Synthesis of Novel Chiral Phase-Transfer Catalysts and Their Application to Asymmetric Synthesis of α-Amino Acid Derivatives

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Abstract: To investigate the electronic and steric influences on enantioselectivities of asymmetric phase-transfer reactions, a series of chiral quaternary ammonium salts were synthesized from *cinchona* alkaloids and 2-chloromethylbenzimidazole or 1-chloromethyl benzotriazole. Using one of the cinchonine-derived alkaloid catalysts, enantioselective alkylations of *N*-(diphenylmethylene) glycine *tert*-butyl ester were efficiently carried out with various alkyl halides to give products in high enantiomeric excess (94–99% ee).

Key words: asymmetric catalysis, alkylation, amino acids, phase-transfer catalysis, *cinchona* alkaloids

Asymmetric alkylation of glycine imines using quaternary ammonium salts as phase-transfer catalysts (PTC) has emerged as a promising transformation because it provides a simple and easily scalable procedure for synthesis of various naturally occurring and synthetic amino acids.[1] Typical chiral PTC catalysts developed for this reaction in the last two decades mainly focused on quaternary ammonium salts derived from *cinchona* alkaloids[2] and binaphthyl.[3]

C_2-Symmetric chiral spiro binaphthol ammonium salts derivatives developed by the Maruoka group have been successfully applied to the highly efficient, catalytic enantioselective synthesis of various amino acids under mild phase-transfer conditions,[3a,b] while these catalysts are expected to be expensive (not derived from the chiral pool and often require multistep syntheses).[1a] *Cinchona* alkaloids quaternary ammonium salts could be easily prepared from cheap commercial natural products, which evoked our greater interests to further study on them. We found that subtle changes in structure of the ammonium salts catalyst often lead to major improvements in the levels of enantioselectivity. In 1989, O'Donnell first introduced *N*-benzyl *cinchona* alkaloid salts as phase-transfer catalysts (first generation) in the asymmetric alkylation of *N*-diphenyl methylene glycine *tert*-butyl ester, which obtained the corresponding product in 66% ee.[4] The second generation of catalysts, the N-alkyl O-alkyl *cinchona* alkaloid salts, were reported in 1994,[5] which gave improvement of enantioselectivities (up to 81% ee). Finally, the third generation of catalyst was described independently by Lygo[6] and Corey[7] in 1997, in which a 9-anthracenylmethyl group was introduced as an effective unit for masking the nitrogen face. Much better results were obtained by replacing the phenyl group with the bulkier anthracenyl moiety, which led to substantially improved enantioselectivities (up to 99.5% ee). Obviously, it is very essential to adjust steric hindrance effect of the catalysts for high enantiomeric induction. However, since asymmetric alkylation of glycine imines is an ion-pair-mediated reaction, the electronic properties of the PTC catalyst may also play a very important role in the transformation. Based on this consideration, we designed and synthesized new chiral quaternary ammonium salts from *cinchona* alkaloids which can maintain the space bulk and change the electronic characteristic of the catalyst. Therefore, various PTC catalysts were prepared from *cinchona* alkaloids and 2-chloromethyl benzimidazole or 1-chloromethylbenzotriazole, respectively (Figure 1). Herein the preliminary result of their catalytic performance is disclosed.

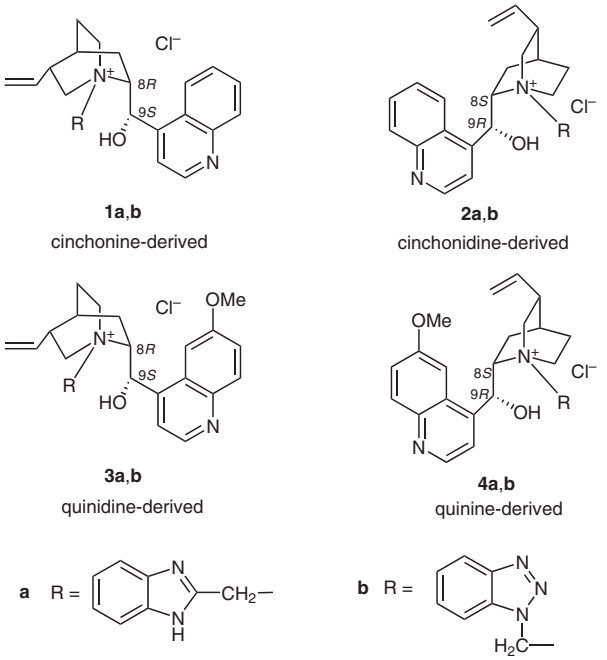

Figure 1 Cinchona-derived phase-transfer catalysts

Cinchona alkaloids, cinchonine, cinchonidine, quinidine, or quinine and 2-chloromethylbenzimidazole or 1-chloromethylbenzotriazole, were stirred at 110 °C in toluene for three hours followed by recrystallization with diethyl

