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Studies on the enantioselective synthesis of α-amino acids via asymmetric phase-transfer catalysis

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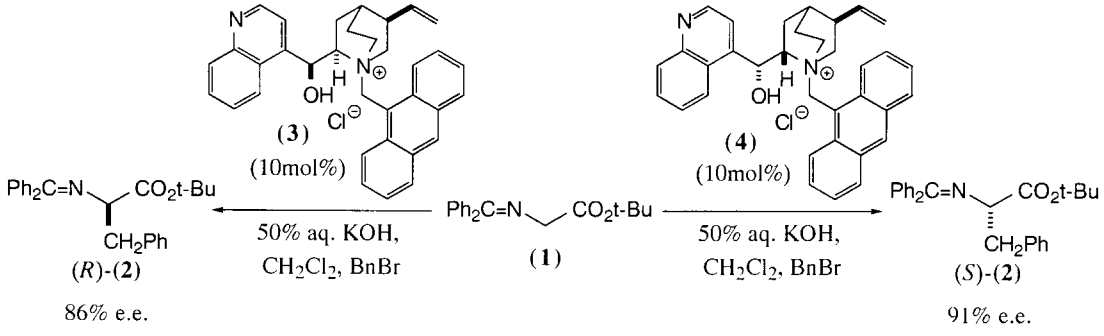
Abstract—In this paper, we describe investigations into the use of *cinchona* alkaloid-derived quaternary ammonium phase-transfer catalysts for the asymmetric alkylation of a benzophenone-derived glycine-imine. Utility of this process is demonstrated by the enantioselective synthesis of a range of α-amino acid esters.

In the preceding paper, we presented details of a study that helped identify *N*-anthracenylmethylcinchonium chloride **3** and *N*-anthracenylmethylcinchonidinium chloride **4** as highly effective 'pre-catalysts' for the asymmetric *C*-benzylation of glycine imine **1** (Scheme 1). In this paper, we report investigations into the utility of these catalysts in the synthesis of α-amino acid esters.[1–4]

One of the initial aims of this work was to develop methodology that was as environmentally benign as possible, and so we briefly investigated the possibility of using organic solvents other than dichloromethane (Table 1). It was found that the asymmetric alkylation could be carried out using both toluene and *tert*-butylmethyl ether, and in both cases the level of enantioselectivity improved slightly (Table 1). Successful reaction was also possible using diethyl ether, however in this case selectivity diminished slightly.

Overall the variation of enantioselectivity with solvent type was only marginally greater than the error levels in our e.e. assay, and so it is likely that any one of these solvents could be used successfully. For the purpose of this study we chose to use toluene since it is somewhat more environmentally acceptable than dichloromethane, and is less volatile than both *tert*-butylmethyl ether and diethyl ether. Toluene also offered the added advantage that it allowed straightforward recovery of the catalyst, which could be removed from the reaction mixture simply by filtering through a short column of magnesium sulfate. If required, the catalyst could then be recovered by washing the magnesium sulfate column with a more polar solvent such as chloroform.



Scheme 1.

Keywords: α-amino acid; enantioselectivity; alkylation; phase-transfer; asymmetric catalysis.
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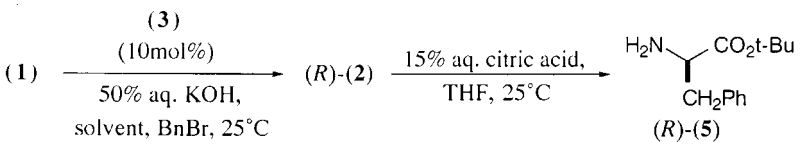
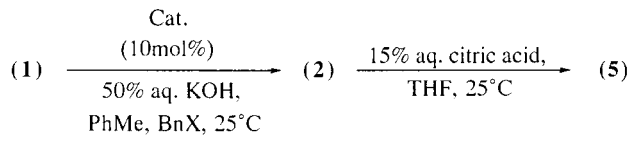
Table 1.



Solvent	% e.e. (**2**)	% Yield (**5**)
CH_2Cl_2	86	73
PhMe	89	63
t-BuOMe	88	67
Et_2O	83	71

Table 2.



X	Cat	Time (h)	% e.e. (**2**)	% Yield (**5**)
Cl	4	18	–	0
Br	3	18	89 (*R*)	63
Br	4	18	91 (*S*)	68
I	4	3	89 (*S*)	77

We next study the effect of efficiency of mixing on the rate and enantioselectivity of the alkylation reaction. It was found that enantioselectivity was not influenced by this, however the rate of reaction was, so for all subsequent studies described in this paper we chose to perform the reactions in conventional round-bottom flasks using magnetic stirring at ca. 1000 rpm. This reaction set-up was chosen since it does not involve any specialised equipment and so should be reproducible in most chemical laboratories.

