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Phase transfer catalyzed asymmetric alkylations of imine glycinamides

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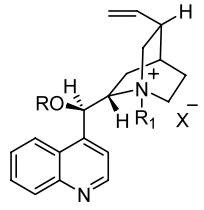
Abstract—Herein we report the use of achiral imine glycinamides as substrates for asymmetric alkylations using chiral phase-transfer catalysts for the first time. Initially tried for obtaining a key intermediate for the synthesis of levobupivacaine, we expanded the study to other *N*-mono and *N*,*N*-disubstituted imine glycinamides. A possible explanation for the lower enantioselectivity observed in the case of alkylation of *N*-monosubstituted as compared to *N*,*N*-disubstituted glycinamides is also provided.

1. Introduction

Phase transfer catalysis (PTC) is a synthetic methodology that has gained importance due to its simplicity and suitability for scale-up. This methodology has been successfully employed especially in the synthesis of both natural and unnatural α-amino acids by enantioselectively alkylating the glycine and alanine Schiff bases using chiral PTC conditions. The chiral PTCs, which have been effectively used are the ones pioneered by O'Donnell[1] **1a** and later improved upon by Lygo **1b**,[2] Corey[3] **1c** and more recently by Jew **1d**.[4] Among the non-cinchona based PTCs, chiral spiro ammonium salts derived from binaphthol are very promising.[5]

However, despite the increasing importance and usefulness of these PTCs in organic reactions, the utility of these catalysts in the asymmetric alkylation of achiral imine glycinamides remain relatively unexplored.[6] There are however, examples of chiral imine glycinamides derived from sultams,[7] ephedrine imidazolidinone,[8] disubstituted pyrrolidines[9] and dimethyloxazolidines.[10]In our studies into the synthesis of leveobupivacaine **2b** which is currently being marketed as its (*S*)-enantiomer, due to its less cardiotoxicity,[11] we wished to try the glycine anion equivalent methodology for making its key amide intermediate **2a**. The amide intermediate can also be used for making the chiral versions of other anesthetics like ropivacaine[12] **2c** and mepivacaine **2d**,[13] which have propyl and methyl attached to nitrogen, respectively.



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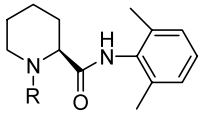

2

a) R = H
b) R = Bu
c) R = Pr
d) R = Me

a) R = H, R1 = benzyl, X = Br
b) R = H, R1 = anthracenylmethyl, X= Cl
c) R = allyl, R1 = anthracenylmethyl, X = Br
d) R = allyl, R1 = 2',3',4'-trifluorobenzyl, X = Br

2. Results and discussion

The amide intermediate **2a** can be made in different ways;[14] one route is through the pipecolic ester **5b** which in turn, can be synthesized through alkylation of benzophenone imine *tert*-butylglycinate **3a** as reported by Corey et al.[15] Alkylation of **3a** with 1-chloro-4-iodobutane and catalyst **1c** according to the reported procedure,[15] using $CsOH{\cdot}H_2O$ as the base gave the same level of enantioselectivity (99%) but a little less (97%) at 0°C (entry 5 and 4 in Table 1).

The other, more direct route would be the alkylation of the imine glycinamide **3b**. Besides reducing the number

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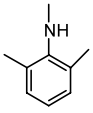
Table 1. Enantioselective phase-transfer-catalysed alkylation of **3a–b** promoted by **1c**

Entry	R (Substrate)	Base[a]	Solvent	Temp. (°C)	Time (hrs.)	ee[b] (%)	Yield[c] (%)
1	 **3b**	50% aq. KOH	CH_2Cl_2	0	24	13	**4b**, 58
2	**3b**	50% aq. KOH	Toluene: $CHCl_3$ (7 : 3)	0	35	16	**4b**, 54
3	**3b**	$CsOH.H_2O$	CH_2Cl_2	-50	28	20	**4b**, 52
4	 **3a**	$CsOH.H_2O$	CH_2Cl_2	0	14	97	**4a**, 78
5	**3a**	$CsOH.H_2O$	CH_2Cl_2	-50	23	99	**4a**, 83

[a]12 equivalent.

[b]Determined using chiral HPLC.

