Asymmetric Organocatalysis of Structurally Well-Defined Chiral Quaternary Ammonium Fluorides

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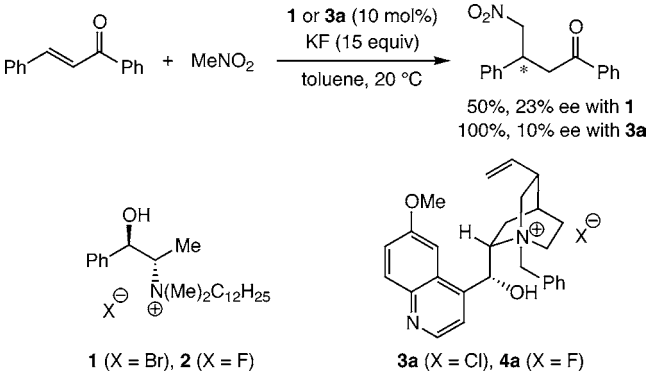
ABSTRACT

Unique organocatalysis of both naturally occurring cinchona alkaloid-derived and purely synthetic chiral quaternary ammonium fluorides in synthetically useful stereoselective bond-forming reactions is overviewed. The development of this chemistry was initiated by the in situ generation of generally hygroscopic ammonium fluorides from the corresponding easy-to-handle ammonium salts in the presence of excess metal fluorides and their direct use for subsequent enantioselective reactions. On the other hand, chiral ammonium fluorides have been prepared by using ion-exchange resins and successfully applied as catalyst to various asymmetric bond formation reactions under homogeneous conditions. In addition, utilization of chiral quaternary ammonium bifluorides as organocatalysts in asymmetric synthesis is described, featuring their characteristic reactivity and selectivity.

Quaternary ammonium fluorides, particularly tetraalkylammonium fluorides, have been widely recognized as a convenient, organic-soluble source of naked fluoride ion. Their utility in modern organic synthesis has been well documented on numerous occasions taking advantage of either the nucleophilic affinity of fluoride ion to a silicon atom or its eminent basicity in aprotic solvents.[1,2] The former property enables the fluoride-mediated generation of nucleophiles from organosilicon compounds, and the latter allows the direct generation of nucleophiles through a deprotonation process, both of which have been utilized for the subsequent selective bond-forming reactions under mild conditions. These synthetically useful metal-free methods have implications for the development of asymmetric versions based on the use of chiral, nonracemic quaternary ammonium fluorides, giving a unique platform for establishing otherwise difficult asymmetric transformations. In this Account, we outline research devoted to the development of structurally well-defined chiral ammonium fluorides and their utilization for various stereoselective carbon−carbon bond formation reactions, providing a basis for future work in this field in view of enantioselective organocatalysis.

Scheme 1



In Situ Generation of Chiral Quaternary Ammonium Fluorides

In 1978, Wynberg and co-workers reported the first example of a chiral quaternary ammonium fluoride-catalyzed Michael addition of nitromethane to chalcone (Scheme 1).[3] The reaction was performed in toluene at 20 °C with 10 mol % of chiral ammonium salt **1** or **3a** and excess potassium fluoride (KF, 15 equiv), yielding the γ-nitroketone with 10−23% enantiomeric excess (ee). The requisite chiral ammonium fluorides **2** and **4a** were generated in situ from the corresponding bromide and chloride through anion exchange with KF. A study of Carpino and Sau showed that a mixture of tetrabutylammonium chloride and potassium fluoride dihydrate ($KF\cdot 2H_2O$) in acetonitrile can be used as a convenient source of fluoride ion.[4] Such in situ generation techniques have obvious synthetic merit because they obviate the preparation and purification of highly hygroscopic anhydrous ammonium fluorides. This is quite advantageous for designing and preparing effective chiral quaternary ammonium fluorides. In this regard, we sought to develop a more efficient combination by focusing on the effect of the counterion of the parent ammonium salts.[5] Since catalytic activity of tetrabutylammonium fluoride (TBAF) in the fluoride ion-catalyzed reactions has been well documented,[6] we employed various tetrabutylammonium salts (TBAX) as a precursor and examined anion exchange with excess $KF\cdot 2H_2O$ in THF. The effectiveness of this procedure was evaluated by subsequently performing

