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Highly efficient polymer supported phase-transfer catalysts containing hydrogen bond inducing functional groups

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Abstract

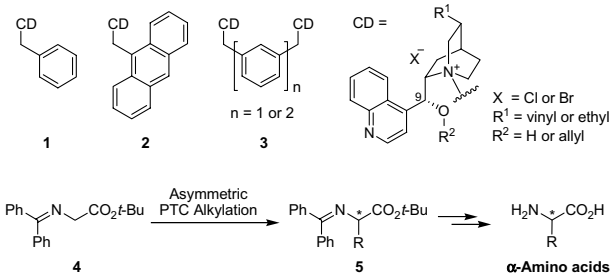
Merrifield resin supported cinchona ammonium salts bearing 2′-fluorobenzene, 2′-cyanobenzene and 2′-*N*-oxypyridine groups were prepared and applied to the phase-transfer catalytic alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester for the enantioselective synthesis of α-amino acids (76–96% ee).

Keywords: Phase-transfer catalyst; Enantioselective synthesis; Polymer-supported catalyst; Cinchona alkaloid

Quaternary ammonium salts derived from cinchona alkaloids have been developed as efficient chiral phase-transfer catalysts (PTCs), which have been successfully applied to various organic reactions, such as alkylation, Michael reaction, aldol condensation, and epoxidation.[1] Especially, intensive studies have been performed on asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) affording a variety of natural and nonnatural α-amino acid derivatives where **1**–**3** have been regarded as representative cinchona-derived PTCs for this purpose (Scheme 1).[2–4]

Beyond these solution phase catalysts, many polymer supported phase-transfer catalysts based on cinchona alkaloids have been developed and employed to various phase-transfer catalytic organic reactions as well.[5] Although catalytic amount of solution phase catalyst is consumed in phase-transfer catalytic reaction, reusable polymer supported catalyst might have far more advantage of a large scale production from both practical and economical viewpoints. Based on the connection site to resin, the polymer supported cinchona catalysts can be classified into three categories (types **6**–**8** as shown in Fig. 1).

Generally, type **6** catalysts showed moderate to good chemical yields with moderate enantioselectivities in the asymmetric alkylation of *N*-(diphenylmethylene)glycine esters.[5a–c] In case of type **7** catalysts, relatively high



Scheme 1. Representative cinchona phase-transfer catalysts and catalytic asymmetric synthesis of α-amino acids under phase-transfer conditions.

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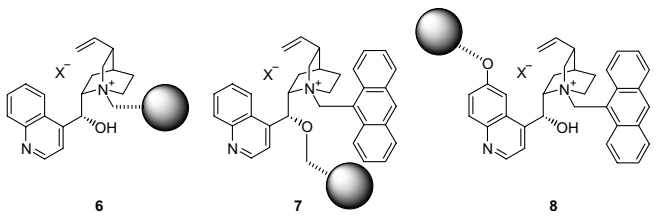


Fig. 1. Polymer supported cinchona phase-transfer catalysts.

enantioselectivities with moderate chemical yields were observed at −50 °C, which may be less practical for large scale production.[5d,e] Type **8** catalysts provided relatively low enantioselectivities even at the condition of −78 °C and solid CsOH base.[5f] In this Letter, we report a new series of polymer supported cinchona-derived ammonium salts in which hydrogen bonding capable functional groups are incorporated in N^+-arylmethyl group, and their application to asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**).

It has been proposed that the high enantioselective catalytic efficiency of cinchona PTCs (**1**–**3**) is due to steric bulkiness of the N^+-arylmethyl group in the catalyst, which enables the *E*-enolate anion of **4** approach only from the opposite direction to N^+-arylmethyl group.[6] However, recent studies from our laboratory demonstrated that the electronic effect of the N^+-arylmethyl unit in the catalyst is also responsible for high enantioselectivity. Catalysts **9**–**11** containing 2′-F, 2′-CN, and 2′-N^+–O^- functional groups showed enhanced enantioselectivity compared to the 2′-H, 2′-C≡CH, and 2′-pyridine analogues, respectively, while they exert virtually the same steric effect (Fig. 2).[7]

We have proposed that the high enantioselectivities might be due to more rigid conformations of catalysts caused by hydrogen bonding (or induced dipole–dipole interaction) involving water between *C*(9)–O and 2′-F, 2′-CN, or 2′-N^+–O^- in each catalyst.[7] We made an attempt to apply the electronic functional group effect into polymer supported phase-transfer catalysts.

