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Three Component Synthesis of β-Amino Carbonyl Compounds Using Indium Trichloride-Catalyzed One-pot Mannich-type Reaction in Water

Teck-Peng Loh,* Sarah B. K. W. Liung, Kee-Leng Tan and Lin-Li Wei

Department of Chemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260

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Abstract—The use of indium trichloride as catalyst in a one-pot Mannich reaction in water gives high yields for the formation of β-aminoketones/esters/acids is described. The catalyst can be recycled when the reaction is complete (Loh T.-P.; Wei L.-L. *Tetrahedron Lett.* **1998**, *39*, 323).

Introduction

The Mannich reaction is a classical method for the preparation of β-amino ketones and aldehydes[2] and has been one of the most important basic reactions in organic chemistry for its use in natural product and pharmaceutical syntheses. However, due to the drastic reaction conditions and the long reaction times, the classical intermolecular Mannich reaction is plagued by a number of serious disadvantages.[2] The Lewis acid-catalyzed condensation of silyl enol ethers or silyl ketene acetals to pre-formed imines is an excellent variant of the classical Mannich reaction.[3–11] However, this Lewis acid-catalyzed three component reaction of aldehydes, amines and silyl enolates in the same vessel has to be carried out under strict anhydrous conditions because many of the imines are unstable in water. In addition, most Lewis acids cannot be used in this one-pot reaction because of the presence of free amines and water produced in the imine formation.

In this article, we propose an efficient one-pot method for the preparation of β-amino esters and ketones from aldehydes using $InCl_3$ as catalyst in pure water. We have also carried out NMR studies to elucidate the role of indium trichloride.

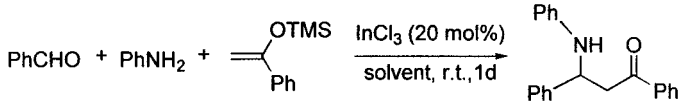
Results and Discussion

This Mannich type reaction using silyl enol ethers or silyl ketene acetals in pure water, to our knowledge, has never been investigated.[1] Nevertheless, we have done so by first trying the Mannich type reaction in polar organic solvents such as THF and acetonitrile (Scheme 1).

Table 1 shows that $InCl_3$ can promote this Mannich type reaction smoothly in both polar organic solvents and pure water.[20] The isolated yields of the product carried out in different solvent systems are comparable.

Further to our research, we have also successfully employed a convenient method for similar Mannich type reactions using aldehydes, amines and ketones at ambient temperature to give various β-amino ketones in good yields. A preview of our work is illustrated below (Scheme 2) and detailed studies are now in progress.

Due to the numerous advantages of using water as a solvent in organic reactions,[12] the following reactions using various aldehydes, such as formaldehyde, 2-pyridine carboxaldehyde, and benzaldehyde with silyl enol ethers **B**–**D** and silyl ketene acetal **A**, have been performed in pure H_2O (Scheme 3).



Scheme 1.

Keywords: one-pot Mannich reaction; β-aminoketones; indium trichloride.
* Corresponding author. Fax: +65-7791691; e-mail: chmlohtp@nus.edu.sg

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Table 1. Mannich reactions in different solvents

Entry	Solvents	Yield[a] (%)
1	CH_3CN	80
2	THF	82
3	H_2O	75

[a] Isolated yield

The catalyst could be recovered and reused after the reactions were complete. The experimental procedure was extremely simple: after normal work-up procedure, the separated aqueous layer could be used for the repeat reaction.

In addition, glyoxylic acid has also been used for the investigations (Scheme 4). The yields of glyoxylic acid reactions ranged from low to moderate (Table 3). Nonetheless, these results demonstrate a convenient method for the preparation of α-amino acids.

We have also attempted reactions using prochiral silyl enol ethers and discovered that the diastereoselectivities were poor, with the *syn* product being the major product. Two sets of reactions using prochiral silyl enol ethers were carried out, one with 1-phenyl-1-trimethylsilyloxypropene **C** and the other with 1-trimethylsiloxycyclopentene **D**. From the results in Table 2, we report that the predominant isomer obtained was always the *syn* isomer, regardless of the stereochemistry of the starting silyl enol ether. Furthermore, the *syn* selectivity improved when the silyl enol ether had a predominant *E* configuration (refer to Table 2). This observation is contrary to previous papers[15–18] that reported on the *anti* selectivity being the major product in the $InCl_3$-catalysed Mannich reaction.[13a,b,14]

We probed the reaction further by performing several experiments involving aliphatic imines derived from alkyl aldehydes (such as valeraldehydes, carboxylcyclohexaldehyde) but found that the yields were poor. Furthermore, the use of alkyl amines (such as benzylamine and methyl benzylamine) also failed to give the desired products which implies that this reaction is limited to non-enolizable imines.

During the course of our investigations, the Mukaiyama–aldol reaction has also been observed in some cases. Compared to the yields of the desired Mannich reaction, the yields of Mukaiyama–aldol reactions were much lower; hence we deduce that in the reaction mixture, free aldehyde and imine could exist together, since the imine formation reaction would be in equilibrium, and these different yields would indicate that the Mannich reaction is faster than the Mukaiyama–aldol reaction. In order to justify our proposal, NMR studies were conducted.

