Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 927–931

TETRAHEDRON: *ASYMMETRY*

New dimeric anthracenyl-derived *Cinchona* quaternary ammonium salts as phase-transfer catalysts for the asymmetric synthesis of α-amino acids

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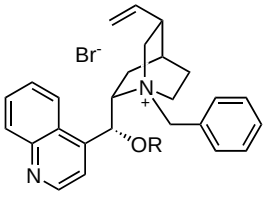
Received 26 April 2002; accepted 30 April 2002

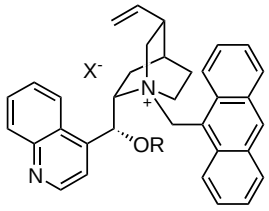
Abstract—New dimeric cinchonidine- and cinchonine-derived ammonium salts which incorporate a dimethylanthracenyl bridge have been prepared and used as phase-transfer catalysts in the asymmetric alkylation of *N*-(diphenylmethylene)glycine esters in good yields and up to 90% ee.

The synthesis of optically active naturally occurring and synthetic α-amino acids using a simple and easily scalable procedure remains as an important synthetic challenge.[1] Of all the strategies developed, the asymmetric alkylation of glycine and alanine Schiff bases using phase-transfer-catalysis (PTC)[1p,2] is probably the most simple, economical and easy to scale up. Thus, the pioneering work of O'Donnell showed that benzyl ammonium salts derived from versatile *Cinchona* alkaloids,[3] such as the cinchonidine-derived **1**, were useful catalysts in the asymmetric alkylation of glycinate imines.[2,4] The results obtained with these catalysts were improved by Lygo[5] and Corey,[6] who changed the *N*-benzyl substituent to a bulkier 9-methylanthryl group as shown in catalyst **2**. In addition, Merrifield resin-bound cinchonidine and cinchonine have been employed as recoverable PTC catalysts.[7] Furthermore, non-*Cinchona* chiral catalysts, such as spiro ammonium[8] and phosphonium salts,[9] TADDOL,[10] binaphthyl-derived amines[10b,11] and salen–metal complexes[12] have also been used in asymmetric PTC alkylations.



R = H, allyl, benzyl

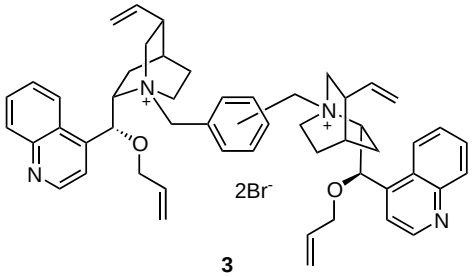
1



R = H, allyl
X = F, Cl, Br

2

Recently, dimeric[13] and trimeric[14] quaternary *Cinchona* catalysts, derived from *o*-, *m*- or *p*-xylene dibromide **3**, and mesitylene tribromide **4**, respectively, have been employed as chiral PTC catalysts achieving good enantioselectivities. In this context, we envisaged that good results could be obtained with this type of *Cinchona*-derived ammonium salts if a bulkier 9,10-dimethylanthryl group was employed as a bridge between the alkaloid moieties, in analogy to Lygo's and Corey's improvements relative to the monomeric catalysts.



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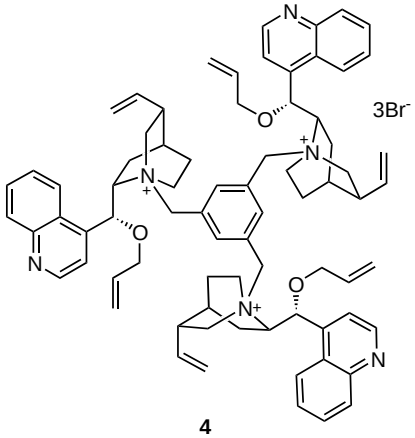

