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Cinchona alkaloid phase-transfer catalysts revisited: influence of substituted aryl groups on the enantioselectivity of glycine ester enolate alkylation

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Abstract—We report herein, the influence of substituted aryl groups in quaternary ammonium salts derived from cinchona alkaloids on enantioselectivity of the alkylation of glycine ester enolates.
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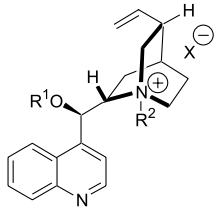
1. Introduction

Asymmetric synthesis using phase-transfer catalysts (PTCs) represent one of the important methodologies in organic chemistry. Since, the pioneering work by Dolling et al.[1] chiral PTCs derived from cinchona alkaloids have been applied to various organic reactions.[2]

In 1989, O'Donnell's group reported the enantioselective PTC alkylations of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**8**) for the synthesis of α-amino acids in enantiomerically pure form using catalyst **1a** derived from cinchonidine.[3] The enantioselective catalytic activity was improved by Lygo and Corey using third generation versions of these catalysts containing an *N*-9-anthracenylmethyl group either with a free OH (**1b**) or with an *O*-allyl group (**1c**), respectively.[4]

When the nitrogen on the bicyclic ring of the cinchona alkaloids are quaternized by the addition of the bulky and rigid anthracenylmethyl group, it seems to give the highest rigidity and steric effect to the catalyst's framework and leads to highly enantioselective alkylations as compared to a benzyl group. Jew et al. found that an *ortho* fluoro substituent on the benzyl group in the quaternary ammonium salt dramatically increased the enantioselectivity in the alkylation of a glycine anion equivalent which was attributed to the electronic effect.[5] They also explored the combination of electronic and steric factor by way of *ortho*-fluoro-dimeric cinchona-derived PTCs.[6] Dimers and trimers of cinchona alkaloids have also been reported by other workers.[7]



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a) R^1 = H, R^2 = benzyl, X= Cl. b) R^1 = H, R^2 = anthracenylmethyl, X= Cl.
c) R^1 = allyl, R^2 = anthracenylmethyl, X= Br. d) R^1 = R^2 = 2-methylnaphthyl, X = Br.

2. Results and discussion

We designed new catalysts having diaryl substitution at the 3- and 4-positions of the *N*-benzyl group in cinchonidinium salts to check how substituted aryl groups affect the asymmetric induction in the benzylation reaction as compared to those having flat linear aryl systems like naphthylmethyl and anthracenylmethyl groups.

For the preparation of new cinchona-derived quaternary ammonium salts, the corresponding 2-, 3- and 4-(bromomethyl)phenyl(diaryl)methanols were prepared, starting from *o*-, *m*- and *p*-toluic acid methyl esters (Scheme 1).

Keywords: Cinchona alkaloids; Phase-transfer catalysts; Asymmetric alkylations.
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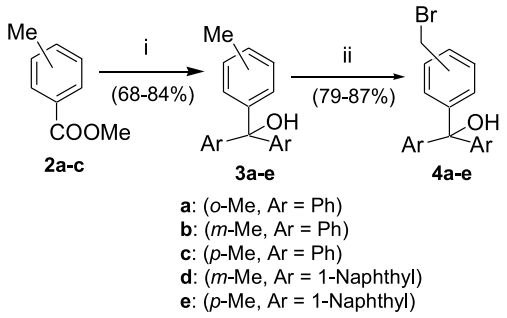
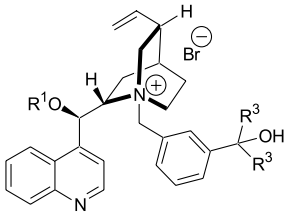


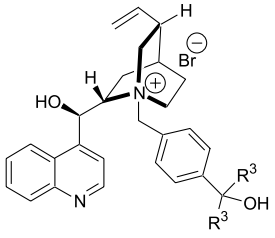
Scheme 1. Reagents: (i) ArBr, Mg, THF; (ii) NBS, CCl_4.

2-, 3- and 4-(Bromomethyl)phenyl(diaryl)methanols thus, prepared were used for quaternization of cinchona alkaloids. This reaction was done in a mixture of acetonitrile and toluene (80:20) at 80 °C. While *meta*- and *para*-(bromomethyl)phenyl(diaryl)methanols formed the quaternary salts in 80–92% yields, the *ortho*-(bromomethyl)phenyl-(diaryl)methanol failed to quaternize cinchonidine.



(**5**): **a**) R^1 = H, R^3 = Ph. **b**) R^1 = H, R^3 = 1-Naphthyl.

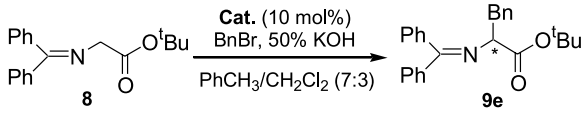
(**6**) R^1 = Allyl, R^3 = 1-Naphthyl.



(**7**): **a**) R^3 = Ph.
b) R^3 = 1-Naphthyl.

