IMPORTANCE OF THE HYDROXYMETHYL - QUINUCLIDINE FRAGMENT IN THE CATALYTIC ASYMMETRIC ALDOL REACTIONS UTILIZING QUATERNARY AMMONIUM FLUORIDES DERIVED FROM CINCHONA ALKALOIDS§

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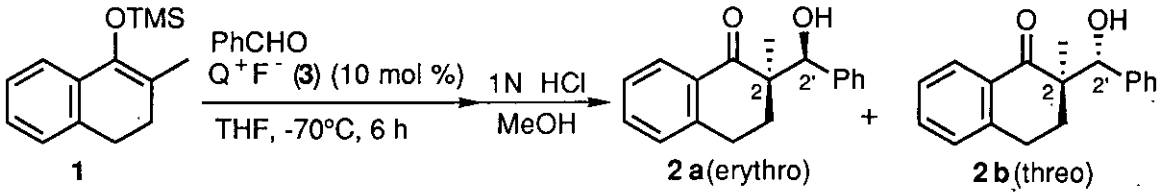
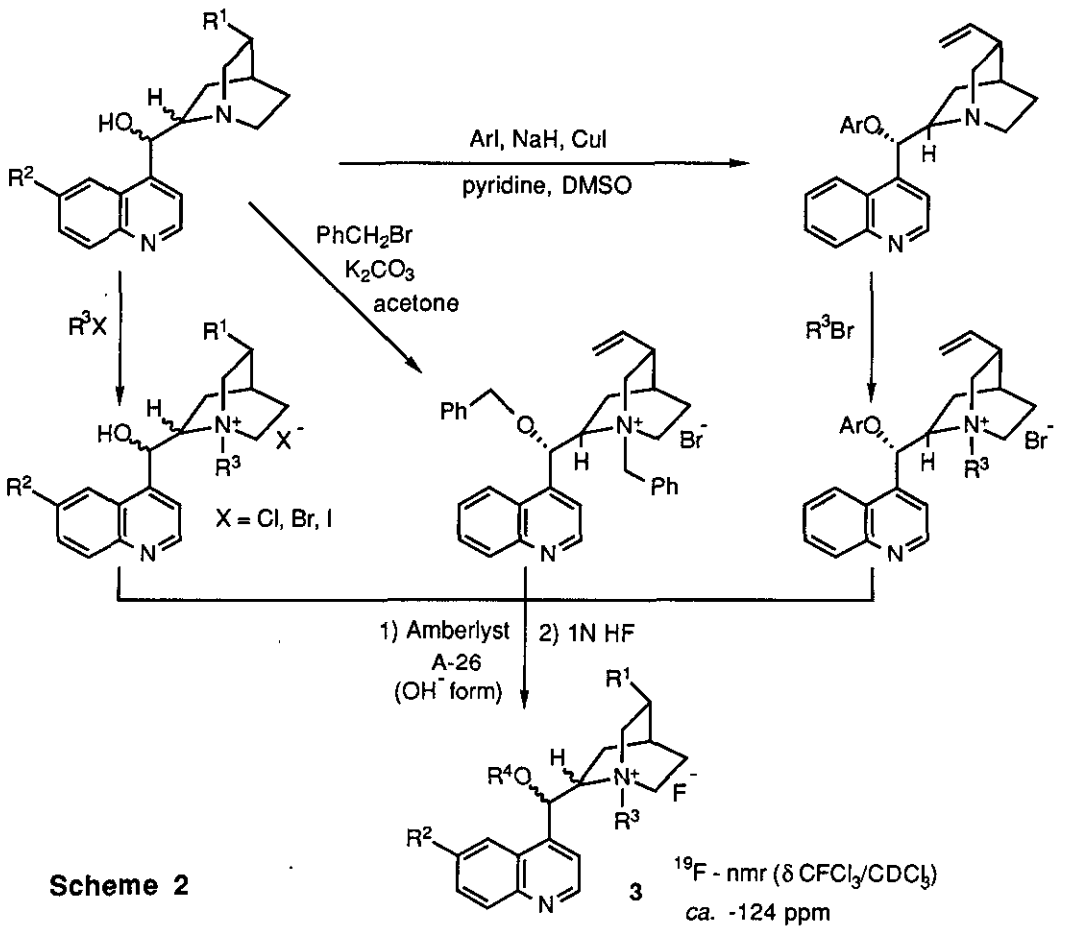
Abstract — The hydroxymethyl-quinuclidine fragment in quaternary ammonium fluorides derived from cinchona alkaloids proved to play an important role on the stereochemical course in the fluoride ion catalyzed aldol reactions.