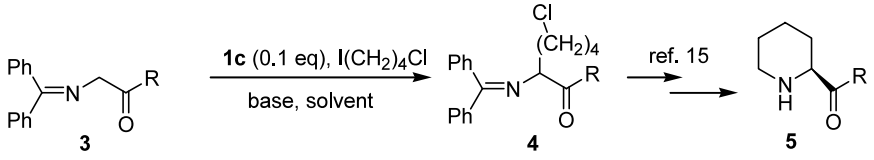
[c]Yields of isolated product.

of steps to the final drug **2b**, glycinamide **3b** is a more stable synthon than the *tert*-butyl ester **3a**. Also, being a sterically hindered amide it can ward off unwanted *N*-alkylation. This was easily prepared[16] from glycine and 2,6-dimethylaniline in 70% yield followed by benzophenone imine[17] protection according to the reported procedure.[18] When we subjected glycinamide **3b** to alkylation with 1-chloro-4-iodobutane, using $CsOH{\cdot}H_2O$ as a base with the catalyst **1c** at −50°C, we got the alkylated product **4b** in only 20% ee (entry 3, Table 1), as detected by chiral HPLC (Scheme 1). We repeated the reaction using various conditions, but the enantioselectivity of the alkylation did not improve significantly (entry 1–3, Table 1).

In order to ascertain the possible reasons for the low enantioselectivities, we repeated the reaction using benzyl bromide as the alkylating agent but using sterically more demanding groups at the amide nitrogen such as *iso*-propyl and *tert*-butyl groups, than the planer 2,6-dimethylbenzene. The enantioselectivity of the alkylation improved to give **6c** and **6d** in 42% and 53% ee, respectively (entries 2 and 3, Table 2). At this point we decided to see if *N*,*N*-disubstituted glycinamides would boost the stereoselectivity. Repeating the alkylation on *N*,*N*-disubstituted imine glycinamides **3e–h** under similar conditions as given in Scheme 2, certainly showed much higher enantioselectivity (ee 67–80%, entries 4–9, Table 2). It should be noted however, that *N*,*N*-dicyclo imine glycinamide did not improve the enantioselectivity (ee 75%, entry 9, Table 2) as compared to *N*,*N*-diethyl imine glycinamide (ee 80%, entry 7, Table 2). This significant increase in enantioselectivity in the alkylation of *N*,*N*-disubstituted imine glycinamides prompted us to carry out modelling studies with various imine glycinamides and the catalysts.

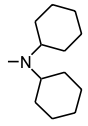
Published X-ray data of *N*-anthracenylmethyl substituted quaternary ammonium salt of cinchona alkaloids[3] show that they have a single accessible binding site for the enolates. Our modelling studies, performed using Sybyl 6.8[19] along similar lines as done previously,[20] showed two possible ion-pair arrangements between the catalyst and the enolate. One ion-pair formed between the catalyst and enolate of imine glycine *tert*-butyl ester and that of the imine *N*,*N*-disubstituted glycinamides must be mainly existing in the most favorable arrangement as shown in Figure 1, which would give rise to the observed (*S*)-alkylated product, but when we consider the mono *N*-substituted glycinamide, like *N*-*tert*-butyl amide **3d**, there is a huge fall in stereoselectivity when compared to that of *O*-*tert*-butyl ester **3a** (53 and 95%, respectively) even though both carry the same sterically bulky *tert*-butyl group (entries 10 and 3, Table 2).

Our modelling studies show that there is a possibility of hydrogen bonding interaction between the amide NH of the enolate of **3d** and the quinoline nitrogen atom when the enolate is placed in the orientation as in Figure 2, which gives rise to the product having opposite stereochemistry. Though this orientation is less favourable due to the steric crowding, as the *tert*-butyl



Scheme 1. Alkylation with 1-chloro-4-iodobutane.

Table 2. Enantioselective phase-transfer-catalysed benzylation of **3a–j** promoted by **1b**

Entry	R (Substrate)	Base[a]	Temp. (°C)	Time (hrs.)	ee[b] (%) (config.)[c]	Yield[d] (%)
1	**3b**	50% aq. KOH	0	8	16 (*S*)	**6b**, 65
2	 **3c**	50% aq. KOH	0	10	42 (*S*)	**6c**, 80
3	 **3d**	50% aq. KOH	0	10	53 (*S*)	**6d**, 84
4	 **3e**	50% aq. KOH	0	25	67 (*S*)	**6e**, 82
5	 **3f**	50% aq. KOH	0	24	66 (*S*)	**6f**, 76
6	 **3g**	50% aq. KOH	0	28	75 (*S*)	**6g**, 78
7*	**3g**	$CsOH.H_2O$	-20	4	80 (*S*)	**6g**, 84
8*	 **3h**	$CsOH.H_2O$	0	5	70 (*S*)	**6h**, 55
9*	**3h**	$CsOH.H_2O$	-20	7	75 (*S*)	**6h**, 60
10	**3a**	50% aq. KOH	0	4	95 (*S*)	**6a**, 85

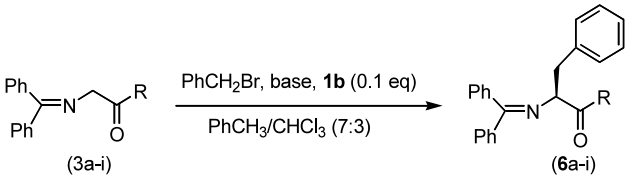
*Reaction done using toluene : CH_2Cl_2 (7:3) as solvent.

