

# A New Trimeric Cinchona Alkaloid as a Chiral Phase-Transfer Catalyst for the Synthesis of Asymmetric $\alpha$ -Amino Acids

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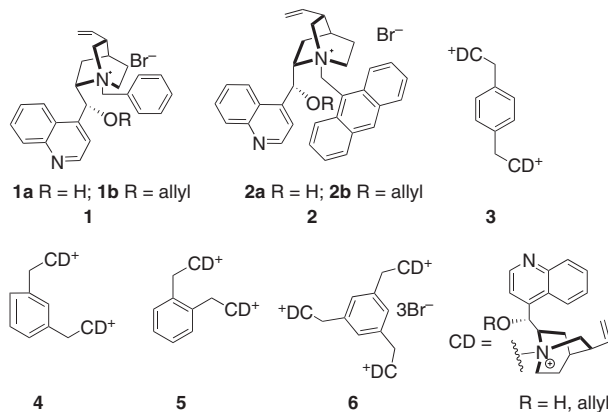
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**Abstract:** A new trimeric cinchona alkaloid, the quaternary ammonium salt,  $\alpha,\alpha',\alpha''$ -tris[*O*(9)-allylcinchonidinium-(4-methylphenoxy)methyl]benzene trichloride, has been synthesized and used as an efficient phase-transfer catalyst in asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with very good yield (up to 97%) and high enantioselectivity (up to 98%).

**Key Words:** enantioselective, cinchona alkaloid, trimeric, Schiff base,  $\alpha$ -amino acid

Phase-transfer catalysis (PTC) is one of the most important and useful methods in synthetic organic reactions because of easy reaction workup, mild reaction conditions, inexpensive and environmental friendly reagents.<sup>1</sup> In the asymmetric version of PTC utilizing chiral phase-transfer catalysts, however, it has not been extensively studied as compared to general enantioselective catalysts. Since the pioneering work of O'Donnel and his co-workers<sup>2</sup> leading to the development of highly practical enantioselective synthesis using cinchona alkaloid quaternary ammonium salts **1** (Figure 1), they are used as chiral PTC (CPTC) for the synthesis of asymmetric  $\alpha$ -amino acids. But the yield and enantiomeric excess (ee) were found to be very poor. Further, Corey<sup>3</sup> and Lygo<sup>4</sup> have studied this independently and reported greatly improved enantioselectivities and chemical yields using cinchona-based anthracenyl-derived catalyst system **2**. Merrifield resin bound cinchonine and cinchonidine catalysts have also been employed as an insoluble chiral component.<sup>5</sup> Some of the researchers have reported on the use of non-cinchona asymmetric catalysts, viz. spiroammonium<sup>6</sup> and phosphonium salts,<sup>7</sup> TADDOL,<sup>8</sup> binaphthyl-derived amines,<sup>8b,9</sup> various transition metal anchored Salen complexes<sup>10</sup> and chiral metal catalysts<sup>11</sup> for the enantioselective alkylation of glycine imines.

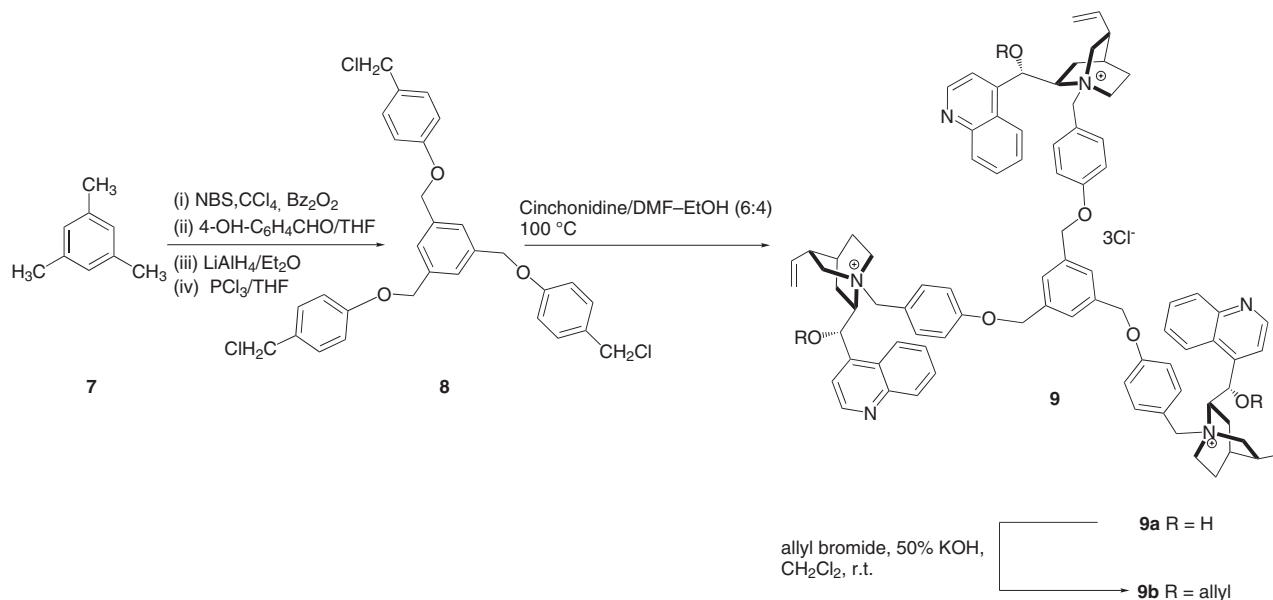
Recently, Jew et al.<sup>12</sup> (**3–5**), Park et al.<sup>13</sup> (**6**) and Najera et al.<sup>14</sup> have reported dimeric and trimeric quaternary cinchona-based chiral catalysts derived from *o*-, *m*-, *p*-xylene dibromide and mesitylene tribromide, respectively. These have been used as chiral PTCs to obtain good ee's but they required a higher amount of aqueous NaOH (50%) which is not environmentally acceptable. Taking in view all the



