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Distinct Advantage of the in Situ Generation of Quaternary Ammonium Fluorides under Phase-Transfer Conditions toward Catalytic Asymmetric Synthesis

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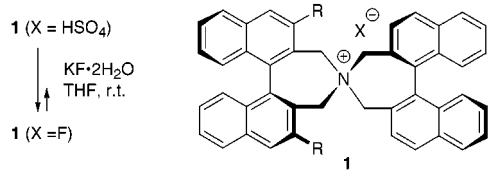
ABSTRACT



Quaternary ammonium fluorides were found to be efficiently generated in situ from the corresponding ammonium hydrogensulfates by treatment with commercially available potassium fluoride dihydrate ($KF·2H_2O$) in THF and directly used as a fluoride source for the generation of carbon nucleophiles from organosilicon compounds. This method can be successfully applied to the preparation of structurally well-defined, C_2-symmetric chiral quaternary ammonium fluorides of type 1 (X = F), thereby allowing catalytic enantioselective Mukaiyama-type aldol reactions under mild conditions.

Triggered by the first utilization of the high affinity of fluoride ion toward silicon atoms in the hydrolysis of trimethylsilyl ether with anhydrous tetrabutylammonium fluoride (TBAF),[1] the synthetic utility of the fluoride-mediated generation of nucleophiles has been intensively visualized in the desilylation of alkynylsilanes,[2] allylic silanes,[3−5] enol silyl ethers,[6,7] and silyl ketene acetals.[8] However, there have been only a few applications to catalytic asymmetric synthesis,[9] including the enantioselective Mukaiyama-type aldol reactions catalyzed by cinchona alkaloid-derived ammonium fluorides independently reported by Shioiri[10] and Corey.[11] This situation is mainly attributable to (i) the troublesome preparation and purification of highly hygroscopic anhydrous ammonium fluorides from the corresponding ammonium salts and (ii) the difficulty of design-

(1) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(2) (a) Nakamura, E.; Kuwajima, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 498. (b) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H.; Akinde, B.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 840.
(3) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043.
(4) (a) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; p 391. (b) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React. (N.Y.)* **1989**, *37*, 57. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(5) Asao, N.; Shibato, A.; Itagaki, Y.; Jourdan, F.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 3177.
(6) (a) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257. (b) Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1980**, *21*, 2085.
(7) (a) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. (b) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932.
(8) (a) Nakamura, E.; Shimizu, M.; Kuwajima, I. *Tetrahedron Lett.* **1976**, 1699. (b) RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.
(9) (a) For the asymmetric Michael addition of nitromethane, see: Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238. (b) For the recent asymmetric trifluoromethylation of aldehydes, see: Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137.
(10) (a) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507. (b) Shioiri, T.; Bohsako, A.; Ando, A. *Heterocycles* **1996**, *42*, 93.
(11) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.

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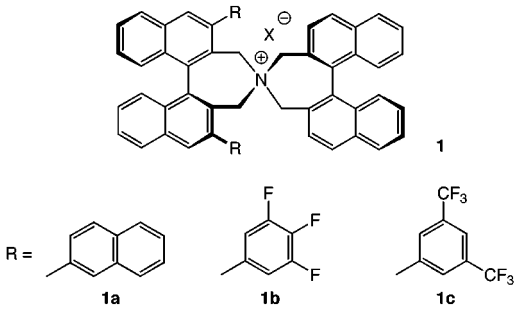
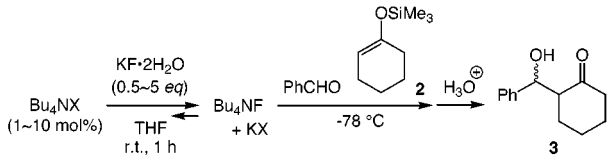
ing and preparing effective chiral quaternary ammonium fluorides for this purpose. Recently, we introduced C_2-symmetric chiral quaternary ammonium bromides **1a** and **1b** (X = Br) as new chiral phase-transfer catalysts and dem-



onstrated their efficiency in the catalytic enantioselective alkylation of protected glycine derivative;[12] this led us to investigate the possibility of preparing quaternary ammonium fluorides in a practical manner, particularly as a fluoride source for the generation of carbon nucleophiles from organosilicon compounds. Here we wish to communicate that quaternary ammonium fluorides can be efficiently generated in situ from the corresponding hydrogensulfates under phase-transfer conditions and directly used for the formation of quaternary ammonium enolates from enol trimethylsilyl ethers. The present approach was successfully applied to the preparation of structurally well-defined, C_2-symmetric chiral quaternary ammonium fluorides, thereby enabling the catalytic asymmetric aldol reactions under mild conditions.