[a]12 equivalent.

[b]Determined using chiral HPLC.

[c]Detremined after hydrolyzing the products and comparing the optical rotation with L-phenylalanine.

[d]Yields of isolated product.



Scheme 2. Alkylation with benzyl bromide.

group is placed between quinoline ring and vinyl substituent, and also due to increased charge separation (loosening of ion-pair), it still seems to form due to the added advantage of hydrogen bonding. This explains the observed fall in the stereoselectivity.

The above explanation also seems to fit in with the difference in the levels of diastereoselectivities observed by Marouka[6] while benzylating the dipeptide Gly-L-Phe. High levels of diastereoselectivities were achieved using chiral spiro ammonium catalysts, where there was no possibility of hydrogen bonding, whereas catalyst **1c** gave poor induction.

All the secondary amides showed low enantioselectivity with **3b** being the least. This is in agreement with the work done earlier on various esters by the O'Donnell's group,[1] where they observed that phenyl esters were sterically less demanding due to their planar structure than *tert*-butyl esters and hence showed worse asymmetric induction.

3. Conclusions

We have shown for the first time that achiral benzophenone imine glycinamides can also be used as suitable substrates for asymmetric alkylations using cinchona derived catalysts under PTC conditions. We have also tried to explain the poorer enantioselectivity of monosubstituted glycinamides as compared to *N*,*N*-disubstituted benzophenone imine glycinamides. On reduction, these compounds are able to yield useful chiral vicinal diamines; work in this direction is in progress.

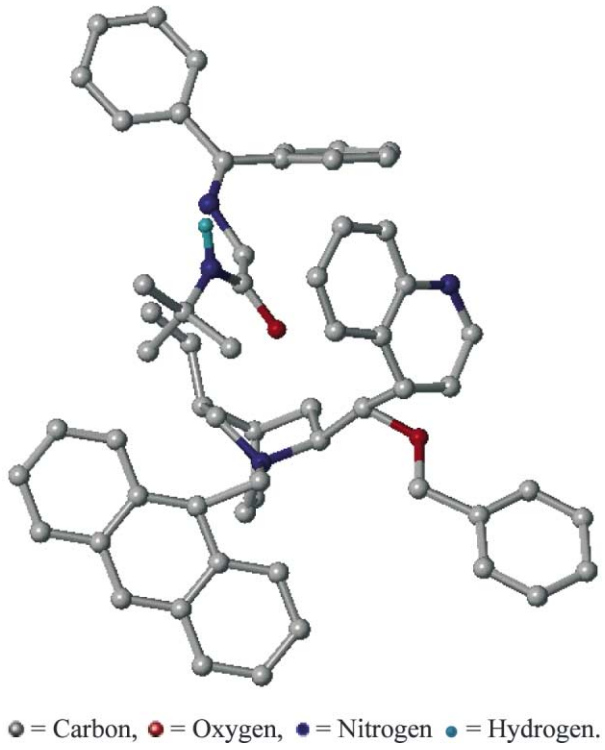


Figure 1. Ion-pair between the catalyst[19] and the (*E*)-enolate of **3d** in the conformation which will give rise to the (*S*)-product.