Among the three kinds of polymer supported phase-transfer catalysts (**6**–**8**, Fig. 1), type **7** afforded the highest enantioselectivity in the alkylation of **4**, which led us to choose *C*(9)–O-connected catalyst **7** as a basic template. We employed Merrifield resin as a solid supporting material. Catalysts **15b**–**d** were prepared in two step sequence from (−)-hydrocinchonidine based on the previous methods (Scheme 2).[4,7] The treatment of (−)-hydrocinchonidine (**12**) with benzyl bromide analogues (**13b**–**d**) in dichloromethane at room temperature (24 h) afforded **14b**–**d**,

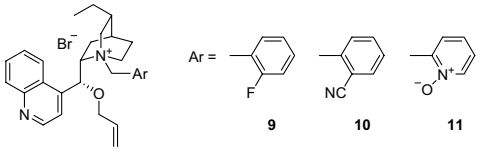
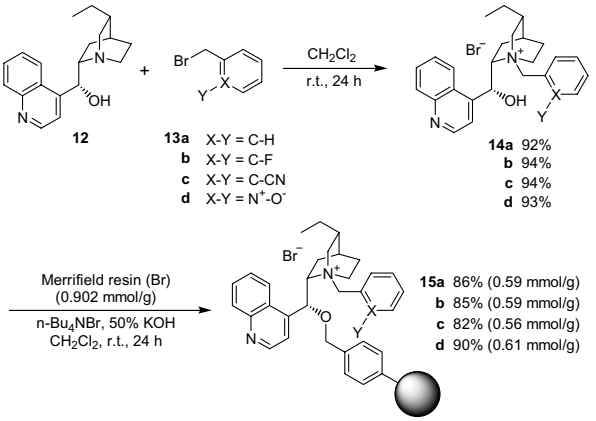


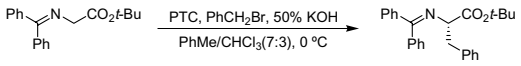
Fig. 2. Electronically modified cinchona PTCs.



Scheme 2. Preparation of Merrifield resin-supported catalysts.

respectively (92–94%) followed by the attachment of **14b**–**d** to Merrifield resin.[8] It should be noted that the activation of Merrifield resin, a halide exchange from chloride to bromide with 2.0 equiv of sodium bromide and 0.1 equiv of tetrabutylammonium bromide (TBAB) in refluxing toluene–water (volume ratio = 10:1), is essential before coupling it with cinchona PTCs **14**. Without this activation process, a retardation of coupling process and low yield was observed. Coupling of activated Merrifield resin and the corresponding cinchona units **14b**–**d** was carried out in the presence of 10 equiv of 50% potassium hydroxide and 0.1 equiv of TBAB in dichloromethane for 24 h at room temperature to give **15b**–**d** (82–90%), respectively. To confirm the electronic effect of 2′-fluoro, 2′-cyano, and 2′-N-oxide functional groups, benzyl analogue **15a** was prepared as a reference by these procedures.

Table 1
Enantioselective phase-transfer catalytic benzylation of *N*-(diphenyl methylene)glycine *tert*-butyl ester (**4**)[a]



Entry	PTC (mol %)	Time (h)	Yield (%)[b]	ee[c,d] (%)
1	**15a** (20)	22	82	69 (*S*)
2	**15b** (20)	7	88	91 (*S*)
3	**15c** (20)	14	83	93 (*S*)
4	**15d** (20)	10	81	95 (*S*)[e]
5	**15d** (2.5)	48	74	90 (*S*)
6	**15d** (5.0)	22	82	91 (*S*)
7	**15d** (10)	14	83	92 (*S*)
8	**15d** (40)	8	81	93 (*S*)

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 20.0 equiv of 50% KOH in the presence of catalyst in PhMe–$CHCl_3$ (7:3) at 0 °C.

