Tetrahedron Letters, Vol. 34, No. 9, pp. 1507-1510, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Chiral Quarternary Ammonium Fluoride. A New Reagent for Catalytic Asymmetric Aldol Reactions

Akira Ando, Toshiro Miura, Toshiaki Tatematsu, and Takayuki Shioiri*

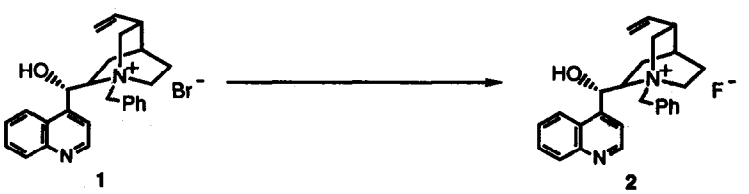
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

Abstract : Catalytic enantioselective aldol reactions of silyl enol ethers with benzaldehyde in high enantiomeric excesses were realized by utilizing chiral quarternary ammonium fluoride.

Catalytic asymmetric synthesis that enables a transformation of prochiral molecules to optical active ones with propagation of chirality has been recognized as one of the most important subjects in modern synthetic organic chemistry. Especially, a development of chiral catalysts for carbon-carbon bond forming reactions represented by aldol reactions has attracted much attention. Although several excellent asymmetric aldol-type reactions which are catalyzed by chiral metal complexes or Lewis acids have been reported,[1] few reports have been known on the use of chiral quarternary ammonium fluorides as a catalyst.[2] Here we report our preliminary results on the novel catalytic asymmetric aldol reactions utilizing a chiral quarternary ammonium fluoride.

We asked a chiral source to cinchonine since quarternary ammonium halides derived from cinchona alkaloids have proved to be excellent as chiral phase transfer catalysts.[3] Thus, preparation of N-benzylcinchonium fluoride (2) from the corresponding bromide 1 were investigated according to the procedures for the preparations of quarternary ammonium fluorides (Scheme 1). In the first two methods (methods A or B), the bromide anion in 1 was directly converted to the fluoride anion by use of the anion exchange resin, Amberlite IRA-410 or Amberlyst A-26, which was prepared as the F^- form beforehand,[4]

Scheme 1

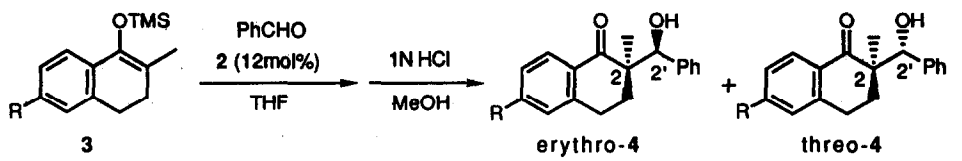


Method A 1) Amberlite IRA-410 F^- form 2) Evaporation
B 1) Amberlyst A-26 F^- form 2) Evaporation
C 1) Amberlyst A-26 OH^- form 2) 1N HF 3) Evaporation
D 1) AgF 2) Filtration 3) Evaporation

and the resulting aqueous solution of **2** was concentrated. In the method C, the bromide **1** was first transformed to the corresponding hydroxide by passing the methanol solution of **1** through Amberlyst A-26 OH^- form. Then the methanolic solution of N-benzylcinchonium hydroxide was neutralized with 1N hydrofluoric acid[5] and the solvents were removed. In the last method D, the bromide **1** was treated with silver fluoride in water overnight[6] followed by filtration and concentration. The fluoride **2** thus obtained was dried over phosphorous pentoxide at 40°C under vacuum overnight, and was used to the following investigations without further purification. The ^{1}H-NMR spectrum of **2** indicated that no decomposition of the N-benzylcinchonium residue took place during the transformation. Furthermore, ^{19}F-NMR spectrum of **2** in CD_2Cl_2 showed the peak centered at ca. -124 ppm ($CFCl_3$ was used as an internal standard), and this value was in agreement with the reported chemical shifts of quarternary ammonium fluorides.[7]

The aldol reaction of silyl enol ethers with aldehydes developed by Kuwajima and co-workers[8] was investigated by using the fluoride **2** as a catalyst (Scheme 2). The silyl enol ethers of 2-methyl-1-tetralone derivatives **3** were allowed to react with benzaldehyde in the presence of 12 mol% of **2** in THF at -70°C for several hours, and then the silylated aldols were hydrolyzed with 1N hydrochloric acid. After a usual work-up, the diastereomeric ratios and the enantiomeric excesses were determined by HPLC measurement having a chiral stationary phase column. The relative and absolute stereochemistries of the products **4** were assigned by the analysis of ^{1}H-NMR spectra of the isolated diastereomers[8b] and those of the corresponding MTPA esters.[9] The results are summarized in Table I.

Scheme 2



3 erythro-**4** threo-**4**

a R=H, **b** R=MeO, **c** R=Cl, **d** R=Br

All four lots of catalysts **2** which were prepared in different ways gave the aldol **4a** in 63-74% yield and the diastereomeric ratios were 70:30-80:20. The enantiomeric excesses of each diastereomers were 67-72% for the erythro isomer and 13-22% for the threo isomer, respectively (entries 1-4). The chemical yields, diastereo- and enantioselectivities were substantially independent on the preparation methods for **2**. THF proved to be the solvent of choice since the enantiomeric excesses dropped when the polar solvent, such as DMF or acetonitrile, was mixed with THF (entries 5 and 6). No aldol was obtained in ether or toluene. Although the hydrogen on the aromatic ring in the substrate **3** was changed to electron donating or withdrawing groups, little effect was observed on the chemical yield and stereoselectivity (entries 7-9).