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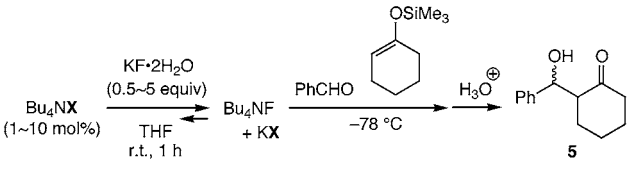
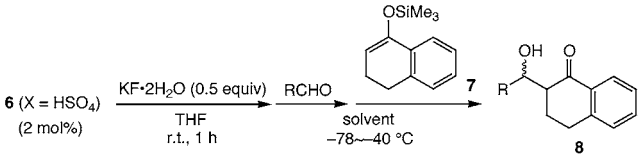
Scheme 2

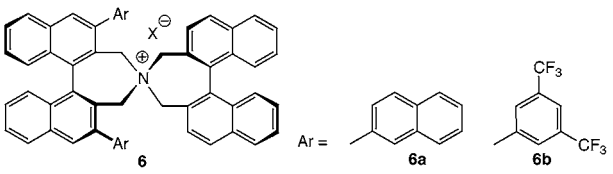


X = I, Br, IO_4, ClO_4, BPh_4, OTf	: no reaction
X = Cl (10 mol%), $KF•2H_2O$ (5 equiv)	: 5% (*erythro*/*threo* = 43:57)
F (10 mol%)	: 89% (40:60)
HSO_4 (10 mol%), $KF•2H_2O$ (5 equiv)	: 91% (25:75)
HSO_4 (10 mol%), $KF•2H_2O$ (0.5 equiv)	: 91% (23:77)
HSO_4 (1 mol%), $KF•2H_2O$ (0.5 equiv)	: 86% (32:68)
F (1 mol%)	: 24% (58:42)

Scheme 3



THF solvent at −78 °C
R = Ph **6a** : 84% (*erythro*/*threo* = 57:43), 31% ee (*erythro* isomer) (*S*,*S*)
6b : 92% (70:30), 76% ee (*S*,*S*)
THF–toluene (2:1) at −78~−40 °C
R = Ph **6b** : 90% (83:17), 84% ee (*S*,*S*)
R = α-Np **6b** : 90% (94:6), 91% ee (*S*,*S*)

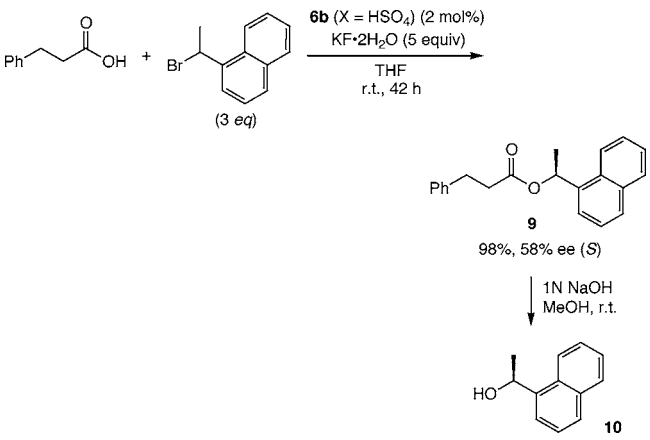


aldol reactions of 1-trimethylsiloxycyclohexene with benzaldehyde in a one-pot reaction under identical conditions. As shown in Scheme 2, the efficiency was indeed profoundly influenced by the anion (X). Although the expected anion exchange was certainly achieved with TBAC to catalyze the cross aldol reaction, the reactivity was far less than that of TBAF itself. Interestingly, comparable catalytic activity was attained by use of $TBAHSO_4$ as a precursor, leading to the formation of the desired β-hydroxy ketone **5** in 91% isolated yield, and it was eventually found that 0.5 equiv of $KF•2H_2O$ was sufficient for a smooth reaction. This 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.

