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TETRAHEDRON: *ASYMMETRY*

Unexpected metal base-dependent inversion of the enantioselectivity in the asymmetric synthesis of α-amino acids using phase-transfer catalysts derived from cinchonidine

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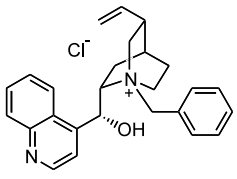
Abstract—New cinchonidinium salts bearing a 3,5-dialkoxybenzyl group show an alkaline metal base-dependent reversal of enantioselectivity when used as phase-transfer catalysts in the asymmetric alkylation of *N*-(diphenylmethylene)glycine isopropyl ester with benzyl bromide. The use of potassium hydroxide as base in this alkylation reaction afforded the (*S*)-enantiomer, whereas using sodium hydroxide under the same conditions afforded the corresponding (*R*)-enantiomer.

Phase-transfer catalysis (PTC) is a synthetic methodology which is increasing in importance nowadays due to its simplicity and its suitability for scale-up.[1] Thus, the synthesis of optically active natural and unnatural α-amino acids by enantioselective alkylation of glycine and alanine Schiff bases using PTC conditions has been widely and successfully explored, being probably the most promising method for the enantioselective synthesis of these important compounds.[2] In addition, many other processes[2f] such as Michael addition,[3a–c] Darzens,[3d] epoxidation,[3e–g] aldol,[3h,i] nitroaldol[3j] and fluorination[3k–m] reactions have recently been performed under asymmetric PTC conditions.

spiro-Ammonium[4] and -phosphonium salts,[5] TADDOL,[6] binaphthyl-derived amines[6b,7] and salen–metal complexes[8] have been used as catalysts in asymmetric PTC reactions for the asymmetric synthesis of α-amino acids. However, *Cinchona* alkaloid-derived quaternary ammonium salts have been the most frequently employed chiral PTC catalyst due to their ready preparation, low cost and their effectiveness as PTCs.[2] For example, the pioneering cinchonidine-derived O'Donnell catalyst[9] **1** or the greatly more efficient Lygo[10] **2** (R = H, X = Cl), and Corey[11] (**2**, R = allyl, X = Br) catalysts have been used for the asymmetric synthesis of (*S*)-α-amino acids. Dimeric[12] and trimeric[13] *Cinchona*-derived catalysts have also been reported, and even solid-supported cinchonidine and cinchonine ammonium salts have been employed as recoverable PTC catalysts.[14] In all cases, the opposite (*R*)-stereochemistry of the final product can be achieved by switching the alkaloid moiety from cinchonidine to cinchonine, both compounds being considered pseudoenantiomers.[2]



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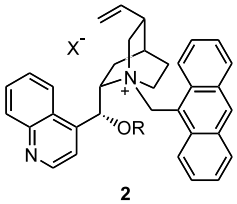

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In this context and as part of our ongoing studies towards the synthesis of *Cinchona* alkaloid-derived dendrimers, suitable for asymmetric PTC reactions using membrane reactors, we prepared *N*-[3,5-di(benzyloxy)benzyl]cinchonidinium bromide **3a**[15] in 68% yield by reaction of (−)-cinchonidine with 1-bromomethyl-3,5-dibenzyloxybenzene).[16] Allylation of **3a** with allyl bromide in 50% aq. KOH afforded allylated ammonium salt **3b**[17] in 73% yield, whereas benzylation of **3a** with benzyl bromide under the same conditions yielded **3c**[18] in 83% yield.