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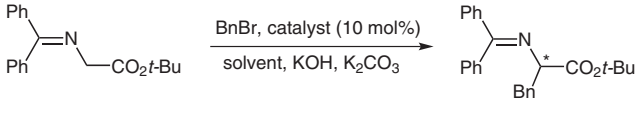
ether to give the corresponding *cinchona* alkaloid catalysts **1a**–**4a**[8] and **1b**–**4b**[9] in 85–93% yields. First, all the quaternary ammonium salts were screened for the effectiveness on the enantioselective phase-transfer benzylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester using 10 mol% of catalysts. Different factors influencing the enantioselectivities including solvent and temperature were also investigated (Table 1).

Table 1 Asymmetric Phase-Transfer Catalytic Benzylation Using *Cinchona*-Derived Catalysts[a]



5 **6e**

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]	Config[d]
1	**1a**	CH_2Cl_2	20	24	70	95	*R*
2	**2a**	CH_2Cl_2	20	24	65	90	*S*
3	**3a**	CH_2Cl_2	20	24	60	73	*R*
4	**4a**	CH_2Cl_2	20	24	61	68	*S*
5	**2b**	CH_2Cl_2	20	12	90	96	*S*
6	**1b**	Et_2O	20	12	55	99	*R*
7	**1b**	toluene	20	18	65	75	*R*
8	**1b**	toluene–CH_2Cl_2	20	12	79	83	*R*
9	**1b**	CH_2Cl_2	20	12	91	99	*R*
10	**1b**	CH_2Cl_2	0	15	85	>99	*R*
11	**1b**	CH_2Cl_2	-20	24	80	>99	*R*
12	**1a**	CH_2Cl_2	-20	36	20	95	*R*
13	**3b**	CH_2Cl_2	20	12	73	75	*R*
14	**4b**	CH_2Cl_2	20	12	69	73	*S*

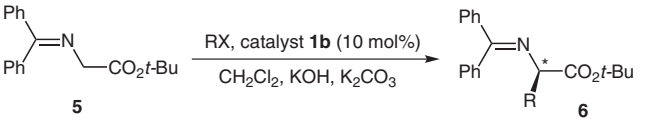
[a] Conditions: **5**/BnBr/catalyst = 1:1.2:0.1 (mmol).
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column with hexane–*i*-PrOH as eluent.
[d] Assigned by comparison with the sign of the specific rotation given in the literature.

As we can see, the absolute configuration of the product was highly dependent upon the absolute configuration of the C8- and C9-positions of the *cinchona* alkaloids. Not surprisingly, the pseudoenantiomeric catalyst pairs gave opposite enantioselectivity in the alkylation reaction. The quaternary ammonium salts derived from quinine and quinidine, with the additional methoxy group, gave lower ee, as compared with the catalysts derived from cinchone and cinchonidine. Generally speaking, both the conversions and the enantioselectivities using **1b**–**4b** were higher than those of **1a**–**4a**. We think the difference of activities and ee may due to their chemical structures. As already known, in the asymmetric phase-transfer catalytic reaction using *cinchona*-derived catalysts with free OH group, the active catalyst was the O-alkylation of the *cinchona* alkaloid quaternary ammonium salt, which was formed in situ during the asymmetric alkylation.[5] In our case, catalysts **1a**–**4a** have an additional NH group, which may induce both N-alkylation and O-alkylation in situ during the catalytic alkylation of **5**, and the new active compounds with larger steric bulk may decrease the catalytic activities. This can also explain the reaction phenomena occurred at low temperature. When using **1a** at –20 °C, the yield decreased dramatically even with much longer time. We further investigated the influence of solvent on enantioselectivities using the optimal catalyst **1b**. CH_2Cl_2 gave the excellent ee (99%) as compared to toluene (75% ee) and toluene–CH_2Cl_2 (7:3; 83% ee). In Et_2O, excellent ee could also be obtained, but the yield was unsatisfactory.