**Figure 1** Cinchona alkaloid quaternary ammonium salts **1–6**

early literature, we envisaged that attempts should be necessarily made to synthesize new chiral phase-transfer catalysts. Thus we prepared  $\alpha,\alpha',\alpha''$ -tris[cinchonidinium-(4-methylphenoxy)methyl]benzene trichloride (**9a**) from cinchonidine and 1,3,5-tris(4-chloromethylphenoxy)methylbenzene (**8**).<sup>15</sup> Cinchonidine (3.5 equiv) and 1,3,5-tris(4-chloromethylphenoxy)methylbenzene were stirred at 100 °C in ethanol–DMF (6:4) for 10 hours followed by *O*(9)-allylation with allyl bromide and 50% aqueous KOH to give  $\alpha,\alpha',\alpha''$ -tris[*O*(9)-allylcinchonidinium(4-methylphenoxy)methyl]benzene trichloride (**9b**) in 87% overall yield (Scheme 1). The efficiency of the trimeric catalysts **9** were studied by enantioselective C-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**10**) using 5 mol% of catalyst along with various alkyl halides and 20% aqueous NaOH in toluene–CH<sub>2</sub>Cl<sub>2</sub> (8:2) at –10 °C for about 15 hours. The enantioselectivities were measured by chiral HPLC analysis of the alkylated imines **12**.

The attainment of higher chemical yield and enantiomeric excess depends on various factors, such as the nature of the electrophiles (steric and electronic), the structure of the CPT catalysts, the nature of the counter ion associated with the CPT catalysts, and the polarity of the solvents. The inorganic base that is associated with the cation of the catalysts (R<sub>4</sub>N<sup>+</sup>) and its concentration were influenced by the formation of chiral quaternary ammonium hydroxide. We analyzed these factors in some depth, with a view to achieve an efficient alkylation of glycine imine **10** using earlier reported procedures.



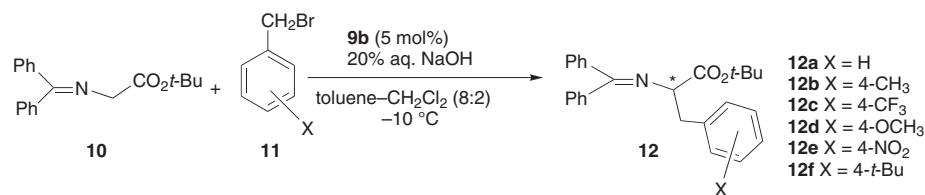
**Scheme 1** Schematic diagram for the synthesis of CPTC catalysts

### The Nature of Electrophiles

The alkylation of glycine imine **10** was carried out with various substituted benzyl halides in the presence of cinchona-derived CPTC's, viz. **9b** in 20% aqueous NaOH and a mixture of toluene and  $\text{CH}_2\text{Cl}_2$  (8:2) at low temperature ( $-10^\circ\text{C}$ ) (Table 1, entries **12a–f**). From the observed results, the enantiomeric excess increases with increasing bulkiness of the substituents on the benzyl moiety, i.e.  $t\text{-Bu} > \text{OCH}_3 > \text{CF}_3 > \text{CH}_3 > \text{H} > \text{NO}_2$ , due to the higher optical induction with the catalyst at the chiral environment

(Table 1, entries **12a–f**). The increased yield and enantiomeric excess are strongly dependent on the optical induction of CPTC's quaternary ammonium salts ( $\text{R}_4\text{N}^+$ ) with enolate of the Schiff base. Thus, *tert*-butyl substituted benzyl bromide provided higher yield of the product whereas *p*-nitrobenzyl bromide gave a lower yield and enantiomeric excess (Table 1, entry **12e** and **12f**) due to the *N*-benzyl group (electrophile =  $\text{NO}_2$ ) that diminishes the  $\pi$ -interaction between the enolate of the substrate and catalyst.

**Table 1** Dependence of Enantioselection (%) on Various Substituted Benzyl Bromide under CPTC Conditions



Entry	Electrophiles	Yield (%) <sup>a</sup>	ee (%)	Abs. Config. <sup>b</sup>
<b>12a</b>	H	42	65	S
<b>12b</b>	$\text{CH}_3$	59	80	S
<b>12c</b>	$\text{CF}_3$	60	87	S
<b>12d</b>	$\text{OCH}_3$	90	91	S
<b>12e</b>	$\text{NO}_2$	75	58	S
<b>12f</b>	<i>t</i> -Bu	93	95	S

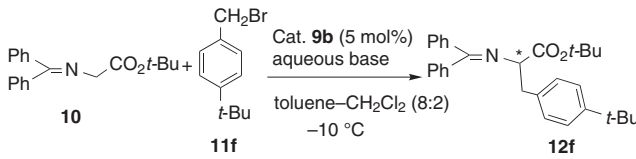
<sup>a</sup> Isolated products were confirmed by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy.

<sup>b</sup> Absolute configurations were determined by chiral HPLC.

### Nature of the Inorganic Bases

Next we carried out the alkylation of glycine imine **10** with 4-*tert*-butylbenzyl bromide in the presence of various inorganic bases like KOH, LiOH, Ca(OH)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> under CPTC condition. The other parameters such as solvents and temperature were kept as constant. From the results, it is very clear that the NaOH afforded better results as compared to other bases (Table 2, entry 1–5) due to weak ionic interaction of Na<sup>+</sup> with the substrate. The highest ee's and yield were observed when 20% aqueous NaOH solution was used (Table 2, entry 2). The chemical yield as well as the ee's were too low when KOH, Ca(OH)<sub>2</sub>, LiOH and K<sub>2</sub>CO<sub>3</sub> were used as bases (Table 2, entries 1, 3–5) due to strong ionic interaction between the quaternary ammonium salts of the CPTC's and substrates of the enolate anion (ion-pair interaction). When the concentration of aqueous NaOH was increased (more than 20%) decomposition of the catalyst occurred (Table 2, entry 6–8). A similar observation was noticed by O'Donnell et al.<sup>16</sup> for the enantioselective alkylation of ketimine in the presence of aqueous 50% NaOH as a base.