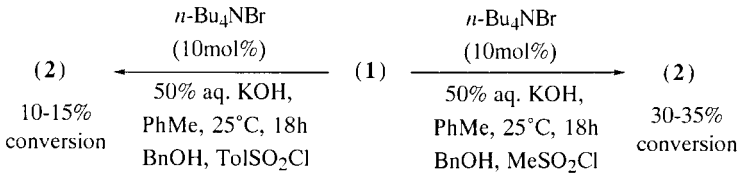
With suitable reaction conditions established, we sought to establish the range of electrophiles that were compatible with the asymmetric alkylation process. Initially variation in the nature of the leaving group was investigated (Table 2).

It was found that imine **1** underwent successful alkylation with both benzyl bromide and benzyl iodide, however no reaction was obtained with the chloride. The iodide led to significantly faster reaction than the bromide, but both resulted in similar levels of enantioselectivity. We also investigated the possibility of using sulfonates derived from benzyl alcohol in this reaction. Toluenesulfonates and methanesulfonates of this type have been reported to be relatively unstable to isolation, but can be generated under phase-transfer catalysed conditions.[5] This offered the interesting possibility of generating the electrophile in situ from benzyl alcohol (Scheme 2). Thus we attempted direct alkylation of the imine **1** via reaction with a mixture of benzyl alcohol and either methanesulfonyl chloride or toluenesulfonyl chloride.

Unfortunately, although we were able to establish that both the methanesulfonate and toluenesulfonate derivatives of benzyl alcohol were rapidly generated under the reaction conditions, the subsequent alkylation was too slow to be synthetically useful.

These results would seem to suggest that moderately reactive alkylating agents are required for efficient alkylation of imine **1**. In order to probe this further we examined a series of alkyl halides of varying structure and reactivity (Table 3). In all cases pre-catalysts **3** and **4** were utilised, since rapid *O*-alkylation of these materials occurs under the alkylation condition. This means that a different catalyst is generated in each case, however was anticipated that this variation in the structure of the active catalysts would not be a problem since we had already demonstrated that the nature of the *O*-alkyl substituent appears to have relatively little effect on enantioselectivity.[6]

As expected, activated alkyl halides such as 2-bromomethylnaphthylene and allyl bromides readily participate in the reaction giving enantioselectivities similar to those observed using benzyl bromide. Simple alkyl iodides such as methyl iodide and *n*-butyl iodide also react giving high levels of enantioselectivity, although isolated yields of the resulting amino acid esters are lower than with most other electrophiles studies. In the case of methylation this appears to be at least in part due to the polar nature of alanine



Scheme 2.

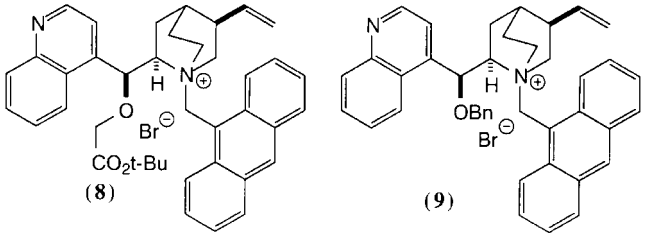
Table 3.

(1) —Cat. (10mol%), 50% aq. KOH→ (6) —15% aq. citric acid, THF, 25°C→ (7)

R–X	Cat	Product	Time (h)	% e.e.[a]	% Yield (7)[b]
CH_2=$CHCH_2Br$	**3**	(*R*)-**6a**	18	88	62
	4	(*S*)-**6a**	18	88	76
CH_2=$C(CH_3)CH_2Br$	**4**	(*S*)-**6b**	18	84[c]	61
CH_3I	**3**	(*R*)-**6c**	3	86	40
	4	(*S*)-**6c**	3	89	41
$CH_3(CH_2)_3I$	**3**	(*R*)-**6d**	18	87	56
	4	(*S*)-**6d**	18	88	42
(2-Naphthyl)CH_2Br	**3**	(*R*)-**6e**	18	82[c]	86
	4	(*S*)-**6e**	18	86[c]	75
t-BuO_2CCH_2Br	**3**	(*R*)-**6f**	18	63[c]	77
	4	(*S*)-**6f**	18	68[c]	67
t-BuO_2CCH_2I	**3**	(*R*)-**6f**	4	67[c]	83
	4	(*S*)-**6f**	4	72[c]	84
$PhCOCH_2Br$	**4**	–	3	–	<30%

[a] Determined by HPLC analysis of crude imine **6** unless otherwise noted.
[b] Overall yield after purification amino ester **7**.
[c] Determined by HPLC analysis of corresponding *N*-benzoyl derivative.

tert-butyl ester, which leads low recovery from the hydrolysis and subsequent chromatographic purification.

