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Synthesis and application of dimeric *Cinchona* alkaloid phase-transfer catalysts: α,α′-bis[*O*(9)-allylcinchonidinium]-*o*, *m*, or *p*-xylene dibromide†

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A dimeric *Cinchona* alkaloid ammonium salt, α,α′-bis[*O*(9)-allylcinchonidinium]-*m*-xylene dibromide 4, has been developed as a new efficient phase-transfer catalyst; the catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester using 4 provided 7 in a high enantiomeric excess (90–99% ee).

Although phase-transfer catalytic reactions have been widely applied in organic synthesis,[1,2] asymmetric synthetic reactions using chiral phase-transfer catalysts have not been extensively studied as compared to general asymmetric synthetic reactions, such as asymmetric dihydroxylation,[3] asymmetric catalytic reduction,[2] and so on. Since the pioneering work of O'Donnell *et al*. (**1a**),[4] the enantioselective alkylation of a prochiral protected glycine derivative, using *Cinchona* alkaloid ammonium salts, has become a very attractive method for the preparation of both natural and unnatural α-amino acids. Especially, the Lygo[5] and Corey[6] groups independently reported the excellent phase-transfer catalysts, *N*-9-anthracenylmethylcinchonidinium chloride (**2a**) and *O*(9)-allyl-*N*-9-anthracenylmethylcinchonidinium bromide (**2b**), respectively, by replacing the phenyl group of **1** with the bulkier anthracenyl moiety. Recently, the Maruoka group developed very efficient non-*Cinchona* catalysts, the C_2-symmetric chiral quaternary ammonium salts prepared from (*S*)-binaphthol.[7]

In connection with the development of Sharpless asymmetric dihydroxylation, the discovery of ligands with two independent *Cinchona* alkaloid units attached to heterocyclic spacers led to considerable increases in both the enantioselectivity and the scope of the substrate.[3] This dimerization effect prompted us to develop dimeric *Cinchona* alkaloid ammonium salts for enantioselective phase-transfer catalytic reactions. In this communication, we report the preparation of new dimeric catalysts, α,α′-bis[*O*(9)-allylcinchonidinium]-*o*, *m*, or *p*-xylene dibromides **3**–**5**, and their application to the catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **6** under mild phase-transfer conditions (Fig. 1).

Compounds **3**–**5** were prepared in two steps from cinchonidine and α,α′-dibromo-*o*, *m*, or *p*-xylene, respectively. Cinchonidine and α,α′-dibromo-*o*-, *m*-, or *p*-xylene were stirred at 100 °C in EtOH–DMF–$CHCl_3$ (v/v = 2.5:3:1)[8] for 6 h followed by *O*(9)-allylation with allyl bromide and 50% aq. KOH, to give the corresponding dimeric *Cinchona* alkaloid catalysts **3**–**5** in 90–92 % overall yields. The enantioselective efficiency of the prepared catalysts was evaluated by enantioselective phase-transfer alkylation using 5 mol% of catalysts **3**–**5** along with **6**, benzyl bromide, and 50% aq. KOH in toluene–$CHCl_3$[4f,9] (v/v = 7:3) at 0 °C or −20 °C for 2–6 h. Surprisingly, the *meta*-dimeric catalyst **4**‡ showed the highest enantioselectivity (*S*-form, 90% ee at 0 °C; 95% ee at −20 °C) among the three dimeric catalysts **3**–**5** (Table 1). The order of enantioselectivity of the three catalysts along with the monomer catalyst **1b** was as follows: *meta*-dimer (**4**) > *para*-dimer (**5**) ≅ monomer (**1b**) ≫ *ortho*-dimer (**3**). The precise mechanism for the high enantioselectivity of **4** is not clear, but it is thought to be similar to the reported mechanism of **2**.[6a] There are two possible conformations, **4a** and **4b**, as shown in Fig. 2. The **4a** conformer seems to be preferred, because of the steric hindrance between the quinoline and *O*-allyl moieties and the *Cinchona* unit (CD^+) in **4b**. In addition, the dramatic increase in the