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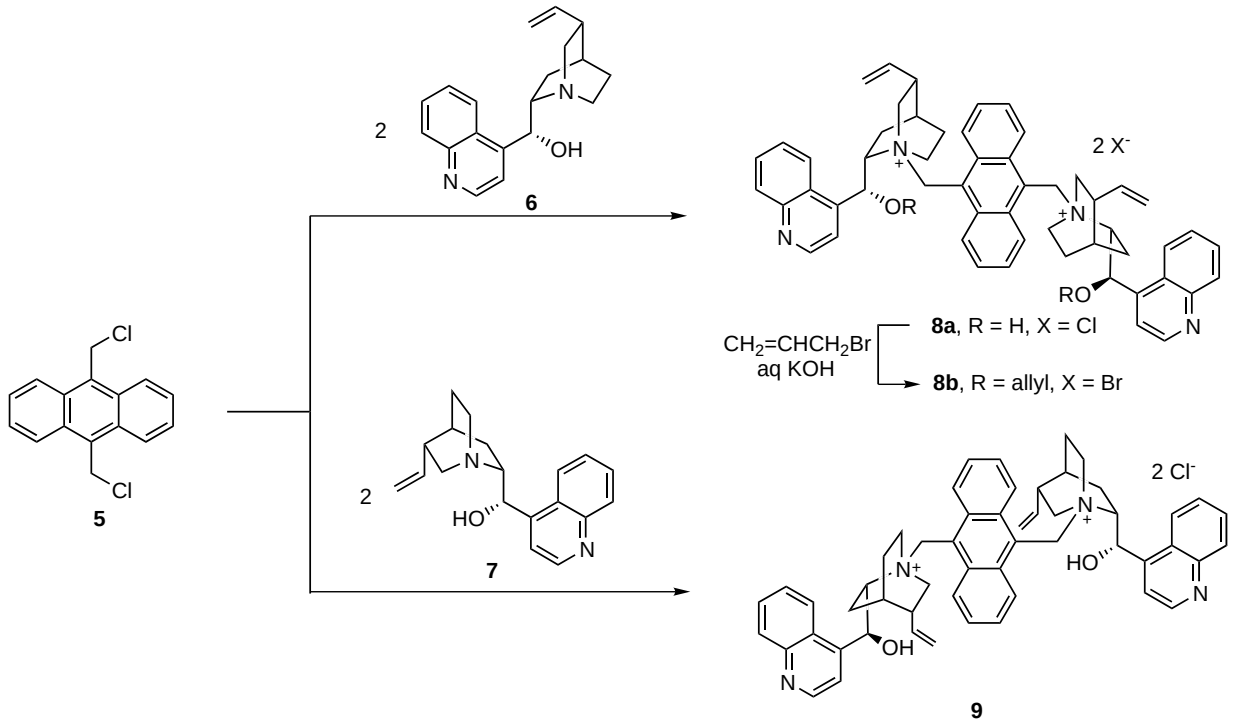
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00211-2

Thus, dimeric cinchonidine-derived ammonium salt **8a**[15] was prepared in 85% yield by reaction of 9,10-di(chloromethyl)anthracene[16] **5** with cinchonidine **6** (2 equiv.) in EtOH/DMF/$CHCl_3$ at 100°C[17] (Scheme 1). *O*(9)-Allylation of **8a** with allyl bromide in 50% aqueous KOH afforded the allylated ammonium salt **8b**[18] in 95% yield. In addition, cinchonine-derived catalyst **9**[19] was prepared in 80% yield following the same methodology as for **8a** but starting from cinchonine **7** (Scheme 1).

A PM3-optimized geometry[20] for the dication of **8a** (Fig. 1) shows the blocking of the anthryl group of one of the faces of the tetrahedron formed by the ammonium ion, whereas the other two faces are blocked by the OH group and the quinuclidine system, respectively. Therefore, only one of the faces is free for coordination with the formed glycine enolate.

These dimeric cinchonidine-derived ammonium salts **8** and **9** were employed as catalysts in the alkylation reaction of glycine-derived *N*-(diphenylmethylene)-glycine alkyl esters **10** with different halides in a biphasic system formed from a mixture of toluene/$CHCl_3$ and 50% aqueous KOH solution (Table 1). The ees of the alkylated products **11** were measured by chiral GLC analysis[21] of the corresponding *N*-trifluoroacetamide esters.[22] The absolute configuration was assigned by the relative retention times of both enantiomers determined previously.[7b]



Scheme 1. Preparation of dimeric *Cinchona* quats.