We have already revealed[1] that catalytic asymmetric aldol reactions of enol silyl ethers with benzaldehyde have been accomplished in good enantiomeric excesses by utilizing a quaternary ammonium fluoride derived from cinchonine.[2,3] We now extended our exploration of quaternary ammonium fluoride catalysts derived from cinchonine to those from the other cinchona alkaloids, and revealed that the reaction course shown in Scheme 1 was mainly dominated by the hydroxymethyl-quinuclidine fragment.



Q^+F^- (3): quaternary ammonium fluorides derived from cinchona alkaloids **Scheme 1**

§ Dedicated to the memory of the late Professor Yoshio Ban whose sudden death is really a great loss to the field of synthetic organic chemistry.



Scheme 2

Table 1. Fluoride Catalysts (3) Derived from Cinchona Alkaloids

Catalyst	R^1	R^2	R^3	R^4	C_8-H	C_9-OR^4	derived from
3a	CH_2=CH	H	$PhCH_2$	H	R	S	cinchonine
3b	CH_2=CH	MeO	$PhCH_2$	H	R	S	quinidine
3c	CH_3CH_2	MeO	$PhCH_2$	H	R	S	quinidine
3d	CH_2=CH	H	$PhCH_2$	Ph	R	S	cinchonine
3e	CH_2=CH	H	$PhCH_2$	1-naphthyl	R	S	cinchonine
3f	CH_2=CH	H	$PhCH_2$	$PhCH_2$	R	S	cinchonine
3g	CH_2=CH	H	4-$CF_3C_6H_4CH_2$	Ph	R	S	cinchonine
3h	CH_2=CH	H	4-$CF_3C_6H_4CH_2$	1-naphthyl	R	S	cinchonine
3i	CH_2=CH	H	4-$MeOC_6H_4CH_2$	H	R	S	cinchonine
3j	CH_2=CH	H	$PhCH_2$	H	S	R	cinchonidine
3k	CH_2=CH	MeO	$PhCH_2$	H	S	R	quinine
3l	CH_2=CH	H	$PhCH_2$	H	R	R	9-epi-cinchonine
3m	CH_2=CH	H	$PhCH_2$	H	S	S	9-epi-cinchonidine

First, various ammonium fluorides (**3**) shown in Table 1 were prepared from cinchona alkaloids. Conversion of the halides to the fluorides was conveniently accomplished by our method using Amberlyst A-26 (OH^- form) followed by 1N hydrofluoric acid,[1] as outlined in Scheme 2. All of the fluorides thus obtained showed a ^{19}F-signal at *ca.* -124 ppm in the ^{19}F-nmr spectra.[4]

With various chiral ammonium fluorides (**3**) in hand, we investigated the aldol reaction shown in Scheme 1. The results summarized in Table 2 suggest that the stereochemical results of the aldol reaction mainly depend on the stereochemistry of the hydroxymethyl-quinuclidine fragment, indicating that the hydroxymethyl-quinuclidine fragment is most responsible for binding with the enolate generated from the enol silyl ether (**1**). Usually, the catalysts derived from cinchonine are more effective than those from cinchonidine. The major product when the catalysts derived from cinchonine and quinidine are used is mainly the erythro isomer (**2a**) which has (2*R*,2'*S*)-configuration in every case. The minor threo isomer (**2b**) has (2*R*,2'*R*)-configuration. Protection of the C-9 hydroxyl group with aryl ones increases the threo isomer. Interestingly the catalysts (**3j**) and (**3k**) derived from cinchonidine and quinine, respectively, change the stereochemical course of the aldol reaction, yielding the threo aldol (**2**) with (2*S*,2'*S*)-configuration as the major product. Although the C-9 hydroxyl group of the catalyst was anticipated to