The usefulness of the present system was then demonstrated by its application to the in situ generation of structurally rigid, C_2-symmetric chiral quaternary ammonium fluorides of type **6** (X = F) from the corresponding hydrogen sulfate **6** (X = HSO_4) and their direct use for the asymmetric aldol reactions (Scheme 3). For instance, mixing **6a** (X = HSO_4, 2 mol %) and $KF•2H_2O$ (0.5 equiv) in THF at room temperature for 1 h and subsequent treatment with benzaldehyde and enol trimethylsilyl ether **7** at −78 °C for 0.5 h gave rise to the desired β-hydroxy ketone **8** (R = Ph) in 84% yield (erythro/threo = 57:42) with 31% ee for the major erythro isomer. Further, employment of **6b** (X = HSO_4) having a 3,5-bis(trifluoromethyl)phenyl group as catalyst precursor resulted in formation of **8** (R = Ph) in 92% yield (erythro/threo = 70:30) with 76% ee (erythro isomer). This beneficial effect of the electron-withdrawing trifluoromethyl group could be understood by tight contact ion pairing of the ammonium enolate due to the decrease of electron density on the nitrogen atom of the catalyst.[7] In addition, the crucial role of toluene as a cosolvent for improvement of the stereoselectivities was uncovered, and the reaction with α-naphthaldehyde under similar conditions exhibited excellent diastereo- and enantioselectivities.[5]

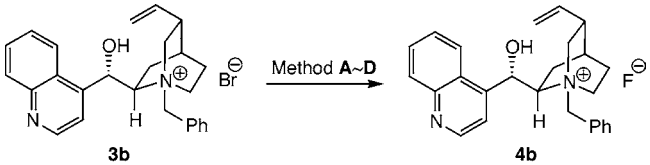
The efficient in situ generation of chiral quaternary ammonium fluorides from the corresponding hydrogen sulfates has also been successfully applied to the facile preparation of optically active esters via alkylative kinetic resolution of secondary alkyl halides. For example, simple stirring of the mixture of 3-phenylpropionic acid, 1-(1-bromoethyl)naphthalene, **6b** (X = HSO_4; 2 mol %) and $KF•2H_2O$ (5 equiv) in THF at room temperature for 42 h gave rise to the desired ester **9** in 98% isolated yield with 58% ee, from which enantioenriched secondary alcohol **10** was readily obtained by basic hydrolysis (Scheme 4).[8]

Scheme 4



Preparation of Chiral Quaternary Ammonium Fluorides and Their Applications to Organocatalytic Asymmetric Bond-Forming Reactions

Shioiri and co-workers systematically investigated the preparation of *N*-benzylcinchonium fluoride **4b** from the corresponding bromide **3b** (Figure 1).[9] In methods A and B, the anion-exchange resins of F^- form were used,[10] while

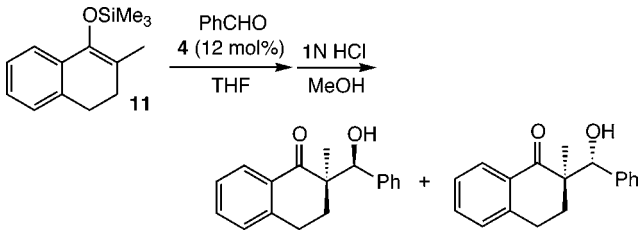


A 1) Amberlite IRA-410 F^- form; 2) Evaporation
B 1) Amberlyst A-26 F^- form; 2) Evaporation
C 1) Amberlyst A-26 OH^- form; 2) 1N HF; 3) Evaporation
D 1) AgF; 2) Filtration; 3) Evaporation

FIGURE 1.

neutralization of the ammonium hydroxide was involved in method C.[11] In method D, silver fluoride (AgF) was employed for the direct anion exchange.[12] The fluoride **4b** thus obtained was dried over P_2O_5 at 40 °C under vacuum overnight. The ^1H NMR analysis of **4b** indicated no decomposition of *N*-benzylcinchonium residue and ^{19}F NMR measurement in CD_2C1_2 showed a peak centered at ca. −124 ppm ($CFCl_3$ as an internal standard).[13] The catalytic activity as well as chiral efficiency of **4b** was then evaluated in the asymmetric aldol reaction of enol silyl ether of 2-methyl-1-tetralone (**11**) with benzaldehyde (Table 1).[9] The chemical yields and diastereo- and enantioselectivities were found to be substantially independent of the preparation method of **4b**.