**Table 2** Influence of Various Bases on Syntheses of  $\alpha$ -Amino Acids



Entry	Aqueous Solution (Base)	Yield (%) <sup>a</sup>	ee (%)	Abs. Config. <sup>b</sup>
1	KOH (20%)	45	59	<i>S</i>
2	NaOH (20%)	93	95	<i>S</i>
3	LiOH (20%)	58	38	<i>S</i>
4	Ca(OH) <sub>2</sub> (20%)	27	25	<i>S</i>
5	K <sub>2</sub> CO <sub>3</sub> (20%)	23	46	<i>S</i>
6	NaOH (30%)	68	83	<i>S</i>
7	NaOH (40%)	60	68	<i>S</i>
8	NaOH (50%)	42	41	<i>S</i>

<sup>a</sup> Isolated products were confirmed by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy.

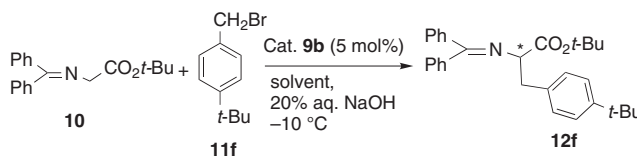
<sup>b</sup> Absolute configurations were determined by chiral HPLC.

### Effect of Solvents on Enantioselective Alkylation of Glycine Imine

The reactivity and also enantioselectivity of the CPTCs are dependent on their solubility and stability in the organic solvent under the PTC conditions. The alkylation reactions were carried out in the presence of various polar or non-polar solvents, the selected solvent results are presented in Table 3. Lower yield of alkylation was observed in pure CH<sub>2</sub>Cl<sub>2</sub> as solvent because the solvent reacted with the aqueous sodium hydroxide (Table 3, entry 1). Moder-

ate yield and ee's were observed when toluene used as solvent due to the poor solubility of the CPTC catalyst (Table 3, entry 2). Catalyst decomposition was observed when polar solvents were used for the alkylation of glycine imine. Generally, the use of pure toluene as solvent is not practical for the alkylation of glycine imine due to the poor solubility of the catalyst. Hence, we have carried out the alkylation reaction in the presence of a mixture of solvents like toluene and CH<sub>2</sub>Cl<sub>2</sub> (8:2), which can improve the solubility as well as influence of the enantioselectivity of the alkylated product (Table 3, entry 6). The addition of dichloromethane to toluene in more than 20% diminished the chemical yield and ee's (Table 3, entries 3–5). The enantioselectivity of the alkylation reaction is strongly dependent on the addition of toluene to the reaction mixture. The increase of toluene amount in the solvent ratio (8:2) influenced the chemical yield (93%) and ee's up to 95% under CPTC conditions at lower concentration of base (Table 3, entries 6–11).

**Table 3** Effect of Solvents on Alkylation of Glycine Imine under CPTC Conditions



Entry	Solvent	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	9	17 ( <i>S</i> )
2	toluene	39	36 ( <i>S</i> )
3	toluene-CH <sub>2</sub> Cl <sub>2</sub> (1:1)	65	71 ( <i>S</i> )
4	toluene-CH <sub>2</sub> Cl <sub>2</sub> (4:6)	57	66 ( <i>S</i> )
5	toluene-CH <sub>2</sub> Cl <sub>2</sub> (3:7)	49	58 ( <i>S</i> )
6	toluene-CH <sub>2</sub> Cl <sub>2</sub> (2:8)	38	46 ( <i>S</i> )
7	toluene-CH <sub>2</sub> Cl <sub>2</sub> (1:9)	19	35 ( <i>S</i> )
8	toluene-CH <sub>2</sub> Cl <sub>2</sub> (9:1)	87	87 ( <i>S</i> )
9	toluene-CH <sub>2</sub> Cl <sub>2</sub> (8:2)	93	95 ( <i>S</i> )
10	toluene-CH <sub>2</sub> Cl <sub>2</sub> (7:3)	82	78 ( <i>S</i> )
11	toluene-CH <sub>2</sub> Cl <sub>2</sub> (6:4)	76	67 ( <i>S</i> )

<sup>a</sup> Isolated products were confirmed by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy.

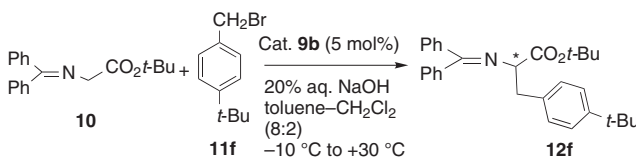
<sup>b</sup> Absolute configurations were determined by chiral HPLC.

### Effect of Temperature on Alkylation of Glycine Imine

The observed yield and ee's are strongly dependent on the reaction temperature. Variation of the temperature also affects the ion pair interaction between the enolate of the substrate and quaternary ammonium of the CPTC's. Some selected results are presented in Table 4. The change in temperature of the alkylation reaction was studied from +30 to -30 °C. From the observed results, the higher yield

and ee's were obtained at  $-10^{\circ}\text{C}$  because at higher temperature the catalyst was decomposed. Hence the optimum temperature for the alkylation reaction is  $-10^{\circ}\text{C}$  (Table 4, entries 1–6). However no influence on the ee was observed when the reaction temperature was lowered at  $-20$  and  $-30^{\circ}\text{C}$  (Table 4, entries 5, 6) due to the lower induction between the enolate of the substrate and catalyst. The same observation was reported by Park et al.<sup>13</sup> for the synthesis of  $\alpha$ -amino acids at a lower temperature of  $-20^{\circ}\text{C}$  in the presence of *ortho*-fluoro dimeric cinchona-derived phase-transfer catalysts.

