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An Unusual Electronic Effect of an Aromatic-F in Phase-Transfer Catalysts Derived from *Cinchona*-Alkaloid

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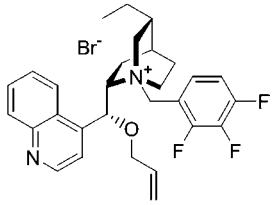
ABSTRACT



Various *N*-benzylcinchonidinium salts were prepared to study electronic factors in the catalytic enantioselective phase-transfer alkylation of glycine anion equivalent. An ortho-fluoro substituent on the benzyl group in the quaternary ammonium salt dramatically increased the enantioselectivity in the alkylation. *O*(9)-Allyl-*N*-2′,3′,4′-trifluorobenzylhydrocinchonidinium bromide (27), which gave the highest enantioselectivity of the catalysts studied, was used to prepare 12 α-alkylated amino acid derivatives in 94∼>99% ee.

Recently, *Cinchona* alkaloid ammonium salts have been developed as efficient chiral phase-transfer catalysts.[1] Since the first application of **1** in the alkylation of glycine imine derivatives by the O'Donnell group,[2] more efficient catalysts **2** were independently developed by the Lygo group[3] and the Corey group[4] by the introduction of the bulky *N*-9-anthracenylmethyl group instead of the *N*-benzyl group in **1**. On the basis of the positive influence of a bulky subunit on the N(1)-position, the dimeric catalysts **3** were also introduced as practical phase-transfer catalysts for the synthesis of both natural and nonnatural α-amino acids (Figure 1).[5]

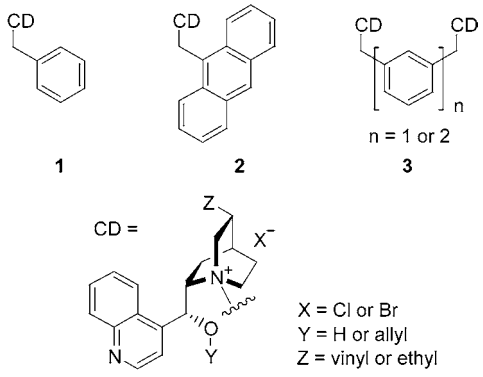


Figure 1. Phase-transfer catalysts derived from *Cinchona* alkaloid.

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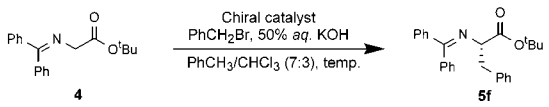
Table 1. Catalytic Enantioselective Phase-Transfer Alkylation[a]



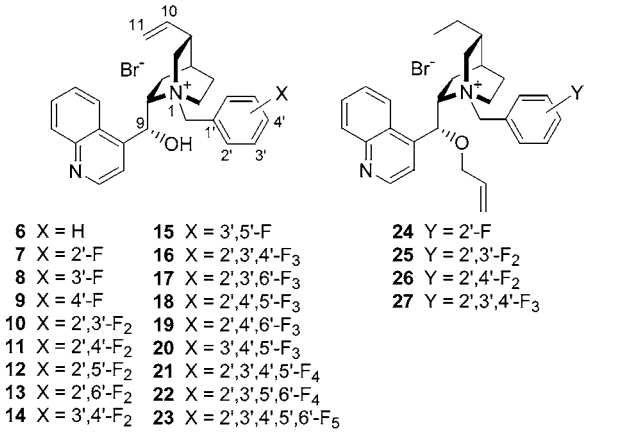
entry	catalyst	temp (°C)	time (h)	yield[b] (%)	% ee[c] (configuration[d])
1	**6**	0	5	92	74 (*S*)
2	**7**	0	6	93	89 (*S*)
3	**8**	0	4	90	74 (*S*)
4	**9**	0	7	92	75 (*S*)
5	**10**	0	6	90	92 (*S*)
6	**11**	0	5	93	90 (*S*)
7	**12**	0	6	89	59 (*S*)
8	**13**	0	7	90	76 (*S*)
9	**14**	0	8	91	71 (*S*)
10	**15**	0	6	88	50 (*S*)
11	**16**	0	5	93	92 (*S*)
12	**17**	0	5	91	66 (*S*)
13	**18**	0	6	88	62 (*S*)
14	**19**	0	5	90	72 (*S*)
15	**20**	0	4	85	50 (*S*)
16	**21**	0	6	91	68 (*S*)
17	**22**	0	7	89	22 (*S*)
18	**23**	0	7	93	54 (*S*)
19	**24**	0	4	90	92 (*S*)
20	**24**	−20	7	88	94 (*S*)
21	**25**	0	4	90	95 (*S*)
22	**25**	−20	6	91	97 (*S*)
23	**26**	0	4	90	92 (*S*)
24	**26**	−20	7	93	95 (*S*)
25	**27**	0	4	90	96 (*S*)
26	**27**	−20	6	92	98 (*S*)

