DOI: 10.1002/chem.200701468

Indium–Silver- and Zinc–Silver-Mediated Barbier–Grignard-Type Alkylation Reactions of Imines by Using Unactivated Alkyl Halides in Aqueous Media

Zhi-Liang Shen, Hao-Lun Cheong, and Teck-Peng Loh*[a]

Abstract: In the presence of In or Zn/AgI/$InCl_3$, an efficient and practical method for the Barbier–Grignard-type alkylation reactions of simple imines by using a one-pot condensation of various aldehydes, amines (including the aliphatic and chiral version), and secondary alkyl iodides has been developed. The reaction proceeded more efficiently in water than in organic solvents. Without the use of CuI, it mainly gave the imine self-reductive coupling product, which was not the alkylated product. Good diastereoselectivities (up to 92:8 dr) were obtained when L-valine methyl ester was used as the substrate.

Keywords: alkylation · imines · indium · silver · water chemistry

Introduction

Organic reactions in aqueous media have attracted tremendous attention because of the many advantages that they offer.[1] For example, organic reactions in aqueous media allow multistep synthesis to be carried out more efficiently without the need for protection–deprotection of the functional groups containing acidic protons. Furthermore, compounds containing water molecules or biomolecules can be used directly. In conjunction with our interest in the development of new organic reactions in aqueous media for the functionalization of biomolecules, our group has extensively studied the indium- or zinc-mediated allylation reactions of carbonyl compounds and imines in aqueous media.[2] However, the analogous metal-mediated alkylation reactions of simple imines in aqueous media have been more difficult and challenging. This is due to the following: 1) Simple imines have lower electrophilicity and, therefore, are less reactive; 2) simple imines are easier to hydrolyze in water, especially aliphatic imines; 3) a simple imine is more prone to undergo a self-coupling reaction to generate diamine than an alkylation reaction in the presence of a metal;[3] and 4) alkyl halide is less reactive relative to allylic halide.

Elegant works by Naito et al. have shown the possibility of carrying out the metal-mediated alkylation of imines in aqueous media.[4–7] However, most of the reported methods are only applicable to activated imines, such as oxime ethers, hydrazones, and glyoxylate imines.[4,5] The limited scope in these reported systems encourages us to search for a new metal-mediated alkylation reaction of simple imines in water.[8] Herein, we report an efficient method for the alkylation of a wide variety of imines by means of a one-pot condensation of aldehydes, amines (including aliphatic and chiral version), and alkyl iodides by using indium–silver and zinc–silver in aqueous media.[9,10]

Results and Discussion

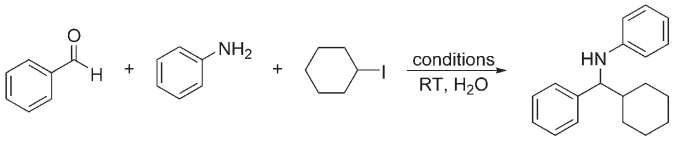
Initial studies were focused on the one-pot reaction of benzaldehyde, aniline, and cyclohexyl iodide by using different metals in water. The results are summarized in Table 1.

As shown in Table 1, among the several metals investigated, both zinc and indium were observed to be effective metals for the activation of the one-pot reaction of benzaldehyde, aniline, and cyclohexyl iodide, to afford the corresponding products in 76 and 88% yields, respectively (entries 6–7). It was important to note that, without the use of AgI, the reaction proceeded sluggishly to give the desired product in only 17% yield (the major product was the imine homocoupling product,[3] entry 8). In addition, the use of $InCl_3$ was also proved to be indispensable for the efficient progress of the alkylation reaction. Without the addition of $InCl_3$, a lower yield of the alkylated product was obtained (51%, entry 9). The utilization of other silver compounds

[a] Z.-L. Shen, H.-L. Cheong, Prof. Dr. T.-P. Loh
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University
Singapore 637371
Fax: (+65) 679-11-961
E-mail: teckpeng@ntu.edu.sg

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

Table 1. Optimization of reaction conditions for the alkylation of imines.



Entry	Conditions	Yield [%][a]
1	Al/AgI/$InCl_3$	<20
2	Mg/AgI/$InCl_3$	<10
3	Fe/AgI/$InCl_3$	32
4	Sn/AgI/$InCl_3$	0
5	Mn/AgI/$InCl_3$	<10
6	Zn/AgI/$InCl_3$	76
7	In/AgI/$InCl_3$	88
8	In/$InCl_3$	17
9	In/AgI	51
10	In/AgCl/$InCl_3$	57
11	In/Ag_2O/$InCl_3$	21
12	In/AgI/$ZnCl_2$	68
13	Zn/AgI/$ZnCl_2$	66

[a] Isolated yield.

(AgCl, Ag_2O) in the place of AgI produced the corresponding product in relatively low yields as compared to AgI (entries 10–11). When other Lewis acid, such as $ZnCl_2$, were used in place of $InCl_3$, the alkylated products could also be obtained albeit in low yields (entries 12–13). Furthermore, it was observed that these reactions proceeded more efficiently in water than in organic solvents.

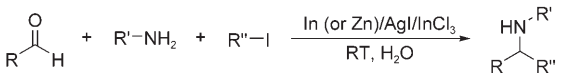
By using the optimized reaction conditions (In or Zn/AgI/$InCl_3$), we continued to carry out the one-pot Barbier–Grignard-type alkylation reaction of simple imines involving various aldehydes, amines, and alkyl iodides in water. The results are outlined in Table 2.