**Table 4** Effect of Temperature on Enantioselective Alkylations of Glycine Imine



Entry	Temp ( $^{\circ}\text{C}$ )	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	30	67	59 ( <i>S</i> )
2	20	73	68 ( <i>S</i> )
3	10	79	76 ( <i>S</i> )
4	$-10$	93	95 ( <i>S</i> )
5	$-20$	87	89 ( <i>S</i> )
6	$-30$	78	77 ( <i>S</i> )

<sup>a</sup> Isolated products were confirmed by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy.

<sup>b</sup> Absolute configurations were determined by chiral HPLC.

We examined next the catalytic efficiency of the CPTCs **9** in phase-transfer alkylation of glycine imine **10** with a variety of alkyl halides **13** to give the alkylated products **14**. Selected results are presented in Table 5. In the case of alkylations, better results were obtained when **9b** was used as a catalyst (Table 5, entries 2, 4, 5, 7–9, 11–13). The observed results show lower yield and ee's when **9a** was used as a catalyst, due to the formation of hydrogen bond between the C9-(OH) of the catalyst with the enolate of the substrates (Table 5, entries 1, 3, 6 and 10). In all entries of the alkylation reactions, the absolute configuration was *S*. In addition, the reaction with 9-bromomethylanthracene (entry 5), 4-bromomethyl-1*H*-indene (entry 8), 3-bromomethyl-1-(toluene-4-sulfonyl)-1*H*-indole (entry 9), 3-bromomethylthiophene (entry 12) and 2-naphthyl bromide (entry 13) afforded the corresponding protected unnatural  $\alpha$ -amino acids, which can be versatile intermediates of various unnatural  $\alpha$ -amino acids, up to 98% ee. In the case of our trimeric catalyst **9**, it showed higher chemical yield and ee's than the previously reported catalysts **4**<sup>12</sup> and **6**<sup>13</sup> under identical reaction conditions (Table 5, entries 1, 2, 14 and 15) due to the minimization of steric hindrance.

In conclusion, the present study has shown that  $\alpha$ -amino acids can be successfully synthesized using two different stable new trimeric cinchona-based chiral phase-transfer catalysts (CPTC) **9a** and **9b**. These two different new chiral PTC's were structurally confirmed by various spectral techniques like FT-IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and mass spectroscopy. The catalytic efficiency was studied by the alkylation of glycine imine and gave very good yields (up to 97%) and ee's (up to 98%) under phase-transfer catalytic conditions. The applications of CPT catalyst **9** to other enantioselective catalytic reactions are currently being studied.

All melting points are uncorrected. The IR spectra were recorded using Shimadzu FT-IR 8300 instrument. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all compounds in  $\text{DMSO}-d_6$  were recorded using Jeol GSX (200, 300 and 400 MHz) NMR spectrometer. The mass spectra were obtained on a using Jeol (HRMS) spectrometer. Column chromatography was performed using silica gel (100–200 mesh size). The enantioselectivities were determined by chiral HPLC analysis using a chiral column (DAICEL Chiralcel OD).

### 1,3,5-Tris(bromomethyl)benzene

Mesitylene (4.0 g, 33.28 mmol), *N*-bromosuccinimide (22.65 g, 116.48 mmol), benzoyl peroxide (2.5 g) and  $\text{CCl}_4$  (75 mL) were taken in a 250-mL round-bottomed flask. The reaction mixture was refluxed in an oil bath for 12 h at  $70^{\circ}\text{C}$ . Then the succinimide formed was removed by filtration and the solvent was evaporated to give a yellow colored solid; yield: 24.52 g (92%); mp  $96^{\circ}\text{C}$ .

FT-IR (KBr): 686, 2956  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.26 (s, 6 H), 7.03 (s, 3 H).

### 1,3,5-Tris(4-chloromethylphenoxy)methyl)benzene (**8**)

1,3,5-Tris(bromomethyl)benzene (3.0 g, 8.41 mmol), *p*-hydroxybenzaldehyde (3.59 g, 29.46 mmol, 3.5 equiv), THF (50 mL) and a catalytic amount of  $\text{K}_2\text{CO}_3$  were taken in a 250-mL round-bottomed flask. The mixture was refluxed for 12 h at  $80^{\circ}\text{C}$ . Then the solvent was removed by distillation to give the crude 1,3,5-tris(4-methoxybenzaldehyde)benzene, which was recrystallized from EtOH; yield: 6.13 g (93%).

### 1,3,5-Tris(4-methoxybenzaldehyde)benzene

FT-IR (KBr): 1698  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 3.8 (s, 6 H), 6.8–7.32 (m, 15 H), 10.32 (s, 3 H).

The above aldehyde was reduced with EtOH in the presence of a catalytic amount of  $\text{LiAlH}_4$  in  $\text{Et}_2\text{O}$  (40 mL). The alcoholic compound was treated with  $\text{PCl}_3$  in the presence of THF to give 1,3,5-tris(4-chloromethylphenoxy)methyl)benzene (**8**). It was purified by silica gel column chromatography using EtOH–benzene (30:70) as an eluent; yield: 4.15 g (83%).

FT-IR (KBr): 722, 1058  $\text{cm}^{-1}$ .

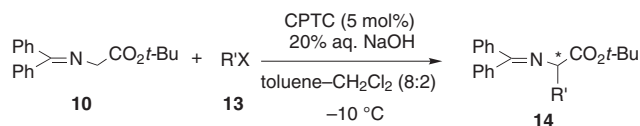
$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.46 (s, 6 H), 5.20 (s, 6 H), 6.67 (d, 6 H,  $J$  = 6.56 Hz), 7.10 (s, 3 H), 7.22 (d, 6 H,  $J$  = 6.56 Hz).