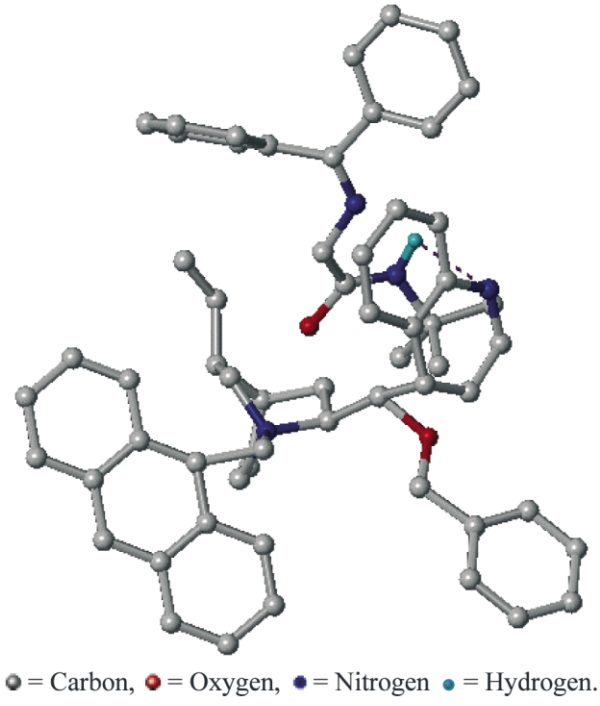


Figure 2. Ion-pair between the catalyst[19] and the (*E*)-enolate of **3d** in the conformation, which will give rise to the (*R*)-product (Hydrogen bonding shown in dotted line)

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C spectra were recorded at 300 MHz Bruker Advance spectrometer 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 spectra data were recorded on a Finnigan-MAT LCMS spectrometer with electron spray ionization and atmospheric pressure ionization modes. Elemental analyses were recorded on a Elementa Vario EL. HPLC was performed on a Shimadzu SPD-10A using chiral phase column (DIACEL Chiralcel, OD-H), with the conditions outlined in the relevant experiment. 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). Molecular modelling studies were done using Sybyl 6.8 installed on an Octane 2 SG workstation.

4.2. General procedure for the preparation of benzophenone imine glycinamides

Benzophenone imine glycinamides were synthesized from the appropriate glycinamide hydrochloride[16] and diphenylmethyl imine[17] according to the reported procedure.[18]

4.2.1. N^1-(2,6-Dimethylphenyl)-N^2-(diphenylmethylene)-glycinamide. Compound **3b** was obtained from N^1-(2,6-dimethylphenyl)-2-aminoacetamide hydrochloride[16] in 82% yield; mp 118–119°C; ν_{max} (KBr) 3330, 3053, 2914, 2881, 1684, 1627, 1499, 1440, 1286, 776, 699; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.30 (s, 6H), 4.16 (s, 2H), 7.11 (s, 3H), 7.20 (d, $J=7.5$ Hz, 2H), 7.34–7.52 (m, 6H), 7.67 (d, $J=7.4$ Hz, 2H), 8.94 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 18.4, 56.6, 127.0, 127.0, 128.0, 128.1, 128.2, 128.8, 128.9, 130.7, 133.8, 135.0, 135.8, 138.4, 168.8, 170.2; MS (*m*/*z*): 344 (24%), 343 (100%). Anal. calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18 Found: C, 80.59; H, 6.50; N, 8.15.

4.2.2. N^2-(Diphenylmethylene)-N^1-isopropylglycinamide. Compound **3c** was obtained from N^1-*iso*propyl-2-aminoacetamide hydrochloride[16] in 87% yield; mp 88–89°C; ν_{max} (KBr) 3345, 3054, 2964, 2871, 1646, 1528, 1314, 1286, 1173, 779, 698; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.25 (d, $J=6.54$ Hz, 6H), 3.93 (s, 2H), 4.17 (m, 1H), 7.13 (d, $J=7.54$ Hz, 2H), 7.2–7.4 (m, 5H), 7.62 (d, $J=7.02$ Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 22.7, 40.7, 56.5, 127.0, 128.1, 128.2, 128.7, 128.8, 130.5, 135.9, 138.6, 169.6, 169.9; MS (*m*/*z*): 282 (22%), 281 (100%). Anal. calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99 Found: C, 76.98; H, 7.28; N, 10.03.

4.2.3. N^1-(*tert*-Butyl)-N^2-(diphenylmethylene)-glycinamide. Compound **3d** was obtained from N^1-

(*tert*-butyl)-2-aminoacetamide hydrochloride[16] in 85% yield; mp 108–109°C; ν_{max} (KBr) 3374, 3080, 2966, 1672, 1623, 1526, 1449, 1286, 1223, 777, 699; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.44 (s, 9H), 3.85 (s, 2H), 7.13 (d, J=7.39 Hz, 2H), 7.14–7.46 (m, 6H), 7.6 (d, J=7.64 Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 28.7, 50.5, 56.9, 127.1, 128.1, 128.6, 128.8, 130.5, 135.9, 138.6, 169.4, 169.5; MS (m/z): 296 (20%), 295 (100%). Anal. calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 80.83; H, 7.41; N, 7.24.

