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Trimeric *Cinchona* alkaloid phase-transfer catalyst: α,α′,α″-tris[*O*(9)-allylcinchonidinium]mesitylene tribromide

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Abstract—A trimeric *Cinchona* alkaloid ammonium salt, α,α′,α″-tris[*O*(9)-allylcinchonidinium]mesitylene tribromide has been prepared as a novel phase-transfer catalyst. The catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester using the trimer catalyst showed high enantioselectivity (90–97% ee).

Phase-transfer catalytic reactions have been widely applied in organic synthesis for the excellent catalytic efficiency.[1] Since the first application of the *Cinchona* alkaloid type phase-transfer catalyst (**1**) for the enantioselective synthesis of α-amino acids by O'Donnell et al.,[2] the development of more efficient catalysts derived from *Cinchona* alkaloid has been extensively studied. Especially, the Lygo and Corey groups independently developed the efficient *Cinchona* type phase-transfer catalysts by replacing the phenyl group of **1** with the bulkier anthracenyl moiety (**2**).[3,4] Recently, the Maruoka group developed very efficient non-*Cinchona* type catalysts, the C_2-symmetric chiral quaternary ammonium salts prepared from (*S*)-binaphthol.[5]

As part of our program toward the development of a more efficient *Cinchona* type phase-transfer catalyst, we introduced bulky environment to the *N*-benzyl group of **1** by the formation of trimer **3** (Fig. 1). In this communication, we report the preparation of novel trimeric α,α′,α″-tris[*O*(9)-allylcinchonidinium]mesitylene tribromide **3** and its application to the catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **5** under mild phase-transfer conditions.

α,α′,α″-Tris[*O*(9)-allylcinchonidinium]mesitylene tribromide **3** was prepared in two steps from (−)-cinchonidine and α,α′,α″-tribromomesitylene[6] **4**. (−)-Cinchonidine (3.3 equiv.) and α,α′,α″-tribromomesitylene were stirred

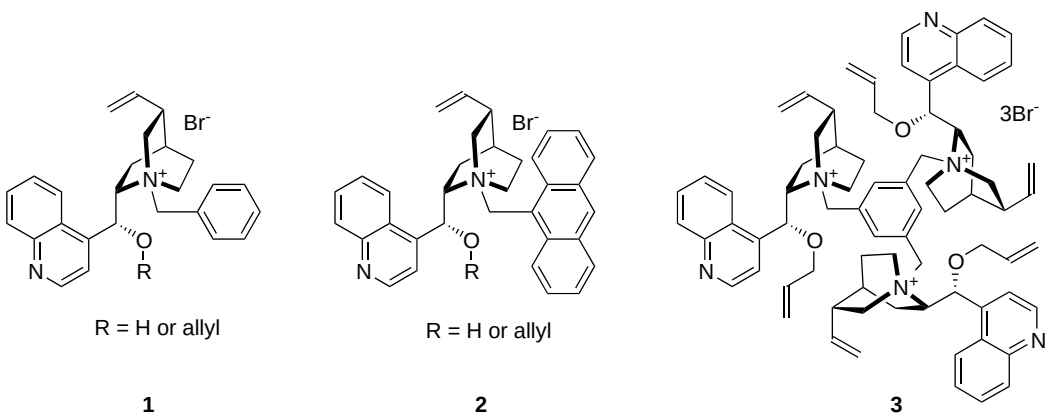

Figure 1.

Keywords: trimeric *Cinchona* alkaloid ammonium salt; phase-transfer catalyst.

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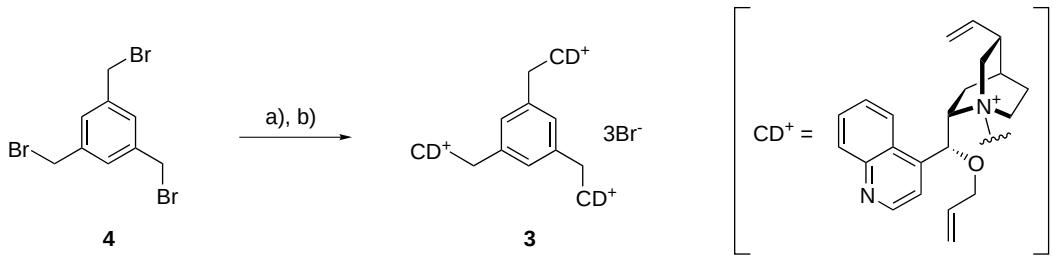
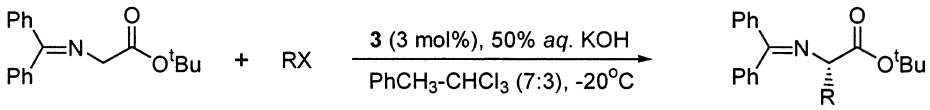
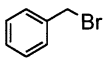
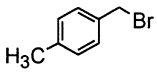
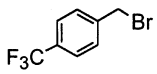
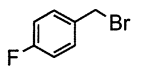
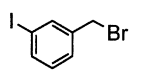
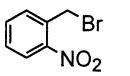
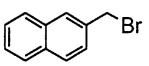
at 100°C in ethanol/DMF/chloroform (volume ratio = 5:6:2)[7] for 6 h followed by *O*(9)-allylation with allyl bromide and 50% aqueous KOH to give **3** in 92% overall yield (Scheme 1).[8] The enantioselective efficiency of the trimeric chiral catalyst **3** was evaluated by enantioselective phase-transfer alkylation using 3 mol% of catalyst **3** along with *N*-(diphenylmethylene)glycine *tert*-butyl ester **5**, alkyl halides and 50% aqueous KOH in toluene/chloroform (volume ratio = 7:3) at −20°C for 10–24 h. The enantioselectivities were determined by chiral HPLC analysis of the alkylated imines **6**. The very high enantioselectivities (*S*-form, 90–97% ee) are shown in Table 1. Not only the enantioselectivity but also the chemical yields are quite high (**6b–j**, 88–95%)



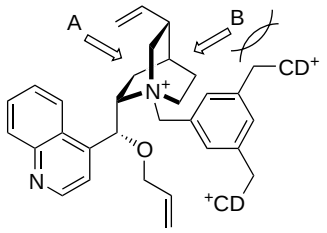
Scheme 1. *Reagents and conditions*: (a) (−)-Cinchonidine (3.3 equiv.), EtOH/DMF/$CHCl_3$ (5:6:2), 100°C, 97%; (b) allyl bromide, 50% KOH, CH_2Cl_2, rt, 95%.