[a] Reaction was carried out with 5.0 equiv of benzyl bromide and 13.0 equiv of 50% aqueous KOH in the presence of 10 mol % **6**−**27** in toluene/chloroform (volume ratio = 7:3) under the given conditions. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of the benzylated imine **5f** using a chiral column (DAICEL Chiralcel OD) with hexanes/2-propanol (volume ratio = 500:2.5) as a solvent. [d] Absolute configuration was determined by comparison of the HPLC retention time with that of an independently prepared authentic sample.[2−5]

Although several efficient catalysts have been developed on the basis of steric factors, the electronic factor was not systematically studied.[6] As part of our program for the mechanistic study of alkylation, we investigated the role of the electronic factor in *Cinchona* alkaloid-type phase-transfer catalysts. Since the ion pair of the quaternary ammonium cation and the anionic substrate is an important intermediate for the chiral induction, the electronic effects of the N(1)-substituents might influence the enantioselectivity. In this letter, we report the role of electronic factors and the unusual aromatic-F effect in alkylations of a glycine anion equivalent involving phase-transfer catalysts.

First, the *N*-benzylcinchonidinium bromide derivatives were prepared from cinchonidine and benzyl bromides substituted at the ortho-, meta-, or para-position with various functional groups such as methyl, *tert*-butyl, methoxy, nitro, halides, and so on. Their catalytic efficiencies were evaluated by enantioselective phase-transfer alkylation, using 10 mol % catalyst, *N*-(diphenylmethylene)glycine *tert*-butyl ester **4**, benzyl bromide, and 50% aqueous KOH in toluene/chloroform (volume ratio = 7:3) at 0 °C for 4−8 h.

We expected that electron-withdrawing functional groups might increase the enantioselectivity by the formation of a tighter binding ion pair, which would lead to a more rigid conformation. However, the meta- and the para-substituted derivatives did not show any significant difference in enantioselectivity, despite their electronic properties (data not shown). In the case of the ortho-substituted derivatives, bulky groups generally reduced the enantioselectivity. Notably, among the ortho-substituted derivatives, the 2′-F derivative **7** (89% ee) showed an enhanced enantioselectivity relative to **6** (74% ee) even though the sizes of F and H are similar (Table 1). A similar aromatic-F effect was previously observed by the replacement of the 3,4,5-trifluorobenzene group with a bulky naphthyl substituent in (*S*)-binaphthol-derived C_2-symmetric chiral catalysts.[7] Also it has been reported that various aromatic-F groups play an important role in the binding of enzyme inhibitors.[8] These findings encouraged us to prepare various F-substituted derivatives (Figure 2).



6 X = H
7 X = 2'-F
8 X = 3'-F
9 X = 4'-F
10 X = 2',3'-F_2
11 X = 2',4'-F_2
12 X = 2',5'-F_2
13 X = 2',6'-F_2
14 X = 3',4'-F_2
15 X = 3',5'-F
16 X = 2',3',4'-F_3
17 X = 2',3',6'-F_3
18 X = 2',4',5'-F_3
19 X = 2',4',6'-F_3
20 X = 3',4',5'-F_3
21 X = 2',3',4',5'-F_4
22 X = 2',3',5',6'-F_4
23 X = 2',3',4',5',6'-F_5
24 Y = 2'-F
25 Y = 2',3'-F_2
26 Y = 2',4'-F_2
27 Y = 2',3',4'-F_3

Figure 2. *N*-(Fluorobenzyl)cinchonidinium bromide derivatives.