4.2.4. *N*-(Diphenylmethylene)-2-oxo-2-pyrrolidin-1-ylethanamine. Compound **3e** was obtained from 2-oxo-2-pyrrolidin-1-ylethylamine hydrochloride[16] in 92% yield; mp 94–95°C; ν_{max} (KBr): 2977, 2876, 1627, 1449, 1425, 1324, 793, 709; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.79–1.97 (m, 4H), 3.48 (q, J=6.61 Hz, 4H), 4.18 (s, 2H), 7.23 (d, J=6.3 Hz, 2H), 7.29–7.46 (m, 6H), 7.64 (d, J=7.79 Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 24.0, 26.0, 45.8, 46.4, 57.3, 127.7, 127.9, 128.4, 128.5, 130.1, 135.9, 139.3, 168.4, 170.8; MS (m/z): 294 (18%), 293 (100%). Anal. calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.96; H, 6.95; N, 9.53.

4.2.5. *N*-(Diphenylmethylene)-2-oxo-2-piperidin-1-ylethanamine. Compound **3f** was obtained from 2-amino-1-piperidino-1-ethanone hydrochloride[16] in 86% yield; mp 73–74°C; ν_{max} (KBr) 3488, 2941, 2856, 1625, 1441, 1253, 1230, 1021, 707; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.57–1.60 (m, 6H), 3.27–3.57 (m, 4H), 4.23 (s, 2H), 7.18–7.49 (m, 8H), 7.63 (d, J=8.05 Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 24.4, 25.4, 26.1, 26.4, 42.9, 45.0, 46.8, 56.9, 127.7, 127.9, 128.1, 128.4, 128.5, 128.5, 129.9, 130.1, 132.3, 135.9, 139.3, 168.1, 170.2; MS (m/z): 294 (18%), 293 (100%). Anal. calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.08. Found: C, 77.80; H, 7.32; N, 8.99.

4.2.6. N^2-(Diphenylmethylene)-N^1,N^1-diethylglycinamide. Compound **3g** was obtained from *N*,*N*-diethyl-2-aminoacetamide hydrochloride[16] in 90% yield; mp 104–105°C; ν_{max} (KBr) 3054, 2975, 2927, 288, 1649, 1480, 1429, 1259, 1144, 773, 701; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.26 (t, J=7.06 Hz, 6H), 3.37 (m, 4H), 4.23 (s, 2H), 7.20–7.23 (m, 2H), 7.26–7.47 (m, 6H), 7.64–7.66 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 12.8, 14.1, 40.0, 41.7, 56.4, 127.6, 127.7, 128.3, 128.4, 129.9, 135.8, 139.2, 168.7, 170.4; MS (m/z): 296 (20%), 295 (100%). Anal. calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.34; H, 7.58; N, 9.49.

4.2.7. N^2-(Diphenylmethylene)-N^1,N^1-dicyclohexylglycinamide. Compound **3h** was obtained from *N*,*N*-dicyclohexyl-2-aminoacetamide hydrochloride[16] in 80% yield; mp 116–117°C; ν_{max} (KBr) 3052, 2928, 2850, 1624, 1443, 1313, 1182, 783, 700; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.05–1.32 (m, 6H), 1.46–1.58 (m, 6H) 1.65–1.76 (m, 7H), 2.49 (bs, 1H), 2.91 (bs, 1H), 3.68 (m, 1H), 4.19 (s, 2H), 7.21 (dd, J=1.42 Hz, J=5.67 Hz, 2H), 7.30–7.48 (m, 6H), 7.64 (d, J=6.76 Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 25.2, 25.8, 26.5, 29.7, 31.2, 55.9, 57.7, 59.1, 127.8, 127.8, 128.3, 128.5, 130.0, 135.9, 139.4, 168.8, 169.9; MS (m/z): 404 (24%), 403 (100%). Anal. calcd for $C_{27}H_{34}N_2O$: C, 80.56; H, 8.51; N, 6.96. Found: C, 80.39; H, 8.64; N, 6.90.

4.3. General procedure for the alkylation of benzophenone imine glycinamide and *tert*-butyl *N*-(diphenylmethylene)glycinate

Alkyl halide (8.4 mmol) was added to a mixture of the appropriate benzophenone imine glycinamide **3b–h** or *tert*-butyl *N*-(diphenylmethylene)glycinate[18] (**3a**, 1.6 mmol) and *N*-anthracenylmethyl cinchonidium bromide[21] (0.16 mmol) in toluene/chloroform (7:3) 10 mL. The reaction mixture was cooled to the appropriate temp, base (16.94 mmol) was added and the resulting mixture stirred vigorously until the starting material had been consumed (4–28 h). The suspension was diluted with diethyl ether (35 mL), washed with water (2×10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude products **4a–b**, **6a–h**. Purification of the residue by silica chromatography afforded the desired products in 58–85% yield. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane/*iso*-propanol, flow rate 0.5 mL, min^{-1}, 20°C, λ 254 nm). The absolute configuration was determined by comparison of the specific rotation of the hydrolyzed product(s) with L-phenylalanine.