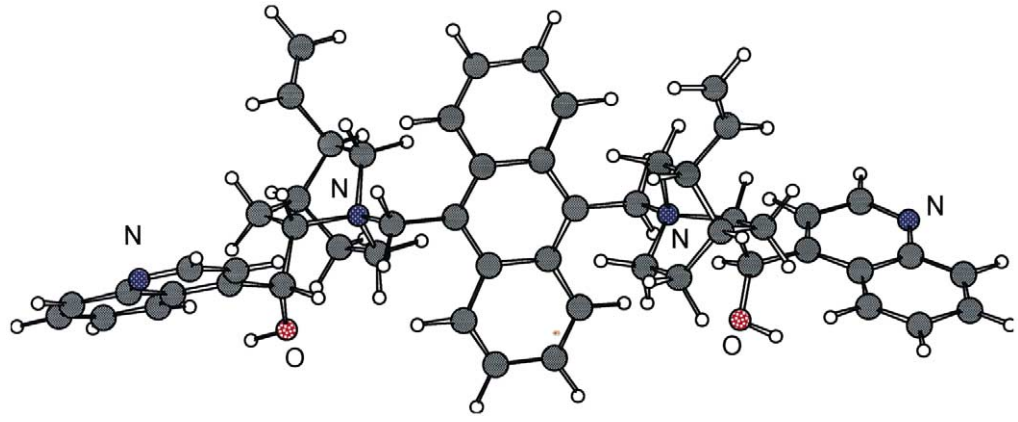
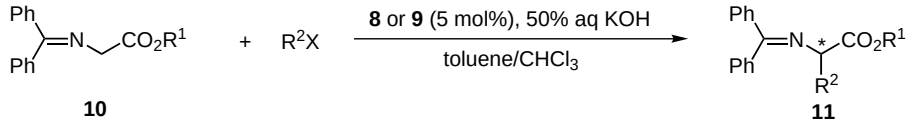


Figure 1. PM3-optimized geometry for the dication of **8a**.

Table 1. Enantioselective PTC alkylations



Entry	R^1	R^2X	Catalyst	Temp. (°C)	Time (h)	Yield (%)[a]	Ee (%)[b]	Abs. Config.[b]
1	*t*Bu	$PhCH_2Br$	**8a**	25	3	95	75	(*S*)
2	*t*Bu	$PhCH_2Br$	**8a**	0	6	88	86	(*S*)
3	*t*Bu	$PhCH_2Br$	**8a**	−20	12	75	86	(*S*)
4	*t*Bu	$PhCH_2Br$	**8a**	−30	24	65	86	(*S*)
5	*i*Pr	$PhCH_2Br$	**8a**	−20	9	95	89	(*S*)
6	*t*Bu	$PhCH_2Br$	**8b**	25	0.5	98	60	(*S*)
7	*t*Bu	$PhCH_2Br$	**8b**	0	1	84	70	(*S*)
8	*t*Bu	$PhCH_2Br$	**8b**	−20	1	72	80	(*S*)
9	*t*Bu	$PhCH_2Br$	**8b**	−50	6	98	86	(*S*)
10	*i*Pr	$PhCH_2Br$	**8b**	−20	3	95	80	(*S*)
11	*t*Bu	$PhCH_2Br$	**9**	25	1	90	73	(*R*)
12	*t*Bu	$PhCH_2Br$	**9**	−20	7	85	86	(*R*)
13	*t*Bu	2-NaphCH_2Br	**8a**	−20	15	76	86	(*S*)
14	*t*Bu	2-NaphCH_2Br	**8b**	−20	2	98	78	(*S*)
15	*t*Bu	4-$CNC_6H_4CH_2Br$	**8a**	−20	18	90	90	(*S*)
16	*t*Bu	4-$CNC_6H_4CH_2Br$	**8b**	−20	2	97	85	(*S*)
17	*t*Bu	4-$CNC_6H_4CH_2Br$	**9**	−20	9	90	84	(*R*)
18	*t*Bu	$CH_2{=}CHCH_2Br$	**8a**	−20	10	60	68	(*S*)
19	*t*Bu	$CH_2{=}CHCH_2Br$	**8b**	−20	2	70	42	(*S*)
20	*t*Bu	$CH{\equiv}CCH_2Br$	**8a**	−20	11	76	70	(*S*)
21	*t*Bu	$CH{\equiv}CCH_2Br$	**8b**	−20	2	67	62	(*S*)
22	*t*Bu	$CH_3CH_2CH_2CH_2I$	**8a**	−20	–	–	–	
23	*t*Bu	$CH_3CH_2CH_2CH_2I$	**8b**	−20	11	65	32	(*S*)

[a] Isolated crude yield determined by ^1H NMR (300 MHz).
[b] Determined by chiral GLC (Ref. 21).