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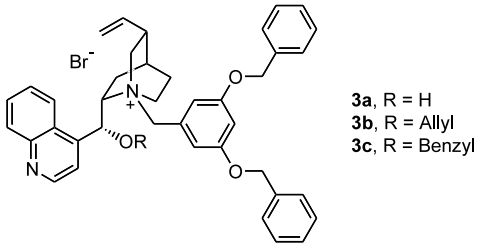
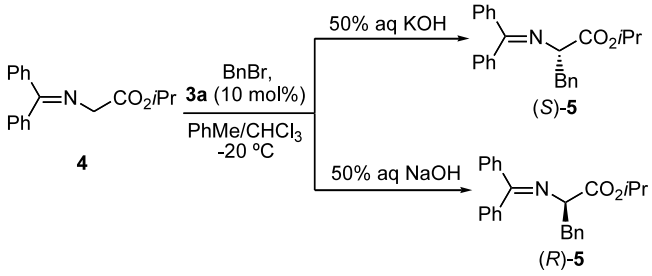
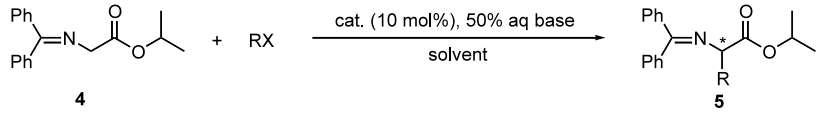
These ammonium salts **3** were employed as PTC catalysts in the alkylation reaction of *N*-(diphenylmethylene)glycine isopropyl ester[19] **4** with benzyl bromide in the biphasic system formed by a mixture of toluene/$CHCl_3$ (7/3 v/v)[12,13] and 50% aq. KOH solution at −20°C (Scheme 1). When **3a** was used as catalyst, the ee of the alkylated product **5** was 58%, measured by chiral GLC analysis[20] of the corresponding *N*-trifluoroacetamide ester (Table 1, entry 1).[21] The absolute configuration was assigned as (*S*) based upon the relative retention times of both enantiomers determined previously.[12b,14b] Surprisingly, when following a routine screening of different reaction conditions, the base was changed from aq. 50% KOH to aq. 50% NaOH solution, a 40% ee of **5** was obtained but of the opposite (*R*)-enantiomer (Table 1, entry 5). When the allylated catalyst **3b** and an aq. 50% KOH was used the ee of (*S*)-**5** increased to 76%. However, no change in the stereochemistry was observed when using aq. 50% NaOH instead of KOH while the ee dropped to 30% (Table 1, compare entries 12 and 13). Similar results were obtained using the benzylated derivative **3c** (Table 1, compare entries 14 and 15).





Scheme 1. Base-dependent enantioselective benzylation of **4**.

Table 1. Enantioselective PTC alkylations



Entry	RX	Catalyst	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)[b]	Abs. config.[b]
1	$PhCH_2Br$	**3a**	KOH	PhMe/$CHCl_3$	−20	3	80	58	(*S*)
2	$PhCH_2Br$	**3a**	KOH	PhMe/$CHCl_3$	−40	7	91	66	(*S*)
3	$PhCH_2Br$	**3a**	NaOH	PhMe/$CHCl_3$	0	3	94	26	(*R*)
4	$PhCH_2Br$	**3a**	NaOH[c]	PhMe/$CHCl_3$	0	1	95	50	(*S*)
5	$PhCH_2Br$	**3a**	NaOH	PhMe/$CHCl_3$	−20	7	96	40	(*R*)
6	$PhCH_2Br$	**3a**	NaOH	PhMe/$CHCl_3$	−40	15	93	40	(*R*)
7	$PhCH_2Br$	**3a**	KOH	PhMe	0	1	96	44	(*S*)
8	$PhCH_2Br$	**3a**	NaOH	PhMe	0	3	93	8	(*S*)
9	$PhCH_2Br$	**3a**	NaOH[c]	PhMe	0	7	76	46	(*S*)
10	$PhCH_2Br$	**3a**	KOH	CH_2Cl_2	0	2	96	34	(*S*)
11	$PhCH_2Br$	**3a**	NaOH	CH_2Cl_2	0	3	98	36	(*S*)
12	$PhCH_2Br$	**3b**	KOH	PhMe/$CHCl_3$	−20	1	84	76	(*S*)
13	$PhCH_2Br$	**3b**	NaOH	PhMe/$CHCl_3$	−20	6	85	30	(*S*)
14	$PhCH_2Br$	**3c**	KOH	PhMe/$CHCl_3$	−20	1	91	72	(*S*)
15	$PhCH_2Br$	**3c**	NaOH	PhMe/$CHCl_3$	−20	9	82	28	(*S*)
16	$PhCH_2Br$	**1**	KOH	PhMe/$CHCl_3$	−20	2	80	54	(*S*)
17	$PhCH_2Br$	**1**	NaOH	PhMe/$CHCl_3$	−20	11	70	24	(*S*)
18	$PhCH_2Br$	**6**	KOH	PhMe/$CHCl_3$	−20	2	98	44	(*S*)
19	$PhCH_2Br$	**6**	NaOH	PhMe/$CHCl_3$	−20	11	80	38	(*R*)
20	4-$CNC_6H_4CH_2Br$	**3a**	KOH	PhMe/$CHCl_3$	−20	3	90	62	(*S*)
21	4-$CNC_6H_4CH_2Br$	**3a**	NaOH	PhMe/$CHCl_3$	−20	14	87	0	
22	2-NaphCH_2Br	**3a**	KOH	PhMe/$CHCl_3$	−20	4	95	60	(*S*)
23	2-NaphCH_2Br	**3a**	NaOH	PhMe/$CHCl_3$	−20	30	95	28	(*S*)
24	$CH_3CH_2CH_2CH_2I$	**3a**	KOH	PhMe/$CHCl_3$	−20	18	65	44	(*S*)
25	$CH_3CH_2CH_2CH_2I$	**3a**	NaOH	PhMe/$CHCl_3$	−20	20	78	32	(*S*)