As shown in Table 1, there are, depending on the position substituted with a fluoro group, quite dramatic variations in

(4) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (c) Corey, E. J.; Bo, Y.; Busch-Peterson, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.

(5) (a) Jew, S.-S.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-G. *Chem. Commun.* **2001**, 1244. (b) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-K.; Huh, H.; Jew, S.-S. *Tetrahedron Lett.* **2001**, *42*, 4645. (c) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.

(6) In early studies, the Merk group found that a *p*-trifluoromethyl group was important for optimal enantioselectivity; see ref 1a. See also refs 1b−c for discussions concerning other catalyst studies.

(7) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

(8) (a) Kim, C.-Y.; Chandra, P. P.; Jain, A.; Christonson, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 9620. (b) Doyon, J. B.; Jain, A. *Org. Lett.* **1999**, *1*, 183. (c) Madder, R. D.; Kim, C.-Y.; Chandra, P. P.; Doyon, J. B.; Baird, T. A., Jr.; Fierke, C. A.; Christonson, D. W.; Voet, J. G.; Jain, A. *J. Org. Chem.* **2002**, *67*, 582.

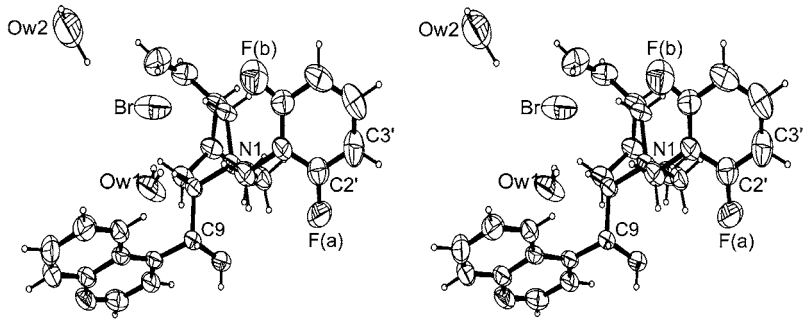


Figure 3. Stereoscopic view of **7** drawn by ORTEPII. Selected atomic distances (Å) and bond angles and torsion angles (deg): N1ΛBr 4.119(2), F(a)ΛO1 4.100(3), F(b)ΛBr 3.492(6); C2−N1−C12 109.8(2), N1−C12−C1′ 113.9(2); C2−N1−C12−C1′−59.6(2), C8−N1−C12−C1′−175.2(2). Non-carbon atoms are drawn as hatched ellipsoids, and hydrogen atoms are drawn as small circles of arbitrary radii.

the enantioselectivity. Generally, a single fluoro group in the ortho-position is critical for enhancement of the induction. With the exception of *o*,*o*′-difluoro groups, which are not effective, the number of fluoro groups on the aromatic ring is not directly related to the enantioselectivity. The best results were obtained with additional fluoro groups on the 3′- and/or 4′-positions (**10**, 92% ee; **11**, 90% ee; **16**, 92% ee).

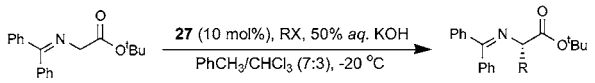
To study the role of 2′-F in the enantioselectivity, an X-ray crystal structure of **7** was obtained (Figure 3).[9] The conformation of **7** is similar to that of the unsubstituted parent **6**.[2b] However, the 2′-F of **7** is disordered; the phenyl group occupies two different conformations in unequal amounts: four parts as F(a) and one part as F(b). This might be due to unfavorable anionic repulsion between the bromide anion and F(b). Another possibility is that conformation F(a) could be favored due to internal hydrogen bonding involving water between F(a) and the C(9)OH group (the distance between these groups in the crystal structure is 4.1 Å). While the exact mechanistic details of the induction are not clear at this time, 2′-F might be involved in internal hydrogen bonding involving water in order to maintain a more rigid catalyst conformation.[10,11]

Another possible reason might be associated with the induced dipole moment by the unsymmetrical introduction of a fluoro group on the benzene ring, which could allow formation of a more favorable ion pair intermediate with the anionic enolate substrate.[6a] The precise mechanistic role of 2′-F is now under investigation.