4.3.1. *tert*-Butyl-*N*-(diphenylmethylene)-L-phenylalaninate. Compound **6a** was obtained from **3a** in 85% yield; pale yellow oil; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.41 (s, 9H), 3.22–3.09 (m, 2H), 4.08 (dd, J=4.98 Hz, J=9.08 Hz, 1H), 6.53–7.62 (m, 15H); R_t HPLC (99.5:0.5, hexane/*iso*propanol, 8.1 min (*S*-isomer) 17.5 min (*R*-isomer)).

4.3.2. *tert*-Butyl-6-chloro-*N*-(diphenylmethylene)-L-norleucinate. Compound **4a** was obtained from **3a** in 83% yield; pale yellow oil; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.30–1.44 (m, 11H), 1.71 (m, 2H), 1.80 (q, J=7.61 Hz, 2H), 3.49 (t, J=6.66 Hz, 2H), 3.92 (t, J=6.46 Hz, 1H), 7.16–7.65 (m, 9H), 7.80 (d, J=7.17 Hz, 1H); R_t HPLC (99.5:0.5, hexane/*iso*propanol, 12.0 min (*S*-isomer) 14.9 min (*R*-isomer)).

4.3.3. 6-Chloro-N^1-(2,6-dimethylphenyl)-N^2-(diphenylmethylene)-L-norleucinamide. Compound **4b** was obtained from **3b** in 58% yield; colourless oil; $[\alpha]_D^{25}$ = −5.8 (*c* 0.5, CH_2Cl_2), ee 20%; ν_{max} (film) 3347, 3062, 2926, 2249, 1715, 1494, 1315, 908, 733; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.55–1.78 (m, 6H), 2.18 (s, 6H), 3.31 (m, 1H), 3.46 (t, J=6.43 Hz), 4.93 (s, 1H), 7.06–7.46 (m, 13H), 8.53 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 18.5, 23.1, 32.2, 34.7, 44.6, 66.0, 127.5, 127.7, 128.1, 128.2, 128.5, 128.8, 128.9, 130.7, 133.7, 135.6, 136.7, 138.3, 169.8, 171.4; MS (m/z): 434 (24%), 433 (100%). Anal. calcd for $C_{27}H_{29}ClN_2O$: C,74.90; H, 6.75; N, 6.47. Found: C, 74.78; H, 6.83; N, 6.43; The enantiomeric excess was determined after reducing the imine to amine; R_t HPLC (hexane/*iso*propanol, 15.2 min (*S*-isomer), 19.8 min (*R*-isomer)).

4.3.4. *N*-(2,6-Dimethylphenyl)-*N*-(diphenylmethylene)-L-phenylalaninamide. Compound **6b** was obtained from **3b** in 65% yield; Colourless oil; $[\alpha]_D^{25} = -4.3$ (*c* 1, CH_2Cl_2), ee 16%; ν_{max} (film) 3340, 3057, 3025, 2920, 2853, 1686, 1621, 1492, 1283, 771, 697; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.20 (s, 6H), 3.18 (dd, $J = 3.57$ Hz, $J = 9.45$ Hz, 1H), 3.33 (dd, $J = 2.98$ Hz, $J = 10.07$ Hz, 1H), 4.33 (dd, $J = 3.07$ Hz, $J = 6.31$ Hz, 1H), 6.46 (d, $J = 6.98$ Hz, 2H), 7.03–7.44 (m, 14H), 7.63 (d, $J = 7.03$ Hz, 2H), 8.26 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 18.4, 41.6, 68.0, 126.3, 127.1, 127.2, 128.1, 128.3, 128.5, 130.2, 130.6, 133.7, 135.0, 135.3, 137.7, 138.8, 170.2, 170.9; MS (*m*/*z*): 434 (38%), 433 (100%). Anal. calcd for $C_{30}H_{28}N_2O$: C, 83.30; H, 6.52; N, 8.18. Found: C, 83.20; H, 6.56; N, 8.13. R_t HPLC (98:2 hexane/*iso*-propanol, 25.62 min (*S*-isomer) 53.44 min (*R*-isomer)).