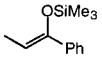
Since catalytic activity of TBAF in the fluoride ion-catalyzed reactions has been well documented,[7] we employed various tetrabutylammonium salts (TBAX) as a precursor and examined the anion exchange under solid−liquid phase-transfer conditions with an excess amount of potassium fluoride dihydrate (KF·2H_2O) in THF.[13] Effectiveness of this method for the in situ generation of TBAF as a fluoride ion source for the formation of carbon nucleophiles was evaluated by subsequently performing aldol reactions of enol trimethylsilyl ethers with benzaldehyde in one pot. As illustrated in Scheme 1, a mixture of TBAX (10 mol %)

Scheme 1



and commercially available KF·2H_2O (5 equiv)[14] in THF was well stirred at room temperature for 1 h and then benzaldehyde (1.2 equiv) and 1-trimethylsiloxycyclohexene (**2**, 1 equiv) were added sequentially at −78 °C. Monitoring

Table 1. In Situ Generated TBAF-Catalyzed Aldol Reaction of Enol Silyl Ethers with Benzaldehyde[a]

entry	enol silyl ether	X of TBAX	KF•2H_2O (equiv)	% yield[b] (ratio)[c]
1	 **2**	I	5	n.r.[d]
2		Br	5	n.r. [71 (45 : 55)][e]
3		Cl	5	5 (43 : 57) [85 (31 : 69)][e]
4		F	0	89 (40 : 60)[f]
5		IO_4	5	n.r. [72 (42 : 58)][e]
6		ClO_4	5	n.r.[d]
7		BPh_4	5	n.r.[d]
8		BF_4	5	n.r. [57 (45 : 55)][e]
9		OTf	5	n.r. [51 (50 : 50)][e]
10		HSO_4	5	91 (25 : 75)
11		HSO_4	0.5	91 (23 : 77)
12		HSO_4	0	n.r.[d]
13		none[f]	5	n.r.[d]
14		HSO_4 (1 mol%)	0.5	86 (32 : 68)[g]
15		F (1 mol%)	0	24 (58 : 42)[g]
16		HSO_4	0.5	92 (96 : 4)
17		HSO_4	0.5	90 (55 : 45)
18	 **4**	HSO_4	0.5	55 (45 : 55)

[a] Unless otherwise specified, the reaciton was carried out with 1.2 equiv of benzaldehyde and 1 equiv of enol silyl ehter in the presence of 10 mol % of TBAX and KF·2H_2O in THF at −78 °C for 0.5 h. [b] Isolated yield. [c] The *erythro/threo* ratio was determined by ^{1}H NMR analysis. [d] n.r. = no reaction even after stirring at rt for several hours. [e] The yields of the reactions at higher temperature are shown in parentheses [−18 °C for 1.5 h (entries 2 and 5); −40 °C for 2 h (entry 3); 0 °C for 0.5 h (entry 8); rt for 2 h (entry 9)]. [f] In the absense of $TBAHSO_4$. [g] At −40 °C for an additional 2 h.

the reactions revealed that the efficiency of the in situ generation of TBAF was profoundly influenced by the anion moiety (X) as summarized in Table 1. Although the expected anion exchange was certainly achieved with TBAB and TBAC to catalyze the present cross aldol reaction, the reactivity was far less than that of TBAF itself (entries 1−4). Interestingly, comparable catalytic activity was attained by

(12) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

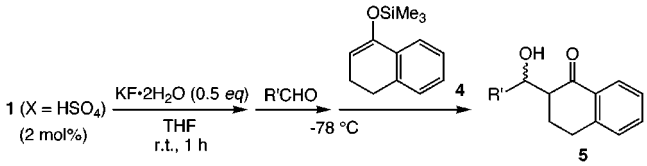
(13) For the use of in situ prepared quaternary ammonium fluoride as a base, see: (a) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931. (b) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