The alkylation reaction of commercially available glycine-derived ester **10** ($R^1 = t$Bu) with benzyl bromide as electrophile was used as a test reaction. Thus, when the cinchonidine-derived **8a** was employed under PTC conditions, the reaction showed an ee of the alkylated product (*S*)-**11** higher when the reaction was performed at 0°C (86%) than when the reaction was performed at rt (75%) (Table 1, entries 1 and 2). However, no influence on the ee was observed when the reaction temperature was lowered at −20 or −30°C (Table 1, entries 3 and 4). In contrast, when allylated cinchonidine derivative **8b** was employed as catalyst, the influence of the temperature was more remarkable and the ee of (*S*)-**11** was notably higher at −20°C (80%) than at rt (60%) or 0°C (70%) (Table 1, entries 6–8), lowering the temperature to −50°C being necessary to match the ee achieved using **8a** at −20°C (86%) (Table 1, entry 9). In addition, the reaction times using **8b** were considerably lower than when **8a** was employed. Interestingly, when the non-commercial isopropyl ester **10** ($R^1 = i$Pr) was used as starting material,[23] the enantioselectivity of (*S*)-**11** was slightly higher or similar than when using the *tert*-butyl derivative **10** ($R^1 = t$Bu), both employing **8a** or **8b** (Table 1, entries 5 and 10). When the cinchonine-derived ammonium salt **9** was used as PTC catalyst, the enantiomeric alkylated product (*R*)-**11** was obtained with ees almost identical to when the *pseudoenantiomeric* cinchonidine-derived ammonium salt **8a** was used (Table 1, compare entries 11 and 12 with entries 1 and 3).

When other benzylic, allylic and propargylic bromides were employed as electrophiles using **10** ($R^1 = t$Bu) as starting material and a reaction temperature of −20°C, a similar tendency of higher reactivity and lower enantioselectivity of **8b** compared to **8a** was observed. Thus, using 4-bromomethylbenzonitrile as electrophile, a 90% ee for (*S*)-**11** in 18 h using **8a** compared to an 85% ee in 2 h using **8b** was obtained (Table 1, entries 15 and 16). In addition, when a non-activated electrophile such as *n*-butyl iodide was used, no reaction was observed when **8a** was used as catalyst, whereas a 65% yield of the corresponding (*S*)-**11** was obtained using **8b**, although with low ee (Table 1, entries 22 and 23).

It can be concluded that dimeric anthracenyl-derived *Cinchona* quaternary ammonium salts are effective catalysts for the enantioselective alkylation of glycine esters for the synthesis of (*S*)- and (*R*)-α-amino acids.

Typical alkylation procedure

A mixture of **10** (0.5 mmol) and the catalyst **8** or **9** (0.025 mmol) in toluene/$CHCl_3$ (7/3 v/v, 2.5 mL) was cooled (see Table 1) and aqueous 50% solution of KOH (0.75 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 (3×15 mL). The organics were dried (Na_2SO_4) and evaporated in vacuo.

Acknowledgements

We thank the Ministerio de Educación y Ciencia (MEC) of Spain (DGICYT, research project PB97-0123) for financial support.