4.3.5. *N*-Isopropyl-*N*-(diphenylmethylene)-L-phenylalaninamide. Compound **6c** was obtained form **3c** in 80% yield; mp 114–115°C; $[\alpha]_D^{25} = -41.4$ (*c* 1, CH_2Cl_2), ee 42%; ν_{max} (KBr) 3380, 3058, 2970, 2919, 1674, 1625, 1502, 1444, 1283, 764, 697; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.14 (dd, $J = 2.77$ Hz, $J = 3.75$ Hz, 6H), 2.99 (dd, $J = 4.20$ Hz, $J = 8.88$ Hz, 1H), 3.15 (dd, $J = 3.29$ Hz, $J = 9.77$ Hz, 1H), 4.11 (dd, $J = 4.68$ Hz, $J = 5.46$ Hz, 2H), 6.48 (d, $J = 6.82$ Hz, 2H), 6.59 (d, $J = 7.81$ Hz, 1H), 7.02–7.58 (m, 13H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 22.3, 22.7, 22.8, 40.8, 41.5, 67.5, 126.2, 127.3, 128.0, 128.1, 128.3, 128.3, 128.5, 130.1, 130.4, 135.5, 137.8, 139.2, 169.6, 171.6; MS (*m*/*z*): 372 (26%), 371 (100%); Anal. calcd for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.95; H, 7.14; N, 7.49; R_t HPLC (95:5 hexane/*iso*propanol, 9.4 min (*S*-isomer), 13.9 min (*R*-isomer)).

4.3.6. *N*-(*tert*-Butyl)-*N*-(diphenylmethylene)-L-phenylalaninamide. Compound **6d** was obtained form **3d** in 84% yield; mp 124–125°C; $[\alpha]_D^{25} = -7.8$ (*c* 1, CH_2Cl_2), ee 53%; ν_{max} (KBr) 3378, 3033, 2964, 2928, 2870, 1664, 1617, 1507, 1447, 1278, 1224, 755, 700; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.35 (s, 9H), 2.99 (dd, $J = 4.22$ Hz, $J = 8.83$ Hz, 1H), 3.14 (dd, $J = 3.25$ Hz, $J = 9.80$ Hz, 1H), 4.03 (dd, $J = 3.32$ Hz, $J = 5.42$ Hz, 1H), 6.86 (d, $J = 6.86$ Hz, 2H), 6.69 (s, 1H), 7.01–7.42 (m, 10H), 7.56 (d, $J = 6.87$ Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 28.7, 41.5, 50.6, 67.9, 126.1, 127.2, 127.9, 128.1, 128.2, 128.4, 130.1, 130.3, 135.4, 137.8, 139.1, 169.0, 171.6; MS (*m*/*z*): 386 (25%), 385 (100%). Anal. calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 80.98; H, 7.48; N, 7.23. R_t HPLC (95:5 hexane/*iso*-propanol, 9.6 min (*S*-isomer), 20.1 min (*R*-isomer)).

4.3.7. (2*S*)-*N*-(Diphenylmethylene)-1-oxo-3-phenyl-1-pyrrolidin-1-ylpropan-2-amine. Compound **6e** was obtained form **3e** in 82% yield; mp 126–127°C; $[\alpha]_D^{25} = -55.9$ (*c* 1, CH_2Cl_2), ee 67%; ν_{max} (KBr) 2974, 2869, 1637, 1437, 1286, 773, 701; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.54–1.64 (m, 4H), 2.72 (t, $J = 5.72$ Hz, 2H), 3.21 (dd, $J = 7.11$ Hz, $J = 5.82$ Hz, 1H), 3.29-3.44 (m, 3H), 4.33 (t, $J = 6.99$ Hz, 1H), 6.87 (d, $J = 3.58$ Hz, 2H), 7.07–7.38 (m, 11H), 7.65 (d, $J = 7.34$ Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 23.7, 25.9, 40.9, 45.7, 45.9, 67.2, 126.2, 127.3, 127.8, 128.0, 128.3, 128.3, 128.7, 129.6, 130.1, 137.0, 138.1, 139.1, 169.2, 170.3; MS (*m*/*z*): 384 (20%), 383 (100%). Anal. calcd for $C_{26}H_{26}N_2O$: C, 81.64; H, 6.85; N, 7.32. Found: C, 81.48; H, 6.93; N, 7.29. R_t HPLC (85:15, hexane/*iso*-propanol, 19.0 min (*S*-isomer), 21.9 min (*R*-isomer)).