[a] Isolated crude yield determined by ^1H NMR (300 MHz).
[b] Determined by chiral GLC (Ref. 20).
[c] A solution of 25% aq. NaOH was used.

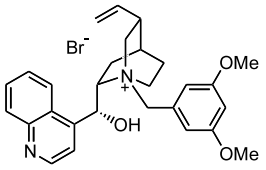
An inversion of stereochemistry in Michael additions under PTC conditions using chiral crown ethers as catalysts, and potassium or sodium *tert*-butoxide as bases has been reported.[22] However, to the best of our knowledge, no such potassium/sodium-dependent stereoselectivity effect has been shown in PTC reactions using ammonium salts as catalysts. These results prompted us to study the origin of this interesting and promising behavior in more detail.

For catalyst **3a**, the influence of the reaction temperature on the enantioselectivity of the process was studied. When KOH was used as base, a 58% ee of (*S*)-**5** was obtained at −20°C (Table 1, entry 1), while at −40°C the value further increased to 66% ee (Table 1, entry 2). In addition, when NaOH was used as base, a 26% ee of (*R*)-**5** was obtained at 0°C (Table 1, entry 3), but lowering the temperature to −20°C afforded 40% ee of (*R*)-**5** (Table 1, entry 5). Further lowering of the reaction temperature to −40°C, did not affect the enantioselectivity of the reaction (Table 1, entry 6).

The nature of the solvent seems to play a very important role in the switching of stereoselectivity when changing the base. Thus, using aq. 50% NaOH as base the (*R*)-enantiomer was the major stereoisomer when the above mentioned toluene/$CHCl_3$ (7/3 v/v) solvent mixture was employed as solvent, whereas in toluene or dichloromethane the (*S*)-enantiomer was always the main one (Table 1, compare entry 3 with entries 8 and 11). It is interesting to note that the presence of a large proportion of toluene seems to markedly increase the proportion of the (*R*)-enantiomer. Thus, when toluene was used as solvent and aq. 50% KOH as base, a 44% ee of (*S*)-**5** was obtained (Table 1, entry 7), whereas when NaOH was used as base the preference towards the (*S*)-enantiomer dropped to just 8% ee (Table 1, entry 8).

The concentration of the base also seems to be crucial to the change in stereoselectivity. Thus, when aq. 25% NaOH solution was employed as base, the reversal in the enantioselectivity was not observed and a 50% ee of (*S*)-**5** was obtained, a 26% ee of (*R*)-**5** being detected when using aq. 50% NaOH (Table 1, compare entries 3 and 6).

It seems reasonable to assume that the presence of the alkoxy groups in the arylmethyl moiety of the catalyst is a key factor in the observed inversion of enantioselectivity, the presence of a free OH also being crucial. Perhaps the alkoxy groups coordinate with the sodium cation in the alcoholate from **3a**, thus forcing a change in the blocking orientation of the arylmethyl moiety of the catalyst. In order to confirm the importance of the alkoxy groups, the alkylation reaction using the mixture of toluene/$CHCl_3$ as solvent was performed at −20°C, but now using O'Donnell's cinchonidine-derived catalyst **1** and 50% aq. KOH and NaOH as bases, respectively. The (*S*)-enantiomer was the major enantiomer, with 54 and 24% ee, respectively (Table 1, entries 16 and 17). In addition, we prepared catalyst **6**[23] (which is related to **3a** but has more simple alkoxy groups), in 89% yield by reaction of (−)-cinchonidine with 1-bromomethyl-3,5-dimethoxybenzene. Catalyst **6** showed identical base-dependent enantioselectivity also found for **3a** in the above mentioned alkylation reaction. Thus, using **6** as PTC catalyst and 50% aq. KOH as base (*S*)-**5** was obtained in 44% ee, whereas the application of 50% aq. NaOH afforded (*R*)-**5** in 38% ee (Table 1, entries 18 and 19).