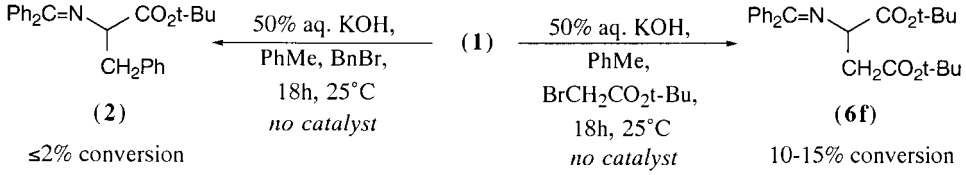


More polar alkylating agents such as *tert*-butyl bromoacetate gave lower enantioselectivities. We confirmed that active catalysts of the type **8** were not inherently less selective repeating these alkylations using catalyst **9**, and it appears that the lower selectivity obtained is largely a consequence of an increased rate of background reaction that is found with this type of electrophile (Scheme 3).

More acidic alkylating agents such as α-bromoacetophenone underwent competing enolisation and polymerisation, resulting in poor yields of the desired amino acid derivatives. This is perhaps not surprising since compounds of this type have been reported to rapidly oligomerise under basic conditions.[7]

The enantioselectivities obtained with non-polar alkylating agents all lie in the range 82–91% (Tables 2 and 3), and this coupled with small variation of enantioselectivity observed on varying the polarity of the organic solvent (Table 1) is consistent with the suggest that the alkylation process is proceeding via a well-organised ion-pair. Published X-ray data on a derivative of salt **4**, and related modelling studies suggest that the *N*-anthracenylmethyl-substituted quaternary ammonium salts have a single accessible ion binding site.[2a] Based on this, and our earlier structure/selectivity studies (see preceding paper) we have identified two possible arrangements for the cinchonidine-derived catalyst **4**-enolate ion-pair (Fig.1).

Ion pair **A** has previously been proposed as the reactive intermediate in alkylations of this type[2a] and is consistent with the sense of stereoselectivity observed, whereas ion-pair **B** would be expected to give rise to lower selectivity, most probably favouring the opposite enantiomer from that observed. Molecular modelling studies suggest that ion-pair arrangement **B** is likely to be less favourable due to the increased charge separation required in order to accommodate the *tert*-butyl group of the enolate in the 'groove' between the quinoline ring and vinyl substituent and that



Scheme 3.

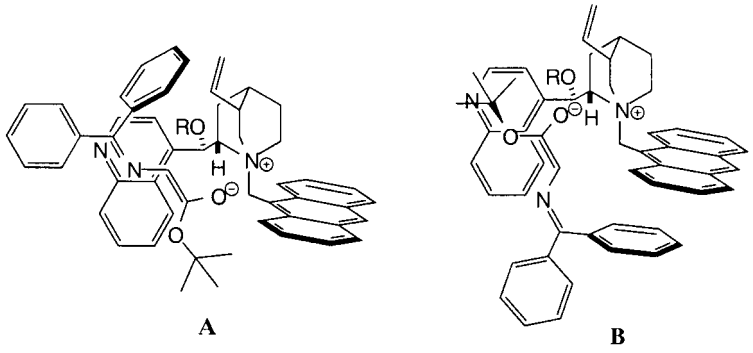
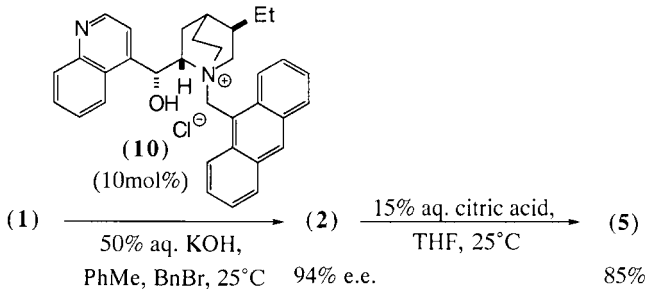


Figure 1.



Scheme 4.

this arrangement would also lead to greater charge separation in the transition state of the alkylation process.

The above model would suggest that modifications to the vinyl-substituent on the quinuclidine may affect the stability of the ion-pair arrangements and so to test this possibility we prepared pre-catalyst **10** and tested it in the standard alkylation reaction (Scheme 4). The resulting imine **2** was obtained in 94% e.e., which represents a slight increase in selectivity over that obtained with the corresponding vinyl-substituted pre-catalyst **4**. This result would seem to be consistent with the ion-pair arrangement **A**, and the slight increase in selectivity may arise as a consequence of further destabilisation alternative of ion-pair arrangements such as **B**. Most significantly, this simple modification to the catalyst structure resulted in a system that is capable of effecting a highly enantioselective benzylation of imine **1** at room temperature.

In conclusion, we have shown that *N*-anthracenylmethyl-substituted cinchona alkaloids are effective catalysts for the enantioselective alkylation of glycine imine **1**. The utility of these catalysts has been illustrated by the preparation of both enantiomeric series of a range of α-amino acid esters.