Using the catalyst **1b**, we also examined the scope and limitations of the enantioselective phase-transfer alkylation of **5** with various alkyl halides with the aids of finely powdered and dried mixture of K_2CO_3 and KOH. Table 2 indicates that high yields (82–92%) and enantioselectivities (94–99% ee) were achieved in the alkylation with 8 alkyl halides.[10] The alkylated imines **6** could be further transformed to the corresponding amino acids[11] by acidic hydrolysis via the known procedure.[7]

In conclusion, novel simple *cinchona* alkaloid ammonium salt catalysts and their catalytic performance were demonstrated. These catalysts, which maintained the steric bulk to mask the nitrogen face and an additional nitrogen atom

Table 2 Asymmetric Phase-Transfer Catalytic Alkylation Using Various Alkyl Halides and Catalyst **1b**[a]



5 **6**

Entry	RX	Product	Time (h)	Yield (%)[b]	ee (%)[c]	Config[d]
1	MeI	**6a**	9	87	97	*R*
2	EtI	**6b**	15	85	96	*R*
3	*n*-BuI	**6c**	11	86	94	*R*
4	CH_2=$CHCH_2Br$	**6d**	12	92	98	*R*
5	BnBr	**6e**	12	91	99	*R*
6	2-Nap-CH_2Br	**6f**	14	83	98	*R*
7	4-*t*-BuBnBr	**6g**	12	82	99	*R*
8	4-F_3CBnBr	**6h**	18	86	97	*R*

[a] Conditions: **5**/RX/**1b** = 1:1.2:0.1 (mmol); reaction temperature: 20 °C.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column with hexane–*i*-PrOH as eluent.
[d] Assigned by comparison with the sign of the specific rotation given in the literature.

in the five-membered ring, showed good activities in the asymmetric alkylation of glycine imines. Among these catalysts, the *N*-benzimidazolemethyl cinchonine quaternary ammonium salt **1b** showed the highest catalytic activity (94–99% ee) in the alkylation of **5**. The advantages of this novel catalyst such as its simple structure, the lower preparation cost, high catalytic efficiency, and easily recovering process imply it may be a potential practical catalyst in industrial synthetic processes for natural and unnatural chiral α-amino acids. Further detailed catalytic mechanism and applications to other various phase-transfer catalytic reactions using **1b** are currently being investigated.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (c) Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266. (d) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (e) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679.

(2) (a) Thierry, B.; Plaquevent, J. C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983. (b) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391. (c) Park, H.; Jeong, B.; Yoo, M.; Park, M.; Huh, H.; Jew, S. *Tetrahedron Lett.* **2001**, *42*, 4645. (d) Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015.

(3) (a) Ooi, T.; Kameda, M.; Maruok, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139. (b) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 1549. (c) Hashimoto, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1599. (d) Han, Z.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555.

(4) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am.Chem. Soc.* **1989**, *111*, 2353.

(5) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.

(6) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.