The catalysts **5–7** were evaluated in the enantioselective phase-transfer benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. The reaction was carried out in toluene/dichloromethane (7:3) at 0 °C and at −20 °C using 50% aqueous KOH as a base under argon (Table 1).

As shown in Table 1, substitution at the *meta*- and *para*-position with diphenyl moieties gave slight increases in the enantioselectivity as compared to the unsubstituted *N*-benzyl group (entries 1–3). The use of bulkier substituents, that is, di(1-naphthyl) moieties in place of di(phenyl) showed an increase in enantiomeric excess (entries 4–5). The *meta*-di(1-naphthyl) substituted catalyst **5b** gave higher enantiomeric excess as compared to the *para*-substituted counterpart **7b** (Scheme 2).



Scheme 2. Benzylation of imine **8** using various catalysts.

The catalyst **5b** was *O*(9)-allylated with allyl bromide in the presence of K_2CO_3 to give the catalyst **6** in 88% yield. The use of catalyst **6** gave high enantiomeric excess (92%) favouring the (*S*)-isomer when the reaction was carried at −20 °C.

Our results show that the quaternary ammonium salts **5–7** containing the triaryl carbinol units provide better steric screens as compared to the naphthylmethyl group (**1d**, 49%)[8] in the asymmetric benzylation of **8**. Among them, *O*(9)-allyl-*N*-[3-(hydroxy-di-naphthalen-1-yl-methyl)-benzyl]cinchonidinium bromide (**6**) seems to give the best steric screen as well as cation rigidity for the formation of close ion-pairs between the bridgehead nitrogen and the enolate of **8**. However, it is less effective than **1c** which has an anthracenylmethyl group in the quaternary ammonium salt.

Taking catalyst **6**, phase-transfer alkylation of **8** with various alkyl halides was carried out. The results obtained for the asymmetric alkylation of **8** with various alkyl halides, using the similar conditions, and at −20 °C are given in Table 2. High enantiomeric excesses up to 94% were obtained with a wide variety of alkylating agents (entries 1–10) for the asymmetric synthesis of α-amino acids (Scheme 3).

3. Conclusion

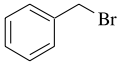
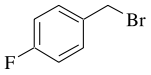
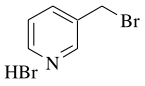
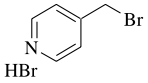
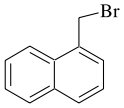
In conclusion, we studied various cinchona alkaloids quaternized by triarylcarbinol units in asymmetric PTC

Table 1. Benzylation of imine **8** using catalysts **1a** and **5–7**

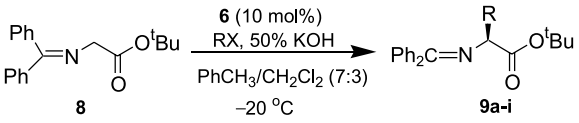
Entry	Catalyst	Time (h)	Temp (°C)	Yield[a] (%)	%ee[b] [config][c]
1	**1a**	10	0	89	66 (*S*)
2	**5a**	12	0	83	73 (*S*)
3	**7a**	18	0	74	72 (*S*)
4	**7b**	18	0	80	80 (*S*)
5	**5b**	16	0	86	84 (*S*)
6	**6**	5	0	90	90 (*S*)
7	**6**	7	−20	92	92 (*S*)

[a] Yields of isolated product.
[b] Based on HPLC analysis using Chiralcel OD-H column with hexanes/2-propanol (99.5:0.5) as eluent.
[c] The absolute configuration was determined by comparision of the HPLC retention time with that of an authentic sample, which was independently synthesized by the reported procedure.[4]

Table 2. Alkylation of imine **8** using catalyst **6**

Entry	RX[a]	Time (h)	Product	Yield[b](%)	%ee[c] [config][d]
1	CH_3CH_2I[e]	8	**9a**[7a]	68	92 (*S*)
2	$CH_3(CH_2)_4CH_2I$[e]	8	**9b**[7a]	78	94 (*S*)
3		3	**9c**[7a]	92	93 (*S*)
4		7	**9d**[7a]	90	93 (*S*)
5		6	**9e**[4b]	93	92 (*S*)
6		6	**9f**[7a]	93	91 (*S*)
7		10	**9g**	87	92 [f]
8		10	**9h**	85	91[f]
9		8	**9i**[4]	89	89 (*S*)

[a] The reaction was carried out with RX (2.0 equiv) and aqueous KOH (50%, 12 equiv) in the presence of **6** (10 mol%) in toluene/CH_2Cl_2 (7:3) at −20 °C.
[b] Yields of isolated products.
[c] Based on chiral HPLC using a Chiralcel OD-H column.
[d] The absolute configuration was determined by comparision of the HPLC retention time with that of an authentic sample, which was independently synthesized by the reported procedure.[4–7]
[e] RX (5.0 equiv) was used.
[f] Absolute configuration not determined.