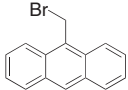

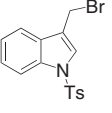

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 47.6, 72.3, 114.7, 125.2, 129.8, 130.5, 141.6, 160.4.

MS:  $m/z$  = 541.07 ( $\text{M}^+$ ).

### $\alpha,\alpha',\alpha''$ -Tris[allylcinchonidinium(4-methylphenoxy)methyl)benzene Trichloride

Compound **8** (0.88 g, 1.95 mmol), cinchonidine (1.72 g, 5.85 mmol, 3 equiv) and DMF–EtOH (6:4) were taken in a 100-mL round-bot-

**Table 5** Enantioselective Catalytic Phase-Transfer Alkylation of Glycine Imine

Entry	R'X	Catalyst	Time (h)	Yield (%) <sup>a</sup>	ee (%)	Abs. Config. <sup>b</sup>
1	PhCH <sub>2</sub> Br	<b>9a</b>	10.0	38	56	<i>S</i>
2	PhCH <sub>2</sub> Br	<b>9b</b>	10.0	42	65	<i>S</i>
3	CH <sub>2</sub> =CHCH <sub>2</sub> Br	<b>9a</b>	10.0	54	53	<i>S</i>
4	CH <sub>2</sub> =CHCH <sub>2</sub> Br	<b>9b</b>	10.0	96	86	<i>S</i>
5		<b>9b</b>	12.5	92	94	<i>S</i>
6	CH≡CCH <sub>2</sub> Br	<b>9a</b>	12.0	93	77	<i>S</i>
7	CH≡CCH <sub>2</sub> Br	<b>9b</b>	12.0	84	90	<i>S</i>
8		<b>9b</b>	12.0	88	92	<i>S</i>
9		<b>9b</b>	10.0	92	89	<i>S</i>
10	CH <sub>3</sub> I	<b>9a</b>	7.5	90	85	<i>S</i>
11	CH <sub>3</sub> I	<b>9b</b>	7.5	92	95	<i>S</i>
12		<b>9b</b>	6.5	89	98	<i>S</i>
13	2-NaphCH <sub>2</sub> Br	<b>9b</b>	7.0	97	96	<i>S</i>
14	PhCH <sub>2</sub> Br	<b>6</b>	10.0	31	53	<i>S</i>
15	PhCH <sub>2</sub> Br	<b>4</b>	10.0	53	61	<i>S</i>

<sup>a</sup> Isolated products were confirmed by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy.<sup>b</sup> Absolute configurations were determined by chiral HPLC.

tomed flask. The mixture was refluxed for 36 h at 100 °C. After completion of reaction time, the solvent was removed by vacuum distillation. The crude compound of **9a** was purified by silica gel column chromatography using acetone–hexane (30:70) as an eluent; yield: 2.44 g (94%); mp 243 °C (dec.).

FT-IR (KBr): 3487, 2934, 1245 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 1.48–1.53 (m, 1 H) 1.65 (t, *J* = 8.60 Hz, 2 H), 1.70 (q, *J* = 11.8 Hz, 2 H), 2.77 (q, *J* = 12.4 Hz, 1 H), 3.24–3.30 (m, 4 H), 4.07–4.15 (m, 1 H), 4.48 (s, 2 H), 5.11 (d, *J* = 13.0 Hz, 1 H), 5.16 (s, 2 H), 5.22 (q, 1 H), 5.40 (br s, 1 H), 6.03 (d, *J* = 15.44 Hz, 2 H), 6.72 (d, *J* = 16.48 Hz, 2 H), 6.93 (d, *J* = 15.04 Hz, 2 H), 7.02 (d, *J* = 14.56 Hz, 1 H), 7.15 (s, 3 H), 7.41 (t, *J* = 10.32 Hz, 1 H), 7.47 (t, *J* = 7.1 Hz, 1 H), 7.76 (d, *J* = 9.36 Hz, 1 H), 8.12 (d, *J* = 8.88 Hz, 1 H), 8.66 (d, *J* = 8.88 Hz, 1 H).

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = -28.3, 30.2, 37.8, 38.4, 61.3, 65.2, 65.8, 69.4, 78.3, 79.4, 114.3, 114.7, 119.6, 123.2, 125.2, 125.5, 126.4, 127.8, 129.2, 130.6, 131.2, 140.2, 141.8, 143.6, 148.6, 149.8, 158.5.

HRMS (FAB): *m/z* calcd for [C<sub>87</sub>H<sub>93</sub>N<sub>6</sub>O<sub>6</sub>]<sup>3+</sup>: 1318.7043; found: 1318.3894.

Anal. Calcd for C<sub>87</sub>H<sub>93</sub>Cl<sub>3</sub>N<sub>6</sub>O<sub>6</sub>: C, 73.33; H, 6.58; N, 5.90. Found: C, 73.19; H, 6.52; N, 5.76.

#### **α,α',α''-Tris[O(9)-allylcinchonidininium(4-methylphenoxy-methyl)]benzene Trichloride**

Compound **9**, allyl bromide, aq 50% KOH and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were taken in a 100-mL round-bottomed flask. The reaction mixture was stirred at r.t. for 24 h. Then the solvent was removed by vacuum distillation and the crude product was purified by column chromatography over silica gel using hexane–MeOH (60:40) as eluent; yield: 1.31 g (87%).

#### **9b**

Mp 231 °C (dec.).

