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Evidence of the Electronic Factor for the Highly Enantioselective Catalytic Efficiency of *Cinchona*-Derived Phase-Transfer Catalysts

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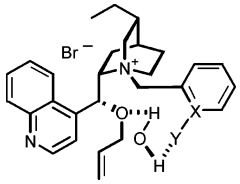
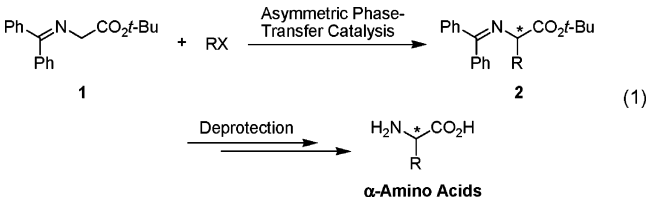
ABSTRACT



The *Cinchona* alkaloid-derived quaternary ammonium salts containing 2′-*N*-oxypyridine and 2′-cyanobenzene moieties were prepared and evaluated as phase-transfer catalysts in the enantioselective alkylation of glycine imine ester 1. The *N*-oxypyridine and cyanobenzene moieties might play an important role to form a rigid conformation by coordinating with H_2O via hydrogen bonding leading to high enantioselectivity (97∼>99% ee), which provides evidence of an electronic factor for the high enantioselective catalytic efficiency in phase-transfer alkylation.

Recently, quaternary ammonium salts derived from *Cinchona* alkaloids have been successfully applied to the asymmetric phase-transfer catalytic alkylation.[1] The asymmetric alkylation of the glycine imine ester **1**, a precursor of the enantioselective synthesis of natural and unnatural α-amino acids, has been studied extensively (eq 1).[2]



It has been proposed that the high enantioselectivity was due to steric bulkiness of the N^+-arylmethyl group in *Cinchona*-derived catalyst. Formation of the geometrically most stable ion pair between *E*-enolate anion of **1** and the bridgehead ammonium cation and the following addition of electrophile accessed exclusively to one face of the ion-paired enolate to yield optically enriched α-amino acid derivatives.

Recent findings from our laboratory demonstrated, however, that the electronic effect of the N^+-arylmethyl unit in the catalyst is also responsible for high enantioselectivity.[3] Catalysts **3** and **4** containing 2′-F showed enhanced enantioselectivity compared to those of nonsubstituted analogues,

(1) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (d) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (e) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (f) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (g) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244. (h) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645. (i) 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. (j) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382.

(2) (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.

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respectively while they exert virtually the same steric effect (Figure 1). We have proposed that the high enantioselectivities might be due to more rigid conformations of catalysts caused by the electronic interactions involving water between C(9)−O and 2′-F in catalyst, for instance, hydrogen bonding or induced dipole−dipole interaction.

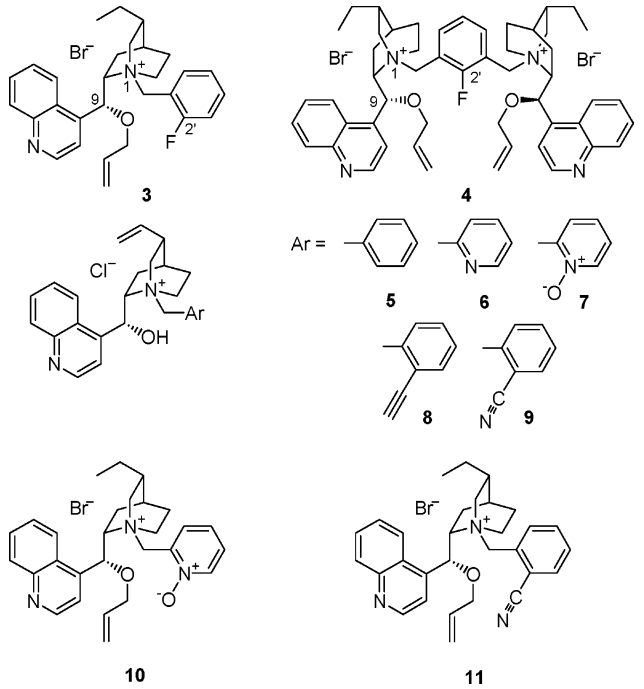


Figure 1. Electronically modified *Cinchona* alkaloid quaternary ammonium salts.