Table 2. Chiral Ammonium Fluoride Catalyzed Aldol Reactions - 1

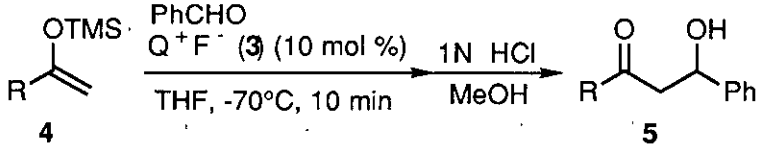
run	catalyst	isolated yield(%)	aldol **2** erythro/threo[a]	% ee erythro(conf.)[b]	threo(conf.)[b]
1	**3a**	74	70/30	70 (R,S)	20 (R,R)
2	**3b**	57	64/36	48 (R,S)	30 (R,R)
3	**3c**	46	61/39	41 (R,S)	23 (R,R)
4	**3d**	90	54/46	55 (R,S)	25 (R,R)
5	**3e**	80	49/51	51 (R,S)	27 (R,R)
6	**3f**	78	69/31	56 (R,S)	4 (R,R)
7	**3g**	37	61/39	14 (R,S)	13 (R,R)
8	**3h**	54	54/46	35 (R,S)	16 (R,R)
9	**3i**	44	76/24	64 (R,S)	17 (R,R)
10	**3j**	35	37/63	5 (R,S)	15 (S,S)
11	**3k**	75	33/67	12 (R,S)	47 (S,S)
12	**3l**	0[c]	-	-	-
13	**3m**	4.5	56/44	1.1 (R,S)	0.05 (R,R)

a) Determined by hplc (SUMICHIRAL OA-4100) analysis. b) Configuration at C-2 and C-2' positions of the major product. c) The reaction does not proceed at all since the catalyst (**3l**) does not dissolve in THF.

provide a directional handle for the ionic interaction *via* hydrogen bond to the enolate anion,[5,6] it is not essential in this reaction since protection of the hydroxyl group little influences the stereochemical outcome. The benzylic group and quinoline ring which might cause the π-π interaction[5,6] are lesser important, and the vinyl group can be replaced with the ethyl group. These results coincide with the proposal by O'Donnell and Lipkowitz[7] in the asymmetric induction of benzophenone imine ester enolates by the benzylcinchoninium ion.[8]

Incidentally, the enol silyl ethers (**4**) from acetophenones and pinacolone were subjected to the fluoride ion catalyzed asymmetric aldol reaction using **3a** and **3j**, as shown in Table 3. Again, stereochemistry of the products depends on the configuration of the hydroxymethyl-quinuclidine fragments, and the catalyst (**3a**) derived from cinchonine is much more effective than **3j** from cinchonidine. Bulkiness of the *tert*-butyl group favors the asymmetric efficiency in the aldol reaction.

Table 3. Chiral Ammonium Fluoride Catalyzed Aldol Reactions - 2



4 **5**

For **4** and **5**: **a**: Ph **b**: 4-ClC_6H_4 **c**: 4-$MeOC_6H_4$ **d**: 2,4-$(MeO)_2C_6H_3$ **e**: Me_3C

run	catalyst	R	product	isolated yield of **5** (%)	% ee	config. of major product
1	**3a**	Ph	**5a**	76	39.5[a]	S[d]
2	**3j**	Ph	**5a**	46	35.5[a]	R[d]
3	**3a**	4-ClC6H4	**5b**	55	42[a]	S[d]
4	**3a**	4-MeOC6H4	**5c**	70	36.5[a]	S[d]
5	**3a**	2,4-(MeO)2C6H3	**5d**	73	25[b]	S[d]
6	**3a**	Me3C	**5e**	62	62[c]	S[e]
7	**3j**	Me3C	**5e**	55	39[c]	R[e]

a) Determined by ^{1}H-nmr analysis of the corresponding acetyl ester in the presence of Eu(hfc)$_3$. b) Determined by ^{1}H-nmr analysis of the corresponding (R)-MTPA ester. c) Determined by hplc (SUMICHIRAL OA-4100) analysis. d) Determined by the specific rotation value (S. H. Mashuragui and R. M. Kellog, *J. Org. Chem.*, 1984, **49**, 2513). e) Determined by the comparison of retention times of hplc (SUMICHIRAL OA-4100).

Although more efficient fluoride catalysts should be explored further, results of the present study are expected to markedly assist in obtaining further insights into the design of new effective catalysts as well as pursuing the mechanistic clarification for the asymmetric aldol reactions.

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REFERENCES AND NOTES

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