3.78–3.98 (m, 1H); ^{19}F NMR ($CDCl_3$) δ −78.8 (d, J=6.6 Hz, 3F); IR (neat) 2957, 2928, 2859, 1467, 1392, 1281, 1254, 1166, 1146, 844, 754, 722, 689 cm^{-1}; MS (EI, m/z) 270 (M^+).

4.1.11. Trimethyl(2,2,2-trifluoro-1-methyl-1-phenylethoxy)silane (4a).[10j] Using the typical procedure, reaction of **3a** (37.3 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **4a** (150.0 mg, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 9H), 1.82 (s, 3H), 7.30–7.45 (m, 3H), 7.57–7.60 (m, 2H); ^{19}F NMR ($CDCl_3$) δ −81.7 (s, 3F); IR (neat) 2961, 1449, 1381, 1297, 1255, 1172, 1105, 1073, 995, 864, 845, 759, 698, 653 cm^{-1}; MS (EI, m/z) 262 (M^+).

4.1.12. 9-(Trifluoromethyl)-9*H*-fluoren-9-yl trimethylsilyl ether (4b).[26] Using the typical procedure, reaction of **3b** (57.5 mg, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **4b** (92.9 mg, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ −0.27 (s, 9H), 7.31 (dt, J=1.2, 7.6 Hz, 2H), 7.74 (dt, J=1.4, 7.6 Hz, 2H), 7.60–7.69 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −80.0 (s, 3F); IR (neat) 3068, 2965, 1964, 1925, 1608, 1451, 1409, 1306, 1253, 1181, 1118, 1082, 970, 943, 925, 889, 868, 843, 761, 739 cm^{-1}; MS (ESI, m/z) 271.1 (M+Na$^+$−TMS).

4.1.13. Trimethyl(1-trifluoromethylcyclohexyloxy)silane (4c).[5a] Using the typical procedure, reaction of cyclohexanone **3c** (33.1 μL, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **4c** (36.6 mg, 48%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 9H), 1.08–1.90 (m, 10H); ^{19}F NMR ($CDCl_3$) δ −82.7 (s, 3F); IR (KBr) 2943, 2865, 1453, 1362, 1310, 1285, 1253, 1158, 1089, 1037, 899, 845, 757, 644; MS (EI, m/z) 240 (M^+).

4.1.14. 2-Benzyl-3-hydroxy-3-trifluoromethyl-2,3-dihydro-isoindol-1-one (4d).[11a] Using the typical procedure, reaction of **3d** (76.0 mg, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.63 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **4d** (104.6 mg, 86%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 9H), 4.55 (d, J=15.8 Hz, 1H), 4.88 (d, J=15.4 Hz, 1H), 7.22–7.37 (m, 5H), 7.56–7.70 (m, 3H), 7.84–7.94 (m, 1H); ^{19}F NMR ($CDCl_3$) δ −79.3 (s, 3F); IR (KBr) 3065, 3035, 2965, 2925, 1715, 1381, 1307, 1258, 1192, 1120, 1084, 987, 965, 952, 895, 875, 849, 726, 705 cm^{-1}; MS (ESI, m/z) 306.0 (M^-−TMS).

4.1.15. (3-Oxo-1-trifluoromethyl-1-trimethylsilanyloxy-1,3-dihydro-isoindol-2-yl)-acetic acid *tert*-butyl ester (4e) and (1-hydroxy-3-oxo-1-trifluoromethyl-1,3-dihydro-isoindol-2-yl)-acetic acid *tert*-butyl ester (4e, OH form).[11a] Using the typical procedure, reaction of **3e** (83.6 mg, 0.32 mmol) with Me_3SiCF_3 (94.6 μL, 0.64 mmol), catalyzed TBAB (10.3 mg, 0.032 mmol), and KF (1.8 mg, 0.032 mmol) in toluene (1 mL) gave **4e** (87.3 mg, 68%) as a colorless oil and its OH form (10.0 mg, 9.4%) as a white solid. Compound **4e**: ^{1}H NMR ($CDCl_3$) δ −0.08 (s, 9H), 1.47 (s, 9H), 3.98 (d, J=17.4 Hz, 1H), 4.24 (d, J=17.2 Hz, 1H), 7.57–7.70 (m, 3H), 7.83–7.94 (m, 1H); ^{19}F NMR ($CDCl_3$) δ −80.1 (s, 3F); IR (neat) 2979, 1757, 1731, 1470, 1414, 1372, 1298, 1256, 1228, 1176, 1068, 981, 892, 876, 849, 744, 721; MS (EI, m/z) 330 (M^+−TMS). Compound **4e** (OH form): ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 4.06 (d, J=18.0 Hz, 1H), 4.76 (d, J=18.0 Hz, 1H), 5.18 (br s, OH), 7.60–7.8 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −79.3 (s, 3F); IR (KBr) 3118, 2981, 2930, 1756, 1712, 1697, 1475, 1423, 1370, 1272, 1228, 1171, 1080, 968, 946, 853, 768, 744, 735, 695, 625, 582, 556; MS (EI, m/z) 332 (M^++1).