1. Experimental

Infra red absorption spectra were recorded on Perkin–Elmer 1600 and 1710 Fourier-transform spectrometers. All the spectra were recorded neat. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 300 or 400 MHz and ^{13}C nuclear magnetic resonance spectra at 75 or 100 MHz on a Bruker AC300 or Bruker Avance 400 spectrometer. All chemical shifts (δ) were referenced to the deuterium lock and are reported in parts per million (ppm). The following abbreviations have been used to describe the signal multiplicity: br (broad), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), m (multiplet), and *J* (coupling constant in Hz). Mass spectra (MS) were recorded at low resolution on Finnigan 4500 instrument with chemical ionisation (CI) using ammonia. Other mass spectra were recorded on Kratos Concept 1-S instrument. Optical rotations ($[\alpha]_D$) are quoted to ±10% accuracy and were measured on an AA-10 monochromatic 589 nm (Optical Activity) polarimeter at room temperature. Melting points (mp) were determined using an electrothermal apparatus and are uncorrected. High performance liquid chromatography (HPLC) was performed using Gilson apparatus with the columns and conditions outlined in the relevant experimental procedures. Enantiomeric excesses determined by HPLC as described in Section 1 were reproducible to ±2%. Thin layer chromatography (TLC) was performed either on plates pre-coated (0.25 mm) with CAMLAB DC-Fertigplatten SIL G-25 UV254 (silica) or plates pre-coated (0.2 mm) with CAMLAB DE-Fertigfolien ALOX N UV254 (neutral alumina). The plates were visualised by the use of a combination of ultraviolet light, iodine, ethanolic vanillin, or aqueous potassium permanganate. Silica gel 60 (particle sizes 40–60 μ) or aluminium oxide 90 active neutral (1077) both supplied by Merck were employed for flash chromatography. Where necessary, solvents and reagents were dried and purified according to recommended procedures.[8] Quaternary ammonium salts **3**,[6] **4**,[6] and **8**[9] were prepared as previously described.

1.1. General procedure for the alkylation of *tert*-butyl *N*-(diphenylmethylene)glycinate (1)

A mixture of *tert*-butyl *N*-(diphenylmethylene)glycinate **1** (100 mg, 0.34 mmol) and the appropriate pre-catalyst (0.034 mmol) in toluene (3 ml) was treated sequentially with the alkyl halide (0.38 mmol) and 50% aqueous potassium hydroxide (0.76 ml, 6.68 mmol). The mixture was then stirred for 3–24 h at room temperature, then the two phases were separated and the toluene solution passed through a short column of magnesium sulfate. The solvent was then removed under reduced pressure to give crude amino acid imine, which was used directly in the subsequent hydrolysis step. The *O*-alkylated catalyst could be recovered in 80–90% yield from the magnesium sulfate column by elution with chloroform, followed by concentration under reduced pressure (bath temp. <40°C).

1.2. General procedure for the hydrolysis of the crude amino acid imines

Hydrolysis of the crude amino acid imines was preformed using the previously reported procedure.[3b] The resulting residue was purified by chromatography on silica gel.

1.2.1. Preparation of *tert*-butyl phenylalaninate (5). Alkylation of imine **1** with benzyl bromide according to the general procedure gave crude *tert*-butyl *N*-(diphenylmethylene)phenylalaninate **2** as a pale yellow oil. R_f (silica gel): 0.6 (9:1, hexane/ethyl acetate). ν_{max} (neat): 2929, 1733 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$) 7.60–6.50 (15H, m, Ar-H), 4.10 (1H, dd, *J*=5.0, 9.0 Hz, H-2), 3.25–3.11 (2H, m, H-3), 1.42 (9H, s, $C(CH_3)_3$). *m/z*: (NH_3, Cl) 386

(M+H$^+$, 100%), 182 (30%). Found [M+H]$^+$ 386.2113 $C_{26}H_{28}NO_2$ requires 386.2120. R_t HPLC (DNPG 'Bakerbon', 98.5:1.5, hexane/dioxane, 254 nm, 0.5 ml/min) 36.8 min (*R*-isomer), 40.4 min (*S*-isomer).

The crude imine **2** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate) to give the product **5** as colourless oil. R_f (silica gel) 0.1 (1:1, ethyl acetate/petroleum ether). ν_{max} (neat): 3379, 2978, 1729 cm^{-1}. ^{1}H NMR δ (300 MHz, $CDCL_3$)[10] 7.45–7.18 (5H, m, Ar-H), 3.65–355 (1H, m, H-2), 3.05–2.99 (1H, dd, *J*=6.0, 14.0 Hz, H-3a), 2.86–2.79 (1H, dd, *J*=6.0, 14.0 Hz, H-3b), 1.61–1.55 (2H, m, NH_2), 1.40 (9H, s, $C(CH_3)_3$). *m/z* (NH_3, Cl) 239 (M+NH_4^+, 75%), 222 (M+H$^+$, 100%), 93 (75%), 76 (60%). Found [M+H]$^+$ 222.1497, $C_{13}H_{20}NO_2$ requires 222.1494.