Table 1. Enantioselective catalytic phase-transfer alkylation[a]



entry	RX	time (h)	% yield[b]	% ee[c] (config.[d])
a	CH_3I	24	65	90 (*S*)
b		18	90	95 (*S*)
c		20	88	90 (*S*)
d		10	94	94 (*S*)
e		20	93	96 (*S*)
f		10	95	97 (*S*)
g		10	95	96 (*S*)
h		24	89	95 (*S*)
i		10	90	92 (*S*)
j		20	95	94 (*S*)

[a]The reaction was carried out with 5.0 equiv of RX and 13.0 equiv of 50% aqueous KOH in the presence of 3 mol % of **3** in toluene/chloroform (volume ratio = 7:3) under the given conditions. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis of the alkylated imine **6** using a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol as solvent; in each case it was established by analysis of racemate of which the enantioisomers were fully resolved. [d]Absolute configuration was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[2,3,4,5]



3

Figure 2.

except **6a** (65%). The alkylated imines **6** could be further transformed to the corresponding α-amino acids by acidic hydrolysis via the known procedure.[2]

It is thought that the high enantioselectivity of **3** is attributed to the steric hindrance of the counter *Cinchona* unit (CD^+) located near the B site as shown in Fig. 2. Because the direction B is blocked by those two *meta*-substituted *Cinchona* units in **3**, the *E*-enolate of *N*-(diphenylmethylene)glycine *tert*-butyl ester **5** forms an ion-pair with **3** from the less hindered direction A. Then, as the *re*-face of enolate can be effectively blocked by the formation of the ion-pair, alkyl halide can approach only the *si*-face of *E*-enolate to give the *S*-form of **6**. The high enantioselectivities indicate that the trimeric catalyst **3** is a very efficient *Cinchona* type phase-transfer catalyst for the synthesis of natural and unnatural α-amino acids.

In conclusion, we prepared the trimeric *Cinchona* alkaloid catalyst **3**. The high enantioselective catalytic efficiency (90–97% ee) and the easy preparation (92% in two steps) could make **3** a practical phase-transfer catalyst for the enantioselective synthesis of α-amino acids.[9] The applications of **3** to other asymmetric catalytic reactions are currently being investigated.

General procedure for enantioselective catalytic alkylation of N-(diphenylmethylene)glycine tert-butyl ester ***5*** *under phase-transfer conditions*: To a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **5** (50 mg, 0.17 mmol) and catalyst **3** (8 mg, 0.0085 mmol) in toluene/chloroform (volume ratio = 7:3, 0.75 mL) was added alkyl halide (0.85 mmol). The reaction mixture was then cooled (−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. 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 **6a**–**j**. The enantioselectivities were determined by chiral HPLC analysis (DAICEL Chiralcel OD, hexane/2-propanol, flow rate = 0.5 or 1.0 mL/min, 23°C, $\lambda = 254$ nm) The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.[2–4]

Acknowledgements

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8. Spectral data for catalyst **3**: mp 201°C (decomp.); $[\alpha]_D^{23}$ −128 (*c* 0.83, $CHCl_3$); IR (KBr) 3437, 2922 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, $J = 4.4$ Hz, 3H), 8.48 (s, 3H), 8.41 (d, $J = 8.3$ Hz, 3H), 8.16 (d, $J = 8.3$ Hz, 3H), 7.88–7.92 (m, 3H), 7.81–7.85 (m, 3H), 7.73 (d, $J = 4.4$ Hz, 3H), 6.59 (s, 3H), 6.17–6.27 (m, 3H), 5.67–5.78 (m, 3H), 5.50 (d, $J = 17.2$ Hz, 3H), 5.42–5.43 (m, 3H), 5.33–5.38 (m, 6H), 5.14–5.18 (m, 3H), 4.96 (d, $J = 10.5$ Hz, 3H),

4.51 (dd, $J=12.7$, 5.2 Hz, 3H), 4.28 (t, $J=11.5$ Hz, 3H), 3.95–4.10 (m, 9H), 3.82–3.89 (m, 3H), 3.71–3.78 (m, 3H), 3.05–3.12 (m, 3H), 2.24–2.35 (m, 3H), 1.98–2.10 (m, 6H), 1.83–1.94 (m, 3H), 1.49 (t, $J=11.4$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.7, 148.5, 141.7, 141.0, 138.6, 134.8, 130.4, 130.1, 129.7, 128.1, 125.5, 124.4, 120.1, 118.2, 116.6, 72.4, 69.7, 68.6, 63.2, 59.4, 51.1, 36.9, 26.2, 24.5, 21.6 ppm; MS (FAB): 1279 $[M-Br]^+$; HRMS (FAB) calcd for $[C_{75}H_{87}N_6O_3Br_2]^+$: 1279.5206, found: 1279.5200.

9. The practicality of our method was confirmed by 1 g scale reaction (benzylation, entry d in Table 1) shown the almost similar chemical yield (93%) and enantioselectivity (95% ee) as small scale reaction.