Designer Chiral Quaternary Ammonium Bifluorides as an Efficient Catalyst for Asymmetric Nitroaldol Reaction of Silyl Nitronates with Aromatic Aldehydes

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The fluoride-mediated generation of nucleophiles from organo-silicon compounds for selective bond-forming reactions occupies an important place in modern organic synthesis.[1] This useful methodology inherently has implication in the development of the asymmetric system based on the use of a chiral nonracemic fluoride ion source represented by chiral quaternary ammonium fluorides. However, such a chemistry remains poorly studied, and only a few successful examples have been reported so far, most of which rely on the use of *cinchona* alkaloid-derived catalysts.[2,3] In this situation, we have been interested for some time in the preparation of a designer chiral C_2-symmetric quaternary ammonium bifluoride of type **1** and its application to catalytic asymmetric carbon−carbon bond-forming reactions.[3c,4] As an initial step and as a valuable chemical transformation in its own right, we communicate herein an efficient, diastereo- and enantioselective nitroaldol reaction of silyl nitronates with aldehydes catalyzed by (*S,S*)-**1** (Scheme 1).

The nitroaldol reaction is a classical yet powerful carbon−carbon bond-forming process in organic chemistry, providing efficient access to valuable synthetic building blocks such as 1,2-amino alcohols and α-hydroxy carboxylic acids.[5] In view of the significant importance of controlling the stereochemistry in an absolute sense, catalytic enantioselective variants utilizing optically active metal catalysts have recently been developed.[6−8] However, no reports have appeared on the asymmetric nitroaldol reaction of silyl nitronates with aldehydes promoted by chiral quaternary ammonium fluorides as organic catalysts, since Seebach and Colvin introduced this useful method for the preparation of 1,2-functionalized nitroalkanols.[9] Therefore, we decided to focus on this transformation.

The requisite chiral C_2-symmetric quaternary ammonium bi-fluoride **1** was found to be readily prepared from the corresponding bromide according to Shioiri's procedure with an appropriate modification.[2b,d] To evaluate the catalytic as well as chiral efficiency of **1**, the reaction of trimethylsilyl nitronate **2a** with benzaldehyde was examined. Thus, treatment of **2a** with benzaldehyde in the presence of **1a** (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 **3a** as a diastereomeric mixture (anti/syn = 74:26) in 83% yield, although the enantioselectivity of major anti isomer turned out to be disappointing (33% ee) (entry 1 in Table 1). Fascinatingly, however, dramatic improvement of both diastereo- and enantioselectivities was achieved by switching the catalyst to **1b** possessing a radially extended 3,3′-substituent (Ar), and the nitroaldol product **3a** was obtained in 92% yield (anti/syn = 92:8) with 95% ee (anti isomer) (entry 2). Further, the catalyst loading can be reduced to 1 mol % without significant loss of reactivity and selectivity (entry 3). The observed high anti selectivity may reflect the acyclic extended transition state mechanism postulated in the fluoride-catalyzed reactions (Figure 1).[9b,10] Judging from the product configuration, we find that the chiral ammonium cation should effectively cover
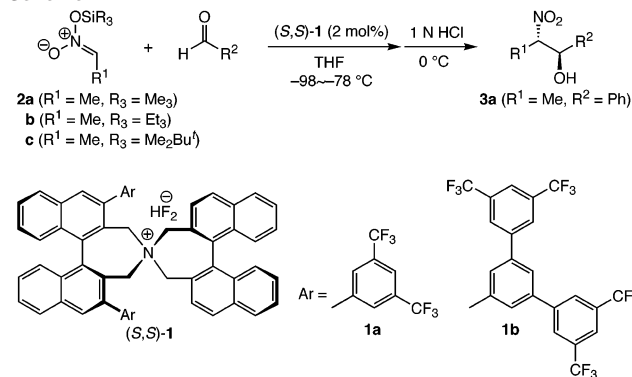
Scheme 1

2a (R¹ = Me, R₃ = Me₃)
 b (R¹ = Me, R₃ = Et₃)
 c (R¹ = Me, R₃ = Me₂Buᵗ)

3a (R¹ = Me, R² = Ph)