FT-IR (KBr): 2967, 1256, 1087 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 1.34–1.40 (m, 1 H) 1.63 (t, *J* = 6.66 Hz, 2 H), 1.75–1.82 (m, 2 H), 2.82–2.89 (m, 1 H), 3.22–



3.29 (m, 4 H), 4.05 (t,  $J = 7.3$  Hz, 2 H), 4.22 (q,  $J = 15.4$  Hz, 1 H), 4.45 (s, 2 H), 5.12 (d,  $J = 15.12$  Hz, 1 H), 5.17 (s, 2 H), 5.20 (q,  $J = 13.6$  Hz, 1 H), 5.43 (br s, 1 H), 5.55–5.60 (m, 1 H), 5.78 (d,  $J = 16.84$  Hz, 2 H), 6.04 (d,  $J = 14.2$  Hz, 2 H), 6.65 (d,  $J = 15.96$  Hz, 2 H), 6.87 (d,  $J = 15.96$  Hz, 2 H), 7.12 (d,  $J = 12.96$  Hz, 1 H), 7.18 (s, 3 H), 7.37 (t,  $J = 5.16$  Hz, 1 H), 7.52 (t,  $J = 5.16$  Hz, 1 H), 7.73 (d,  $J = 16.44$  Hz, 1 H), 8.21 (d,  $J = 12.88$  Hz, 1 H), 8.43 (d,  $J = 13.2$  Hz, 1 H).

$^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ):  $\delta = -26.6, 33.4, 36.8, 38.4, 61.7, 65.5, 66.9, 69.7, 70.8, 78.3, 79.5, 114.3, 114.5, 115.7, 119.7, 122.2, 125.5, 125.8, 126.9, 127.2, 129.2, 131.6, 131.2, 135.4, 142.2, 143.8, 144.6, 147.8, 150.1, 155.6$ .

HRMS (FAB):  $m/z$  calcd for  $[\text{C}_{96}\text{H}_{105}\text{N}_6\text{O}_6]^{3+}$ : 1438.8023; found: 1438.7896.

Anal. Calcd for  $\text{C}_{96}\text{H}_{105}\text{Cl}_3\text{N}_6\text{O}_6$ : C, 74.62; H, 6.85; N, 5.44. Found: C, 74.46; H, 6.61; N, 5.39.

#### Alkylation of Glycine Imine **10**; General Procedure

A solution of glycine imine **10** (0.5 mmol) in toluene- $\text{CH}_2\text{Cl}_2$  (8:2) was treated sequentially with the appropriate catalyst **9** (5 mol%), alkylating agent **11** or **13** (0.5 mmol), and 20% aq NaOH (0.5 mL) (see Tables 1 and 5). The resulting mixture was stirred at  $-10^\circ\text{C}$  for about 1–15 h. The aqueous layer was extracted with EtOAc (5  $\times$  5 mL), and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give the crude product **12 or 14**. This was dissolved in THF (5 mL) and 15% aq citric acid (1.5 mL) was added. The mixture was stirred vigorously at r.t. for 1 h, and then diluted with  $\text{H}_2\text{O}$  (5 mL). The mixture was extracted with  $\text{Et}_2\text{O}$  (2  $\times$  5 mL) to remove any excess alkylating agent and benzophenone, then the aqueous layer was basified with  $\text{K}_2\text{CO}_3$ . Extraction with EtOAc (3  $\times$  5 mL) followed by drying ( $\text{Na}_2\text{SO}_4$ ) and concentration under reduced pressure gave the crude  $\alpha$ -amino acid *tert*-butyl ester, which can be generally purified by passing through a plug of silica gel (Tables 1 and 5). The enantioselectivities were measured by chiral HPLC analysis (DAICEL Chiralcell OD, hexane-propan-2-ol, flow rate 0.5  $\mu\text{L}/\text{min}$ , at  $25^\circ\text{C}$ ,  $\lambda = 254$  nm). The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the earlier reported procedure.<sup>2,3</sup>

#### *tert*-Butyl 3-Phenyl-2-diphenylmethyleaminopropanoate [(S)-**12a**]

Synthesized following the general procedure and according to the reaction condition listed in Table 1; yield: 0.21 g, 42%;  $[\alpha]_{\text{D}}^{25} -13.4$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3025, 2906, 1710, 1525, 1235  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta = 1.45$  (s, 9 H), 3.25 (d, 2 H,  $J = 8.4$  Hz), 4.35 (t, 1 H,  $J = 4.0$  Hz), 7.12–7.35 (m, 15 H).

$^{13}\text{C}$  NMR (50 MHz, DMSO- $d_6$ ):  $\delta = 27.4, 37.6, 61.9, 73.0, 124.7, 125.3, 128.4, 128.9, 129.5, 130.8, 137.5, 141.6, 160.8, 176.9$ .

MS:  $m/z = 385.19$  ( $\text{M}^+$ ).

HRMS:  $m/z$  calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}_2$ : 386.2042; found: 386.1897.

#### *tert*-Butyl 3-(4-Trifluoromethylphenyl)-2-diphenylmethyleaminopropanoate [(S)-**12c**]

Synthesized following the general procedure and according to the reaction condition listed in Table 1; yield: 0.13 g, 60%;  $[\alpha]_{\text{D}}^{25} -14.3$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3076, 2904, 1732, 1610, 1230  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 1.32$  (s, 9 H), 3.25–3.29 (d, 2 H,  $J = 12.0$  Hz), 4.32–4.38 (t, 1 H,  $J = 9.0$  Hz), 7.05–7.09 (d, 2 H,  $J = 12.0$  Hz), 7.41–7.44 (d, 2 H,  $J = 9.0$  Hz), 7.47–7.76 (m, 10 H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta = 26.2, 37.3, 61.6, 73.2, 119.6, 125.3, 128.2, 128.6, 129.2, 130.5, 137.4, 143.8, 164.5, 178.2$ .

MS:  $m/z = 453.18$  ( $\text{M}^+$ ).