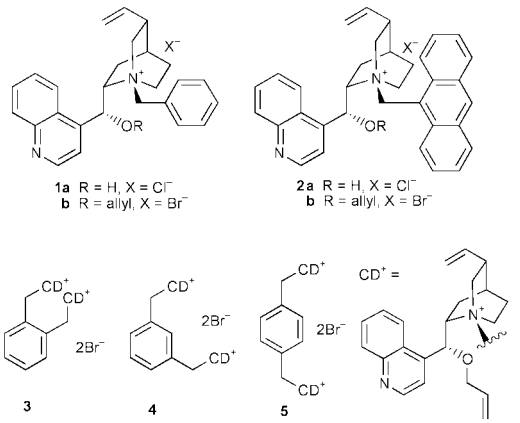
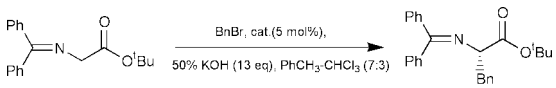


Fig. 1

Table 1 Enantioselective catalytic phase-transfer alkylation



6 → 7g

Entry	Catalyst	Temp./°C	Time/h	% yield[a]	% ee[b] (Config.)[c]
1	**1b**	0	2	92	75 (*S*)
2	**1b**	−20	5	94	81 (*S*)
3	**3**	0	3	90	31 (*S*)
4	**3**	−20	6	88	35 (*S*)
5	**4**	0	2	91	90 (*S*)
6	**4**	−20	5	94	95 (*S*)
7	**5**	0	4	92	80 (*S*)
8	**5**	−20	6	92	86 (*S*)

[a] Isolated yield of purified material. [b] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD). [c] Absolute configuration was determined by comparison of the HPLC retention time with the authentic samples independently synthesized by the reported procedure.[4–7]

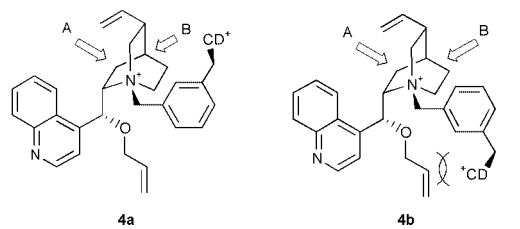
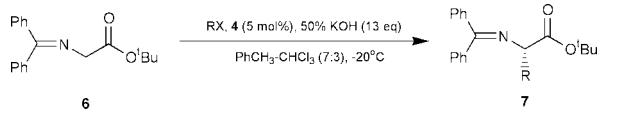


Fig. 2

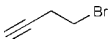
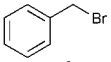
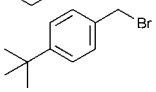
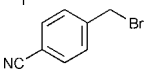
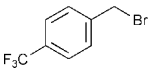
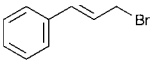
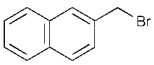
† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b1/b102584h/

 DOI: 10.1039/b102584h

Table 2 Enantioselective catalytic phase-transfer alkylation



6 7

Entry	RX	Time/h	% Yield[a]	% ee[b] Config.[c]
a	CH_3I	3	72	90 (*S*)
b	CH_3CH_2I	10	50	92 (*S*)
c	$CH_3(CH_2)_4CH_2I$	5	64	99 (*S*)
d		4	86	94 (*S*)
e		4	88	97 (*S*)
f		3	92	90 (*S*)
g		5	94	95 (*S*)
h		5	87	95 (*S*)
i		8	75	96 (*S*)
j		6	98	95 (*S*)
k		8	90	90 (*S*)
l		5	96	90 (*S*)

[a] Isolated yield of purified material. [b] Enantiopurity was determined by HPLC analysis of the alkylated imine **7** using a chiral column (DAICEL Chiralcel OD) with hexane–propan-2-ol (500/2 for **7a**, **7b**, **7g**, **7h**, **7j**, **7k**, **7l**; 500/1 for **7c**, **7d**, **7e**, **7f**; 500/5 for **7i**) as solvent. [c] Absolute configuration was determined by comparison of the HPLC retention time with the authentic samples independently synthesized by the reported procedure.[4–7]

enantioselectivity from **1b** to **4** implies that the *Cinchona* unit (CD^+) is located near the B site. Consequently, as the direction B is sterically hindered by the counter *Cinchona* unit in **4**, the *E*-enolate of **6** forms an ion-pair with **4** from the less hindered direction A. We expect that as the *re*-face of the enolate can be effectively blocked by the formation of the ion-pair, the alkyl halide can approach only the *si*-face of *E*-enolate, to give the *S*-form. The lack of a difference in the enantioselectivity between the *para*-dimer **5** and the monomer **1b** implies that the *Cinchona* units of the *para*-dimer **5** do not sterically affect each other. In the case of the *ortho*-dimer **3**, the severe steric repulsion between the two *Cinchona* units may lead to a less efficient conformation for enantioselectivity. Generally, the lower temperature (−20 °C) yielded higher enantioselectivity (Table 1). Catalyst **4** was chosen for the further investigation of the enantioselective phase-transfer alkylation with various alkyl halides. Table 2 indicates the results obtained for the alkylation of **6** with various alkyl halides, using catalyst **4** under the same reaction conditions as in Table 1, except for the temperature (−20 °C). The very high enantioselectivities (90–99% ee) shown in Table 2 indicate that catalyst **4** is a very efficient enantioselective phase-transfer catalyst for the synthesis of natural and unnatural α-amino acids.