Scheme 3. Alkylation of imine **8** using catalyst **6**.

reactions. *O*(9)-Allyl-*N*-[3-(hydroxy-di-naphthalen-1-yl-methyl)-benzyl]cinchonidinium bromide (**6**) proved to be the best as it gave very high ees in the alkyated products of **8**. The applications to other types of phase-transfer catalytic reactions using **6** are currently being investigated. Further, it would be interesting to synthesize and study the catalysts where R^3 aryl carbinol units can be heteroaromatic or further substituted aromatic systems.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C spectra were recorded at 300 and 75 MHz using a Bruker Advance spectrometer, respectively, with chemical shifts in ppm and tetramethylsilane as the internal standard. Infra-red absorption spectra were recorded on a Nicolet Impact 410 spectrometer; the frequencies in the IR spectra are indicated in cm^{-1}. Mass spectral data were recorded on a Finnigan-MAT LCMS spectrometer. Elemental analyses were recorded on an Elementa Vario EL. HPLC was performed on a Shimadzu SPD-10A using a chiral phase column (DAICEL Chiralcel OD and Chiralcel OD-H, 254 nm). TLC was performed on plates pre-coated (0.25 mm) with silica gel 60, Merck F-254. The plates were visualized by the use of a combination of UV (254 nm) and iodine. Column chromatography was carried out with silica gel Merck 60 (80–230 mesh).

4.2. General procedure for the synthesis of 2- or -3 or 4-methylphenyl(diphenyl)methanol

Under argon, to a suspension of magnesium turnings (5.9 g, 246 mmol) in dry tetrahydrofuran (100 mL) was added bromobenzene (26.3 mL, 249 mmol) dropwise at such a rate so as to maintain a gentle reflux over a period of 0.5 h. After stirring the reaction mixture for 1 h at rt, a solution of 2-, 3- or 4-toluic acid methyl esters (15 g, 99.8 mmol) in tetrahydrofuran (25 mL) was added dropwise and the stirring continued for 5 h at 50 °C. The reaction mixture was cooled to rt, poured onto ice and acidified with 2 N HCl. The aqueous layer was extracted with chloroform (3× 60 mL) and the combined organic layers dried over Na_2SO_4 and concentrated. Purification of the residue oil by column chromatography on silica gel (hexane/EtOAc, 95:5) gave 2- or -3 or 4-methylphenyl(diphenyl)methanols as white solids (70–84%).

4.2.1. 2-Methylphenyl(diphenyl)methanol (3a). 19.2 g, yield 70%; mp 100–101 °C; IR (KBr) ν 3468, 3058, 3027, 2929, 2863, 1598, 1509, 1445, 1328, 1153, 1007 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.77 (s, 1H), 7.09–7.33 (m, 14H); MS (APCI): *m/z* 257 (M^+-OH, 100). Anal. Calcd for C, 87.56; H, 6.61. Found C, 87.14; H, 6.78.

4.2.2. 3-Methylphenyl(diphenyl)methanol (3b). 22.5 g, yield 82%; mp 62–63 °C; IR (KBr) ν 3462, 3049, 2928, 1594, 1490, 1440, 1321, 1154, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.79 (s, 1H), 7.09–7.33 (m, 14H); MS (APCI): *m/z* 274 (M^+), 257. Anal. Calcd for C, 87.56; H, 6.61. Found C, 87.18; H, 6.71.

4.2.3. 4-Methylphenyl(diphenyl)methanol (3c). 23.1 g, yield 84%; mp 72–73 °C; IR (KBr) ν 3466, 3058, 1597, 1489, 1444, 1325, 1156, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.96 (s, 1H), 7.17–7.32 (m, 14H); MS (APCI) *m/z* 274 (M^+), 257, 197, 105. Anal. Calcd for C, 87.56; H, 6.61. Found C, 87.23; H, 6.67.

4.3. General procedure for the synthesis of 2-, 3- or 4-(bromomethyl)phenyl(diphenyll)methanol

To a solution of 3- or 4-methylphenyl(diphenyl)methanol (5.0 g, 18.2 mmol) in CCl_4 (50 mL) at 70 °C was added *N*-bromosuccinimide (3.24 g, 18.2 mmol) and benzoyl peroxide (88 mg, 0.36 mmol) in two portions. The solution was stirred under reflux for 5 h and cooled to rt, washed successively with 10% $NaHCO_3$, water and brine, dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo to afford the product as oils in 79–85% yield, which was used without purification for the next step.

4.3.1. [2-(Bromomethyl)phenyl](diphenyl)methanol (4a). 5.5 g, yield 85%; IR (neat) ν 3452, 3046, 1593, 1478, 1444, 1325, 1156, 1006 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52 (s, 2H), 5.18 (s, 1H), 7.10–7.33 (m, 14H); MS (APCI): *m/z* 337 ($M^+ - OH$), 335, 257, 255.

4.3.2. [3-(Bromomethyl)phenyl](diphenyl)methanol (4b). 5.2 g, yield 80%; IR (neat) ν 3442, 3029, 2923, 1598, 1442, 1356, 1148, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.82 (s, 1H), 4.48 (s, 2H), 7.22–7.48 (m, 14H); MS (APCI): *m/z* (%) 354 (M^+), 352 (M^+), 337, 274.