[b] Isolated yields.

[c] Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexanes–2-propanol as eluents.

[d] Absolute configuration was assigned by comparison of retention times of both enantiomers determined previously.[2–4]

[e] It was reported that the PTC **11**, the unsupported counterpart of **15d**, gave **5d** in 94% chemical yield and 96% ee under the same conditions (the reaction time: 5 h).[7b]

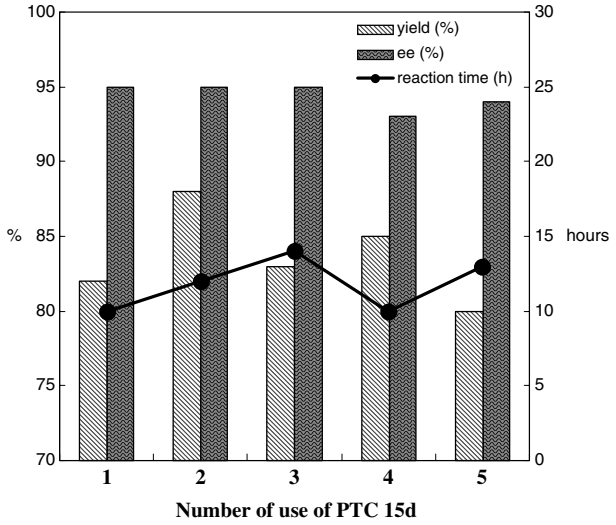


Fig. 3. Relationship between chemical/optical yield and reaction time according to the number of use of the PTC **15d**.

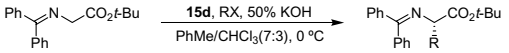
The capability of the catalysts **15b–d** along with **15a** was evaluated by the benzylation of **4** with 20 mol % of each solid supported catalyst, benzyl bromide, and 50% KOH in toluene–chloroform (volume ratio = 7:3) at 0 °C.[9] As shown in Table 1, all of the functional group incorporated catalysts (**15b–d**) showed quite enhanced enantioselectivity with faster reaction rate compared to the reference **15a**, which is in agreement with previous results.[7] Among the catalysts, *N*-oxy derivative **15d** showed the highest enantioselectivity (**15b**, 91% ee; **15c**, 93% ee; **15d**, 95% ee). These cumulative findings along with our previous results strongly support that the electronic effects of the functional groups play integral role of increasing of enantioselectivity in asymmetric phase-transfer catalytic alkylation. The best catalyst **15d** was chosen for investigation of the optimal amount of catalyst loading. As shown in Table 1, the optimal amount of **15d** was 20 mol %. Generally, the larger amount of the catalyst showed the faster reaction rate with slightly increased enantioselectivity except for 40 mol % loading (93% ee), which showed slightly decreased enantioselectivity than 20 mol % (95% ee).

Our next focus was on the reusability of **15d**. After the first benzylation (10 h, 81%, 95% ee) of **4** in the presence of 20 mol % of **15d**, the catalyst was recovered and subsequently used in the second benzylation. No decrease of enantioselectivity (12 h, 88%, 95% ee) was observed with the recovered **15d** (Fig. 3). Even the 5th recycle of the catalyst conserved enantioselectivity (13 h, 80%, 94% ee). The reusability of **15d** without any decrease of enantioselectivty demonstrates **15d** as an efficient and economical polymer supported phase-transfer catalyst.

Further alkylation with various alkylating reagents under the optimal reaction condition using **15d** was performed. High enantioselectivities (76–96% ee) shown in Table 2 indicate that the polymer supported recyclable PTC **15d** is a very efficient catalyst for the practical asymmetric synthesis of α-amino acids.

In conclusion, we developed a series of Merrifield resin supported hydrocinchonidine-derived ammonium salts **15b–d** incorporated the functional groups having an ability of hydrogen bonding. Very high enantioselectivities were obtained in the alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) under mild reaction conditions, and **15d** showed the highest catalytic efficiency. The easy preparation and recyclable capability without decrease of enantioselectivity of **15d** make this catalyst very practical for the synthesis of optically active α-amino acids in industrial process. Further application to other phase-transfer catalytic reactions is currently under investigation.