1.2.2. Preparation of *tert*-butyl 2-aminopent-4-enoate (7a). Alkylation of imine **1** with allyl bromide according to the general procedure gave crude *tert*-butyl 2-[(diphenylmethylene)amino]pent-4-enoate **6a** as a pale yellow oil. R_f (silica gel): 0.7 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat): 2978, 1732, 1661 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCL_3$), 7.80–7.14 (10H, m, Ar-H), 5.78–5.65 (1H, m, H-4), 5.10–4.98 (2H, m, H-5a, H-5b), 4.01 (1H, dd, *J*=5.5, 7.5 Hz, H-2), 2.66–2.60 (2H, m, H-3a), 1.43 (9H, s, $CC(CH_3)_3$). *m/z*: (NH_3, Cl) 336 (M+H$^+$, 100%). Found [M+H]$^+$ 336.1972 $C_{22}H_{26}NO_2$ requires 336.1963. R_t HPLC (DNPG Bakerbond, 98.5:1.5, hexane/dioxane, 254 nm, 0.5 ml/min) 28.4 min (*R*-isomer), 31.0 min (*S*-isomer).

The crude imine **6a** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate) to-give the product **7a** as colourless oil. R_f (silica gel): 0.3 (ethyl acetate). ν_{max} (neat): 3379, 2978, 1729, 1661 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$)[11] 5.80–5.66 (1H, m, H-4), 5.28–5.10 (2H, m, H-5a, H-5b), 3.49–3.36 (1H, m, H-2), 2.51–2.31 (2H, m, H-3a, H-3b), 2.15–1.75 (2H, m, NH_2), 1.44 (9H, s, $C(CH_3)_3$). *m/z*: (NH_3, Cl) 172 (M+H$^+$, 100%). Found [M+H]$^+$ 172.1337 $C_9H_{18}NO_2$ requires 172.1337.

1.2.3. Preparation of *tert*-butyl 2-amino-4-methylpent-4-enoate (7b). Alkylation of imine **1** with 3-bromo-2-methylpropene according to the general procedure gave crude *tert*-butyl *N*-(diphenylmethylene)alaninate **6b** as a pale yellow solid. R_f (silica gel): 0.4 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat): 2974, 1733, 1660 cm^{-1}. ^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.65–7.16 (10H, m, Ar-H), 4.74 (1H, br s, H-5a), 4.08 (1H, br s, H-5b), 4.08 (1H, dd, *J*=5.0, 8.5 Hz, H-2), 2.63 (1H, br dd, *J*=5.0, 13.5 Hz, H-3a), 2.56 (1H, ddd, *J*=0.5, 8.5, 13.5 Hz, H-3b), 1.52 (3H, s, CH_3), 1.45 (9H, s, $CC(CH_3)_3$). *m/z*: (ES+) 350 (M+H$^+$, 100%), 294 (70%). Found [M+H]$^+$ 350.2107 $C_{23}H_{28}NO_2$ requires 350.2120.

The crude imine **6b** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate) to give the product **7b** as colourless oil. R_f (silica gel): 0.3 (1:3, petroleum ether/ethyl acetate). ν_{max} (neat): 3416, 2976, 1734, 1623 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$) 4.85 (1H, br s, H-5a), 4.78 (21H, br s, H-5b), 3.55–3.44 (1H, m, H-2), 2.46 (1H, br dd, *J*=5.0, 13.5 Hz, H-3a), 2.46 (1H, br dd, *J*=8.5, 13.5 Hz, H-3b), 1.76 (3H, s, CH_3), 1.62–1.50 (2H, m, NH_2), 1.46 (9H, s, $C(CH_3)_3$). *m/z*: (NH_3, Cl) 172 (M+H$^+$, 100%). ^{13}C NMR δ (100 MHz, $CDCl_3$) 174.9, 141.7, 113.9, 81.2, 53.1, 43.9, 28.1, 22.0.

1.2.4. Preparation of (*R*)-*tert*-butyl alaninate (7c). Alkylation of imine **1** with methyl iodide according to the general procedure gave crude *tert*-butyl *N*-(diphenylmethylene)-alaninate **6c** as a pale yellow oil. R_f (silica gel): 0.6 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat): 2977, 1732 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$) 7.80–7.15 (10H, m, Ar-H), 4.02 (1H, q, *J*=6.5 Hz, H-2), 1.43 (9H, s, $C(CH_3)_3$), 1.38 (3H, d, *J*=6.5 Hz, CH_3. *m/z*: (NH_3, Cl) 310 (M+H$^+$, 100%). Found [M+H]$^+$ 310.1800 $C_{20}H_{24}NO_2$ requires 310.1807. R_t HPLC (DNPG Bakerbond, 98.5:1.5, hexane/dioxane, 254 nm, 0.5 ml/min) 32.6 min (*R*-isomer), 35.0 min (*S*-isomer).