4.3.8. (2*S*)-*N*-(Diphenylmethylene)-1-oxo-3-phenyl-1-piperidin-1-ylpropan-2-amine. Compound **6f** was obtained form **3f** in 76% yield; mp 120–121°C; $[\alpha]_D^{25} = -48.7$ (*c* 1, CH_2Cl_2), ee 66%; ν_{max} (KBr) 2925, 2858, 1624, 1496, 1443, 1219, 998, 694, 775; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.10 (bs, 1H), 1.25 (bs, 1H), 1.50 (m, 4H), 3.09-3.18 (m, 2H), 3.28-3.34 (m, 2H), 3.51 (m, 2H), 4.51 (dd, $J = 1.44$ Hz, $J = 6.17$ Hz, 1H), 6.80 (m, 2H), 7.06–7.67 (m, 13H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 24.5, 25.6, 26.2, 40.9, 41.9, 43.4, 46.2, 47.2, 50.4, 66.3, 126.3, 127.5, 127.7, 127.9, 128.2, 128.3, 128.4, 128.7, 129.4, 129.7, 130.1, 136.5, 138.3, 139.3, 169.0, 169.9; MS (*m*/*z*): 398 (10%), 397 (100%); Anal. calcd for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06. Found: C, 81.69; H, 7.31; N, 6.99. R_t HPLC (90:10 hexane/*iso*-propanol, 12.3 min (*S*-isomer), 14.3 min (*R*-isomer)).

4.3.9. *N*,*N*-Diethyl-*N*-(diphenylmethylene)-L-phenylalaninamide. Compound **6g** was obtained form **3g** in 84% yield; mp 111–112°C; $[\alpha]_D^{25} = -51.8$ (*c* 1, CH_2Cl_2), ee 80%; ν_{max} (KBr) 3058, 3022, 2970, 2930, 1648, 1611, 1446, 1260, 1078, 792, 701; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 0.72 (t, $J = 7.04$ Hz, 3H) 1.04 (t, $J = 7.04$ Hz, 3H), 2.92–3.11 (m, 3H), 3.24-3.38 (m, 3H), 4.42 (t, $J = 6.72$ Hz, 1H), 6.84 (d, $J = 4.29$ Hz, 2H), 7.05–7.39 (m, 11H), 7.64 (d, $J = 6.91$ Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 12.8, 14.2, 40.5, 41.1, 66.0, 126.2, 127.4, 127.8, 128.1, 128.2, 128.3, 128.4, 128.7, 129.6, 130.1, 136.5. 138.2, 139.3, 168.8, 170.6; MS (*m*/*z*): 386 (20%), 385 (100%). Anal. calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 81.12; 7.58; N, 7.24. R_t HPLC (95:5, hexane/*iso*propanol, 21.6 min (*S*-isomer), 27.5 min (*R*-isomer)).

4.3.10. *N*,*N*-Dicyclohexyl-*N*-(diphenylmethylene)-L-phenylalaninamide. Compound **6h** was obtained form **3h** in 60% yield; Pale yellow oil; $[\alpha]_D^{25} = -25.2$ (*c* 0.5, MeOH), ee 75%; ν_{max} (film) 3048, 3022, 2930, 1625, 1446, 1319, 1260, 1098, 772, 701; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.03–1.29 (m, 6H), 1.42–1.53 (m, 6H) 1.62–1.70 (m, 7H), 2.40 (bs, 1H), 2.91–3.0 (m, 2H), 3.24 (dd, $J = 3.25$ Hz, $J = 9.87$ Hz, 1H), 3.59 (m, 1H), 4.29 (t, $J = 6.92$ Hz, 1H), 6.82 (d, $J = 3.55$ Hz, 2H), 7.09–7.48 (m, 11H), 7.65 (d, $J = 6.76$ Hz, 2H); ^{13}C NMR δ ($CDCl_3$, 300 MHz) 25.3, 25.7, 26.8, 29.9, 31.2, 55.2, 59.3, 67.2, 126.2, 127.3, 127.8, 128.0, 128.3, 128.4, 128.7, 129.5, 130.1, 135.9, 138.7, 169.2, 170.2; MS (*m*/*z*): 495.3 (10%), 494 (25%), 493 (100%); Anal. calcd for $C_{34}H_{40}N_2O$: C, 82.88; H, 8.18; N, 5.69. Found: C, 82.74; H, 8.29; N, 5.63. R_t HPLC (98:2, hexane/*iso*-propanol, 8.1 min (*S*-isomer), 17.5 (*R*-isomer)).

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