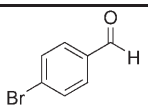
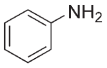
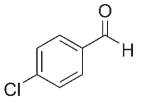
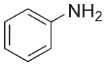
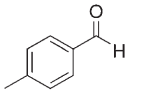
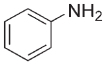
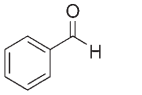
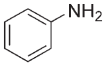
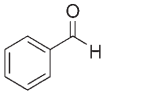
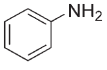
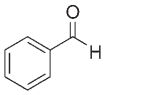
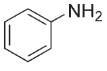
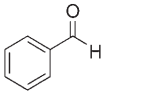
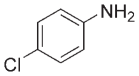
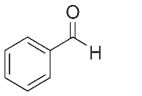
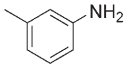
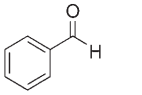
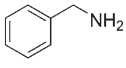
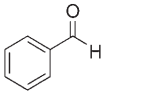
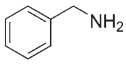
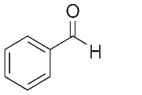
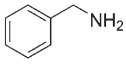
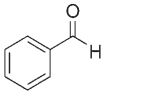
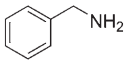
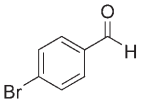
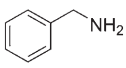
As shown in Table 2, indium–silver and zinc–silver efficiently mediated one-pot reactions of various aldehydes, amines, and alkyl iodides in water at ambient temperature. The corresponding alkylated products were furnished in moderate to good yields.[11] It is worth noting that the indium–silver system works well even for aliphatic amines, such as benzylamine, to generate the desired products in moderate to good yields (entries 9–14).

With the success of using aliphatic amines, such as benzylamine, for Barbier–Grignard-type alkylation reactions of imines in water, we were encouraged to apply this reaction system to chiral imines in the hope of providing a new method for the synthesis of enantiomerically enriched amino compounds.

By using L-valine methyl ester as a substrate, it was found that the one-pot reaction involving benzaldehyde and cyclohexyl iodide worked well in the presence of In/AgI/$InCl_3$ (in a 1:1 mixture of MeOH and H_2O) to afford the desired product both in good yield and with good diastereoselectivity (77% yield, 89:11 dr).[12] However, a poor yield (<30%) of the desired product was obtained when the same reaction was carried out by using Zn/AgI/$InCl_3$. Therefore, In/AgI/$InCl_3$ was chosen to apply to one-pot alkylation reactions of

Table 2. One-pot alkylation reactions of simple imines in water.[a]



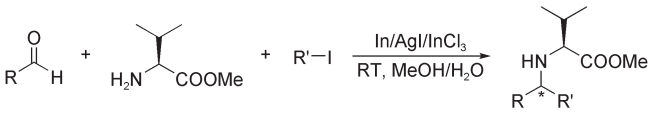
Entry	RCHO	R′NH_2	R″I	Yield [%][b] In	Yield [%][b] Zn
1				64	83
2				68	85
3				94	82
4				88	76
5				67	43
6				90[c]	45[d]
7				73[e]	65
8				85[e]	76
9				68[e,f]	30[e,f]
10				82[e,f]	48[e,f]
11				76[e,f]	53[e,f]
12				72[e,f,g]	39[e,f,h]
13				58[e,f]	16[e,f]
14				75[e,f]	37[e,f]

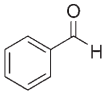
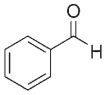
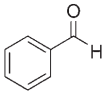
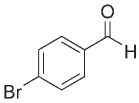
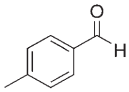
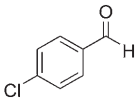
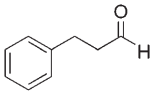
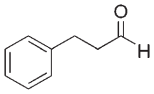
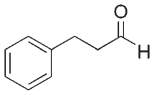
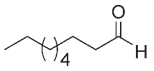
[a] Unless otherwise noted, the reaction was carried out at room temperature for 1 d by using In or Zn (6 equiv), AgI (4 equiv), $InCl_3$ (0.1 equiv), aldehyde (1 equiv), amine (1.2 equiv), alkyl iodide (5 equiv), and water (10 mL). [b] Isolated yield. [c] Diastereomeric ratio: 55:45. [d] Diastereomeric ratio: 50:50. [e] By using MeOH/H_2O 1:1. [f] By using 2 equiv of amine. [g] Diastereomeric ratio: 67:33. [h] Diastereomeric ratio: 65:35.

various aldehydes, alkyl iodides, and L-valine methyl ester in aqueous media. The results are listed in Table 3.

As shown in Table 3, the one-pot reaction employing various aldehydes, alkyl iodides, and L-valine methyl ester condensed efficiently in the presence of In/AgI/$InCl_3$ to generate the desired products in moderate to good yields and with good diastereoselectivities. It is worth noting that even aliphatic aldehydes (hydrocinnamaldehyde and nonyl aldehyde, entries 7–10) were also demonstrated to be good substrates for this reaction and good yields and diastereoselectivities of the corresponding products were obtained. The chiral auxiliary can be easily removed by reported procedures (diisobutylaluminum hydride (DIBAL-H) reduction followed by H_5IO_6-mediated oxidative cleavage of the corresponding amino alcohol) to afford the optically active amines.[13]

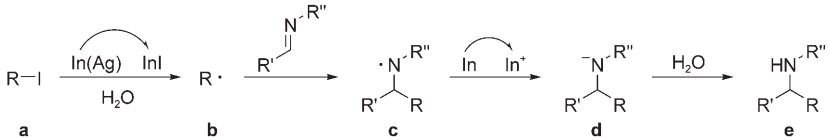
Table 3. One-pot alkylation reactions of simple imines by using L-valine methyl ester.[a]



Entry	RCHO	R'I	Yield [%][b]	dr
1			72	89:11
2			82	92:8
3			65	90:10
4			53	88:12
5			86	89:11
6			66	89:11
7			74	85:15
8			80	87:13
9			87	89:11
10			72	86:14

[a] The reaction was carried out at room temperature for 1 d by using In (6 equiv), AgI (4 equiv), $InCl_3$ (1 equiv), aldehyde (1 equiv), amine (2 equiv), alkyl iodide (5 equiv), MeOH (5 mL), and water (5 mL). [b] Isolated yield.

A plausible reaction mechanism has been proposed, as shown in Scheme 1. The reaction was initiated by a single-electron transfer from indium–silver (or zinc–silver) to alkyl iodide **a** to generate an alkyl radical **b**, which attacked the imine (which has been activated by $InCl_3$) to furnish a radical intermediate **c**. Subsequent indium (or zinc)-promoted reduction of intermediate **c** and the quenching of the generated amino anion **d** in the presence of water afforded the desired product **e**.



Scheme 1. Proposed reaction mechanism.