(14) Potassium fluoride dihydrate was purchased from Kanto Chemical Co., Ltd. It was finely ground and dried under reduced pressure for 20 min at ambient temperature before use. We also attempted the aldol reaction of **2** with benzaldehyde using finely powdered, anhydrous KF on the assumption, as judged from the previous reports,[7] that rigorous exclusion of water might possibly increase the catalytic efficiency. However, significant rate retardation was observed and only a trace amount of aldol product **3** was obtained under similar conditions, suggesting the importance of *omega phase* [KF(nH_2O)] for facile anion exchange under the solid−liquid phase-transfer condition,[21] which is obviously critical in the present system.

use of $TBAHSO_4$ as a precursor, where the aldol reaction was completed within 30 min at −78 °C and the desired β-hydroxy ketone **3** was obtained in 91% isolated yield (entry 10).[15] Optimization of the reaction conditions showed that 0.5 equiv of $KF·2H_2O$ was sufficient for the smooth reaction (entry 11). It should be added that the aldol reaction did not proceed at all in the absence of either $TBAHSO_4$ or $KF·2H_2O$ under otherwise identical conditions as included in Table 1 (entries 12 and 13). Noteworthy is that this phase-transfer system was advantageous, especially when the reaction was conducted with a reduced amount of $TBAHSO_4$ (1 mol %), where the catalytic activity of the in situ generated TBAF was found to be markedly enhanced compared to 1 mol % of TBAF itself (entries 14 vs 15). The generality of the present method was clearly demonstrated with the enol trimethylsilyl ethers of several representative ketone substrates (entries 16−18).

Among the enol trimethylsilyl ethers examined, tetralone-derived **4** on reaction with benzaldehyde under the optimized reaction conditions gave the corresponding aldol product in 55% yield (entry 18 in Table 1) accompanied by the formation of tetralone, indicating the insufficient nucleophilicity of the intermediary quaternary ammonium enolate toward aldehyde carbonyl. This result suggested that rational modification of the structure of the cationic quaternary ammonium moiety might increase the enolate reactivity. Taking account of the high reactivity of C_2-symmetric chiral quaternary ammonium bromide **1a** (X = Br) observed in our recent study on the asymmetric synthesis of α-amino acids,[16] we undertook the utilization of the corresponding hydrogensulfate **1a** (X = HSO_4) which, if successful, would lead directly to the catalytic asymmetric aldol processes. Fortunately, we found that mixing only 2 mol % of **1a** (X = HSO_4) and $KF·2H_2O$ (0.5 equiv) in THF at room temperature for 1 h and subsequent treatment with benzaldehyde (R′ = Ph) and enol trimethylsilyl ether **4** at −78 °C for 0.5 h gave rise to the desired β-hydroxy ketone **5** (R′ = Ph) in 84% yield as a mixture of diastereomers (*erythro*/*threo* = 57:42), though the enantiomeric excess of the major *erythro* isomer was not yet satisfactory (31% ee) as shown in Table 2 (entry 1). Further, the profound effect of the structurally well-defined catalyst on the reactivity as well as the selectivity was emphasized by the fact that the employment of newly designed **1c** (X = HSO_4) as the catalyst precursor resulted in formation of the aldol product **5** (R′ = Ph) in 92% yield (*erythro*/*threo* = 70:30) with 76% ee for the major *erythro* isomer (entry 2).[17] This beneficial effect of the electron-withdrawing trifluoromethyl group could be understood by tight contact ion pairing of the possible ammonium enolate due to the decrease of electron density on the nitrogen atom of the catalyst.[18] An additional unique feature uncovered in the present system is the crucial role of toluene as a cosolvent for improvement of the stereoselectivities, i.e., when the reaction was performed in THF−toluene (volume ratio = 2:1), **5** (R′ = Ph) was obtained in 90% yield (*erythro*/*threo* = 83:17) with 84% ee for *erythro* isomer (entry 3). Moreover, the reactions with α-naphthaldehyde and phenanthrene-9-carboxaldehyde under similar conditions exhibited excellent diastereo- and enantioselectivities (entries 4 and 5).[19] Since ammonium hydro-

Table 2. Asymmetric Aldol Reactions of **4** with Aldehydes Catalyzed by in Situ Generated C_2-Symmetric Chiral Quaternary Ammonium Fluorides[a]



entry	aldehyde (R')	ammonium hydrogensulfate	% yield[b]	*erythro*/*threo*[c]	% ee[d] (config)[e]
1	Ph	**1a** (X = HSO_4)	84	57:42	31 (*S*,*S*)[f]
2		**1c** (X = HSO_4)	92	70:30	76 (*S*,*S*)
3		**1c** (X = HSO_4)	90	83:17	84 (*S*,*S*)[g]
4	α-Naph	**1c** (X = HSO_4)	90	94:6	91 (*S*,*S*)[g]
5	9-phenanthryl	**1c** (X = HSO_4)	88	95:5	90 (*S*,*S*)[g]