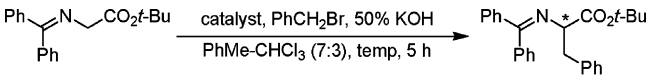
Hydrogen bonds are important because of the effects that they have on the properties of compounds. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it often plays a significant role in determining reaction rates by influencing the conformation of molecules,[4] and it is also important in maintaining the three-dimensional structures of protein and nucleic acid molecules.[5] In addition to CO_2H, OH, and NH that are typical functional groups to form hydrogen bonds, *N*-oxypyridine and cyanobenzene were reported to form a stable crystal structure by internal hydrogen bonding, similar to fluorobenzenes.[6] These reports prompted us to prepare new *Cinchona* alkaloid-derived ammonium salts bearing *N*-oxypyridine and cyanobenzene moieties at 2′ position which were expected to show similar electronic effects as those with 2′-F-phenyl ring (**3**, **4**).

N^+-(1-Oxypyridin-2-ylmethyl)-*cinchona* catalyst **7** and N^+-(1-cyanobenzyl)-*cinchona* catalyst **9** were prepared from (−)-cinchonidine along with 2-chloromethylpyridine-1-oxide and 2-cyanobenzyl chloride, respectively by previously reported methods.[3] To confirm the electronic effect of the *N*-oxide and cyano group functionality, 2′-pyridine analogue **6** and 2′-acetylene analogue **8** were prepared, respectively.

Figure 2. Stereoview of plausible hydrogen bonding between catalyst **10** and H_2O.

The capability of the catalysts **6**−**9** along with **5** on the introduction of enantioselectivity was evaluated by the benzylation of **1** with 5 mol % of each catalyst, benzyl bromide, and 50% aqueous KOH in toluene−chloroform (volume ratio = 7:3) at 0 °C for 5 h (Table 1). As shown in Table 1, the replacement of phenyl ring (**5**, 70% ee) with pyridine (**6**, 61% ee) resulted in a decrease in the enantioselectivity. In contrast, the *N*-oxypyridine derivative (**7**, 90%

Table 1. Evaluation of Catalytic Efficiency Using Catalytic Phase-Transfer Benzylation[a]



1 2e

entry	catalyst	T (°C)	yield[b] (%)	% ee[c] (config[d])
1	**5**	0	92	70 (*S*)
2	**6**	0	95	61 (*S*)
3	**7**	0	92	90 (*S*)
4	**8**	0	90	75 (*S*)
5	**9**	0	95	92 (*S*)
6	**10**	0	94	96 (*S*)
7	**10**	−20	95	98 (*S*)
8	**11**	0	94	96 (*S*)
9	**11**	−20	96	98 (*S*)

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 10.0 equiv of 50% aqueous KOH in the presence of 5.0 mol % of catalyst in toluene/chloroform (7:3) under the given temperature conditions. [b] Isolated yields. [c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2e** using a chiral column (Chiralcel OD) with hexanes/2-propanol (500:2.5) as the eluent. [d] The absolute configuration was confirmed by comparison of the HPLC retention time of an authentic sample, which was synthesized independently by reported procedures.[1−3]

(3) (a) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I. Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497.

(4) For reviews of the effect of hydrogen bonding on reactivity, see: (a) Sadekov, I. D.; Minkin, V. I.; Lutskii, A. E. *Russ. Chem. Rev.* **1970**, *39*, 179. (b) Hibbert, F.; Emsley, *J. Adv. Phys. Org. Chem.* **1990**, *26*, 255.

(5) (a) Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1988**, *71*, 258. (b) Hodgkin, E. E.; Clark, J. D.; Miller, K. R.; Marshall, G. R. *Biopolymers* **1990**, *30*, 533. (c) Di Blasio, B.; Pavone, V.; Lombardi, A.; Pedone, C.; Benedetti, E. *Biopolymers* **1993**, *33*, 1037. (d) Toniolo, C.; Crisma, M.; Formaggio, F.; Valle, G.; Cavicchioni, G.; Précigoux, G.; Aubry, A.; Kamphius, J. *Biopolymers* **1993**, *33*, 1061. (e) Toniolo, C. *Jassen Chim. Acta* **1993**, *11*, 10. (f) Karle, I. L.; Rao, R. B.; Prasad, S.; Kaul, R.; Balaram, P. *J. Am. Chem. Soc.* **1994**, *116*, 10355. (g) Formaggio, F.; Pantano, M.; Crisma, M.; Bonora, G. M.; Toniolo, C.; Kamphius, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1097. (h) Benedetti, E. *Biopolymers* **1996**, *40*, 3. (i) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048.

ee) gave considerable enhancement in enantiomeric excess, which implied *N*-oxypyridine moiety plays a crucial role in enantioselectivity.