Conclusion

We have developed an efficient and practical method for the Barbier–Grignard-type alkylation reaction of simple imines in aqueous media. This one-pot three-component condensation of various aldehydes, amines, and alkyl iodides in aqueous media, in the presence of In or Zn/AgI/$InCl_3$ allows easy construction of a large library of amines. This method is practical and it works with a wide variety of aldehydes, amines (including aliphatic amines), and secondary alkyl iodides. The mild reaction conditions, moderate to good yields, good to excellent diastereoselectivities, and the simplicity of the reaction procedure make this method attractive for scale-up purposes. Efforts to apply this method for the synthesis of complex molecules as well as expanding it to the intramolecular version are currently in progress.

Experimental Section

General method: Analytical TLC was performed by using Merck 60 F254 precoated silica-gel plates (0.2 mm thickness). Subsequent to elution, plates were visualized by using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with an acidic solution of ceric molybdate or an ethanol solution of ninhydrin. Flash-column chromatography was performed by using Merck silica gel 60 with freshly distilled solvents. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 and Bruker AMX 400 spectrophotometer by using TMS as an internal standard. HRMS spectra were obtained by using Finnigan MAT95XP GC/HRMS (Thermo Electron Corporation). IR spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The proportion of diastereomers was determined from the integration of ^1H and ^{13}C NMR spectra.

Materials: Deionised water was used in all reactions. All aldehydes were purified before use. All commercially available amines (nonchiral amine) and alkyl iodides were used directly without purification. Commercially

available chiral amines (hydrochloride form) were washed with saturated aqueous sodium carbonate solution before use. The following commercial-grade reagents were also used without further purification: indium (powder, −100 mesh, 99.99%, Aldrich), zinc (powder, 98%, Alfa Aesar), silver(I) iodide (99.9%, Strem), and indium trichloride (Strem).

General procedure for the alkylation reaction of imines derived from an aromatic amine and aromatic aldehyde: Water (10 mL), aldehyde (0.5 mmol), amine (0.6 mmol), and $InCl_3$ (0.05 mmol) were added to a 10 mL round-bottomed flask. After stirring for 10 min at room temperature, indium or zinc (3 mmol), silver iodide (2 mmol), and alkyl iodide (2.5 mmol) were added sequentially to the reaction system. The reaction was stirred vigorously at room temperature for 1 d. After reaction, it was then extracted by using diethyl ether (20 mL × 3), washed with brine, dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated in vacuo to give the crude product. Silica-gel column chromatography by using ethyl acetate and hexane as the eluent afforded the desired product.

General procedure for the alkylation reaction of imines derived from aliphatic amine (including benzylamine and L-valine methyl ester): MeOH (5 mL), H_2O (5 mL), aldehyde (0.5 mmol), amine (1.0 mmol), and $InCl_3$ (with 0.05 mmol for benzylamine, 0.5 mmol for L-valine methyl ester) were added to a 10 mL round-bottomed flask. After stirring for 4 h at room temperature, indium (3 mmol), silver iodide (2 mmol), and alkyl iodide (2.5 mmol) were added sequentially to the reaction system. The reaction mixture was stirred vigorously at room temperature for 1 d. After reaction, it was extracted by using diethyl ether (20 mL × 3), washed with brine, dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated in vacuo to give the residue. Silica-gel column chromatography by using ethyl acetate and hexane (with 1% v/v triethyl amine) as the eluent afforded the desired product.

***N*-Phenyl-[1-(*p*-bromophenyl)-1-cyclohexylmethyl]amine (Table 2, entry 1)**: $R_f = 0.61$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$–1.26 (m, 6H), 1.49–1.85 (m, 5H), 4.05 (d, $J = 6.03$ Hz, 1H), 4.09 (brs, 1H), 6.44 (d, $J = 7.80$ Hz, 2H), 6.60 (t, $J = 7.32$ Hz, 1H), 7.02–7.07 (m, 2H), 7.13–7.17 (m, 2H), 7.37–7.40 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.4$ (C), 141.7 (C), 131.3 (2CH), 129.1 (2CH), 120.4 (C), 128.9 (2CH), 117.2 (CH), 113.1 (2CH), 62.9 (CH), 44.7 (CH), 30.1 (CH_2), 29.3 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 26.3 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu} = 3422$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{19}H_{22}NBr$: 343.0936; found: 342.0828 $[M-H]^+$.

***N*-Phenyl-[1-(*p*-chlorophenyl)-1-cyclohexylmethyl]amine (Table 2, entry 2)**: $R_f = 0.59$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.95$–1.29 (m, 5H), 1.42–1.85 (m, 6H), 4.07 (s, 1H), 4.09 (s, 1H), 6.43–6.46 (m, 2H), 6.58–6.63 (m, 1H), 7.02–7.08 (m, 2H), 7.19–7.26 ppm (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 147.4$ (C), 141.2 (C), 132.3 (C), 129.1 (2CH), 128.6 (2CH), 128.4 (2CH), 117.2 (CH), 113.2 (2CH), 62.8 (CH), 44.8 (CH), 30.1 (CH_2), 29.4 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 26.3 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu} = 3426$ cm^{-1} (NH); HRMS: *m*/*z*: calcd for $C_{19}H_{22}ClN$: 299.1441; found: 298.1346 $[M-H]^+$.

***N*-Phenyl-[1-(*p*-methylphenyl)-1-cyclohexylmethyl]amine (Table 2, entry 3)**: $R_f = 0.63$ (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$–0.90 (m, 1H), 0.95–1.26 (m, 5H), 1.50–1.74 (m, 4H), 1.85–1.88 (m, 1H), 2.27 (s, 3H), 4.06 (d, $J = 6.20$ Hz, 1H), 4.09 (brs, 1H), 6.47 (d, $J = 7.89$ Hz, 2H), 6.57 (t, $J = 7.20$ Hz, 1H), 7.01–7.15 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.8$ (C), 139.5 (C), 136.1 (C), 129.0 (2CH), 128.8 (2CH), 127.1 (2CH), 116.8 (CH), 113.1 (2CH), 63.0 (CH), 44.9 (CH), 30.2 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 21.0 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu} = 3424$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{25}N$: 279.1987; found: 278.1897 $[M-H]^+$.