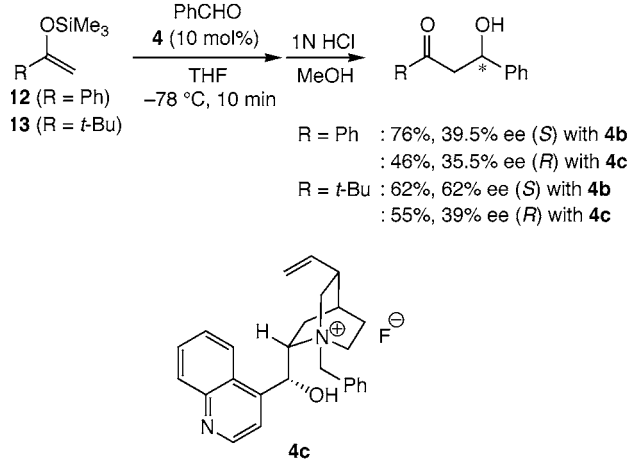
Table 1. Asymmetric Aldol Reactions of Enol Silyl Ether 11 with Benzaldehyde Catalyzed by Chiral Quaternary Ammonium Fluorides 4b



					% ee	
entry	catalyst	preparation method	% yield	erythro/ threo	erythro (config)	threo (config)
1	**4b**	A	74	75:25	72 (*R*,*S*)	22 (*R*,*R*)
2	**4b**	B	63	71:29	67 (*R*,*S*)	13 (*R*,*R*)
3	**4b**	C	74	70:30	70 (*R*,*S*)	20 (*R*,*R*)
4	**4b**	D	66	80:20	71 (*R*,*S*)	16 (*R*,*R*)

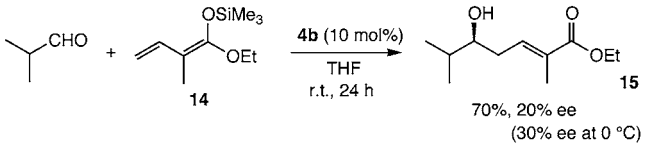
Further examination on the fluoride ion-catalyzed asymmetric aldol reaction of the enol silyl ethers prepared from acetophenone (**12**) and pinacolone (**13**) with benzaldehyde using **4b** and its peudoenantiomer **4c** revealed the dependence of the stereochemistry of the reactions on the hydroxymethyl-quinuclidine fragment of the catalyst (Scheme 5).[9,14]

Scheme 5

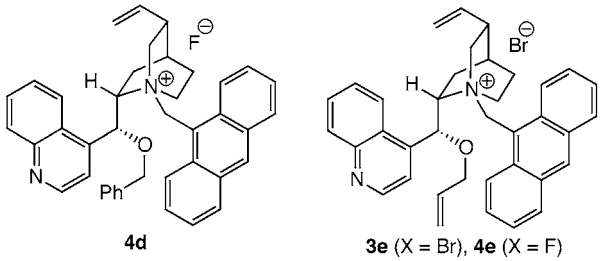


Campagne and Bluet recently reported the catalytic asymmetric vinylogous Mukaiyama (CAVM) reaction of aldehydes with dienol silyl ether **14** using chiral ammonium fluorides as an activator. For example, the CAVM reaction of isobutyraldehyde with **14** in the presence of 10 mol % of **4b** in THF at room temperature led to the formation of the vinylogous aldol product **15** in 70% yield with 20% ee, and the enantiomeric excess was improved to 30% ee by conducting the reaction at 0 °C (Scheme 6).[15]

Scheme 6



Corey and Zhang utilized chiral quaternary ammonium fluoride **4d** possessing a 9-anthracenylmethyl group on

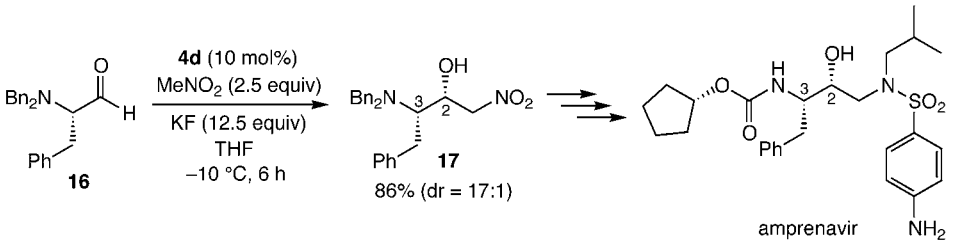


nitrogen for the face-selective nitroaldol reaction of nitromethane with protected (*S*)-phenylalaninal directed toward the practical stereoselective synthesis of amprenavir,[16] an important second generation of HIV protease inhibitor with a number of clinical advantages over first generation agents. A THF solution of *N*,*N*-dibenzyl-(*S*)-phenylalaninal (**16**) was added to a mixture of **4d**, nitromethane, and finely ground KF in THF at −10 °C (Scheme 7). After the mixture was stirred for 6 h, the desired nitro alcohol **17** was isolated in 86% yield with a diastereomeric ratio of 17:1, from which amprenavir was synthesized in a five-step sequence.[17]