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In order to determine if other alkyl halides behave similarly in this base-dependent stereoselective reaction, we performed the alkylation with 4-(bromomethyl)benzonitrile as electrophile. When aq. 50% KOH was used as base, a 62% ee of (*S*)-**5** was obtained, but with aq. 50% NaOH, a dramatic effect on the (*S*)-preference was observed and complete loss of enantiomeric excess was seen (Table 1, entries 20 and 21). Other halides such as 2-(bromomethyl)naphthalene or butyl iodide did not show the inversion of configuration effect (Table 1, entries 22–25).

We conclude that an opposite (*S*) and (*R*) enantioselectivity in the PTC alkylation reactions of glycine esters with benzyl bromide can be achieved using a single cinchonidine-derived ammonium salt as catalyst and only changing the nature of the inorganic base from KOH to NaOH. Further studies directed to understand the nature of this change in the stereoselectivity and to the design of more versatile and efficient new alkaline metal-dependent catalysts are now underway.

Typical alkylation procedure: A mixture of **4** (0.5 mmol, 140 mg), benzyl bromide (2.5 mmol, 425 μL) and the catalyst **3** or **6** (0.05 mmol) in toluene/$CHCl_3$ (7/3 v/v, 2.5 mL) was cooled (see Table 1) and an aq. 50% solution of KOH (0.75 mL) or NaOH (0.55 mL) was added. The mixture was vigorously stirred and monitored by GLC. When the reaction was finished, water (15 mL) was added and the mixture was extracted with AcOEt (3 x 15 mL). The organics extracts were combined and dried (Na_2SO_4) then evaporated to dryness in vacuo.

Acknowledgements

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15. **Compound 3a**: mp 215°C. $[\alpha]_D^{25} = -160$ (*c* 1, $CHCl_3$). IR (KBr) *v* 3187, 2939, 2878, 1602, 1454, 1381, 1320, 1152, 1058, 858, 745, 696 cm^{-1}. ^1H NMR (300 MHz, $CHCl_3$) δ 0.90 (1H, m), 1.41 (1H, m), 1.80 (1H, m), 2.23 (1H, m), 2.56 (1H, app t, $J=11.5$), 2.94 (1H, br t, $J=10.5$) 3.78 (1H, br d, $J=12.8$,), 3.78 (1H, br d, $J=12.8$,), 4.08 (1H, m,), 4.89 (1H, m), 5.08 (4H, dd, $J=17.7$, 12.2), 5.31 (2H, d, $J=4.3$), 5.37 (d, $J=11.6$, 1H), 5.89 (1H, d, $J=11.6$), 6.42 (1H, br s), 6.49 (1H, s), 6.68 (1H, d, $J=5.5$), 6.88 (2H, s), 7.05 (2H, m), 7.28 (6H, m), 7.49 (4H, d, $J=7.3$), 7.61 (1H, m), 7.83 (1H, d, $J=4.6$), 8.15 (1H, m), 8.78 (1H, d, $J=4.6$). ^{13}C NMR (75 MHz, $CHCl_3$) δ 22.7, 25.3, 26.4, 37.9, 50.2, 60.0, 62.2, 65.5, 66.7, 70.0, 104.7, 112.9, 118.0, 119.9, 123.2, 123.7, 127.7, 127.95, 128.0, 128.7, 128.9, 129.1, 136.2, 137.0, 149.0, 159.3.
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17. **Compound 3b**: mp 164°C. $[\alpha]_D^{25} = -136$ (*c* 1, $CHCl_3$). IR (KBr) *v* 3409, 3040, 2939, 2878, 1596, 1454, 1381, 1347, 1300, 1159, 1072, 937, 857, 743, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (1H, m), 1.65 (1H, m), 2.00–2.23 (5H, m), 2.41 (1H, m), 2.90 (1H, t, $J=11.7$), 3.25 (1H, m), 3.98 (1H, dd, $J=12.5$, 6.7), 4.15 (2H, m), 4.22 (1H,

