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Highly efficient *ortho*-fluoro-dimeric cinchona-derived phase-transfer catalysts

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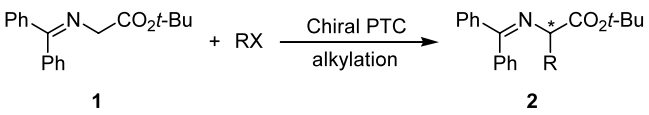
Abstract—A series of cinchona alkaloid-derived dimeric quaternary ammonium salts were prepared as chiral phase-transfer catalysts by the introduction of various functional groups on the phenyl ligand. Among them, the 2-F-substituted derivative **21** showed the highest enantioselectivity in the alkylation of the glycine anion equivalent **1** (97 to >99% ee).

Cinchona alkaloids are popular as chiral sources for various efficient catalysts, due to their various functional groups, commercial availability, and low cost. Recently, their *N*(1)-alkylated ammonium salts were developed as efficient chiral phase-transfer catalysts.[1] Since the first introduction of *N*(1)-benzylcinchoninium chloride by the Dolling group,[2] the O'Donnell group elegantly applied the cinchona-derived quaternary ammonium salts to the catalytic enantioselective synthesis of natural and unnatural α-amino acids via the asymmetric alkylation of glycinate imine **1** (Fig. 1).[3]

The enantioselective catalytic efficiency was improved by the increase bulkiness of the *N*(1)-substituents, through the replacement of the benzyl group with the 9-anthracenylmethyl group[4–6] or the formation of a dimer (**3**, **4**)[7,8] or a trimer (**5**).[9] Recently, we reported the electronic role of the cinchona alkaloid-derived phase-transfer catalysts in the alkylation of the glycine anion equivalent **1**, and the unusual aromatic-F effect in the selectivity.[10] Among the various functional groups substituted on the phenyl ring of *N*(1)-benzylcinchonidinium bromide, the *ortho*-fluoro group increases the enantioselectivity in the alkylation (**6**–**8** in Figure 2).[10] These findings prompted us to investigate the electronic effect in the dimeric system. In this communication, we describe the aromatic-F effect in the alkylation of a glycine anion equivalent involving cinchona alkaloid-derived dimeric phase-transfer catalysts.



1 2

Figure 1.

New dimeric cinchona-derived quaternary ammonium salts were prepared in two steps from (–)-cinchonidine (CD) (**9**–**20**) or (–)-hydrocinchonidine (HCD) (**21**) and the corresponding 1,3-bis(bromomethyl)benzenes, substituted at the 2- or 5-position with various functional groups in 85–95% overall yields.[7,11] Their catalytic efficiencies were evaluated by the enantioselective phase-transfer alkylation, using 5 mol% of catalyst, *N*-(diphenylmethylene)glycine *tert*-butyl ester **1**, benzyl bromide, and 50% aqueous KOH in toluene/chloroform (volume ratio = 7:3) at 0 or −20°C (Table 1).[12]

As shown in Table 1, no significant electronic effect on the enantioselectivity was observed in the series of 5-substituted derivatives (**15**–**20**), except for **18** (entry 11). In the case of the 2-substituted derivatives (**9**–**14**, entries 2–9), the enantioselectivities generally decreased only in proportion to the bulkiness of the functional group, not the electronic properties. The bulky substituents might lead to unfavorable conformations as a result of the severe steric hindrance. However, the 2-F catalyst **9** (94% ee) showed enhanced enantioselectivity, as compared to that of the reference catalyst **3** (90% ee, entry 1), in accordance with our previous results.[10] While the exact mechanistic details of the improvement in enantioselectivity are not clear at this time, the