4.3.3. [4-(Bromomethyl)phenyl](diphenyl)methanol (4c). 5.1 g, yield 79%; IR (neat) ν 3432, 3059, 2923, 1598, 1445, 1409, 1386, 1228, 11545, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81 (br s, 1H), 4.52 (s, 2H), 7.24–7.48 (m, 14H); MS (APCI): *m/z* 354 (M^+), 352 (M^+), 273, 105.

4.4. General procedure for the synthesis of 3- or 4-methylphenyl-di(1-naphthyl)methanol

Under argon, to a suspension of magnesium turnings (5.9 g, 246 mmol) in dry tetrahydrofuran (100 mL) was added a solution of 1-bromonaphthalene (51.2 g, 247 mmol) in tetrahydrofuran (40 mL) slowly at such a rate so as to maintain a gentle reflux over a period of 0.5 h. After stirring the reaction mixture for 2 h at 50 °C, a solution of 3- or 4-toluic acid methyl ester (15 g, 99.8 mmol) in tetrahydrofuran (25 mL) was added drop wise and the stirring continued for 8 h at 60 °C. The reaction mixture was cooled to rt, poured onto ice and acidified with 2 N HCl. The aqueous layer was extracted with chloroform (2×100 mL) the combined organic layers dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by crystallization from toluene/hexane gave the product as white solid (68–72%).

4.4.1. 3-Methylphenyl-di(1-naphthyl)methanol (3d). 27 g, yield 72%; mp 180–183 °C decomp.; IR (KBr) ν 3550, 3043, 2922, 1599, 1505, 1395, 1341, 1222, 1148, 1050, 1011 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.60 (s, 1H), 6.84 (d, J=7.1 Hz, 2H), 7.09–7.24 (m, 8H), 7.38 (t, J=7.3 Hz, 2H), 7.77 (d, J=8.1 Hz, 2H), 7.84 (d, J=8.1 Hz, 2H), 8.25 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.7, 85.2, 124.3, 125.1, 125.3, 125.5, 127.8, 127.9, 128.3, 128.6, 128.8, 129.1, 131.4, 135.1, 137.6, 142.2, 146.8; MS (APCI): *m/z* (%) 357 ($M^+ - OH$, 100). Anal. Calcd for C, 89.81; H, 5.92. Found C, 89.67; H, 5.98.

4.4.2. 4-Methylphenyl-di(1-naphthyl)methanol (3e). 25.4 g, yield 68%; mp 188–190 °C decomp.; IR (KBr) ν 3546, 3041, 2916, 1599, 1506, 1395, 1342, 1311, 1183, 1154, 998 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.57 (s, 1H), 6.85 (d, J=7.1 Hz, 2H), 7.11–7.26 (m, 8H), 7.37 (t, J=7.1 Hz, 2H), 7.77 (d, J=8.0 Hz, 2H), 7.83 (d, J=8.0 Hz, 2H), 8.26 (d, J=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.4, 84.5, 123.6, 124.6, 124.8, 125.7, 126.8, 127.1, 127.6, 128.0, 128.1, 128.5, 129.6, 130.7, 134.4, 136.0, 141.6, 143.3; MS (APCI): *m/z* (%) 357 ($M^+ - OH$, 100). Anal. Calcd for C, 89.81; H, 5.92. Found C, 89.59; H, 6.01.

4.5. General procedure for the synthesis of 3- and 4-bromomethylphenyl-di(1-naphthyl)methanol

The procedure discussed in Section 4.3 was followed.

4.5.1. [3-(Bromomethyl)phenyl][di(1-naphthyl)]methanol (4d). 4.9 g, yield 82%; mp 159–163 °C decomp.; IR (KBr) ν 3541, 3046, 1598, 1507, 1359, 1342, 1216, 1149, 1008 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 (s, 1H), 4.4 (s, 2H), 6.83 (d, J=7.1 Hz, 2H), 7.19–7.41 (m, 10H), 7.79 (d, J=7.9 Hz, 2H), 7.84 (d, J=8.0 Hz, 2H), 8.2 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 34.2, 85.6, 122.4, 125.8, 125.9, 126.0, 126.1, 128.4, 128.5, 128.7, 128.8, 128.9, 129.1, 129.2 (2C), 129.3, 129.8, 131.6, 135.5, 138.1, 142.2, 148.0; MS (APCI): *m/z* (%) 437 ($M^+ - OH$, 74), 435 (74), 390 (40), 357 (100).