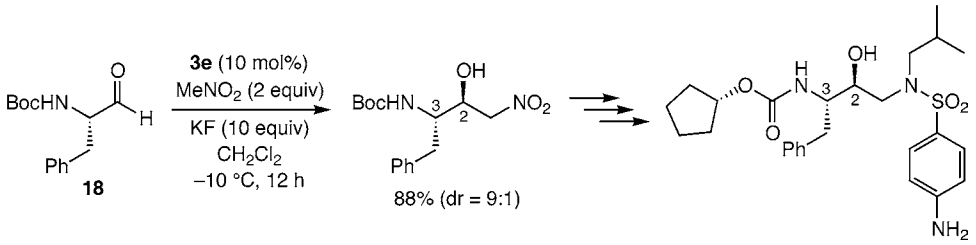
The asymmetric synthesis of the C(2) diastereomer of amprenavir was also accomplished similarly starting from *N*-*tert*-butoxycarbonyl-(*S*)-phenylalaninal (**18**), where the requisite chiral ammonium fluoride **4e** was generated in situ from the corresponding bromide **3e** in the initial nitro aldol process (Scheme 8).[17]

Iseki, Nagai, and Kobayashi prepared cinchonine-derived **4f** and **4g** from the corresponding bromides by the method B and realized the asymmetric trifluoromethylation of aldehydes and ketones with trifluoromethyltrimethylsilane (Me_3SiCF_3) catalyzed by these ammonium fluorides (Scheme 9).[18] Although the enantioselectivities are not sufficiently high, this reaction system should offer a new access to various chiral trifluoromethylated molecules of analytical and medicinal interests through appropriate modifications.

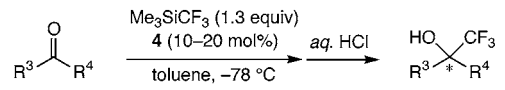
Scheme 7

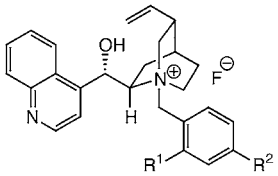


Scheme 8



Scheme 9



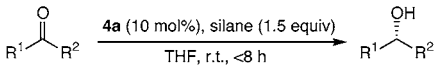


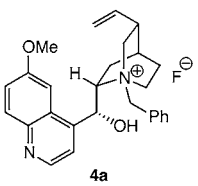
R^3	R^4	4 (mol%)	% yield	% ee
Ph	H	**4f** (10)	>99	37 (*R*)
Ph	H	**4g** (20)	>99	46 (*R*)
Ph	Me	**4f** (20)	91	48 (*R*)
Ph	*i*-Pr	**4f** (20)	87	51 (*R*)

4f (R^1 = H, R^2 = CF_3)
4g (R^1 = R^2 = CF_3)

The hydrosilylation of carbonyl compounds with polymethylhydrosiloxane (PMHS) or other alkoxysilanes can be catalyzed by TBAF with high efficiency.[19] The asymmetric version of this process has been developed by Lawrence and co-workers using chiral ammonium fluorides **4** prepared via the method **C**.[20] The reduction of acetophenone was performed with trimethoxysilane (1.5 equiv) and 10 mol % of **4a** in THF at room temperature, giving phenethyl alcohol quantitatively with 51% ee (*R*) (Scheme 10). In the reduction of propiophenone, slightly higher enantioselectivity was observed. When tris(trimethylsiloxy)silane was used as a hydride source, the enantioselectivity was increased, though prolonged reaction time was required. Although significant rate acceleration was observed with PMHS, the stereoselectivity was unfortunately decreased.

Scheme 10





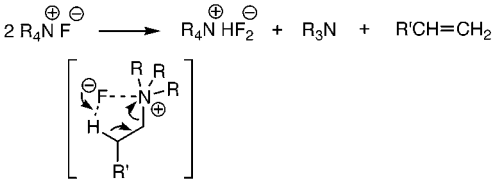
R^1	R^2	silane	% yield	% ee
Ph	Me	$(MeO)_3SiH$	100	51
Ph	Et	$(MeO)_3SiH$	83	65
Ph	Me	$(Me_3SiO)_3SiH$	78	65 (for 28 h)
Ph	Me	PMHS	98	28