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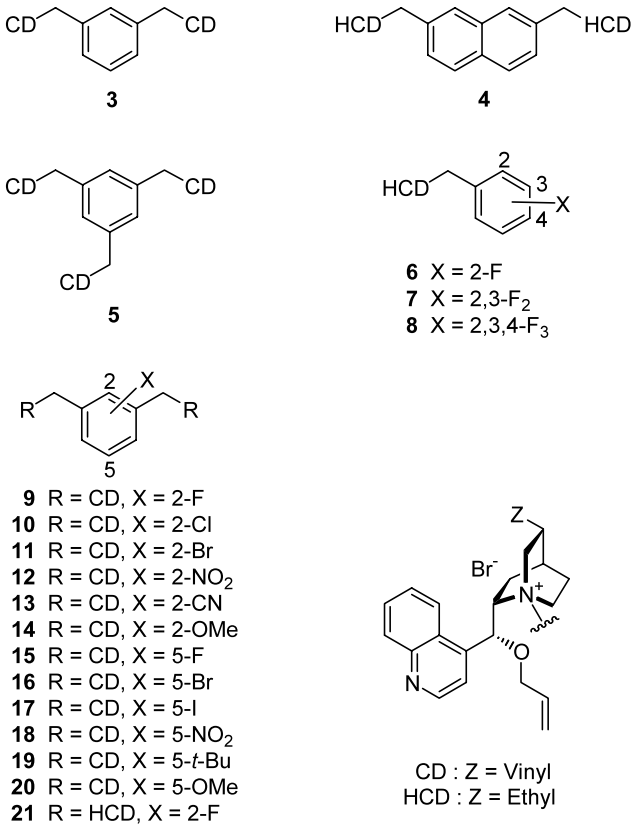
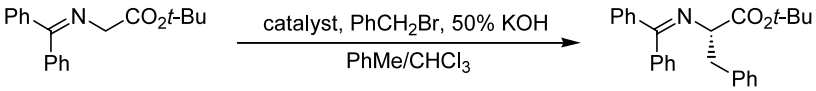


Figure 2.

aromatic F might be involved in internal hydrogen bonding involving water in order to maintain a more rigid catalyst conformation.[10] The corresponding 2-F catalyst derived from (+)-cinchonine gave (*R*)-**2d** in a slightly lower enantioselectivity (89% ee) compared to **9** at 0°C. In order to improve the catalytic efficiency of **9**, its hydro-derivative (**21**) was prepared and the catalytic efficiency was measured. In agreement with the general tendency, enhanced enantioselectivity was observed (96% ee at 0°C, entry 14), and the lower reaction temperature (−20°C) gave even higher enantioselectivity (98% ee at −20°C, entry 15). Catalyst **21** was chosen for further investigation with various alkyl halides.[12] The quite high enantioselectivities (97 to >99% ee), shown in Table 2, indicate that catalyst **21** is a very efficient phase-transfer catalyst for the enantioselective synthesis of both natural and unnatural α-amino acids.

In conclusion, a series of *meta*-dimeric cinchona alkaloid phase-transfer catalysts were prepared to study the electronic effect in the catalytic enantioselective phase-transfer alkylation of the glycine anion equivalent **1**. Among them, only the 2-fluoro substituted catalysts (**9**, **21**) showed greatly enhanced catalytic activities. Especially, 1,3-bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl]-2-fluorobenzene dibromide **21** is a highly effective catalyst for the asymmetric phase-transfer alkylation in the synthesis of chiral α-amino acids. Applications of **21** to other enantioselective phase-transfer reactions are currently being investigated.

Table 1. Enantioselective catalytic phase transfer benzylation of **1**[a]



1 **2d**

Entry	Catalyst	Temp. (°C)	Time (h)	% Yield[b]	% ee[c] (config.)[d]
1	**3**	0	2	91	90 (*S*)
2	**9**	0	6	93	94 (*S*)
3	**10**	0	6	92	74 (*S*)
4	**11**	0	7	90	67 (*S*)
5	**12**	0	6	87	55 (*S*)
6	**13**	0	5	94	78 (*S*)
7	**14**	0	10	90	30 (*S*)
8	**15**	0	8	91	86 (*S*)
9	**16**	0	10	91	88 (*S*)
10	**17**	0	20	85	89 (*S*)
11	**18**	0	6	90	66 (*S*)
12	**19**	0	8	92	88 (*S*)
13	**20**	0	10	89	87 (*S*)
14	**21**	0	6	94	96 (*S*)
15	**21**	−20	8	94	98 (*S*)

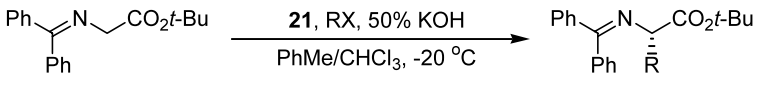
[a] The reaction was carried out with 5.0 equiv. of benzyl bromide and 13.0 equiv. of 50% aqueous KOH in the presence of 5.0 mol% of catalyst in toluene/chloroform (7:3) under the given conditions.

[b] Isolated yield.