dd, $J=12.5$, 5.1), 4.43 (1H, d, $J=11.7$), 4.58 (1H, m), 4.77 (1H, m), 5.02 (1H, d, $J=10.4$), 5.14 (1H, d, $J=11.9$), 5.20 (1H, d, $J=11.9$), 5.38 (3H, m), 5.66 (1H, m), 6.05 (1H, m), 6.15 (1H, s), 6.39 (1H, d, $J=11.6$), 6.75 (1H, s), 7.15 (2H, s), 7.25–7.36 (6H, m), 7.49 (4H, m), 7.78 (1H, t, $J=7.6$), 7.94 (1H, m), 8.13 (1H, d, $J=8.4$), 8.81 (1H, d, $J=8.4$), 8.95 (1H, d, $J=4.4$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 25.1, 26.7, 37.7, 51.1, 59.6, 62.1, 66.1, 70.2, 104.2, 113.0, 118.3, 119.8, 124.5, 125.1, 127.8, 127.9, 128.4, 129.1, 129.8, 130.2, 132.4, 136.1, 136.4, 139.8, 148.4, 149.3, 159.7.

18. Compound **3c**: mp 154°C. $[\alpha]_D^{25}=-60$ (c 1, $CHCl_3$). IR (KBr) ν 3032, 2929, 1608, 1454, 1378, 1305, 1158, 1040, 840, 758, 702 cm^{-1}. ^{1}H NMR (300 Hz, $CDCl_3$) δ 0.85–0.96 (1H, m), 1.26 (1H, m), 1.55 (1H, m), 2.02–2.34 (4H, m), 2.83–2.94 (1H, m), 3.96 (1H, m), 4.30 (1H, m), 4.67 (2H, m), 4.91–5.15 (6H, m), 5.32 (2H, m), 5.67 (1H, m), 5.96 (1H, m), 6.50–6.57 (4H, m), 6.90 (1H, s), 7.28–7.47 (16 H, m), 8.08 (1H, m), 8.24–8.36 (1H, m), 8.56 (1H, m), 9.31 (1H, m). ^{13}C NMR (75 Hz, $CDCl_3$) δ 22.2, 24.8, 26.6, 29.6, 37.7, 50.9, 53.4, 59.4, 61.4, 62.4, 70.1, 72.4, 104.6, 112.8, 118.5, 119.2, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5, 129.2, 129.4, 129.5, 132.3, 135.2, 136.0, 136.3, 136.4, 137.6, 150.2, 159.6.
19. Prepared in 80% overall yield by reaction of glycine with thionyl chloride in the presence of *iso*-propanol (see: Patel, R.; Price, S. *J. Org. Chem.* **1965**, *30*, 3575–3576), followed by treatment of the crude with benzophenone imine (see: O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666).
20. Chirasil-LVal (Chrompack), 1 min 85°C, 2°C/min to 180°C. Reference racemic samples were prepared using tetrabutylammonium bromide as phase-transfer catalyst.
21. Obtained after hydrolysis of the imine with 2 M aq. HCl and further reaction with trifluoroacetic anhydride. See: Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2380.
22. Dehmlow, E. V.; Knufinke, V. *Liebigs Ann. Chem.* **1992**, 283–285.
23. **Compound 6**: mp 203°C. $[\alpha]_D^{25}=-201$ (c 1, $CHCl_3$). IR (KBr) ν 3422, 3221, 2993, 2946, 1602, 1468, 1354, 1307, 1206, 1159, 1065, 931, 857, 783 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 (1H, m), 1.84 (2H, m), 2.0 (2H, m), 2.49 (1H, m), 3.25 (2H, m), 3.80 (6H, s), 3.88 (1H, m), 4.13 (1H, m), 4.65 (1H, m), 4.91 (1H, d, $J=10.0$), 5.29 (1H, m), 5.37–5.48 (1H, m), 5.59 (1H, d, $J=11.7$), 5.81 (1H, d, $J=11.7$), 6.25 (1H, s), 6.51 (1H, br s), 6.58 (1H, d, $J=6.5$), 6.90 (2H, s), 7.16 (2H, m), 7.66 (1H, d, $J=6.5$), 7.82 (1H, d, $J=4.3$), 8.16 (1H, d, $J=8.2$), 8.80 (1H, d, $J=4.3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 25.2, 26.4, 37.9, 50.5, 55.5, 60.4, 62.4, 65.0, 67.1, 102.2, 111.6, 117.9, 119.8, 122.9, 123.6, 127.5, 128.5, 128.8, 129.4, 136.0, 144.9, 146.8, 149.2, 160.5.