4.5.2. 4-Bromomethylphenyl-di(1-naphthyl)methanol (4e). 5.3 g, yield 87%; mp 168 °C decomp.; IR (neat) ν 3542, 3040, 2922, 2863, 1504, 1498, 1340, 1229, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 1H), 4.41 (s, 2H), 6.82 (d, J=7.1 Hz, 2H), 7.15–7.26 (m, 8H), 7.39 (t, J=7.1 Hz, 2H), 7.76 (d, J=8.0 Hz, 2H), 7.83 (d, J=8.0 Hz, 2H), 8.23 (d, J=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.5, 85.6, 124.1, 124.7, 125.7, 125., 125.9, 126.0 (2C), 128.6, 128.7, 128.7, 128.8, 128.9, 129.2, 129.3, 129.5, 129.7, 131.6, 135.5, 137.0, 142.1, 147.6; MS (APCI): *m/z* (%) 437 ($M^+ - OH$, 74), 435 (100), 391 (35), 357 (25).

4.6. General procedure for the synthesis of quaternary ammonium salts from cinchona alkaloids

A suspension of cinchonidine (1.0 g, 3.39 mmol) and 3- or 4-(bromomethyl)phenyl][di(aryl)]methanol (3.73 mmol) in acetonitrile/toluene (50:50, 20 mL) was stirred at 80 °C under argon for 6 h. The reaction mixture was cooled to rt, the solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, MeOH/$CHCl_3$ 5:95) to afford the products [**7a–b**, **9a–b**] as crystalline solids (80–92%).

4.6.1. *N*-[3-(Hydroxy-diphenyl-methyl)-benzyl]cinchonidinium bromide (5a). Yield 88%; mp 209–210 °C decomp.; $[\alpha]_D^{30}$ −71.24 (*c* 0.52, MeOH); IR (KBr) *ν* 3424, 3173, 3061, 2955, 1614, 1454, 1294, 1158, 1146, 1034, 1016, 928 cm^{-1}; ^1H NMR ($CDCl_3$+ CD_3OD) *δ* 1.28–1.31 (m, 1H), 1.73 (m, 1H), 2.00–2.22 (m, 3H), 2.56 (br s, 1H), 3.14–3.25 (m, 1H), 3.47–3.51 (m, 1H), 3.86 (t, *J*=8.5 Hz, 1H), 4.52 (m, 1H), 4.98 (d, *J*=10.4 Hz, 1H), 5.05 (d, *J*=4.4 Hz, 1H), 5.09 (d, *J*=9.9 Hz, 1H), 5.45–5.56 (m, 2H), 6.59 (s, 1H), 7.18–7.33 (m, 14H), 7.56–7.65 (m, 2H), 7.69 (d, *J*=7.4 Hz, 1H), 7.75 (s, 1H), 7.82 (d, *J*=4.5 Hz, 1H), 8.02 (d, *J*=7.6 Hz, 1H), 8.08 (d, *J*=7.3 Hz, 1H), 8.82 (d, *J*=4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD) *δ* 21.3, 24.5, 26.2, 37.5, 50.9, 60.4, 63.6, 64.3, 67.9, 81.0, 117.2, 119.7, 122.6, 124.2, 126.3, 126.9, 127.6, 127.6, 128.2, 129.0, 129.5, 130.1, 132.0, 132.8, 136.2, 145.4, 146.4, 146.9, 148.4, 149.2; MS (APCI): *m/z* (%) 568 (M^+−Br, 32), 567 (100), 549 (29). Anal. Calcd for $C_{39}H_{39}BrN_2O_2$: C, 72.33; H, 6.07; N, 4.33. Found: C, 71.57; H, 6.14; N, 4.26.

4.6.2. *N*-[4-(Hydroxy-diphenyl-methyl)-benzyl]cinchonidinium bromide (7a). Yield 92%; mp 205–206 °C decomp.; $[\alpha]_D^{30}$ −75.5 (*c* 0.56, MeOH); IR (KBr) *ν* 3194, 1592, 1508, 1446, 1422, 1381, 1321, 1281, 1183, 1159, 1110, 1018, 938 cm^{-1}; ^1H NMR ($CDCl_3$+ CD_3OD) *δ* 1.40 (t, *J*=11.3 Hz, 1H), 1.88 (m, 1H), 2.06 (s, 1H), 2.14–2.29 (m, 2H), 2.27 (br s, 1H), 3.30 (s, 1H), 3.62–3.70 (m, 1H), 3.98 (t, *J*=8.9 Hz, 1H), 4.43 (m, 1H), 4.97 (d, *J*=10.4 Hz, 1H), 4.99 (d, *J*=12.2 Hz, 1H), 5.12 (d, *J*=12.4 Hz, 1H), 5.17 (d, *J*=7.5 Hz, 1H), 5.48 (s, 1H), 5.61–5.72 (m, 1H), 6.65 (s, 1H), 7.25–7.34 (m, 12H), 7.50 (d, *J*=8.2 Hz, 2H), 7.67 (d, *J*=8.2 Hz, 2H), 7.80 (t, *J*=7.7 Hz, 1H), 7.88 (t, *J*=7.8 Hz, 1H), 7.99 (d, *J*=4.5 Hz, 1H), 8.13 (d, *J*=8.2 Hz, 1H), 8.28 (d, *J*=8.3 Hz, 1H), 8.96 (d, *J*=4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$+ CD_3OD) *δ* 22.5, 25.9, 28.0, 39.1, 52.8, 54.8, 62.1, 64.8, 66.4, 69.4, 82.6, 117.5, 121.4, 124.2, 126.2, 127.2, 128.3, 128.9, 129.3, 129.4, 129.8, 130.0, 131.7, 134.2, 138.7, 148.1, 148.4, 148.5, 150.5, 151.1; MS (APCI): *m/z* (%) 568 (M^+−Br, 20), 567 (48), 549 (100). Anal. Calcd for $C_{39}H_{39}BrN_2O_2$: C, 72.33; H, 6.07; N, 4.33. Found: C, 71.80; H, 6.23; N, 4.09.