***N*-Phenyl-(1-phenyl-1-cyclohexylmethyl)amine (Table 2, entry 4)**: $R_f = 0.57$ (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$–1.26 (m, 5H), 1.47–1.54 (m, 1H), 1.60–1.76 (m, 4H), 1.86–1.89 (m, 1H), 4.10 (d, $J = 6.32$ Hz, 1H), 4.12 (brs, 1H), 6.48 (d, $J = 7.72$ Hz, 2H), 6.59 (t, $J = 7.44$ Hz, 1H), 7.02–7.06 (m, 2H), 7.18–7.21 (m, 1H), 7.27–7.28 ppm (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 147.8$ (C), 142.7 (C), 129.0 (2CH), 128.2 (2CH), 127.2 (2CH), 126.7 (CH), 116.9 (CH), 113.1 (2CH), 63.4 (CH), 44.9 (CH), 30.2 (CH_2), 29.4 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 26.3 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu} = 3426$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{19}H_{23}N$: 265.1830; found: 265.1810 $[M]^+$.

***N*-Phenyl-(2-methyl-1-phenylpropyl)amine (Table 2, entry 5)**: $R_f = 0.63$ (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.82$ Hz, 3H), 0.97 (d, $J = 6.78$ Hz, 3H), 1.97–2.08 (m, 1H), 4.10 (s, 1H), 4.12 (s, 1H), 6.49 (d, $J = 7.62$ Hz, 2H), 6.60 (t, $J = 7.30$ Hz, 1H), 7.03–7.08 (m, 2H), 7.16–7.29 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.7$ (C), 142.6 (C), 129.0 (2CH), 128.2 (2CH), 127.2 (2CH), 126.8 (CH), 117.0 (CH), 113.2 (2CH), 63.8 (CH), 34.9 (CH), 19.7 (CH_3), 18.6 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu} = 3426$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{16}H_{19}N$: 225.1517; found: 224.1434 $[M-H]^+$.

***N*-Phenyl-(2-methyl-1-phenylbutyl)amine (Table 2, entry 6)**: $R_f = 0.63$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): two isomers: $\delta = 0.85$–0.94 (m, 12H), 1.10–1.32 (m, 2H), 1.42–1.65 (m, 2H), 1.76–1.81 (m, 2H), 4.07 (brs, 2H), 4.20 (d, $J = 5.82$ Hz, 1H), 4.29 (d, $J = 4.89$ Hz, 1H), 6.48 (d, $J = 8.05$ Hz, 4H), 6.57–6.62 (m, 2H), 7.02–7.08 (m, 4H), 7.17–7.21 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$): two isomers: $\delta = 147.7$ (2C), 142.9 (C), 142.3 (C), 129.0 (2CH), 129.0 (2CH), 128.2 (2CH), 128.1 (2CH), 127.3 (2CH), 127.0 (2CH), 126.7 (CH), 126.6 (CH), 116.9 (2CH), 113.1 (2CH), 113.1 (2CH), 62.5 (CH), 61.4 (CH), 41.8 (CH), 41.5 (CH), 26.8 (CH_2), 25.3 (CH_2), 16.1 (CH_3), 14.4 (CH_3), 12.0 (CH_3), 11.8 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu} = 3428$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{21}N$: 239.1674; found: 238.1592 $[M-H]^+$.

***N*-(*p*-Chlorophenyl)-(1-phenyl-1-cyclohexylmethyl)amine (Table 2, entry 7)**: $R_f = 0.62$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$–1.28 (m, 5H), 1.49–1.53 (m, 1H), 1.57–1.76 (m, 4H), 1.84–1.88 (m, 1H), 4.04 (d, $J = 6.16$ Hz, 1H), 4.14 (brs, 1H), 6.39 (d, $J = 8.79$ Hz, 2H), 6.97 (d, $J = 8.79$ Hz, 2H), 7.17–7.30 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 146.3$ (C), 142.1 (C), 128.8 (2CH), 128.2 (2CH), 127.1 (2CH), 126.9 (CH), 121.4 (C), 114.2 (2CH), 63.4 (CH), 44.8 (CH), 30.1 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.3 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu} = 3428$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{19}H_{22}ClN$: 299.1441; found: 299.1432 $[M]^+$.

***N*-(*m*-Methylphenyl)(1-phenyl-1-cyclohexylmethyl)amine (Table 2, entry 8)**: $R_f = 0.61$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.01$–1.23 (m, 5H), 1.49–1.53 (m, 1H), 1.62–1.71 (m, 4H), 1.84–1.88 (m, 1H), 2.17 (s, 3H), 4.08–4.10 (m, 2H), 6.27 (d, $J = 7.90$ Hz, 1H), 6.34 (s, 1H), 6.41 (d, $J = 7.30$ Hz, 1H), 6.92 (t, $J = 7.70$ Hz, 1H), 7.14–7.27 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 147.8$ (C), 142.8 (C), 138.6 (C), 128.9 (CH), 128.1 (2CH), 127.1 (2CH), 126.6 (CH), 117.9 (CH), 114.0 (CH), 110.1 (CH), 63.3 (CH), 44.9 (CH), 30.2 (CH_2), 29.4 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 21.6 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu} = 3381$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{25}N$: 279.1987; found: 278.1901 $[M-H]^+$.

***N*-Benzyl-(1-phenyl-1-cyclohexylmethyl)amine (Table 2, entry 9)**: $R_f = 0.41$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$–1.26 (m, 5H), 1.37–1.41 (m, 1H), 1.48–1.73 (m, 5H), 1.94–1.98 (m, 1H), 3.35 (d, $J = 7.18$ Hz, 1H), 3.43 (d, $J = 13.24$ Hz, 1H), 3.62 (d, $J = 13.25$ Hz, 1H), 7.18–7.34 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 143.0$ (C), 140.9 (C), 128.2 (2CH), 128.1 (4CH), 128.0 (2CH), 126.7 (2CH), 68.0 (CH), 51.6 (CH_2), 44.3 (CH), 30.2 (CH_2), 29.9 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.3 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu} = 3431$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{20}H_{25}N$: 279.1987; found: 278.1903 $[M-H]^+$.