The crude imine **6c** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate) to give the product **7c** as colourless oil. R_f (silica gel): 0.1 (ethyl acetate). ν_{max} (neat): 3369, 2931, 1732 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$)[11] 3.45–3.35 (1H, m, H-2), 1.43 (1H, s, $C(CH_3)_3$), 1.26 (3H, d, *J*=7.0 Hz, H-3a, H-3b, H-3c). *m/z*: (NH_3, Cl) 146 (M+H$^+$, 100%), 90 (65%). Found [M+H]$^+$ 146.1182 $C_7H_{16}NO_2$ requires 146.1182.

1.2.5. Preparation of *tert*-butyl 2-aminohexanoate (7d). Alkylation of imine **1** with 1-iodobutane according to the general procedure gave crude *tert*-butyl 2-[(diphenylmethylene)amino]hexanoate **6d** as a pale yellow oil. R_f (silica gel): 0.8 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat): 2957, 1733 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$) 7.81–7.15 (10H, m, Ar-H), 3.90 (1H, dd, *J*=7.5 Hz, H-2), 1.91–1.84 (2H, m, H-3a, H-3b), 1.43 (9H, s, $C(CH_3)_3$), 1.39–1.15 (4H, m, H-4a, H-4b, H-5a, H-5b), 0.90–0.81 (3H, t, *J*=7.0 Hz, CH_3). *m/z*: (NH_3, Cl) 352 (M+H$^+$, 100%). Found [M+H]$^+$ 352.2279 $C_{23}H_{30}NO_2$ requires 352.2276. R_t HPLC (DNPG Bakerbond, 99:1, hexane/dioxane, 254 nm, 0.5 ml/min) 29.9 min (*R*-isomer), 34.2 min (*S*-isomer).

The crude imine **6d** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate) to give the product **7d** as colourless oil. R_f (silica gel): 0.2 (ethyl acetate). ν_{max} (neat): 3381, 2957, 1729 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$)[10] 3.51–3.25 (1H, m, H-2), 2.32–1.86 (2H, m, NH_2), 1.78–1.51 (2H, m, H-3a, H-3b), 1.45 (9H, s, $C(CH_3)_3$), 1.39–1.20 (4H, m, H-4a, H-4b, H-5a, H-5b), 0.95–0.82 (3H, m, CH_3). *m/z*: (NH_3, Cl) 188 (M+H$^+$, 100%), 132 (60%), 86 (70%). Found [M+H]$^+$ 188.1659 $C_{10}H_{22}NO_2$ requires 188.1650.

1.2.6. Preparation of *tert*-butyl 2-amino-3-(2-naphthyl) propanoate (7e). Alkylation of imine **1** with 2-naphthylmethyl bromide according to the general procedure gave crude *tert*-butyl 2-[(dephenylmethylene) amino]-3-(2-naphthyl)propanoate **6e** as a pale yellow oil. R_f (silica gel): 0.7 (9:1, petroleum ether/ethyl acetate). ν_{max}: (neat) 3056, 1732 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$)

7.88–7.15 (17H, m, Ar-H), 6.61–6.51 (1H, m, Ar-H), 4.28 (1H, dd, *J*=4.5, 9.0 Hz, H-2), 3.44 (1H, dd, *J*=4.5, 13.5 Hz, H-3a), 3.35 (1H, dd, *J*=9.0, 13.5 Hz, H-3b), 1.47 (9H, s, $C(CH_3)_3$). *m/z*: (NH_3, Cl) 436 ($M+H^+$, 100%). Found $[M+H]^+$ 436.2284 $C_{30}H_{30}NO_2$ requires 436.2276.

The crude imine **6e** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate) to give the product **7e** as colourless oil. R_f (silica gel): 0.3 (ethyl acetate). ν_{max} (neat): 3380, 2976, 1729 cm^{-1}. ^1H NMR: δ (300 MHz, $CDCl_3$) 7.81–7.71 (3H, m, H-4′, H-5′, H-8′), 7.65 (1H, s, H-1′), 7.47–7.31 (3H, m, H-3′, H-6′, H-7′), 3.80–3.52 (1H, m, H-2), 3.20 (1H, dd, *J*=5.5, 13.5 Hz, H-3a), 3.00 (1H, dd, *J*=8.0, 13.5 Hz, H-3b), 1.8–1.52 (2H, m, NH_2), 1.41 (9H, s, $C(CH_3)_3$). *m/z*: (NH_3, Cl) 272 ($M+H^+$, 100%). Found $[M+H]^+$ 272.1659 $C_{17}H_{22}NO_2$ requires 272.1650.