4a

Preparation of Chiral Quaternary Ammonium Bifluorides and Their Use as Organocatalysts for Asymmetric Carbon–Carbon Bond-Forming Reactions

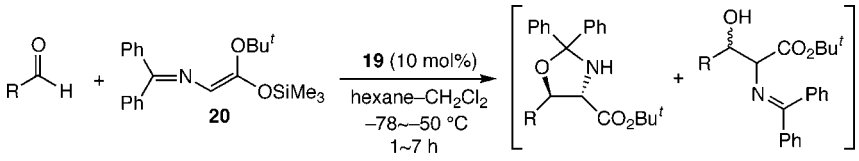
Tetraalkylammonium fluoride ($R_4N^+F^-$) is well-known to be highly receptive to protic compounds such as hydrogen halides and water, affording nonstoichiometric hydrogen-bonded adducts, $R_4N^+F^-(HY)_n$, in nonpolar solvents. This property reasonably accounts for the hygroscopic nature of ammonium fluorides. However, under strictly anhydrous conditions, intramolecular interactions are predominant resulting in self-destruction of the tetraalkylammonium cation via Hoffman elimination to furnish tetraalkylammonium bifluoride, trialkylamine, and olefin (Scheme 11).[21] Therefore, the resulting tetraalkylammonium bifluoride, $R_4N^+HF_2^-$, is more stable than the parent fluoride and is expected to be easy to handle, though its reactivity and selectivity in organic synthesis have scarcely been investigated, especially in the field of asymmetric catalysis.

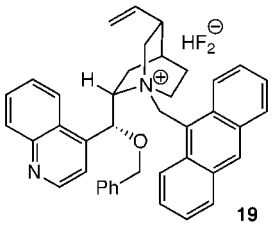
Scheme 11



Recently, Corey and co-workers prepared the cinchonidine-derived bifluoride **19** from the corresponding bromide by passage of a methanolic solution through a column of Amberlyst A-26 OH^- form and subsequent neutralization with 2 equiv of 1 N HF solution and evaporation (the modified method C). The catalytic activity and chiral efficiency of **19** (dried over P_2O_5 under vacuum) have been demonstrated by the development of a Mukaiyama-type aldol reaction of ketene silyl acetal **20** with aldehydes under mild conditions, giving mostly *syn*-

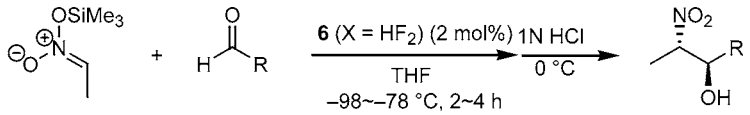
Scheme 12





R	% yield	*syn*-**21**/*anti*-**21**	% ee *syn*-**21**	% ee *anti*-**21**
i-Pr	70	6:1	95	83
c-Hex	81	13:1	88	46
$Cl(CH_2)_3$	48	1:1	82	86

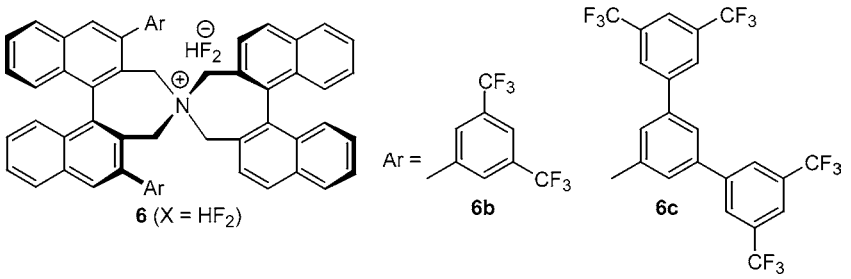
Scheme 13



R = Ph **6b** : 83% (*anti*/*syn* = 74:26), 33% ee (*anti* isomer)
6c : 92% (92:8), 95% ee

R = *p*-Me-C_6H_4 **6c** : 92% (94:6), 97% ee

R = *p*-F-C_6H_4 **6c** : 94% (83:17), 90% ee



β-hydroxy-α-amino esters **21** as the major diastereomer with good to excellent enantiomeric excesses (Scheme 12).[22]

The nitroaldol reaction of silyl nitronates with aldehydes promoted by ammonium fluorides, originally introduced by Seebach and Colvin in 1978,[23] is a useful method for the preparation of 1,2-functionalized nitroalkanols. We have recently succeeded in developing an asymmetric version of high efficiency and stereoselectivity by using a designer chiral quaternary ammonium bifluoride of type **6** as catalyst, which was readily prepared from the corresponding bromide by the modified method **C** (Scheme 13).[24]