***N*-Benzyl-(1-phenyl-1-cyclopentylmethyl)amine (Table 2, entry 10)**: $R_f = 0.30$ (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$–1.11 (m, 1H), 1.23–1.67 (m, 6H), 1.77 (s, 1H), 1.86–1.96 (m, 1H), 2.00–2.14 (m, 1H), 3.32 (d, $J = 9.06$ Hz, 1H), 3.43 (d, $J = 13.29$ Hz, 1H), 3.61 (d, $J = 13.29$ Hz, 1H), 7.18–7.31 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 144.0$ (C), 140.9 (C), 128.3 (2CH), 128.1 (4CH), 127.9 (2CH), 126.8 (CH), 126.7 (CH), 68.1 (CH), 51.5 (CH_2), 47.4 (CH), 30.5 (CH_2), 30.3 (CH_2), 25.3 (CH_2), 25.0 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu} = 3418$ cm^{-1} (NH); HRMS (EI): *m*/*z*: calcd for $C_{19}H_{23}N$: 265.1830; found: 264.1760 $[M-H]^+$.

***N*-Benzyl-(2-methyl-1-phenylpropyl)amine (Table 2, entry 11)**: $R_f = 0.30$ (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.74$ (d, $J = 6.80$ Hz, 3H), 0.97 (d, $J = 6.67$ Hz, 3H), 1.81 (brs, 1H), 1.84–1.92 (m, 1H), 3.34 (d, $J = 6.96$ Hz, 1H), 3.46 (d, $J = 13.30$ Hz, 1H), 3.65 (d, $J = 13.29$ Hz, 1H), 7.23–7.35 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$):

δ=142.9 (C), 141.0 (C), 128.3 (2CH), 128.1 (4CH), 128.0 (2CH), 126.8 (CH), 126.8 (CH), 68.7 (CH), 51.7 (CH_2), 34.5 (CH), 19.7 (CH_3), 19.5 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3401 cm^{-1} (NH); HRMS (EI): *m/z*: calcd for $C_{17}H_{21}N$: 239.1674; found: 238.1589 $[M-H]^+$.

***N*-Benzyl-(1-phenyl-2-methylbutyl)amine (Table 2, entry 12)**: R_f=0.38 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): two isomers: δ=0.70–0.93 (m, 6H), 0.95–1.26 (m, 1H), 1.32–1.71 (m, 2H), 1.79 (br s, 1H), 3.43–3.49 (m, 2H), 3.61–3.68 (m, 1H), 7.19–7.35 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$): two isomers: δ=143.2 (C), 142.7 (C), 141.0 (C), 140.9 (C), 128.3, 128.2, 128.2, 128.2, 128.0, 128.0, 128.0, 126.7, 126.7 (overall 20CH), 67.0 (CH), 66.9 (CH), 51.7 (CH_2), 51.7 (CH_2), 41.4 (CH), 40.9 (CH), 26.1 (CH_2), 26.1 (CH_2), 15.6 (CH_3), 15.3 (CH_3), 11.8 (CH_3), 11.4 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3345 cm^{-1} (NH); HRMS (EI): *m/z*: calcd for $C_{18}H_{23}N$: 253.1830; found: 252.1740 $[M-H]^+$.

***N*-Benzyl-[1-(*p*-bromophenyl)-1-cyclohexylmethyl]amine (Table 2, entry 13)**: R_f=0.47 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.78–1.20 (m, 5H), 1.37–1.73 (m, 6H), 1.88–1.92 (m, 1H), 3.33 (d, *J*=6.88 Hz, 1H), 3.41 (d, *J*=13.27 Hz, 1H), 3.60 (d, *J*=13.23 Hz, 1H), 7.15 (d, *J*=8.24 Hz, 2H), 7.22–7.31 (m, 5H), 7.44 ppm (d, *J*=8.28 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=142.1 (C), 140.7 (C), 131.1 (2CH), 129.9 (2CH), 128.3 (2CH), 128.1 (2CH), 126.8 (CH), 120.4 (C), 67.4 (CH), 51.6 (CH_2), 44.3 (CH), 30.1 (CH_2), 29.7 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.2 ppm (CH_2); IR (NaCl, neat): $\tilde{\nu}$=3350 cm^{-1} (NH); HRMS (EI): *m/z*: calcd for $C_{20}H_{24}BrN$: 357.1092; found: 356.1000 $[M-H]^+$.

***N*-Benzyl-[1-(*p*-methylphenyl)-1-cyclohexylmethyl]amine (Table 2, entry 14)**: R_f=0.37 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.75–1.26 (m, 5H), 1.38–1.72 (m, 6H), 1.94–1.98 (m, 1H), 2.34 (s, 3H), 3.32 (d, *J*=7.12 Hz, 1H), 3.43 (d, *J*=13.23 Hz, 1H), 3.62 (d, *J*=13.24 Hz, 1H), 7.10–7.31 ppm (m, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=141.0 (C), 139.9 (C), 136.1 (C), 128.7 (2CH), 128.2 (2CH), 128.1 (2CH), 128.0 (2CH), 126.7 (CH), 67.7 (CH), 51.6 (CH_2), 44.3 (CH), 30.3 (CH_2), 29.9 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 21.1 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3402 cm^{-1} (NH); HRMS (EI): *m/z*: calcd for $C_{21}H_{27}N$: 293.2143; found: 292.2065 $[M-H]^+$.

2-[(1-Cyclohexyl-1-phenylmethyl)amino]-3-methylbutyric acid methyl ester (Table 3, entry 1): R_f=0.65 (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): major isomer: δ=0.83 (d, *J*=6.73 Hz, 3H), 0.90 (d, *J*=6.81 Hz, 3H), 0.83–1.01 (m, 2H), 1.04–1.12 (m, 2H), 1.17–1.29 (m, 1H), 1.36–1.39 (m, 1H), 1.45–1.52 (m, 1H), 1.60–1.61 (m, 2H), 1.72–1.83 (m, 2H), 1.89–1.94 (m, 2H), 2.71 (d, *J*=6.32 Hz, 1H), 3.17 (d, *J*=6.92 Hz, 1H), 3.69 (s, 3H), 7.13–7.29 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): major isomer: δ=176.4 (CO), 142.5 (C), 128.6 (2CH), 127.7 (2CH), 126.8 (CH), 67.3 (CH), 64.5 (CH), 51.2 (CH_3), 44.4 (CH), 31.8 (CH), 29.9 (CH_2), 29.7 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 19.5 (CH_3), 18.6 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3445 (NH), 1732 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{19}H_{29}NO_2$: 303.2198; found: 304.2245 $[M+H]^+$.