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15. Compound **8a**: mp 197°C (decomp.). $[\alpha]_D^{25}$ −579 (*c* 0.5, $CHCl_3$). IR (KBr) *v* 3396, 2947, 1643, 1585, 1468, 1063, 925, 776, 537 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.21–1.36 (2H, m), 1.71–1.91 (2H, m), 2.12–2.21 (2H, m), 2.68–2.76 (1H, m), 3.36–3.45 (1H, m), 3.54–3.68 (1H, m), 3.84–3.86 (1H, m), 4.44–4.69 (2H, m), 4.99–5.09 (2H, m), 5.68–5.78 (1H, m), 5.98–6.03 (1H, d, $J=13.4$), 6.58–6.62 (1H, d, $J=13.4$), 7.09 (1H, s), 7.46 (1H, s), 7.98–7.99 (4H, m), 8.19–8.22 (1H, d, $J=7.3$), 8.69–8.71 (1H, d, $J=8.5$), 8.95–8.98 (1H, d, $J=8.5$) 9.08–9.10 (1H, d, $J=4.9$), 9.15–9.18 (1H, d, $J=8.5$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.6, 24.6, 25.4, 37.2, 51.3, 54.3, 60.4, 64.9, 67.8, 116.4, 120.4, 124.3, 124.6, 126.0, 126.9, 126.9, 127.2, 129.5, 129.8, 133.0, 133.0, 138.6, 145.8, 147.7, 150.3. MS (ESI) 828 $[M-Cl]^+$.
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18. Compound **8b**: mp 156°C. $[\alpha]_D^{25}$ −282 (*c* 1, $CHCl_3$). IR (KBr) *v* 3402, 3073, 2936, 1589, 1515, 1450, 1066, 924, 765 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.43–1.47 (1H, m), 1.95 (1H, m), 2.07 (1H, m), 2.21 (1H, m), 2.36 (1H, m), 2.81 (1H, m), 3.56 (2H, m), 3.72–3.80 (1H, m), 3.89–3.99 (3H, m), 4.27–4.30 (2H, m), 4.47–4.63 (2H, m), 4.99–5.07 (1H, m), 5.14–5.31 (1H, m), 5.41–5.53 (1H, m), 5.64–5.82 (1H, m), 5.88–6.10 (1H, m), 6.23–6.36 (1H, m), 6.57–6.62 (1H, d, $J=13.4$), 7.08 (1H, s), 7.68–7.69 (1H, m), 7.76–7.97 (3H, m), 8.14–8.24 (1H, m), 8.66 (1H, m), 9.02–9.03 (1H, d, $J=4.9$), 9.12 (1H, d, $J=3.7$), 9.23–9.25 (1H, d, $J=7.3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.5, 24.5, 25.6, 36.8, 51.5, 54.5, 60.1, 67.5, 69.2, 71.9, 116.5, 117.3, 119.6, 123.4, 124.6, 125.4, 126.1, 127.2, 129.8, 129.9, 132.9, 133.2, 134.0, 137.8, 138.4, 140.9, 141.2, 148.0, 148.1, 150.2. MS (ESI) 952 $[M-Br]^+$.
19. Compound **9**: mp 194°C (decomp.). $[\alpha]_D^{25}$ +400 (*c* 0.5, $CHCl_3$). IR (KBr) *v* 3389, 3187, 2946, 1636, 1589, 1454, 1060, 931, 780, 541 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.66 (2H, m), 1.75 (2H, m), 2.26–2.34 (1H, m), 2.76–2.84 (1H, m), 3.19–3.21 (1H, d, $J=6.1$), 3.45–3.61 (1H, m), 4.02–4.19 (2H, m), 4.38 (1H, m), 4.51 (1H, m), 5.05–5.10 (1H, m), 5.16–5.19 (1H, d, $J=9.8$), 5.89–6.01 (1H, m), 6.07–6.11 (1H, d, $J=13.4$), 6.39–6.44 (1H, d, $J=13.4$), 7.00 (1H, s), 7.61 (1H, s), 7.90–7.99 (4H, m) 8.18–8.22 (1H, d, $J=8.5$), 8.74–8.77 (1H, d, $J=7.3$), 8.85 (1H, m), 9.08–9.10 (1H, d, $J=4.9$), 9.15 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.8, 24.5, 26.8, 37.7, 54.7, 55.8, 57.7, 66.9, 68.1, 117.6, 121.4, 125.4, 125.7, 127.7, 127.8, 128.1, 128.3, 130.6, 130.8, 133.9, 134.2, 139.0, 146.6, 148.8, 151.3. MS (ESI) 828 $[M-Cl]^+$.
20. Performed using the PC GAMESS version (Granovsky, A. A. http://classic.chem.msu.su/gran/gamess/index.html) of the GAMESS (US) QC package: Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
21. 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.
22. Obtained after HCl(g)/Et_2O hydrolysis of the imine and further reaction with trifluoroacetic anhydride: Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363–2380.
23. Prepared in 80% overall yield by reaction of glycine with thionyl chloride in the presence of isopropanol: Patel, R.; Price, S. *J. Org. Chem.* **1965**, *30*, 3575–3576; followed by treatment of the crude with benzophenone imine: O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666.