(*S,S*)-**1**   Ar =   **1a**   **1b**

Table 1. Asymmetric Nitroaldol Reaction of Silyl Nitronates with Aromatic Aldehydes Catalyzed by Chiral Quaternary Ammonium Bifluoride **1**[a]

entry	R¹	R₃	R²	react time (h)	% yield[b] (anti/syn)[c]	% ee[d] (config)[e]
1[f]	Me	Me₃ (**2a**)	Ph	2	83 (74:26)	33 (1*R*,2*S*)
2				3	92 (92:8)	95 (1*R*,2*S*)
3[g,h]				4	90 (90:10)	93 (1*R*,2*S*)
4		Et₃ (**2b**)		3	94 (85:15)	92 (1*R*,2*S*)
5		*t*-BuMe₂ (**2c**)		5	45 (57:43)	11 (1*R*,2*S*)
6[h]		Me₃ (**2a**)	*p*-Me-Ph	4	92 (94:6)	97
7			*p*-F-Ph	4	94 (83:17)	90
8			β-Np	4	88 (92:8)	93
9	Et		Ph	4	94 (90:10)	91
10	BnO(CH₂)₂		Ph	4	70 (87:13)	91

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of **2** and aldehyde in the presence of 2 mol % (*S,S*)-**1b** in THF (0.075 M substrate concentration) at −98 °C for 1 h and at −78 °C for the given reaction time. [b] Isolated yield. [c] Determined by ¹H NMR analysis. [d] Enantiomeric excess of the major *anti*-**3** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AS) with hexane-2-propanol or ethanol as solvent. Optical purity of the minor *syn*-**3** was generally lower (3−45% ee). [e] Absolute configuration of *anti*-**3a** was assigned, after conversion to the corresponding N-protected amino alcohol, by comparison of the HPLC retention time with that of the authentic sample independently prepared from commercially available (1*R*,2*S*)-(−)-norephedrine. [f] Use of (*S,S*)-**1a** as catalyst. [g] 0.15 M substrate concentration with 1 mol % (*S,S*)-**1b**. [h] Additional stirring at −40 °C for 1 h.

the *si*-face of the nitronate and the selective approach of aldehyde from the *re*-face should result.[11] It is important to note that the reaction of triethylsilyl nitronate **2b** with benzaldehyde under the influence of **1b** afforded **3a** in comparable chemical yield and with stereoselectivity (94%, anti/syn = 85:15, 92% ee for anti isomer) (entry 4), while substantial retardation of rate and diminished enantioselectivity were observed in the case of *tert*-butyldimeth-
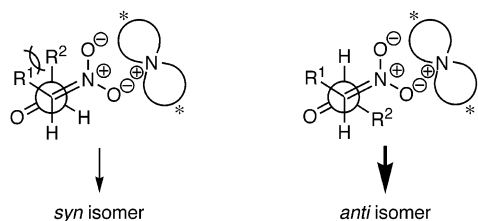
syn isomer   *anti* isomer

Figure 1.

ylsilyl nitronate **2c**, probably due to the difficulty of generating chiral ammonium nitronate (entry 5).

Further investigation was conducted with trimethylsilyl nitronate **2a** and various aromatic aldehydes in the presence of **1b** (2 mol %). The results listed in Table 1 clearly show the potential of this new asymmetric nitroaldol protocol, being complementary to Shibasaki's method using heterobimetallic complexes.[6c,e] Both diastereo- and enantioselectivity seemed to be subtly affected by the electronic nature of aldehydes (entries 6−8).[12] The present method was applicable to other silyl nitronates derived from simple nitroalkanes, where eminent catalytic activity and a high level of stereoselectivity were attained; see Table 1 (entries 9 and 10).

In conclusion, the highly enantio- and anti selective nitroaldol reaction of silyl nitronates with aldehydes has been accomplished using designer *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride **1b** as an efficient organic catalyst. Further detailed investigations on the mechanism as well as the scope and limitations of the present asymmetric system are currently being conducted in our laboratory.

Supporting Information Available: Representative experimental procedures and spectroscopic characterization of all new compounds including stereochemical assignment (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) ^{19}F NMR measurement of a solution of **1b** in THF-d_8 at −78 °C showed the signal of HF_2^- at δ −149.8 ppm. With the addition of **2a** (2.4 equiv) at −78 °C, the sharp signal of trimethylsilyl fluoride appeared at δ −157.61 ppm, supporting generation of the corresponding chiral ammonium nitronate.

(12) Attempted reaction of silyl nitronate **2a** with heteroaromatic aldehyde, 2-furaldehyde, under similar conditions gave the corresponding nitroaldol **3** with moderate enantioselectivity [97% (anti/syn = 85:15), 77% ee (anti isomer)]. We also investigated aliphatic aldehydes in the nitroaldol reaction with **2a** (at −78 °C for 0.5 h and −20 °C for 3 h), and the following results imply the present limitation of this method: 3-phenylpropanal [98% (anti/syn = 21:79), 46% ee (anti isomer), and 33% ee (syn isomer)]; cyclohexanecarboxaldehyde [87% (anti/syn = 43:57), 33% ee (anti isomer), and 20% ee (syn isomer)].

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