Initial investigation showed that treatment of trimethylsilyl nitronate **22a** with benzaldehyde (R = Ph) in the presence of **6b** (X = HF_2, 2 mol %) in THF at −98 °C for 1 h and at −78 °C for 1 h and subsequent hydrolysis with 1 N HCl at 0 °C resulted in clean formation of the corresponding nitroalkanol **23** (R = Ph) in 83% yield (anti/syn = 74:26) with 33% ee (anti isomer). Notably, the poor diastereo- and enantioselectivities were dramatically improved by switching the catalyst to **6c** (X = HF_2) possessing a radially extended 3,3′-aromatic substitutent (Ar), and **23** (R = Ph) was obtained in 92% yield (anti/syn = 92:8) with 95% ee (anti isomer). This asymmetric nitroaldol protocol tolerates various aromatic aldehydes to afford *anti*-nitroaldols selectively, being complementary to Shibasaki's method using heterobimetallic complexes that gives *syn*-nitroaldols as major products.[25]

The observed high anti selectivity may reflect the acyclic extended transition state mechanism postulated in the fluoride-catalyzed reactions (Figure 2).[26] Judging from the product configuration, chiral ammonium cation should effectively cover the *si*-face of the nitronate and the selective approach of aldehyde from the *re*-face should result.

During the course of our study on these asymmetric nitroaldol reactions catalyzed by chiral ammonium bifluorides **6** (X = HF_2), we attempted the reaction of **22a** with *trans*-cinnamaldehyde, a representative α,β-unsatur-

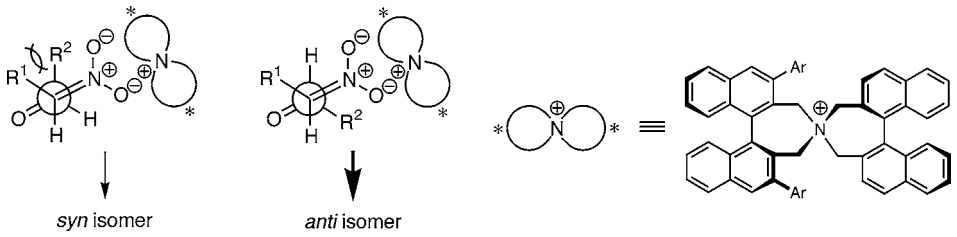
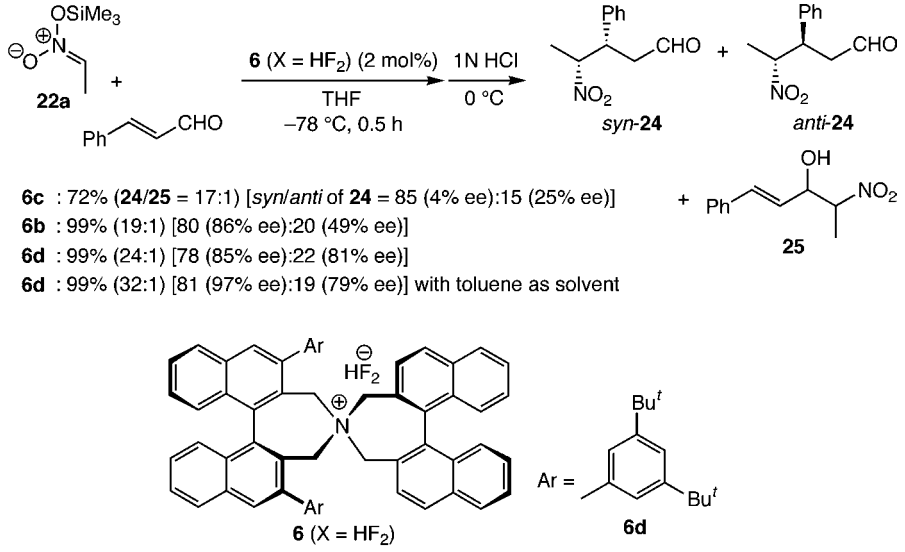


FIGURE 2.