4.6.3. *N*-[3-(Hydroxy-di-naphthalen-1-yl-methyl)-benzyl]cinchonidinium bromide (5b). Yield 80%; mp 188–190 °C decomp.; $[\alpha]_D^{30}$ −59.43 (*c* 0.85, MeOH); IR (KBr) *ν* 3215, 3047, 2944, 1597, 1508, 1454, 1391, 1336, 1314, 1232, 1164, 1038, 928 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.82–0.87 (m, 1H), 1.37 (m, 1H), 1.64 (br s, 1H), 1.89–2.02 (m, 3H), 2.92 (br s, 1H), 3.85 (m, 1H), 4.22 (m, 1H), 5.11–5.24 (m, 3H), 5.79 (m, 1H), 6.52 (m, 2H), 6.49 (m, 2H), 7.20–7.35 (m, 15H), 7.70–7.81 (m, 8H), 8.04 (m, 1H), 8.27 (m, 1H), 8.61 (d, *J*=4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 21.5, 24.7, 26.3, 29.6, 50.6, 60.5, 63.6, 68.8, 84.9, 117.5, 120.1, 124.2, 124.5 (2C), 125.4, 126.4, 127.5, 128.1, 128.3, 128.6, 129.0, 129.3, 129.5, 130.1, 131.3, 132.8, 134.9, 135.0, 136.1, 141.4, 141.6, 147.5, 148.4, 149.8; MS (APCI): *m/z* (%) 667 (M^+−Br, 20), 650 (42), 649 (100). Anal. Calcd for $C_{47}H_{43}BrN_2O_2$: C, 75.49; H, 5.80; N, 3.75. Found: C, 74.89; H, 5.92; N, 3.62.

4.6.4. *O*(9)-Allyl-*N*-[3-(hydroxy-di-naphthalen-1-yl-methyl)-benzyl]cinchonidinium bromide (6). To a suspension of **5b** (0.500 g, 0.668 mmol) and allyl bromide (0.160 g, 1.33 mmol) in CH_2Cl_2 (10 mL) was added K_2CO_3 (0.184 g, 1.33 mmol). The resulting mixture was stirred vigorously at rt for 12 h. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3×20 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 90:10) to afford **6** as yellow solid (0.463 g, 88%); mp 195–196 °C (decomp.); $[\alpha]_D^{30}$ −44.26 (*c* 0.30, MeOH); IR (KBr) *ν* 3393, 3040, 2929, 1608, 1450, 1340, 1287, 1166, 1063, 1040, 928 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 1.87–2.03 (m, 3H), 2.8 (m, 1H), 3.24 (br s, 1H), 3.72 (br s, 1H), 4.06–4.49 (m, 3H), 4.72 (m, 2H), 4.98 (m, 1H), 4.99 (d, *J*=9.8 Hz, 1H), 5.16 (d, *J*=9.7 Hz, 2H), 5.30 (d, *J*=17.3 Hz, 1H), 5.53–5.59 (m, 2H), 5.97 (m, 1H), 6.63 (m, 1H), 6.80 (m, 1H), 6.93 (d, *J*=7.05 Hz, 2H), 7.26–7.61 (m, 11H), 7.72–7.90 (m, 7H), 8.09 (d, *J*=8.4 Hz, 1H), 8.33 (m, 2H), 8.70 (m, 2H), 8.86 (d, *J*=4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 22.4, 25.1, 26.6, 37.6, 50.2, 59.4, 62.2, 65.6, 70.1, 85.0, 118.3, 119.0, 119.6, 124.5, 124.6, 125.2, 125.3, 126.3, 128.3, 128.4, 128.7, 129.1, 129.7, 129.9, 130.2, 130.8, 131.2, 132.2, 133.4, 135.0, 135.9, 139.8, 141.6, 148.3, 149.2; MS (APCI): *m/z* (%) 707 (M^+−Br, 100). Anal. Calcd for $C_{50}H_{47}BrN_2O_2$: C, 76.23; H, 6.01; N, 3.56. Found: C, 75.79; H, 6.24; N, 3.49.