2-[(1-Cyclopentyl-1-phenylmethyl)amino]-3-methylbutyric acid methyl ester (Table 3, entry 2): R_f=0.61 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.81 (d, *J*=6.78 Hz, 3H), 0.88 (d, *J*=6.82 Hz, 3H), 0.99–1.12 (m, 1H), 1.16–1.26 (m, 1H), 1.32–1.46 (m, 2H), 1.48–1.69 (m, 3H), 1.72–1.85 (m, 1H), 1.88–2.13 (m, 3H), 2.70 (d, *J*=6.30 Hz, 1H), 3.14 (d, *J*=8.77 Hz, 1H), 3.70 (s, 3H), 7.14–7.28 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=176.3 (CO), 143.6 (C), 128.2 (2CH), 127.9 (2CH), 126.9 (CH), 67.6 (CH), 64.4 (CH), 51.2 (CH_3), 47.6 (CH), 31.7 (CH), 30.2 (CH_2), 30.0 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 19.4 (CH_3), 18.5 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3447 (NH), 1734 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{18}H_{27}NO_2$: 289.2042; found: 288.1964 $[M-H]^+$.

2-[(2-Methyl-1-phenylpropyl)amino]-3-methylbutyric acid methyl ester (Table 3, entry 3): R_f=0.61 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.73 (d, *J*=6.81 Hz, 3H), 0.84 (d, *J*=6.78 Hz, 3H), 0.91 (d, *J*=6.81 Hz, 3H), 0.96 (d, *J*=6.69 Hz, 3H), 1.75–1.87 (m, 2H), 1.90 (br s, 1H), 2.72 (d, *J*=6.39 Hz, 1H), 3.17 (d, *J*=6.73 Hz, 1H), 3.69 (s, 3H), 7.13–7.30 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=175.8 (C), 141.7 (C), 128.6 (2CH), 127.9 (2CH), 127.1 (CH), 68.2 (CH), 64.6 (CH), 51.3 (CH_3), 34.5 (CH), 31.6 (CH), 19.4 (CH_3), 19.3 (2CH_3), 18.7 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3443 (NH), 1732 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{16}H_{25}NO_2$: 263.1885; found: 262.1805 $[M-H]^+$.

2-{[1-Cyclohexyl-1-(*p*-bromophenyl)methyl]amino}-3-methylbutyric acid methyl ester (Table 3, entry 4): R_f=0.61 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.84 (d, *J*=6.76 Hz, 3H), 0.90 (d, *J*=6.78 Hz, 3H), 0.98–1.92 (m, 12H), 2.69 (d, *J*=6.28 Hz, 1H), 2.87 (br s, 1H), 3.17 (d, *J*=6.97 Hz, 1H), 3.70 (s, 3H), 7.13 (d, *J*=8.22 Hz, 2H), 7.40 ppm (d, *J*=8.22 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=175.7 (CO), 141.0 (C), 131.0 (2CH), 130.3 (2CH), 120.7 (C), 66.9 (CH), 64.6 (CH), 51.4 (CH_3), 44.1 (CH), 31.6 (CH), 29.9 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.1 (2CH_2), 19.4 (CH_3), 18.6 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3447 (NH), 1734 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{19}H_{28}BrNO_2$: 381.1303; found: 380.1224 $[M-H]^+$.

2-{[1-Cyclohexyl-1-(*p*-methylphenyl)methyl]amino}-3-methylbutyric acid methyl ester (Table 3, entry 5): R_f=0.61 (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): major isomer: δ=0.83 (d, *J*=6.68 Hz, 3H), 0.90 (d, *J*=6.76 Hz, 3H), 0.94–1.93 (m, 13H), 2.32 (s, 3H), 2.72 (d, *J*=6.40 Hz, 1H), 3.14 (d, *J*=6.88 Hz, 1H), 3.68 (s, 3H), 7.06–7.14 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): major isomer: δ=176.4 (CO), 139.4 (C), 136.2 (C), 128.4 (4CH), 66.9 (CH), 64.5 (CH), 51.1 (CH_3), 44.5 (CH), 31.8 (CH), 29.9 (CH_2), 29.7 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 21.1 (CH_3), 19.4 (CH_3), 18.6 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3447 (NH), 1734 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{20}H_{31}NO_2$: 317.2355; found: 316.2272 $[M-H]^+$.

2-{[1-Cyclohexyl-1-(*p*-chlorophenyl)methyl]amino}-3-methylbutyric acid methyl ester (Table 3, entry 6): R_f=0.63 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.83 (d, *J*=6.75 Hz, 3H), 0.89 (d, *J*=6.81 Hz, 3H), 0.95–1.90 (m, 13H), 2.66 (d, *J*=6.40 Hz, 1H), 3.16 (d, *J*=6.75 Hz, 1H), 3.70 (s, 3H), 7.17–7.26 ppm (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=176.2 (CO), 141.1 (C), 132.4 (C), 129.9 (2CH), 127.9 (2CH), 66.7 (CH), 64.6 (CH), 51.3 (CH_3), 44.4 (CH), 31.8 (CH), 29.9 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 26.2 (2CH_2), 19.5 (CH_3), 18.5 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3447 (NH), 1732 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{19}H_{28}ClNO_2$: 337.1809; found: 336.1722 $[M-H]^+$.

2-[(1-Cyclohexyl-3-phenylpropyl)amino]-3-methylbutyric acid methyl ester (Table 3, entry 7): R_f=0.30, 0.39 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.86 (d, *J*=6.66 Hz, 3H), 0.90 (d, *J*=6.79 Hz, 3H), 0.94–1.35 (m, 5H), 1.44–1.87 (m, 10H), 2.13 (q, *J*=5.12 Hz, 1H), 2.58 (t, *J*=8.25 Hz, 2H), 2.92 (d, *J*=6.54 Hz, 1H), 3.59 (s, 3H), 7.04–7.20 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=176.4 (CO), 143.1 (C), 128.3 (2CH), 128.2 (2CH), 125.5 (CH), 65.5 (CH), 61.3 (CH), 51.2 (CH_3), 40.5 (CH), 32.6 (CH_2), 32.2 (CH), 31.7 (CH_2), 29.3 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 19.4 (CH_3), 18.9 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3449 (NH), 1736 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{21}H_{33}NO_2$: 331.2511; found: 330.2411 $[M-H]^+$.