#### *tert*-Butyl 3-(4-Methoxyphenyl)-2-diphenylmethyleaminopropanoate [(S)-**12d**]

Synthesized following the general procedure and according to the reaction condition listed in Table 1; yield: 0.18 g, 90%;  $[\alpha]_{\text{D}}^{25} -17.3$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3042, 2965, 1698, 1555, 1236, 786  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta = 1.32$  (s, 9 H), 3.10 (s, 3 H), 3.24 (d, 2 H,  $J = 10.0$  Hz), 4.45 (t, 1 H,  $J = 4.0$  Hz), 7.02 (d, 2 H,  $J = 6.0$  Hz), 7.38 (d, 2 H,  $J = 4.0$  Hz), 7.47–7.85 (m, 10 H).

$^{13}\text{C}$  NMR (50 MHz, DMSO- $d_6$ ):  $\delta = 24.5, 37.7, 62.3, 71.3, 120.2, 127.5, 129.4, 130.4, 131.9, 132.5, 133.7, 137.5, 141.6, 161.3, 179.0$ .

MS:  $m/z = 415.18$  ( $\text{M}^+$ ).

HRMS:  $m/z$  calcd for  $\text{C}_{27}\text{H}_{29}\text{NO}_3$ : 415.2397; found: 415.2186.

#### *tert*-Butyl 3-(4-Nitrophenyl)-2-diphenylmethyleaminopropanoate [(S)-**12e**]

Synthesized following the general procedure and according to the reaction condition listed in Table 1; yield: 0.16 g, 75%;  $[\alpha]_{\text{D}}^{25} -16.7$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3055, 2910, 1725, 1560, 1467, 1223, 1075  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta = 1.15$  (s, 9 H), 3.12 (d, 2 H,  $J = 6.0$  Hz), 4.25 (t, 1 H,  $J = 5.0$  Hz), 7.23–7.66 (m, 14 H).

MS:  $m/z = 430.18$  ( $\text{M}^+$ ).

#### *tert*-Butyl 3-(4-*tert*-Butylphenyl)-2-diphenylmethyleaminopropanoate [(S)-**12f**]

Synthesized following the general procedure and according to the reaction condition listed in Table 1; yield: 0.21 g, 93%;  $[\alpha]_{\text{D}}^{25} -28.2$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3050, 2915, 1705, 1555, 1450, 1224, 1065  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta = 1.35$  (s, 9 H), 2.16 (s, 9 H), 3.25 (d, 2 H,  $J = 8.4$  Hz), 4.36 (t, 1 H,  $J = 6.4$  Hz), 6.92–7.67 (m, 14 H).

$^{13}\text{C}$  NMR (50 MHz, DMSO- $d_6$ ):  $\delta = 24.8, 28.4, 39.5, 65.7, 73.2, 76.4, 122.2, 128.9, 130.2, 131.5, 132.8, 134.7, 135.5, 141.6, 165.2, 185.1$ .

MS:  $m/z = 441.52$  ( $\text{M}^+$ ).

#### *tert*-Butyl 3-(2-Allyl)-2-diphenylmethyleaminopropanoate [(S)-**14**, $\text{R}' = \text{CH}_2\text{CH}=\text{CH}_2$ ] (Table 5, Entry 4)

Synthesized following the general procedure and according to the reaction condition listed in Table 5; yield: 0.15 g, 96%;  $[\alpha]_{\text{D}}^{25} -19.2$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3065, 2926, 1720, 1629, 1245  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta = 1.40$  (s, 9 H), 2.65 (t, 2 H,  $J = 5.7$  Hz), 4.25 (t, 1 H,  $J = 6.6$  Hz), 4.95 (d, 2 H,  $J = 8.4$  Hz), 5.72 (m, 1 H), 7.15–7.60 (m, 10 H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta = 28.3, 35.2, 57.4, 71.4, 114.6, 127.6, 128.5, 130.5, 137.8, 161.7, 175.9$ .

MS:  $m/z = 321.41$  ( $\text{M}^+$ ).

#### *tert*-Butyl 3-(9-Methylanthracenyl)-2-diphenylmethyleaminopropanoate [(S)-**14**, $\text{R}' = \text{methylanthracenyl}$ ] (Table 5, Entry 5)

Synthesized following the general procedure and according to the reaction condition listed in Table 5; yield: 0.22 g, 92%;  $[\alpha]_{\text{D}}^{25} -21.3$  ( $c = 0.2$ ,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3024, 2875, 1710, 1598, 1225  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz, DMSO- $d_6$ ):  $\delta = 1.40$  (s, 9 H), 3.70 (d, 2 H,  $J = 5.16$  Hz), 4.35 (t, 1 H,  $J = 6.0$  Hz), 7.07–78.02 (m, 19 H).

$^{13}\text{C}$  NMR (50 MHz, DMSO- $d_6$ ):  $\delta$  = 27.2, 33.5, 61.4, 73.5, 124.6, 125.3, 125.8, 126.2, 128.2, 128.6, 129.1, 130.2, 131.3, 132.3, 132.6, 137.4, 165.7, 182.6.

MS:  $m/z$  = 485.49 ( $\text{M}^+$ ).

**tert-Butyl 3-(Inden-3-yl)-2-diphenylmethyleaminopropanoate [(S)-12, R' = inden-3-yl] (Table 5, Entry 8)**

Synthesized following the general procedure and according to the reaction condition listed in Table 5; yield: 0.19 g, 88%;  $[\alpha]_{\text{D}}^{25}$  –26.4 ( $c$  = 0.2,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3058, 2920, 1720, 1684, 1217  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  = 1.35 (s, 9 H), 3.22 (d, 2 H,  $J$  = 13.8 Hz), 3.35 (d, 2 H,  $J$  = 11.4 Hz), 4.24 (t, 1 H,  $J$  = 7.83 Hz), 6.38 (dd, 2 H,  $J$  = 7.5, 8.1 Hz), 6.95 (t, 1 H,  $J$  = 7.4 Hz), 7.04 (dd, 2 H,  $J$  = 6.6, 7.4 Hz), 7.14–7.80 (m, 10 H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  = 24.5, 29.2, 30.3, 62.4, 72.9, 121.4, 123.5, 125.8, 127.0, 128.4, 128.6, 129.0, 130.2, 134.2, 135.5, 137.7, 140.3, 163.4, 182.4.