4.1.16. Enantioselective trifluoromethylation of 1a: (*R*)-1-(2′-naphthyl)-2,2,2-trifluoroethanol (2a).[11b] A mixture of *N*-(3,5-bistrifluoromethyl)benzyl cinchonium bromide (19.3 mg, 0.032 mmol) and KF (0.93 mg, 0.016 mmol) in toluene (1.0 mL) was stirred at room temperature for 1 h under N_2 atmosphere. After addition of **1a** (50.0 mg, 0.32 mmol), reaction mixture was cooled to 0 °C. And then Me_3SiCF_3 (95 μL, 0.64 mmol) was added and reaction temperature was gradually increased to room temperature over 1 h. After stirring for 18 h, the reaction was quenched with water, and to the mixture was added 1 M HCl aqueous solution (1 mL) and THF (1 mL), and stirred for 1 h. The aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane=90:10). Product (*R*)-**2a** was obtained in 54% yield, 40% ee as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.59 (br d, OH), 5.11–5.29 (m, 1H), 7.51–7.59 (m, 3H), 7.85–7.95 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −78.1 (d, J=7.0 Hz, 3F). The ee of the product was determined by HPLC using a Daicel Chiralcel OJ-H column (*n*-hexane/*i*-PrOH=90:10, flow rate 1.0 mL/min, λ=254 nm, τ_R=16.1 min, τ_S=24.9 min); $[\alpha]_D^{25}$ −13.5 (*c* 0.36, $CHCl_3$, 40% ee). The absolute configuration of **2a** was assigned to (*R*) by the relative retention times of the (*R*/*S*)-isomers reported in the literature.[11b]

4.1.17. *N*-3,5-Bis(trifluoromethylbenzyl)cinchonium bromide (5g). A solution of cinchonine (200 mg, 0.68 mmol) and 2,5-bis(trifluoromethylbenzyl)bromide (150 μL, 1.08 mmol) in THF (20 mL) was refluxed under N_2 atmosphere. After 12 h, the reaction mixture was concentrated under reduced pressure and recrystallized from ether/CH_2Cl_2 to give **5g** (347 mg, 85%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 0.60–0.95 (m, 1H), 1.40–1.95 (m, 3H), 2.09 (t, J=10.8 Hz, 1H), 2.34 (q, J=7.4 Hz, 1H), 2.55 (q, J=10.4 Hz, 1H), 3.05 (t, J=10.8 Hz,1H), 4.00–4.20 (m, 2H), 4.57 (t, J=10.4 Hz, 1H), 5.16–5.29 (m, 2H), 5.61 (d, J=12.2 Hz, 1H), 5.74–5.91 (m, 1H), 6.51 (s, 2H), 6.66 (d, J=11.8 Hz, 1H), 6.98 (quint, J=7.2 Hz, 2H), 7.53 (d, J=8.2 Hz, 1H), 7.78–7.81 (m, 2H), 8.20–8.30 (br s, 3H), 8.80 (d, J=4.4 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −62.8 (s, 6F); IR (KBr) 3216, 1592, 1510, 1459, 1373, 1279, 1180, 1135, 1002, 920, 906, 775, 711, 683 cm^{-1}; MS (ESI, *m/z*) 522.2 (M^+–Br); $[\alpha]_D^{25}$ +102.9 (*c* 1.0, $CHCl_3$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.024.

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