2-[(1-Cyclopentyl-3-phenylpropyl)amino]-3-methylbutyric acid methyl ester (Table 3, entry 8): R_f=0.43, 0.55 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.96 (d, *J*=6.72 Hz, 3H), 1.00 (d, *J*=6.75 Hz, 3H), 1.20–1.26 (m, 2H), 1.50–2.00 (m, 11H), 2.24–2.30 (m, 1H), 2.52–2.82 (m, 2H), 3.07 (d, *J*=6.63 Hz, 1H), 3.68 (s, 3H), 7.15–7.29 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=176.3 (CO), 143.4 (C), 128.3 (2CH), 128.3 (2CH), 125.5 (CH), 64.9 (CH), 60.7 (CH), 51.2 (CH_3), 43.0 (CH), 33.5 (CH_2), 32.0 (CH), 30.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 19.6 (CH_3), 19.0 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$=3449 (NH), 1736 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{20}H_{31}NO_2$: 317.2355; found: 316.2285 $[M-H]^+$.

3-Methyl-2-[(2-methyl-1-phenethylpropyl)amino]butyric acid methyl ester (Table 3, entry 9): R_f=0.43, 0.55 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ=0.88 (d, *J*=3.78 Hz, 3H), 0.90 (d, *J*=3.78 Hz, 3H), 0.94 (d, *J*=6.78 Hz, 3H), 0.98 (d, *J*=6.76 Hz, 3H), 1.49–1.96 (m, 5H), 2.21 (q, *J*=5.25 Hz, 1H), 2.67 (t, *J*=8.35 Hz, 2H), 3.01 (d, *J*=6.51 Hz, 1H), 3.67 (s, 3H), 7.13–7.29 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ=176.4 (CO), 143.1 (C), 128.3 (2CH), 128.3 (2CH), 125.6 (CH), 65.5 (CH), 62.0 (CH), 51.2 (CH_3), 32.5 (CH_2), 32.3 (CH), 31.9 (CH_2), 30.1 (CH), 19.4 (CH_3), 18.9 (CH_3), 18.7

(CH_3), 18.1 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$ = 3449 (NH), 1736 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{18}H_{29}NO_2$: 291.2198; found: 290.2117 $[M-H]^+$.

2-[(1-Cyclohexylnonyl)amino]-3-methylbutyric acid methyl ester (Table 3, entry 10): R_f = 0.53, 0.62 (EtOAc/hexane 1:8); ^{1}H NMR (300 MHz, $CDCl_3$): major isomer: δ = 0.86–0.96 (m, 9H), 1.16–1.29 (m, 21H), 1.58–1.85 (m, 6H), 2.11–2.12 (m, 1H), 2.99 (d, *J* = 6.60 Hz, 1H), 3.69 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): major isomer: δ = 176.5 (CO), 65.6 (CH), 61.6 (CH), 51.2 (CH_3), 40.7 (CH), 32.1 (CH), 31.9 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 19.3 (CH_3), 18.9 (CH_3), 14.1 ppm (CH_3); IR (NaCl, neat): $\tilde{\nu}$ = 3455 (NH), 1736 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{21}H_{41}NO_2$: 339.3137; found: 338.3055 $[M-H]^+$.

2-[(1-Cyclohexyl-1-phenylmethyl)amino]-2-phenylacetic acid methyl ester:[12] R_f = 0.55, 0.59 (EtOAc/hexane 1:8); ^{1}H NMR (400 MHz, $CDCl_3$): isomer 1: δ = 0.83–0.96 (m, 1H), 1.05–1.27 (m, 5H), 1.40–1.43 (m, 1H), 1.55–1.62 (m, 3H), 1.75–1.78 (m, 1H), 1.97–2.00 (m, 1H), 3.41 (d, *J* = 7.05 Hz, 1H), 3.71 (s, 3H), 4.13 (s, 1H), 7.25–7.33 ppm (m, 10H); isomer 2: δ = 0.69–0.79 (m, 1H), 0.84–0.94 (m, 1H), 1.02–1.08 (m, 2H), 1.12–1.26 (m, 2H), 1.50–1.56 (m, 3H), 1.69–1.73 (m, 1H), 2.06–2.09 (m, 1H), 2.55 (brs, 1H), 3.01 (d, *J* = 7.81 Hz, 1H), 3.56 (s, 3H), 4.09 (s, 1H), 7.11–7.13 (m, 2H), 7.22–7.33 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): isomer 1: δ = 174.5 (CO), 142.2 (C), 138.8 (C), 128.6 (2CH), 128.4 (2CH), 128.1 (2CH), 127.8 (CH), 127.1 (3CH), 67.4 (CH), 62.8 (CH), 51.9 (CH_3), 44.3 (CH), 30.0 (CH_2), 29.7 (CH_2), 26.5 (CH_2), 26.2 ppm ($2CH_2$); isomer 2: δ = 173.3 (CO), 142.1 (C), 138.3 (C), 128.5 (2CH), 128.1 (4CH), 128.0 (2CH), 127.9 (CH), 126.9 (CH), 64.7 (CH), 62.4 (CH), 52.2 (CH_3), 43.9 (CH), 30.2 (CH_2), 30.0 (CH_2), 26.5 (CH_2), 26.2 ppm ($2CH_2$); IR (NaCl, neat): $\tilde{\nu}$ = 3447 (NH), 1738 cm^{-1} (C=O); HRMS (EI): *m/z*: calcd for $C_{22}H_{27}NO_2$: 337.2042; found: 336.1946 $[M-H]^+$.

Acknowledgement

We gratefully acknowledge the Nanyang Technological University, A* STAR (no. M47110000), and Ministry of Education (no. M45110000) for funding this research.