In conclusion, we prepared the dimeric *Cinchona* alkaloid ammonium salt catalysts **3**–**5** to enhance catalytic efficiency by the dimerization effect. Among the dimeric catalysts, the *meta*-isomer (**4**) showed the highest catalytic activity (90–99% ee) in the alkylation of **6**. The high catalytic efficiency, the easy preparation, and the lower preparation cost relative to **2a,b** could make **4** a practical catalyst in industrial synthetic processes for natural and unnatural chiral α-amino acids. Applications to other various types of phase-transfer catalytic reactions using **4** are currently being investigated.

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Notes and references

‡ All new compounds gave satisfactory analytical and spectral data.

Selected data for **4**: mp 181 °C (decomp.); $[\alpha]^{25}_D$ −156 (*c* 0.320, $CHCl_3$); IR (KBr) 3437, 2922 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 9.03 (d, *J* = 4.4 Hz, 2 H), 8.35 (d, *J* = 8.3 Hz, 2 H), 8.15 (d, *J* = 9.0 Hz, 3 H), 7.97 (d, *J* = 7.5 Hz, 2 H), 7.90–7.86 (m, 2 H), 7.81–7.76 (m, 3 H), 7.72 (d, *J* = 4.4 Hz, 2 H), 6.53 (s, 2 H), 6.22–6.16 (m, 2 H), 5.78–5.70 (m, 2 H), 5.49 (d, *J* = 17.2 Hz, 2 H), 5.37–5.28 (m, 4 H), 5.20–5.14 (m, 4 H), 4.99 (d, *J* = 10.5 Hz, 2 H), 4.46 (dd, *J* = 12.5, 5.3 Hz, 2 H), 4.06–4.03 (m, 6 H), 3.82–3.76 (m, 2 H), 3.69–3.64 (m, 2 H), 3.51–3.40 (m, 2 H), 2.84–2.75 (m, 2 H), 2.34–2.26 (m, 2 H), 2.15–2.00 (m, 4 H), 1.92–1.81 (m, 2 H), 1.51–1.42 (m, 2 H); δ_C (100 MHz, DMSO-d_6) 150.6, 148.4, 141.7, 139.3, 138.3, 135.9, 134.6, 130.3, 130.0, 129.9, 128.8, 127.9, 125.4, 124.1, 120.0, 118.0, 116.9, 72.3, 69.7, 68.2, 63.4, 59.3, 51.2, 37.2, 26.3, 24.5, 21.2; MS (ESI): 772 $[M]^{2+}$; HRMS (ESI) calcd for $[C_{52}H_{60}N_4O_2]^{2+}$: 772.4716, found: 772.4739.

Representative procedure for enantioselective catalytic alkylation of **6** *under phase-transfer conditions (benzylation)*: to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **6** (50 mg, 0.17 mmol) and chiral catalyst **4** (8 mg, 0.0085 mmol) in toluene–$CHCl_3$ (v/v = 7:3, 0.75 mL) was added benzyl bromide (0.1 mL, 0.85 mmol). The reaction mixture was then cooled (−20 °C), 50% aq. KOH (0.25 mL) was added, and the reaction mixture was stirred at −20 °C until the starting material had been consumed (5 h). The suspension was diluted with 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 on silica gel (hexane:EtOAc = 50:1) afforded the desired product **7g** (61 mg, 94% yield) as a colorless oil. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD, hexane:propan-2-ol = 500:2.5, flow rate = 1.0 ml min^{-1}, 23 °C, λ = 254 nm; retention times *R* (minor) 12.2 min, *S* (major) 22.5 min, 95% ee). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.[4–7]

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9 The optimal solvent condition was determined by benzylation of **6** at −20 °C using **4**. Toluene–$CHCl_3$ (v/v, 7:3) gave the highest enantioselectivity (95% ee) compared to toluene (87% ee), CH_2Cl_2 (85% ee), $CHCl_3$ (90% ee), and toluene–CH_2Cl_2 (v/v, 7:3, 93% ee).