(7) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(8) **Procedure for the Synthesis of 1a–4a**
To a suspension of *cinchona* alkaloid (10 mmoL) in toluene (40 mL) was added 2-chloromethylbenzimidazole (10.5 mmoL), and the mixture was stirred at reflux for 3 h (TLC with CH_2Cl_2–MeOH = 15:1). The mixture was cooled to r.t. and filtered. The solids were collected and recrystallized in Et_2O to afford the pure product.
Compound **1a**: white solid (prepared from cinchonine); yield 93%; mp 182–183 °C; $[\alpha]_D^{25}$ +68 (*c* 0.5, EtOH). IR (KBr): 3425, 2947, 1637, 1510, 1458, 1402, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.87 (d, *J* = 4.6 Hz, 1 H), 7.83–7.80 (m, 2 H), 7.51–7.45 (m, 3 H), 7.27–7.16 (m, 4 H), 6.70–6.67 (m, 2 H), 6.60 (s, 1 H), 6.30 (d, *J* = 13.8 Hz, 1 H), 5.93 (m, 1 H), 5.30–5.23 (m, 3 H), 4.85 (m, 1 H), 4.71 (t, *J* = 5.2 Hz, 1 H), 4.07 (t, *J* = 11.2 Hz, 1 H), 3.97 (t, *J* = 8.5 Hz, 1 H), 3.07 (m, 1 H), 2.62 (m, 1 H), 2.35–1.78 (m, 4 H), 0.87 (m, 1 H). MS: *m/z* (%) 425 ([M–Cl]$^+$, 5), 424 (10), 293 (40), 159 (20), 132 (100). Anal. Calcd for $C_{27}H_{29}ClN_4O$: C, 70.34; H, 6.34; N, 12.15. Found: C, 70.32; H, 6.30; N, 12.18.
Compound **2a**: white solid (prepared from cinchonidine); yield 90%; mp 175–176 °C. $[\alpha]_D^{25}$ –34 (*c* 0.5, EtOH). IR (KBr): 3423, 3238, 2960, 1641, 1620, 1591, 1508, 1456, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 4.4 Hz, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 7.79 (d, *J* = 4.6 Hz, 1 H), 7.64–7.01 (m, 7 H), 6.77 (s, 1 H), 6.57–6.46 (m, 1 H), 6.14 (d, *J* = 13.8 Hz, 1 H), 5.46–5.24 (m, 2 H), 5.02 (m, 2 H), 4.72 (d, *J* = 13.6 Hz, 1 H), 4.05 (s, 1 H), 3.63–3.50 (m, 2 H), 2.68 (d, *J* = 5.0 Hz, 1 H), 2.20 (s, 1 H), 2.07–1.85 (m, 4 H), 1.24 (m, 1 H), 1.11 (m, 1 H). MS: *m/z* (%) = 425 (5) [M – Cl]$^+$, 424 (10), 293 (55), 159 (15), 136 (40), 132 (100). Anal. Calcd for $C_{27}H_{29}ClN_4O$: C, 70.34; H, 6.34; N, 12.15. Found: C, 70.37; H, 6.31; N, 12.14.
Compound **3a**: pink solid (prepared from quinidine); yield 90%; mp 210–212 °C (dec.); $[\alpha]_D^{25}$ +112 (*c* 0.2, EtOH). IR (KBr): 3425, 2935, 1624, 1512, 1437, 1242, 1028, 743 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 8.78 (d, *J* = 4.6 Hz, 1 H), 8.03 (d, *J* = 9.4 Hz, 1 H), 7.92 (d, *J* = 4.8 Hz, 1 H), 7.74–7.13 (m, 6 H), 6.76 (d, *J* = 1.7 Hz, 1 H), 6.12–6.03 (m, 1 H), 5.35–5.27 (m, 3 H), 5.08 (d, *J* = 10.0 Hz, 1 H), 4.76 (t, *J* = 10.0 Hz, 1 H), 4.15 (t, *J* = 9.0 Hz, 1 H), 3.97 (s, 3 H), 3.90 (m, 2 H), 3.42 (m, 1 H), 2.79 (m, 1 H), 2.41 (t, *J* = 2.0 Hz, 1 H), 2.31 (s, 1 H), 1.89–1.98 (m, 4 H), 1.03 (m, 1 H). MS: *m/z* (%) = 455 (5) [M – Cl]$^+$, 454 (10), 324 (35), 189 (20), 136 (100). Anal. Calcd for $C_{28}H_{31}ClN_4O_2$: C, 68.49; H, 6.36; N, 11.41. Found: C, 68.52; H, 6.33; N, 11.37.
Compound **4a**: pink solid (preapred from quinine); yield 85%, mp 170–172 °C (dec.); $[\alpha]_D^{25}$ –50 (*c* 0.2, CH_2Cl_2). IR (KBr): 3403, 1622, 1510, 1242, 1028, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 4.4 Hz, 1 H), 7.97 (d, *J* = 9.1 Hz, 1 H), 7.79 (d, *J* = 4.4 Hz, 1 H), 7.66–7.17 (m, 6 H), 6.90 (s, 1 H), 6.59 (s, 1 H), 5.80 (d, *J* = 13.0 Hz, 1 H), 5. 51–5. 40 (m, 2 H), 5.17 (d, *J* = 7.1 Hz, 1 H), 5.00 (m, 2 H), 4.06 (d, *J* = 6.3 Hz, 2 H), 3.94 (t, *J* = 8.5 Hz, 1 H), 3.61 (s, 3 H), 3.29 (m, 1 H), 2.68 (d, *J* = 4.4 Hz, 1 H), 2.34 (s, 1 H), 2.26–1.83 (m, 4 H), 1.20 (m, 1 H). MS: *m/z* (%) = 455 (10) [M – Cl]$^+$, 454 (15), 123 (80), 136 (40), 132 (100). Anal. Calcd for $C_{28}H_{31}ClN_4O_2$: C, 68.49; H, 6.36; N, 11.41. Found: C, 68.54; H, 6.40; N, 11.39.