[1] Organic reactions in water, for reviews see: a) C. J. Li, *Acc. Chem. Res.* **2002**, *35*, 533; b) C. I. Herrerías, X. Q. Yao, Z. P. Li, C. J. Li, *Chem. Rev.* **2007**, *107*, 2546; c) K. K. Chauhan, C. G. Frost, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3015; d) B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347; e) G. Babu, P. T. Perumal, *Aldrichimica Acta* **2000**, *33*, 16; f) T. P. Loh in *Science of Synthesis* (Ed.: H. Yamamoto), Georg Thieme Verlag Stuttgart, New York, **2004**, pp. 413; g) C. J. Li, T. H. Chan, *Tetrahedron* **1999**, *55*, 11149; h) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095; i) C. J. Li, *Chem. Rev.* **1993**, *93*, 2023; j) C. J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68; k) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563; l) S. Kobayashi, A. K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209; m) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751.

[2] a) R. B. Wang, C. M. Lim, C. H. Tan, B. K. Lim, K. Y. Sim, T. P. Loh, *Tetrahedron: Asymmetry* **1995**, *6*, 1825; b) X. R. Li, T. P. Loh, *Tetrahedron: Asymmetry* **1996**, *7*, 1535; c) T. P. Loh, G. Q. Cao, J. Pei, *Tetrahedron Lett.* **1998**, *39*, 1453; d) T. P. Loh, X. R. Li, *Eur. J. Org. Chem.* **1999**, 1893; e) T. P. Loh, J. R. Zhou, Z. Yin, *Org. Lett.* **1999**, *1*, 1855; f) T. P. Loh, J. R. Zhou, *Tetrahedron Lett.* **1999**, *40*, 9115; g) T. P. Loh, J. R. Zhou, *Tetrahedron Lett.* **2000**, *41*, 5261; h) T. P. Loh, J. M. Huang, K. C. Xu, *Tetrahedron Lett.* **2000**, *41*, 6511; i) T. P. Loh, H. Y. Song, *Synlett* **2003**, 2119; j) T. P. Loh, Z. Yin, H. Y. Song, K. L. Tan, *Tetrahedron Lett.* **2003**, *44*, 911; k) J. M. Huang, K. C. Xu, T. P. Loh, *Synthesis* **2003**, 755.

[3] a) N. Kalyanam, G. V. Rao, *Tetrahedron Lett.* **1993**, *34*, 1647; b) M. R. Pitts, J. R. Harrison, C. J. Moody, *J. Chem. Soc. Perkin Trans. 1* **2001**, *9*, 955; c) T. Tsukinoki, S. Nagashima, Y. Mitoma, M. Tashiro, *Green Chem.* **2000**, *2*, 117; d) M. P. Dutta, B. Baruah, A. Boruah, D. Prajapati, J. S. Sandhu, *Synlett* **1998**, 857; e) B. Baruah, D. Prajapati, J. S. Sandhu, *Tetrahedron Lett.* **1995**, *36*, 6747.

[4] For reviews see: a) H. Miyabe, M. Ueda, T. Naito, *Synlett* **2004**, 1140, and references therein; b) H. Miyabe, T. Naito, *Org. Biomol. Chem.* **2004**, *2*, 1267; for examples, see: c) H. Miyabe, M. Ueda, T. Naito, *J. Org. Chem.* **2000**, *65*, 5043; d) H. Miyabe, M. Ueda, A. Nishimura, T. Naito, *Tetrahedron* **2004**, *60*, 4227; e) H. Miyabe, M. Ueda, A. Nishimura, T. Naito, *Org. Lett.* **2002**, *4*, 131; f) H. Miyabe, M. Ueda, T. Naito, *Chem. Commun.* **2000**, 2059; g) M. Ueda, H. Miyabe, A. Nishimura, H. Sugino, T. Naito, *Tetrahedron: Asymmetry* **2003**, *14*, 2857; h) H. Miyabe, A. Nishimura, M. Ueda, T. Naito, *Chem. Commun.* **2002**, 1454; i) M. Ueda, H. Miyabe, H. Sugino, T. Naito, *Org. Biomol. Chem.* **2005**, *3*, 1124.

[5] For the alkylation of activated perfluorophenyl aromtic aldimines see: X. Y. Liu, S. Z. Zhu, S. W. Wang, *Synthesis* **2004**, 683.

[6] For the alkylation of simple imines with limited substrates (only three pieces of data were reported) see: T. Huang, C. C. K. Keh, C. J. Li, *Chem. Commun.* **2002**, 2440.

[7] Recently, a radical-type alkylation reaction of imines by using Ti^{III} and PhN_2^+ in acidic aqueous media has been reported with limited substrates and moderate selectivities: R. Cannella, A. Clerici, N. Pastori, E. Regolini, O. Porta, *Org. Lett.* **2005**, *7*, 645.

[8] For the alkylation of aldehydes in aqueous media see: C. C. K. Keh, C. M. Wei, C. J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 4062.

[9] In the process of our research, studies on Barbier–Grignard-type alkylation reactions of simple imines in aqueous media, a comparable result has been obtained by using a In/CuI/$InCl_3$ system; see: Z. L. Shen, T. P. Loh, *Org. Lett.* **2007**, in press.

[10] For reviews on indium-mediated organic reactions see: a) T. P. Loh, G. L. Chua, *Chem. Commun.* **2006**, 2739; b) K. K. Chauhan, C. G. Frost, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3015; c) P. Cintas, *Synlett* **1995**, 1087; d) J. Podlech, T. C. Maier, *Synthesis* **2003**, 633; e) V. Nair, S. Ros, C. N. Jayan, B. S. Pillai, *Tetrahedron* **2004**, *60*, 1959; f) J. Auge, N. Lubin-Germain, J. Uziel, *Synthesis* **2007**, 1739.

[11] For primary iodide and tertiary iodide, the one-pot reaction of benzaldehyde, aniline, and *n*-hexyl iodide or *tert*-butyl iodide proceeded sluggishly under optimized conditions to give the desired products in very low yields. No desired products were obtained when the reaction system was applied to alkyl bromide and alkyl chloride.

[12] Application of the optimized reaction conditions to other chiral amines, such as (*S*)-(+)-2-phenylglycine methyl ester, gave the corresponding product in 62% yield, and with a 50:50 dr (separable isomers).

[13] T. P. Loh, S. L. Chen, *Org. Lett.* **2002**, *4*, 3647.

Received: September 16, 2007
Published online: December 4, 2007