MS:  $m/z$  = 423.12.

**tert-Butyl 3-[(1-Toluene-4-sulfonyl)indol-3-yl]-2-diphenylmethyleaminopropanoate [(S)-12, R' = (1-toluenesulfonyl)indol-3-yl] (Table 5, Entry 9)**

Synthesized following the general procedure and according to the reaction condition listed in Table 5; yield: 0.18 g, 92%;  $[\alpha]_{\text{D}}^{25}$  –19.2 ( $c$  = 0.2,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3025, 2910, 1715, 1522, 1235  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  = 1.36 (s, 9 H), 2.44 (s, 3 H), 3.12 (d, 2 H, 8.07 Hz), 4.35 (t, 1 H,  $J$  = 5.20 Hz), 6.8 (s, 1 H), 7.22 (dd, 2 H,  $J$  = 7.92, 8.04 Hz), 7.52 (dd, 2 H,  $J$  = 7.5, 8.4 Hz).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  = 27.2, 38.6, 61.7, 73.4, 125.7, 127.3, 128.4, 128.9, 129.5, 130.7, 137.2, 140.6, 164.8, 172.9.

MS:  $m/z$  = 385.19 ( $\text{M}^+$ ).

HRMS:  $m/z$  calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}_2$ : 386.2042; found: 386.1897.

**tert-Butyl 3-(Methyl)-2-diphenylmethyleaminopropanoate [(S)-12, R' = Me] (Table 5, Entry 11)**

Synthesized following the general procedure and according to the reaction condition listed in Table 5; yield: 0.14 g, 92%;  $[\alpha]_{\text{D}}^{25}$  –15.7 ( $c$  = 0.2,  $\text{CHCl}_3$ ).

FT-IR (KBr):  $\delta$  = 3022, 2919, 1710, 1520, 1233  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  = 1.40 (s, 9 H), 1.52 (d, 3 H,  $J$  = 9.42 Hz), 4.17 (q, 1 H,  $J$  = 13.95 Hz), 6.8–7.45 (m, 10 H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  = 17.8, 27.2, 55.6, 73.2, 128.4, 129.3, 130.5, 137.4, 155.4, 176.6.

MS:  $m/z$  = 309.38 ( $\text{M}^+$ ).

**tert-Butyl 3-(3-Thiophenyl)-2-diphenylmethyleaminopropanoate [(S)-12, R' = 3-thiophenyl] (Table 5, Entry 12)**

Synthesized following the general procedure and according to the reaction condition listed in Table 5; yield: 0.17 g, 89%;  $[\alpha]_{\text{D}}^{25}$  –27.3 ( $c$  = 0.2,  $\text{CHCl}_3$ ).

FT-IR (KBr): 3060, 2925, 1720, 1618, 1232  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  = 1.27 (s, 9 H), 3.27 (d, 2 H,  $J$  = 7.8 Hz), 4.22 (t, 1 H,  $J$  = 7.02 Hz), 6.02 (s, 1 H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  = 29.3, 32.1, 62.4, 74.5, 121.5, 126.8, 128.2, 129.1, 129.7, 130.6, 137.2, 138.4, 165.4, 168.8.

MS:  $m/z$  = 391.29 ( $\text{M}^+$ ).

## References

- (1) For general reviews on asymmetric PTC, see: (a) O'Donnell, M. J. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, **2000**. (b) Shioiri, T.; Arai, S. *Stimulating Concepts in Chemistry*; Vogtle, F.; Stoddart, J. F.; Shibasaki, M., Eds.; Wiley: New York, **2000**. (c) Nelson, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1583.
- (2) (a) O'Donnell, M. J.; Benett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181. (c) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591. (d) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (e) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775. (f) O'Donnell, M. J.; Delgado, F.; Pottorf, R. *Tetrahedron* **1999**, *55*, 6347.
- (3) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (b) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (c) Corey, E. J.; Bo, Y.; Busch-Peterson, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.
- (4) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1389. (c) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389. (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671.
- (5) (a) Zhang, Z.; Wang, Y.; Hodge, P. *React. Funct. Polym.* **1999**, *41*, 37. (b) Chinchilla, R.; Mazon, P.; Najera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277.
- (6) (a) Ooi, T.; Kameda, M. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Ooi, T.; Tayama, E.; Doda, K.; Takeuchi, M.; Maruoka, K. *Synlett* **2000**, 1500. (c) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.
- (7) (a) Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807. (b) Manabe, K. *Tetrahedron* **1998**, *54*, 14456.
- (8) (a) Belokon, Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Vyskocil, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851. (b) Belokon, Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Singh, I.; Parmar, V. S.; Vyskocil, S.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041.
- (9) (a) Belokon, Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Vyskocil, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1723. (b) Belokon, Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S. R.; Vyskocil, S.; North, M.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 1948. (c) Casas, J.; Najera, C.; Sansano, J. M.; Gonzalez, J.; Saa, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699.
- (10) (a) Belokon, Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. L. *Tetrahedron Lett.* **1999**, *40*, 6105. (b) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245.
- (11) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, T. *Tetrahedron Lett.* **2002**, *43*, 9539.
- (12) Jew, S.; Jeong, B.; Yoo, M.; Park, H.; Huh, H. *Chem. Commun.* **2001**, 1244.
- (13) Park, H.; Jeong, B.; Yoo, M.; Park, M.; Huh, H.; Jew, S. *Tetrahedron Lett.* **2001**, *42*, 4645.
- (14) Chinchilla, R.; Mazon, P.; Najera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927.
- (15) Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **2002**, *43*, 1909.
- (16) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.