(9) **Procedure for the synthesis of 1b–4b**
To a suspension of the *cinchona* alkaloid (10 mmoL) in 40 mL toluene was added 1-chloromethylbenzotriazole(10.5 mmoL), and the mixture was stirred at reflux for 3 h (TLC with CH_2Cl_2–MeOH = 15:1). The solvent was evaporated under reduced pressure. The pure product was attained by chromatography using CH_2Cl_2–MeOH as eluent.
Compound **1b**: white solid (prepared from cinchonine); yield 85%; mp 170–172 °C; $[\alpha]_D^{25}$ +148 (*c* 0.5, EtOH). IR (KBr): 3424, 2949, 1631, 1505, 1510, 1456, 1418, 1289, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.81–8.79 (m, 1 H), 8.73 (d, *J* = 7.9 Hz, 1 H), 8.65 (d, *J* = 8.1 Hz, 1 H), 8.04–8.01 (m, 1 H), 7.97–7.87 (m, 3 H), 7.73–7.61 (m, 1 H), 7.45–7.38 (m, 2 H), 6.86 (s, 1 H), 5.76–5.73 (m, 1 H), 5.22–5.14 (m, 2 H), 4.98–4.83 (m, 1 H), 4.86–4.75 (m, 1 H), 4.08–3.87 (m, 1 H), 3.81–3.75 (m, 1 H), 3.70–3.54 (m, 2 H), 2.95–2.89 (m, 1 H), 2.63–2.54 (m, 1 H), 2.31–1.89 (m, 5 H), 1.29–1.26 (m, 1 H). Anal. Calcd for $C_{26}H_{28}ClN_5O$: C, 67.59; H, 6.11; N, 15.16. Found: C, 67.54; H, 6.16; N, 15.20. ESI-MS: 426 [M – Cl]$^+$.
Compound **2b**: white solid (prepared from cinchonidine); yield 89%; mp 230–240 °C (dec.); $[\alpha]_D^{25}$ –154 (*c* 0.5, EtOH).

IR (KBr): 3398, 3243, 2955, 1629, 1498, 1455, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.82–8.81 (m, 1 H), 8.69 (d, *J* = 7.8 Hz, 1 H), 8.45–8.41 (m, 1 H), 7.95–7.77 (m, 4 H), 7.49–7.37 (m, 3 H), 7.20 (s, 1 H), 6.79 (s, 1 H), 5.42–5.31 (m, 1 H), 5.13–5.08 (m, 1 H), 4.98 (d, *J* = 10.2 Hz, 1 H), 4.26–4.23 (m, 1 H), 3.69–3.56 (m, 2 H), 3.22–3.19 (m, 1 H), 2.52 (s, 1 H), 1.72–1.57 (m, 1 H), 1.09–1.01 (m, 1 H), 2.11–1.93 (m, 5 H). Anal. Calcd for $C_{26}H_{28}ClN_5O$: C, 67.59; H, 6.11; N, 15.16. Found: C, 66.94; H, 6.20; N, 15.19. ESI-MS: 426 $[M - Cl]^+$.