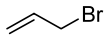
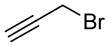
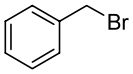
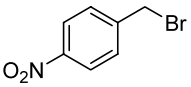
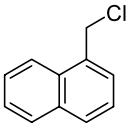
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2d** by using a chiral column (Chiralcel OD) with hexanes/2-propanol (500:2.5) as solvent.

[d] The absolute configuration was determined by comparison of the HPLC retention time that of an authentic sample, which was synthesized independently by reported procedures.[4–10]

Table 2. Catalytic enantioselective phase transfer alkylation of **1** with some representative alkyl halides in the presence of **21** (5 mol%)[a]



1 **2**

entry	RX	time (h)	% yield[b]	% ee[c] (config.)[d]
a	$CH_3(CH_2)_4CH_2I$	12	81	>99 (*S*)
b		6	92	97 (*S*)
c		4	94	98 (*S*)
d		8	94	98 (*S*)
e		4	91	>99 (*S*)
f		6	90	97 (*S*)

[a] The reaction conditions were same as Table 1 except reaction temperature and alkyl halides.
[b] Isolated yield.
[c] The enantiopurity was determined by HPLC analysis of the alkylated imine **2** by using a chiral column (Chiralcel OD) with hexanes/2-propanol as solvent.
[d] The absolute configuration was assigned by the relative retention times of both enantiomers determined previously.[4–10]

Acknowledgements

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11. All new compounds gave satisfactory analytical and spectral data. Selected data for **21**: mp 187°C (decomp.); $[\alpha]_D^{25}$ −135 (*c* 0.500, $CHCl_3$); IR (KBr) 3399, 2960, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6); 9.02 (d, $J=4.4$ Hz, 2H), 8.27 (d, $J=8.3$ Hz, 2H), 8.14 (d, $J=7.6$ Hz, 2H), 8.07–8.02 (m, 2H), 7.90–7.85 (m, 2H), 7.80–7.76 (m, 2H), 7.70–7.63 (m, 3H), 6.48 (s, 2H), 6.14–6.05 (m, 2H), 5.44 (d, $J=17.3$ Hz, 2H), 5.36 (d, $J=12.7$ Hz, 2H), 5.25 (d, $J=9.3$ Hz, 2H), 4.91 (d, $J=12.0$ Hz, 2H), 4.35–4.29 (m,

2H), 4.19–4.11 (m, 2H), 4.05–3.99 (m, 4H), 3.65–3.61 (m, 2H), 3.40–3.31 (m, 4H), 2.28–2.24 (m, 2H), 2.07–2.04 (m, 2H), 2.03–1.96 (m, 2H), 1.87–1.76 (m, 4H), 1.52–1.46 (m, 2H), 1.26–1.20 (m, 4H), 0.68 (t, $J=7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CHCl_3$-*d*); 149.7, 148.4, 140.6, 193.2, 132.9, 129.9, 128.5, 125.2, 123.9, 118.7, 116.2, 70.1, 65.7, 62.8, 51.5, 35.2, 31.4, 26.3, 25.3, 23.9, 22.5, 22.0, 20.1, 15.1, 14.0, 11.2; MS (FAB): 874 $[M\text{-}Br]^+$; HRMS (FAB) calcd for $[C_{52}H_{63}FN_4O_2Br]^+$: 874.4118, found: 874.4144.

12. Representative procedure for the catalytic enantioselective phase-transfer alkylation of **1** in the presence of catalyst **21** (benzylation): Benzyl bromide (0.1 mL, 0.85 mmol) was added to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **1** (50 mg, 0.17 mmol) and the chiral catalyst **21** (8.1 mg, 0.0085 mmol) in toluene/chloroform (7:3, 0.75 mL). The reaction mixture was then cooled to −20°C, 50% aqueous KOH (0.25 mL) was added, and the reaction mixture was stirred at −20°C until the starting material had been consumed (8 h). The suspension was diluted with ethyl ether (20 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography afforded the benzylated imine **2d** (61 mg, 94% yield) as a colorless oil. The enantiomeric excess of **2d** was determined by a chiral HPLC analysis [Chiralcel OD column, hexane:2-propanol = 500:2.5, flow rate = 1.0 mL/min, 23°C, $\lambda = 254$ nm, retention times *R* (minor) 12.2 min, *S* (major) 22.5 min, 98% ee]. The absolute configuration was determined by comparison of the HPLC retention times and the $[\alpha]_D$ value with the reported data of an authentic sample.[4–10]