4.6.5. Synthesis of *N*-[4-(hydroxy-di-naphthalen-1-yl-methyl)-benzyl]cinchonidinium bromide (7b). Yield 83%; mp 196–197 °C decomp.; $[\alpha]_D^{30}$ −72.92 (*c*, 0.80, MeOH); IR (KBr) *ν* 3400, 2944, 1634, 1502, 1388, 1159, 1115, 1018, 920 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 1.49 (m, 1H), 1.54 (m, 1H), 1.99–2.07 (m, 2H), 2.63 (br s, 1H), 3.08–3.34 (m, 2H), 3.63 (br s, 1H), 3.87 (m, 1H), 4.62 (m, 1H), 4.78 (d, *J*=6.8 Hz, 1H), 4.99 (d, *J*=11.8 Hz, 1H), 5.41–5.47 (m, 2H), 5.77 (d, *J*=12.2 Hz, 1H), 6.77 (s, 1H), 6.80 (t, *J*=7.9 Hz, 1H), 7.12–7.16 (m, 3H), 7.26–7.47 (m, 6H), 7.67–7.89 (m, 10H), 8.00–8.30 (m, 5H), 8.65 (s, 1H), 8.73 (d, *J*=4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) *δ* 23.9, 24.7, 26.5, 37.6, 51.1, 54.7, 62.5, 66.3, 68.3, 84.9, 117.6, 118.7, 120.1, 122.7, 123.0, 124.3, 125.3, 125.9, 127.1, 127.7, 127.8, 128.6, 128.7, 129.1, 129.2, 129.6, 131.2, 132.1, 133.6, 135.0, 136.2, 136.9, 141.6, 144.9, 147.3, 149.6; MS (APCI): *m/z* (%) 667 (M^+−Br, 25), 650 (50), 649 (100). Anal. Calcd for $C_{47}H_{43}BrN_2O_2$: C, 75.49; H, 5.80; N, 3.75. Found: C, 74.98; H, 6.04; N, 3.58.

4.7. General procedure for enantioselective catalytic alkylation of 8 under phase-transfer conditions

To a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester[9] (0.050 g, 0.17 mmol) and **6** (0.013 g, 0.017 mmol) in toluene/dichloromethane (7:3, 2 mL) was added alkyl halide (0.34 mmol). The reaction mixture was cooled to −20 °C, 50% aqueous KOH (0.25 mL) was added and the resulting mixture stirred vigorously until the starting material had been consumed (3–10 h). The suspension was diluted with diethyl ether (30 mL), washed with water (2×10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. Purification of the residue by flash chromatography (SiO_2, Hexane/EtOAc, 98:2) afforded the desired products in 68–93% yield.

4.7.1. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino] butanoate (9a).[7a] Oil, yield 68%; IR (film) *ν* 3060, 2926,

2854, 1732, 1662, 1625, 1446, 1367, 1284, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) 0.87 (t, $J=7.6$ Hz, 3H), 1.44 (s, 9H), 1.87–1.91 (m, 2H), 4.01 (dd, $J=8.0$, 5.2 Hz, 1H), 7.17 (dd, $J=4.4$, 1.6 Hz, 2H), 7.30–7.44 (m, 6H), δ 7.65 (m, 2H); MS (MALDI): m/z 324 ($M^+ +1$); R_t HPLC (Chiralcel OD, 254 nm, 1 mL/min, 95.5:0.5, hexane/2-propanol, $t_S=11.6$ min, $t_R=13.3$ min).

4.7.2. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino] octanoate (9b).[4b] Oil, yield 78%; IR (film) ν 2954, 2856, 1735, 1627, 1456, 1448, 1391, 1365, 1249, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, $J=6.8$ Hz, 3H), 1.26–1.23 (m, 8H), 1.44 (s, 9H), 1.86 (m, 2H), 3.98 (t, $J=6.7$ Hz, 1H), 7.18 (dd, $J=5.1$, 2.0 Hz, 2H), 7.32–7.43 (m, 5H), 7.64–7.79 (m, 3H); MS (MALDI): m/z 380 ($M^+ +1$); R_t HPLC (Chiralcel OD, 254 nm, 1 mL/min, 95.5:0.5, hexane/2-propanol, $t_S=10.5$ min, $t_R=12.2$ min).

4.7.3. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]pent-4-enoate (9c).[7a] Oil, yield 92%; IR (film) ν 3061, 2928, 2930, 1734, 1624, 1598, 1576, 1446, 1367, 1277, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.65 (m, 2H), 4.0 (dd, $J=7.6$, 5.5 Hz, 1H), 4.99–5.09 (m, 2H), 5.72 (m, 1H), 7.17 (m, 2H), 7.30–7.47 (m, 6H), 7.64 (m, 2H); MS (MALDI): 336 [$M^+ +1$]; R_t HPLC (Chiralcel OD-H, 254 nm, 0.5 mL/min, 99.5:0.5, hexane/isopropanol, $t_S=10.5$ min, $t_R=12.0$ min).

4.7.4. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]pent-4-ynoate (9d).[7a] Oil, yield 90%; IR (film) ν 3642, 3290, 2968, 1728, 1622, 1447, 1369, 1328, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.96 (t, $J=2.4$ Hz, 1H), 2.77 (m, 2H), 4.15 (dd, $J=5.4$, 7.6 Hz, 1H), 7.23–7.48 (m, 8H), 7.63–7.67 (m, 2H); MS (MALDI): m/z 332 ($M^+ -1$); R_t HPLC (Chiralcel OD, 254 nm, 1 mL/min, 99.8:0.2, hexane/isopropanol, $t_S=18.4$ min, $t_R=21.2$ min).