Compound **3b**: white solid (prepared from quinidine); yield 88%; mp 190–195 °C (dec.); $[\alpha]_D^{25}$ +149 (*c* 0.5, EtOH). IR (KBr): 3428, 2946, 1623, 1508, 1460, 1239 cm^{-1}. ^1H NMR (300 MHz, CD_3Cl): δ = 8.63 (d, *J* = 8.1 Hz, 1 H), 8.46 (d, *J* = 4.2 Hz, 1 H), 7.83–7.78 (m, 4 H), 7.40–7.37 (m, 2 H), 7.21–7.11 (m, 1 H), 6.87 (s, 1 H), 5.80–5.68 (m, 1 H), 5.15–5.10 (m, 2 H), 4.87–4.80 (m, 1 H), 4.25–4.22 (m, 2 H), 3.85 (s, 3 H), 3.66–3.57 (m, 1 H), 3.06–3.03 (m, 1 H), 2.55–2.35 (m, 3 H), 2.33–2.31 (m, 1 H), 2.17 (t, *J* = 12.0 Hz, 1 H), 1.87–1.71 (m, 3 H), 1.25–1.21 (m, 1 H). ESI-MS: 456.6 $[M - Cl]^+$. Anal. Calcd for $C_{27}H_{30}ClN_5O_2$: C, 65.91; H, 6.15; N, 14.23. Found: C, 65.89; H, 6.19; N, 14.21.

Compound **4b**: white solid (prepared from quinine); yield 90%; mp 160–162 °C; $[\alpha]_D^{25}$ –122 (*c* 0.5, EtOH). IR (KBr): 3421, 1621, 1506, 1460, 1352, 1235 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.68 (s, 1 H), 8.65 (d, *J* = 4.5 Hz, 1 H), 7.95–7.93 (m, 1 H), 7.91 (d, *J* = 3.3 Hz, 1 H), 7.78 (d, *J* = 4.2 Hz, 1 H), 7.66–7.64 (m, 1 H), 7.56 (d, *J* = 13.5Hz, 1 H), 7.47 (t, *J* = 7.2 Hz, 1 H), 7.36 (d, *J* = 7.5 Hz, 1 H), 6.97 (s, 1 H), 5.46–5.34 (m, 1 H), 5.07 (br s, 1 H), 4.96–4.91 (m, 2 H), 4.14–4.11 (m, 2 H), 3.98 (s, 3 H), 3.71 (t, *J* = 11.4 Hz, 1 H), 3.13 (d, *J* = 11.4 Hz, 1 H), 2.77–2.52 (m, 4 H), 2.19–2.18 (m, 1 H), 2.08–1.99 (m, 2 H), 1.98–1.85 (m, 1 H), 1.27–1.25 (m, 1 H). ESI-MS: 456.6 $[M - Cl]^+$. Anal. Calcd for $C_{27}H_{30}ClN_5O_2$: C, 65.91; H, 6.15; N, 14.23. Found: C, 65.94; H, 6.20; N, 14.29.

(10) **Representative Procedure for Enantioselective Catalytic Alkylation of 5 under Phase-Transfer Conditions**

To a mixture of *N*-(diphenylmethylene) glycine *tert*-butyl ester (**5**, 295 mg, 1 mmol) and chiral catalyst **1b** (46.2mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added BnBr (205 mg, 1.2 mmol). Then a finely powdered and dried mixture of K_2CO_3 (138 mg, 1 mmol) and KOH (56 mg, 1 mmol) was added to the reaction mixture. The resulting suspension was then vigorously stirred at 20 °C till the reaction was complete (TLC, PE–EtOAc = 20:1). The suspension was diluted with CH_2Cl_2 (10 mol), washed with H_2O (2 × 30 mL), dried over MgSO4, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on SiO_2 (PE–EtOAc = 20:1 to 10:1) afforded the desired product **6e** (258 mg, 91% yield) as a colorless oil. The ee was determined by chiral HPLC analysis [DAICEL Chiralcel OD, hexane–*i*-PrOH (98:2), flow rate = 0.4 mL/min, 23 °C, λ = 259 nm; t_R (*R*, major) = 12.2 min; t_R (*S*, minor) = 15.5 min, 99% ee]. The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.

(11) **Acidic Hydrolysis of Alkylated Imine 6e to the Corresponding (*R*)-Phenylalanine**

The crude alkylated imine **6e** was treated by refluxing 4 h in HCl (4 mL, 6 mol/L), followed by neutralization of the amine hydrochloride using propylene oxide (0.8 mL) in EtOH. After being filtrated and washed with precooled Et_2O and EtOH, the (*R*)-phenylalanine was attained in 75% yield, $[\alpha]_D^{25}$ +32 (*c* 1.0, H_2O), lit. $[\alpha]_D^{25}$ +33.7 (*c* 2.0, H_2O).

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