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of aldehyde and 1 equiv of enol trimethylsilyl ether **4** in the presence of 2 mol % of **1** (X = HSO_4) and 0.5 equiv of $KF·2H_2O$ in THF at −78 °C for 0.5 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Enantiopurity of *erythro* isomer of **5** was determined by HPLC analysis using a chiral column [DAICEL Chiralcel OJ (for entries 1−3) and Chiralpak AD (for entries 4 and 5)] with hexane−2-propanol as solvent. [e] Determined by ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters (Yamaguchi, S. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1, p 125.). Absolute configuration of the aldol product with benzaldehyde was also confirmed, after reduction of its trifluoroacetate with 10% Pd/C, H_2, by comparison with the optical rotation of the known (*R*)-2-benzyltetralone (Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun*. **1990**, 1657.). [f] 20% ee for *threo* isomer. [g] Use of THF−toluene (volume ratio = 2:1) as solvent and the reaction was performed at −40 °C for 0.5−1 h.

(15) After the mixture of $TBAHSO_4$ (10 mol %) and $KF·2H_2O$ (5 equiv) in THF was stirred at room temperature for 1 h, the resulting supernatant solution was transferred to another flask and treated with benzaldehyde (1.2 equiv) and 1-trimethylsiloxycyclohexene (**2**, 1 equiv) at −78 °C for 30 min, producing β-hydroxy ketone **3** in 85% yield with an *erythro*/*threo* ratio of 23:77.

(16) For example, alkylation of *tert*-butyl glycinate−benzophenone Schiff base with **1a** (X = Br; 1 mol %) and benzyl bromide (1.2 equiv) in toluene−50% KOH aqueous solution (volume ratio = 3:1) at 0 °C for 30 min gave the corresponding benzylation product in 95% yield (96% ee),[12a] while reaction with TBAB (1 mol %) under otherwise identical conditions afforded the product in 41% yield (Ooi, T.; Doda, K.; Maruoka, K. Unpublished results). Upon assuming that the interfacial mechanism is operative in this system,[22] structurally well-defined **1a** (X = Br) could enhance the rate of ion-exchange with potassium enolate of the glycine derivative initially formed at the interface and effectively extract the enolate anion deep into the toluene phase with the aid of its lipophilicity, leading to the observed reactivity enhancement. In addition, **1a** (X = Br) does not suffer from Hofmann elimination because of the unique *N*-spiro structure without β-hydrogen, which would also contribute to the high reactivity.

(17) Use of **1b** (X = HSO_4) slightly lowered the enantioselectivity (73% ee) in this case.

(18) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (b) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.

(19) Unfortunately, attempted reaction of **4** with 3-phenylpropanal under similar conditions gave rise to the aldol product in only 14% yield with an *erythro*/*threo* ratio of 46:54, and the enantioselectivity of the *erythro* isomer was determined to be 46% ee. We also investigated other enol silyl ethers in the aldol reaction with α-naphthaldehyde under the optimized conditions, and the following results imply the present limitation of our approach: 1-trimethylsiloxyindene [94% yield, 80% ee (*erythro* isomer; *erythro*/*threo* = 96:4), 1-trimethlysiloxycyclohexene (**2**) [80% yield, 29% ee (*erythro* isomer; *erythro*/*threo* = 71:29)].

gensulfates can be conveniently prepared from the corresponding bromides without the use of typical anion-exchange resins and simple recrystallization generally provides essentially pure salts,[20] preparation and purification of each chiral ammonium fluoride would no longer be prerequisite. This represents a distinct advantage of our approach for the elaboration of effective chiral quaternary ammonium fluorides, which should play a crucial role in the development of still unexplored fluoride ion-catalyzed asymmetric carbon−carbon bond-forming reactions.

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(20) Dehmlow, E. V.; Vehre, B.; Broda, W. *Synthesis* **1985**, 508.

(21) Liotta, C. L.; Berkner, J.; Wright, J.; Fair, B. In *Phase-Transfer Catalysis*; Halpern, M. E., Ed.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; Chapter 3.

(22) (a) Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 960. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.