Table 2
Enantioselective phase-transfer catalytic alkylation of **4**[a]



Entry	RX	Time (h)	Yield[b] (%)	ee[c,d] (%)
a	Iodomethane	48	60	76 (*S*)
b	Allyl bromide	14	75	88 (*S*)
c	2-Methylallyl bromide	12	78	90 (*S*)
d	Benzyl bromide	10	81	95 (*S*)
e	2-Methylbenzyl bromide	14	84	94 (*S*)
f	3-Methylbenzyl bromide	14	87	95 (*S*)
g	4-Methylbenzyl bromide	15	81	90 (*S*)
h	4-Fluorobenzyl bromide	7	84	90 (*S*)
i	2-Nitrobenzyl bromide	8	76	90 (*S*)
j	2-Chlorobenzyl bromide	8	80	96 (*S*)
k	3-Chlorobenzyl bromide	8	76	92 (*S*)
l	2-Bromomethylnaphthalene	11	78	94 (*S*)

[a] The reaction was carried out with 5.0 equiv of alkylating reagents and 20.0 equiv of 50% KOH in the presence of 20 mol % of **15d** in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yields.
[c] Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexane–2-propanol as eluents.
[d] Absolute configuration was assigned by comparison of retention times of both enantiomers determined previously.[2–4]

Acknowledgment

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8. *Representative procedure for the preparation of Merrifield resin supported catalyst* (**15d**): To a suspension of Merrifield resin (Br) (1.0 g, 0.90 mmol), tetrabutylammonium bromide (30.0 mg, 0.09 mmol), and *N*-(1-oxypyridin-2-ylmethyl)hydrocinchonidinium bromide (**14d**) (8.89 g, 1.8 mmol) in dichloromethane (20 mL) was added 50% aq potassium hydroxide (1.0 mL, 9.0 mmol). The resulting mixture was stirred at room temperature for 24 h. The solid was filtered, and successively washed with water, dioxane, CH_2Cl_2, and MeOH. The solid was dried in vacuo for 14 h at room temperature and for 2 h at 100 °C to afford **15d**. IR (KBr): 3434, 3024, 2920, 1633, 1492, 1451, 1026, 758, 698, 545 544 cm^{-1}; Elemental Anal: N, 2.50%, loading: 0.61 mmol/g, 90% yield.
9. *Procedure of the asymmetric benzylation of* **4** *under phase-transfer conditions*: To an ice-cooled mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) (25 mg, 0.085 mmol) and **15d** (30 mg, 0.017 mmol) in toluene–chloroform (7:3, 0.6 mL) was added benzyl bromide (50 μL, 0.43 mmol) at 0 °C. Then 50% aq potassium hydroxide (0.1 mL) was added and the resulting mixture was stirred at 0 °C until the starting material **4** had been consumed. The suspension was filtered, and the filter cake was washed with ethyl ether to afford the recovered catalyst **15d**. The filtrate was washed with water, and the combined filtrate and washings was dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes–EtOAc = 50:1) afforded the benzylated imine **5d** (26.3 mg, 81%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2H), 7.38–7.22 (m, 6H), 7.20–7.17 (m, 3H), 7.12–7.02 (m, 2H), 6.8 (d, $J = 7.0$ Hz, 2H), 4.08 (dd, $J = 4.4$, 4.8 Hz, 1H), 3.25–3.10 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.3, 139.6, 138.4, 136.4, 130.0, 129.9, 128.7, 128.2, 128.1, 128.0, 127.9, 127.7, 126.1, 81.1, 67.9, 39.6, 28.0 ppm; MS (FAB): m/z 386 $[M+H]^+$. The enantiomeric excess of the product was determined by a chiral HPLC analysis [Chiralcel OD-H column, hexanes–2-propanol = 500:2.5, flow rate = 1.0 mL/min, 23 °C, $\lambda = 254$ nm, retention times *R* (minor) 10.6 min, *S* (major) 23.2 min, 95% ee]. The absolute configuration was determined by comparison of the HPLC retention times with the reported data of an authentic sample.[2–5]