1.2.7. Preparation of *tert*-butyl 3-(carbo-*tert*-butoxy)-2-aminopropanoate (7f). Alkylation of imine **1** with either *tert*-butyl bromoacetate or *tert*-butyl iodoacetate according to the general procedure gave crude *tert*-butyl 3-(carbo-*tert*-butoxy)-2-[(diphenylmethylene) amino]propanoate **6f** as a pale yellow oil. ν_{max} (neat): 2978, 1730 cm^{-1}. ^1H NMR: δ (300 MHz, $CDCl_3$) 7.65–7.14 (10H, m, Ar-H), 4.35 (1H, dd, *J*=6.0, 8.0 Hz, H-2), 2.90 (1H, dd, *J*=6.0, 15.5 Hz, H-3a), 2.74 (1H, dd, *J*=8.0, 15.5 Hz, H-3b, 1.42 (18H, s, 2×$C(CH_3)_3$). *m/z*: (NH_3, Cl) 410 ($M+H^+$, 25%), 352 (100%). Found $[M+H]^+$ 410.2339 $C_{25}H_{32}NO_4$ requires 410.2331.

The crude imine **6f** was then hydrolysed according to the general procedure above and the residue purified by chromatography on silica gel (ethyl acetate to give the product **7f** as colourless oil. R_f (silica gel): 0.3 (ethyl acetate). ν_{max} (neat): 3387, 1732 cm^{-1}. ^1H NMR: δ (300 MHz, $CDCl_3$) 3.68–3.50 (1H, m, H-2), 2.72–2.48 (2H, m, H-3a, H-3b), 2.19–1.80 (2H, m, NH_2), 1.41 (18H, s, 2×$C(CH_3)_3$). *m/z*: (NH_3, Cl) 246 ($M+H^+$, 100%), 190 (75%). Found $[M+H]^+$ 246.1703 $C_{12}H_{24}NO_4$ requires 246.1705.

1.3. General procedure for *N*-benzoylation of amino acid *tert*-butyl esters

A solution of the amino acid ester (0.32 mmol) and triethylamine (0.35 mmol) in chloroform (1 ml) was cooled to 0°C under argon. Benzoyl chloride (0.35 mmol) was then added and the solution stirred at 0°C for 20 min and then at room temperature for 1 h. The solution was then washed with 3 M hydrochloric acid (1 ml), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the product.

1.3.1. *N*-Benzoylation of *tert*-butyl 2-amino-4-methylpent-4-enoate (7b). Amino acid ester **7b** was reacted with benzoyl chloride according to the above general procedure. The residue obtained was purified by chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the corresponding *N*-benzoate as a colourless solid. R_f (silica gel): 0.3 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat); 3303, 1737, 1640 cm^{-1}. ^1H NMR: δ (400 MHz, $CDCl_3$) 7.79–7.72 (5H, m, Ar-H), 6.65 (1H, br d, *J*=7.5 Hz, NH), 4.87 (1H, br s, H-5a), 4.80 (1H, br s, H-5b), 4.86–4.78 (1H, m, H-2), 2.64 (1H, ddd, *J*=0.5, 5.5, 13.5 Hz, H-3a), 2.52 (1H, *J*=0.5, 7.5, 13.5 Hz, H-3b), 1.81 (3H, s, CH_3), 1.49 (9H, s, $C(CH_3)_3$). ^{13}C NMR: δ (100 MHz, $CDCl_3$) 171.5, 166.8, 141.0, 134.1, 131.6, 128.5, 127.0, 114.5, 82.3, 51.4, 40.9, 28.0, 22.0. *m/z*: (ES+) 353 ($M+Na^+$+CH_3CN, 100%), 312 ($M+Na^+$, 9%) Found $[M+Na^++CH_3CN]^+$ 353.1817 $C_{19}H_{26}N_2O_3$ requires 353.1841. R_t HPLC (Chiralcel OD-H, 95:5, hexane/IPA, 232 nm, 0.9 ml/min) 7.1 min (*R*-isomer), 21.9 min (*S*-isomer).

1.3.2. *N*-Benzoylation of *tert*-butyl 2-amino-3-(2-naphthyl)propanoate (7e). Amino acid ester **7e** was reacted with benzoyl chloride according to the above general procedure. The residue obtained was purified by chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the corresponding *N*-benzoate as a colourless solid. R_f (silica gel): 0.3 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat): 3330 (N–H), 1726 (C═O), 1648 (C═O) cm^{-1}. ^1H NMR: δ (300 MHz, $CDCl_3$) 7.83–7.29 (12H, m, Ar-H), 6.69 (1H, br d, *J*=7.5 Hz, NH), 5.07–5.01 (1H, m, H-2), 3.49–3.33 (2H, m, H-3a, H-3b), 1.42 (9H, s, $C(CH_3)_3$). ^{13}C NMR: δ (100 MHz, $CDCl_3$) 170.7, 166.7, 134.1, 133.8, 133.3, 132.5, 131.7, 128.6, 128.3, 128.0, 127.8, 127.7, 127.5, 127.0, 126.1, 125.6, 82.7, 54.0, 38.1, 28.0. *m/z*: (NH_3, Cl) 376 ($M+H^+$, 100%), 320 (80%), 198 (65%), 105 (80%). Found $[M+H]^+$ 376.1889 $C_{24}H_{26}NO_3$ requires 376.1912. R_t HPLC (Chiralcel OD-H, 9:1, hexane/IPA, 232 nm, 0.5 ml/min) 18.7 min (*S*-isomer), 31.1 min (*R*-isomer).