4.7.5. *tert*-Butyl-*N*-(diphenylmethylene)-L-phenylalaninate (9e).[7a] Yield 93%; ^1H NMR δ ($CDCl_3$) 1.41 (s, 9H), 3.22–3.09 (m, 2H), 4.08 (dd, $J=5.0$, 9.1 Hz, 1H), 6.53–7.62 (m, 15H); R_t HPLC (Chiralcel OD-H, 254 nm, 0.5 mL/min, 99.5:0.5, hexane/isopropanol, $t_S=25.4$ min $t_R=17.5$ min).

4.7.6. *tert*-Butyl (2*S*)-3-(4-fluorophenyl)-2-[(diphenylmethylene)amino]propanoate (9f).[7a] Yield 93%; IR (neat) ν 2977, 2928, 1726, 1626, 1508, 1446, 1369, 1285, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.15 (dd, $J=13.4$, 8.6 Hz, 1H), 3.22 (dd, $J=13.4$, 4.8 Hz, 1H), 4.06 (dd, $J=8.6$, 4.8 Hz, 1H), 6.69 (d, $J=7.1$ Hz, 2H), 6.85–7.02 (m, 4H), 7.30–7.41 (m, 6H), 7.56–7.58 (m, 2H); R_t HPLC (Chiralcel OD, 254 nm, 1 mL/min, 99.5:0.5, hexane/isopropanol, $t_S=8.1$ min, $t_R=13.5$ min).

4.7.7. *tert*-Butyl 2-[(diphenylmethylene)amino]-3-pyridin-3-ylpropanoate (9g). Yield: 87%; $[\alpha]_D^{25}$ -184.32 (c 1, CH_2Cl_2); IR (neat) ν 2958, 2869, 1739, 1450, 1425, 1286, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.25 (dd, $J=5.3$, 3.3 Hz, 2H), 4.95 (dd, $J=5.9$, 3.3 Hz, 1H), 6.87 (d, $J=6.2$ Hz, 2H), 7.23 (dd, $J=4.9$, 2.8 Hz, 1H), 7.39–7.58 (m, 7H), 7.76 (d, $J=7.0$ Hz, 2H), 8.44 (s, 1H), 8.48 (d, $J=4.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9, 36.6, 67.1, 81.4, 122.9, 127.4, 128.2, 128.4, 128.6, 129.9, 130.3, 132.3, 133.8, 136.1, 137.3, 139.1, 147.6, 170.8; MS (MALDI): m/z 386 (M^+); R_t HPLC (Chiralcel OD-H, 254 nm, 0.5 mL/min, 98:2, hexane/isopropanol, $t_S=20.4$ min, $t_R=22.8$ min). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.58; H, 6.84; N, 7.18.

4.7.8. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]-3-pyridin-4-ylpropanoate (9h). Yield 85%; $[\alpha]_D^{25}$ -180.03 (c 1, CH_2Cl_2); IR (neat) ν 2941, 2856, 1736, 1456, 1253, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.24 (t, $J=6.7$ Hz, 2H), 4.97 (dd, $J=6.4$, 5.9 Hz, 1H), 6.82 (d, $J=6.8$ Hz, 1H), 7.15 (d, $J=5.7$ Hz, 2H), 7.40–7.54 (m, 7H), 7.74 (d, $J=7.2$ Hz, 2H), 8.50 (d, $J=5.5$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.9, 36.5, 65.2, 81.2, 122.3, 127.2, 128.2, 128.2, 129.9, 130.8, 132.2, 133.8, 135.9, 137.2, 139.1, 148.6, 170.7; MS (MALDI): m/z 386 (M^+); R_t HPLC (Chiralcel OD-H, 254 nm, 0.5 mL/min, 98:2, hexane/isopropanol, $t_R=44.6$ min, $t_S=48.8$ min). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.54; H, 6.86; N, 7.16.

4.7.9. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]-3-(1-naphthyl)propanoate (9i).[4] Yield 89%; IR (film) ν 3054, 2975, 1730, 1622, 1576, 1446, 1367, 1287, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 3.56 (dd, $J=12.9$, 8.2 Hz, 1H), 3.86 (dd, $J=12.9$, 3.8 Hz, 1H), 4.30 (dd, $J=8.2$, 3.8 Hz, 1H), 6.68 (br s, 2H), 6.96 (t, $J=7.5$ Hz, 2H), 7.12–7.34 (m, 8H), 7.39 (ddd, $J=8.7$, 6.9, 1.2 Hz, 1H), 7.50–7.72 (m, 4H); R_t HPLC (Chiralcel OD, 254 nm, 1 mL/min, 95.5:0.5, hexane/2-propanol, $t_S=24.3$ min, $t_R=21.6$ min).

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