Scheme 14

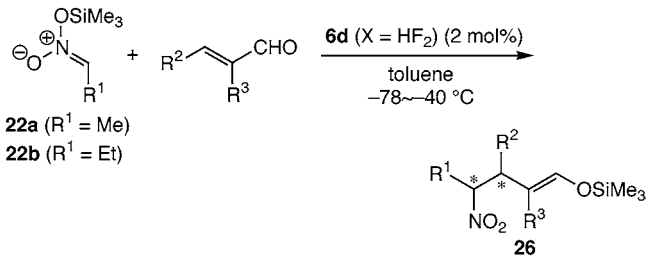


ated aldehyde, under the influence of **6c** (X = HF_2, 2 mol %) in THF at −78 °C. The starting aldehyde was consumed within 30 min at this temperature and, surprisingly, the 1,4-addition product **24** was obtained predominantly as a diastereomeric mixture with concomitant formation of the initially expected nitroaldol (1,2-addition product) **25** [72% combined yield, **24**/**25** = 17:1, syn/anti of **24** = 85 (4% ee):15 (25% ee)] (Scheme 14). It is noteworthy that achiral TBAF gave rise to a mixture of **24** and **25** in a ratio of 1.1:1 (76% yield, syn/anti = 61:39 for **24**). Although the observed enantiomeric excesses were still low at this stage, these results strongly implied that regio- and stereochemistry of the fluoride-catalyzed addition of silyl nitronates to α,β-unsaturated aldehydes could be precisely controlled by a designer chiral quaternary ammonium bifluoride of type **6** via the in situ formation of chiral ammonium nitronates, allowing a direct access to optically active γ-nitro aldehydes, very useful precursors of various complex organic molecules including aminocarbonyls. This should provide a unique yet powerful strategy for achieving the hitherto difficult catalytic asymmetric Michael addition to α,β-unsaturated aldehydes.[27]

From this standpoint, we pursued a thorough examination of the effect of the catalyst substituent (Ar) and reaction conditions on the reactivity and selectivity of this reaction. As also shown in Scheme 14, the sterically less congested **6b** (X = HF_2) exerted high catalytic activity, affording the products quantitatively with high regio- and diastereoselectivity (**24**/**25** = 19:1, syn/anti of **24** = 80:20), and the enantioselectivity of the major *syn*-**24** was drastically improved to 86% ee. Further, **24** was obtained with even higher regioselectivity and comparable stereoselectivity when the catalyst **6d** (X = HF_2) having the 3,5-di-*tert*-butylphenyl substituent was employed. Moreover, the use of toluene as solvent led to almost exclusive formation of the 1,4-adduct (**24**/**25** = 32:1) with similar diastereoselectivity (syn/anti = 81:19), and critical enhancement of the enantioselectivity was attained (97% ee).[28]

The significant synthetic advantage of this approach is the isolation of regio- and stereo-defined enol silyl ethers of optically active γ-nitro aldehydes as an attractive Mukaiyama donor, not readily accessible by ordinary asymmetric methodologies (Scheme 15). For instance,

Scheme 15



22	R^2, R^3	% yield (*syn*/*anti*)	% ee of **26** (major isomer)
22a	Ph, H	90 (83:17)	97
22b	Ph, H	87 (90:10)	98
22a	Ph, Me	90 (5:95)	95

after the reaction of **22a** with *trans*-cinnamaldehyde under the optimized conditions, the resulting mixture can be directly purified by silica gel column chromatography to give optically active enol silyl ether **26a** in 90% yield. High levels of catalytic efficiency and stereoselectivity were also available in the Michael addition of silyl nitronate **22b**. The introduction of an alkyl substituent at the α-carbon of enals can be well accommodated, as excellent diastereo- and enantiofacial differentiation have been achieved with α-methyl-*trans*-cinnamaldehyde.[28]

Conclusion

It is fair to say that asymmetric synthesis using chiral quaternary ammonium fluorides is still an underdeveloped field and the various useful stereoselective bond-forming processes described here are probably just a beginning in exploring its vast synthetic potential, particularly in combination with the knowledge of organosilicon chemistry. We believe the key issue to be addressed is the rational molecular design of chiral quaternary ammonium cations with appropriate steric and electronic properties, which are expected to be readily tunable to impart a sufficient reactivity as well as an ideal chiral environment to the requisite nucleophile involved in the desired chemical transformation. Continuous accumulation of information regarding the relationship between the structure of fluoride salts and their reactivity and selectivity promises to create a solid basis for this field, eventually offering a unique yet reliable tool for sophisticated bond construction events with rigorous stereocontrol under mild conditions.

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