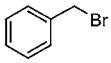
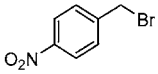
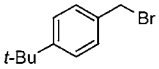
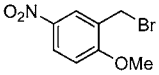
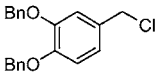
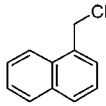
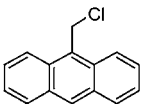
Dihydro and C(9)*O*-allyl derivatives of **7**, **10**, **11**, and **16** were prepared by the reported method,[5] and their catalytic efficiencies were evaluated (**24**−**27**). In agreement with previous reports,[2b,c,3a] all of these catalysts gave higher enantioselectivities than those with a free C(9)OH group (92−96% ee at 0 °C). Use of lower temperature improved the enantioselectivity (94−98% ee at −20 °C).

The best enantioselectivity was obtained with catalyst **27**, which was chosen for further investigation with various alkyl halides. Table 2 shows the results obtained for the alkylation of **4** with various alkyl halides, using catalyst **27** under the same reaction conditions as those in Table 1, except that the reaction was conducted at −20 °C. Very high enantioselectivities (94∼>99% ee) are shown in Table 2, indicating that catalyst **27** is a very efficient asymmetric phase-transfer

Table 2. Catalytic Enantioselective Phase-Transfer Alkylation[a]



4 **5**

entry	RX	time (h)	yield (%)	% ee (Config.)
a	CH_3I	12	60	94 (*S*)
b	$CH_3(CH_2)_4CH_2I$	18	65	>99 (*S*)
c		9	95	96 (*S*)
d		8	90	96 (*S*)
e		3	94	97 (*S*)
f		6	96	98 (*S*)
g		7	90	96 (*S*)
h		6	92	99 (*S*)
i		9	90	98 (*S*)
j		8	93	97 (*S*)
k		16	85	>99 (*S*)
l		10	95	97 (*S*)

[a] With the exception of the alkyl halide used and the reaction temperature, the reaction conditions and determination of the enantiopurity and absolute configuration were same as that in Table 1.

catalyst for the synthesis of natural and nonnatural α-amino acids.

In conclusion, various N-(substituted-benzyl)cinchonidinium salts were prepared for study of the electronic factors in the catalytic enantioselective phase-transfer alkylation of glycine anion equivalent **4**. Unexpectedly, a 2′-F substituent dramatically increased the enantioselectivity in the alkylation. Among the F-substituted derivatives, *O*(9)-allyl-*N*-2′,3′,4′-trifluorobenzylhydrocinchonidinium bromide, **27**, showed the highest enantioselectivity. The easy and efficient preparation of **27** makes it an attractive catalyst for the preparation of various α-amino acid derivatives in high enantioselectivity.

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Supporting Information Available: Representative experimental procedures and an X-ray crystal structure of **7** and spectroscopic characterizations of catalyst **27** and alkylated imines **5i** and **5l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Crystallographic data of **7**: $C_{26}H_{28}BrFN_2O \cdot 1.5\ H_2O$, bright yellow prism, 0.30 × 0.30 × 0.30 mm, tetragonal, space group $P4_12_12$ (no. 92), $a = b = 10.029(1)$ Å, $c = 47.637(7)$ Å, $V = 4791(1)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.415$ g/cm^3, μ(Cu Kα) = 26.6 cm^{-1}, $T = 298$ K. Details of structural results were deposited to the Cambridge Crystallographic Data Center as deposit no. 190336. These data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax, +44 1223 336033; e-mail, deposit@ccdc.cam.ac.uk).

(10) Alkylations under anhydrous conditions using 10 mol % catalyst, the *O*(9)-allyl derivative of **6** or **7** along with *N*-(diphenylmethylene)glycine *tert*-butyl ester **4**, benzyl bromide, and NaH in toluene/CH_2Cl_2 (volume ratio = 7:3) at 0 °C for 12 h both gave the same enantioselectivity (62% ee).

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