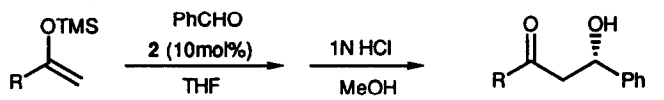
When the silyl enol ethers **5** and **7** were subjected to the similar reaction conditions, the aldols **6** and **8** were obtained in 65% and 62% yield, respectively (Scheme 3). The enantiomeric excess of **6** was 39%ee and the absolute configuration of the major isomer was (S).[10] On the other hand, (S)-**8** of 62%ee[11] was obtained when **7** was used. The last example shows that the aromatic portion in the substrate is not necessarily needed to get good stereoselectivity in this reaction.

Table I Asymmetric Aldol Reactions of Silyl Enol Ethers with Benzaldehyde Catalyzed Chiral Ammonium Fluoride 2[a]

entry	substrate	preparation method for 2	isolated yield of 4(%)	erythro/threo[b]	%ee[b] erythro[c]	%ee[b] threo[c]
1	3a	A	74	75/25	72	22
2	3a	B	63	71/29	67	13
3	3a	C	74	70/30	70	20
4	3a	D	66	80/20	71	16
5[d]	3a	C	74	88/12	2	1
6[e]	3a	C	65	73/27	44	6
7	3b	C	73	76/24	68	30
8	3c	C	73	82/18	66	21
9	3d	C	67	81/19	66	15

a) Experimental conditions as in the typical procedure. b) Diastereomeric ratios and enantiomeric excesses determined by HPLC(Sumichiral OA-4100) analysis. c) In entries 1-6, the absolute configurations of major isomer were (2R, 2'S) for the erythro isomer and (2R, 2'R) for the threo isomer, respectively. d) THF-DMF(2 : 8) was used as a solvent. e) THF-MeCN(7 : 3) was used as a solvent.

Scheme 3



5 R=Ph
7 R=*t*-Bu

6 R=Ph 65%, 39%ee
8 R=*t*-Bu 62%, 62%ee

Thus, the catalytic enantioselective aldol reactions up to 70%ee were realized by utilizing the chiral quarternary ammonium fluoride 2. These results would promise a new development of asymmetric synthesis. Further investigations including mechanistic studies are in progress.

The typical procedures for the preparation of the catalyst 2 by the method C and the aldol reaction are as follows: Amberlyst A-26 (Cl^- form, 2.5 g, 10 meq) was transformed into the OH^- form by passing 1N aq. NaOH until complete exchange of the chloride anion was achieved. The column was washed with water until neutral, and then with methanol. A solution of the bromide 1 (464 mg, 1.0 mmol) in methanol (20 mL) was slowly passed through the column and the column was washed with methanol. The eluent was neutralized until pH ≈ 7 with 1N aq. HF, and the solvents were removed *in vacuo*. The residue was co-evaporated with benzene-acetonitrile (1:1) three times and dried over phosphorous pentoxide at 40°C under vacuum overnight. The fluoride 2 (428 mg) was obtained as an amorphous solid and used to the next step without further purification.

To a solution of the fluoride **2** (49 mg, 0.12 mmol) in THF (8 mL) were added successively benzaldehyde (0.11 ml, 1.1 mmol) and a solution of the silyl enol ether **3a** (233 mg, 1.0 mmol) in THF (2 mL) at -70°C under Ar. After 6h, water (2 mL) was added and the mixture was warmed to room temperature and concentrated. The residue in methanol (10 mL) was treated with 1N aq. HCl (0.3 mL) at room temperature for 2 h. Usual work-up followed by chromatographic purification gave the aldol **4a** (198 mg, 74%). The diastereomeric ratio (erythro : threo = 70 : 30) and the enantiomeric excesses (70%ee for the erythro and 20%ee for the threo isomer, respectively) were determined by HPLC measurement (column : Sumichiral OA-4100, solvent : hexane : 1,2-dichloroethane : ethanol = 280:19:1, flow rate : 1.0ml/min).

Acknowledgements: This work was supported in part by research grants from the Ministry of Education, Science and Culture, Japan and the Japan Research Foundation for Optically Active Compounds. We are grateful to Mr. T. Watanabe for his able preparative assistance.

References and note

1. For recent catalytic aldol processes, see: (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041. (b) Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *Chem. Lett.* **1991**, 831. (c) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365 and references cited therein.
2. Only one asymmetric Michael reaction catalyzed by chiral ammonium fluoride prepared *in situ* has been reported see: Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc. Chem. Commun.* **1978**, 238.
3. Masui, M.; Ando, A; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835 and references cited therein.
4. (a) Pless, P. *J. Org. Chem.* **1974**, *39*, 2644. (b) Miller, J. M.; Cater, S. R.; So, K.-H.; Clark, J. H. *Can. J. Chem.* **1979**, *57*, 2629. (c) Colonna, S.; Re, A.; Gelbard, G.; Cesarotti, E. *J. Chem. Soc. Perkin Trans. I* **1979**, 2248.
5. (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) Kuwajima, I.; Murofushi, T.; Nakamura, E.; *Synthesis* **1976**, 602.
6. Hayami, J.; Uno, N.; Kaji, A. *Tetrahedron Lett.* **1968**, 1385.
7. Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A. *Synthesis* **1988**, 953 and references cited therein.
8. (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.
9. Yamaguchi, S. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1 p125-152.
10. The enantiomeric excess of **6** was determined by ^{1}H-NMR analysis of the corresponding acetyl ester in the presence of Eu(hfc)$_3$, and the absolute configuration was determined by the comparison of specific rotation value, see: Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513.
11. The enantiomeric excess and the absolute configuration of **8** were determined according to the same procedure as that used in the case of **4a**.

(Received in Japan 7 November 1992)