The 2′-CN-catalyst **9** also showed dramatic enhancement (92% ee) compared to the reference catalyst **5**. However, despite the steric similarity to the 2′-CN catalyst **9**, the 2′-acetylene analogue **8** showed only marginal increase in enantioselectivity (75% ee), suggesting that the nitrogen atom in the 2′-CN moiety is important in the increase of enantioselectivity.

We speculate that the difference in enantioselectivity between pyridine (**6**) and *N*-oxypyridine (**7**) derivatives, and acetylenylbenzene (**8**) and cyanobenzene (**9**) derivatives might be caused by the electronegativity requirement for hydrogen bonding. The results are in agreement with those of the 2′-F-containing catalysts.[3] Therefore, the results herein along with our previous findings support the hypothesis that hydrogen bonding between water and *Cinchona* catalyst could provide the more rigid conformation leading to high enantioselectivity (Figure 2).

We then further prepared **10** and **11** to enhance the catalytic efficiency in two steps from (−)-hydrocinchonidine. It has been reported that *O*-allyl derivatives are more efficient catalysts than their free OH analogues.[1,3] The same tendency was observed in 3-ethyl derivatives versus 3-vinyl analogues.[1,3] In line with general tendencies described above, the enantioselectivity was enhanced to 96% ee at 0 °C in the both case of **10** and **11** (entries 6 and 8), and improved to even higher enantiomeric excess (98% ee) at lower reaction temperature (−20 °C, entries 7 and 9). Moreover, when **10** and **11** were employed for the alkylation with various alkyl halides, excellent enantioselectivities (97∼>99% ee) were obtained in both nonactive aliphatic and active alkyl halides as shown in Table 2.

In conclusion, N(1)-2′-*N*-oxypyridinylmethyl and N(1)-2′-cyanobenzyl derivatives of *Cinchona* alkaloid were developed as electronically modified version of chiral phase-transfer catalysts. Considerable enhancement of catalytic efficiency in the enantioselective phase-transfer alkylation of the glycine anion equivalent **1** was observed. The new evidences might indicate that the electronic factor could be an important factor in enantioselectivity along with conventional steric bulkiness. N(1)−O(9)-cyclized *Cinchona* ammonium salts and non-*Cinchona* quaternary ammonium salts containing F, *N*-oxypyridine, and cyanobenzene groups are now under investigation.

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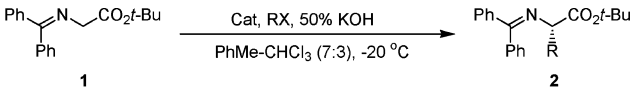
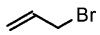
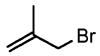
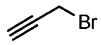
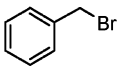
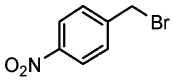
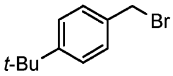
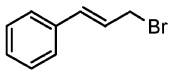
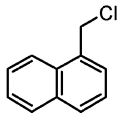
(6) (a) Ulku, D.; Huddle, B. P.; Morrow, J. C. *Acta Crystallogr.* **1971**, *B27*, 432. (b) Thalladi, V. R.; Weiss, H.-C.; Blaeser, D.; Boese, R.; Nangia, A.; Desiraju, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 8702.

Table 2. Catalytic Enantioselective Phase-Transfer Alkylation Using Catalysts **10** and **11**[a]



entry	RX	cat.	time (h)	yield[b] (%)	% ee[c] (config.[d])
a	$CH_3(CH_2)_4CH_2I$	**10**	20	80	>99 (*S*)
b		**11**	20	72	>99 (*S*)
c		**10**	7	94	97 (*S*)
d		**11**	7	93	96 (*S*)
e		**10**	7	97	98 (*S*)
f		**11**	7	95	97 (*S*)
g		**10**	5	93	98 (*S*)
h		**11**	7	92	98 (*S*)
i		**10**	7	93	98 (*S*)
j		**11**	7	96	98 (*S*)
k		**10**	6	92	98 (*S*)
l		**11**	7	93	98 (*S*)
m		**10**	7	95	97 (*S*)
n		**11**	7	92	99 (*S*)
o		**10**	7	95	97 (*S*)
p		**11**	7	93	97 (*S*)
q		**10**	15	86	98 (*S*)
r		**11**	20	85	98 (*S*)

[a] The reaction conditions were same as Table 1 except in the case of the alkyl halides. [b] Isolated yields. [c] The enantiopurity was determined by HPLC analysis of the alkylated imine **2** using a chiral column (Chiralcel OD) with hexanes/2-propanol as eluents. [d] The absolute configuration was assigned by the relative retention times of both enantiomers determined previously.[1−3]

Supporting Information Available: Experimental procedures and spectroscopic characterizations of the new catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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