1.3.3. *N*-Benzoylation of *tert*-Butyl 3-(carbo-*tert*-butoxy)-2-aminopropanoate (7f). Amino acid ester **7f** was reached with benzoyl chloride according to the above general procedure. The residue obtained was purified by chromatography on silica gel (9:1, petroleum ether/ethyl acetate) to give the corresponding *N*-benzoate as a colourless solid. R_f (silica gel): 0.3 (9:1, petroleum ether/ethyl acetate). ν_{max} (neat): 3339, 1732, 1652 cm^{-1}. ^1H NMR: δ (300 MHz, $CDCl_3$) 7.79 (2H, m, Ar-H), 7.51–7.39 (3H, m, Ar-H), 7.20 (1H, br d, *J*=8.0 Hz, NH), 4.89–4.83 (1H, m, H-2), 2.97 (1H, dd, *J*=4.0, 17.0 Hz, H-3a), 2.84 (1H, dd, *J*=4.0, 17.0 Hz, H-3b), 1.46 (9H, s, $C(CH_3)_3$), 1.42 (9H, s, $C(CH_3)_3$). ^{13}C NMR: δ (100 MHz, $CDCl_3$) 170.5, 170.0, 166.9, 134.1, 131.7, 128.6, 127.1, 82.5, 81.6, 49.5, 37.5, 28.1, 27.9. *m/z*: (NH_3, Cl) 350 ($M+H^+$, 100%), 244 (75%), 105 (75%). Found $[M+H]^+$ 350.1954 $C_{19}H_{28}NO_5$ requires 350.1967. R_t HPLC (Chiralcel OD-H, 94:6, hexane/IPA, 232 nm, 0.5 ml/min) 12.5 min (*R*-isomer), 15.2 min (*S*-isomer).

1.3.4. Preparation of (2*S*,5*R*,1′*R*)-1-(1-anthracenyl)-methyl-5-ethylene-2-[1-benzyloxy-1-(quinol-4-yl)]methyl-1-azoniabicyclo[2.2.2]octane bromide (9). A solution of the salt **4** (0.70 g, 1.34 mmol) in dichloromethane (10 ml) was prepared at room temperature with benzyl bromide (0.46 ml, 3.89 mmol). 50% aqueous sodium hydroxide (0.35 ml, 0.44 mmol) was added and the reaction was stirred for 1.5 h. Water (5 ml) was then added and the aqueous layer was extracted with dichloromethane (5 ml) and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

The residue was purified by chromatography on silica gel (19:1, dichloromethane/methanol) to give the product (0.52 g, 66%) as a yellow solid. R_f (silica gel): 0.6 (19:1, dichloromethane/methanol). $[\alpha]_D = -195$ (c=0.8, $CHCl_3$). Mp 130–131°C. ν_{max} (neat): 3426, 2955 cm^{-1}. ^1H NMR: δ ($CDCl_3$, 300 MHz) 9.76 (1H, d, J=8.5 Hz, Ar-H), 9.49–9.18 (1H, m, Ar-H), 9.12–8.9 (1H, m, Ar-H), 8.57 (1H, s, Ar-H), 8.23 (1H, d, J=8.5 Hz, Ar-H), 8.12–7.70 (6H, m, Ar-H), 7.67–7.44 (7H, m, Ar-H), 7.40–7.29 (1H, m, Ar-H), 7.21–7.07 (1H, m, Ar-H), 6.99–6.75 (2H, m, H-1a″, H-1′), 6.08–5.79 (2H, m, H-1b″, H-1‴), 5.67–5.40 (1H, m, H-2), 5.16 (1H, d, J=17.0 Hz, H-2a‴), 5.09–4.85 (4H, m, H-1a‴, H-1b‴, H-2b‴, H-6a), 4.55–4.40 (1H, m, H-7a), 3.05–2.75 (1H, m, H-7b), 2.73–2.54 (1H, m, H-6b), 2.42–2.1.71 (4H, m, H-3a, H-4, H-8a, H-8b), 1.66–1.48 (1H, m, H-5), 1.47–1.30 (1H, m, H-3b). ^{13}C NMR: δ (75 MHz, $CDCl_3$) 148.8, 136.7, 136.4, 134.1, 133.2, 132.2, 131.5, 130.9, 130.0, 129.2, 128.9, 128.8, 128.6, 127.5, 127.1, 126.0, 125.5, 124.8, 123.3, 118.5, 118.1, 75.5, 71.5, 66.5, 61.3, 55.3, 51.1, 38.7, 26.5, 25.9, 23.7. m/z: FAB: m/z 575 (M^+-Br, 40%), 385 (25%), 191 (100%). Found $[M-Br]^+$ 575.3059 $C_{41}H_{39}N_2O$ requires 575.3062.

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