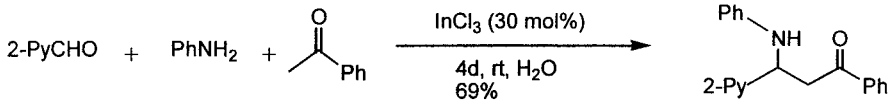
NMR Studies of the $InCl_3$ Catalyzed Mannich-type Reaction in D_2O

Aldimine vs benzaldehyde

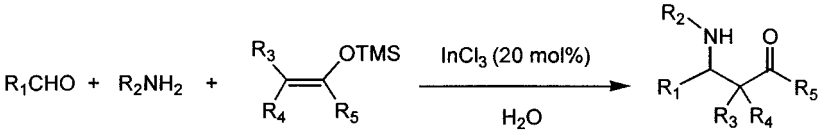
First, we investigated the Mannich-type reaction of benzaldehyde (0.5 mmol) and aniline (0.6 mmol) with 1-phenyl-1-trimethylsilyloxyethene (1.0 mmol) in D_2O (5 mL) with and without $InCl_3$ (20 mol%). The progress of reaction was monitored by ^1H NMR in D_2O. The reaction mixture was extracted with $CDCl_3$ and the extract was also examined directly.

Without the addition of $InCl_3$, the spectra of the reaction mixture in both D_2O and $CDCl_3$ (extracted into $CDCl_3$) showed the progress of the formation of imine (benzaldehyde with aniline) and no products from the aldol reaction and Mannich type reaction were observed.

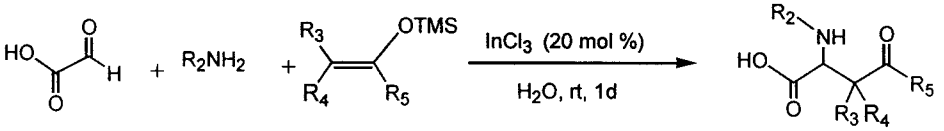
On the contrary, in the presence of $InCl_3$ (20 mol%), the ratio of benzaldehyde/imine/Mannich-product in the Mannich reaction was 28:59:13 after 7 h of mixing. After 22.5 h, the ratio was 21:34:45 and no aldol product was observed.



Scheme 2.

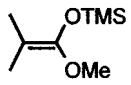
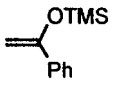
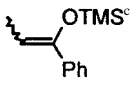


Scheme 3.



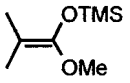
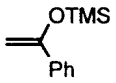
Scheme 4. ***1–3***: R_3=R_4=Me, R_5=OMe; ***1***: R_2=Ph; ***2***: R_2=4-ClC_6H_5; ***3***: R_2 = 4-$CH_3OC_6H_5$; ***4***: R_2=4-ClC_6H_5, R_3=R_4=H, R_5=Ph.

Table 2. Synthesis of β-amino ketones in water

Entry	Aldehyde (R^1)	Amine (R^2)	Yield (%)[a]		(*syn*/*anti*)[b]	
						
			A	**B**	**C**	**D**
1	H	Ph	30, 8[d]	91 (88)[e]	58	46
2	Ph	Ph	54	75 (74)[e]	80 (57:43)	68 (59:41)
3	2-Py	Ph	92	94	70[f] (69:31)	60 (52:48)
4	H	4-ClPh	21	85	78	60
5	Ph	4-ClPh	23	60	26 (60:40)	17 (74:26)
6	2-Py	4-ClPh	90	91	55[g] (57:43)	35 (64:36)
7	H	4-CH_3OPh	35, 17[h]	86	41, 5[i]	20
8	Ph	4-CH_3OPh	30	40	45 (51:49)	11 (76:24)
9	2-Py	4-CH_3OPh	90	90	70[j] (66:34)	20 (76:24)

[a] Isolated yield.
[b] The diastereoselectivity was determined by ^{1}H NMR.
[c] *E*/*Z*=4:1.
[d] Yield of $PhN(CH_2C(CH_3)_2CO_2CH_3)_2$.
[e] Yield (in parenthesis) obtained from separated aqueous layer from previous reaction containing $InCl_3$.
[f] The yield of aldol product was 10%.
[g] The yield of aldol products was 23%.
[h] Yield of 4-$CH_3OPhN(CH_2C(CH_3)_2CO_2CH_3)_2$.
[i] The yield of 4-$CH_3OPh(CH_2(CH_3)CHCOPh)_2$.
[j] The yield of aldol product was 11%.

Table 3. Synthesis of α-amino acid in water using glyoxylic acid

Entry	Amine (R^2)	Yield (%)[a]	
			
		A	**B**
1	Ph	~10	–[b]
2	4-ClPh	31	63
3	4-CH_3OPh	10	–[b]

[a] Isolated yield.
[b] Decomposed.

Next, the competitive reaction was carried out in the presence of excess benzaldehyde. The experimental procedure is as follows: benzaldehyde (1 mmol), aniline (0.5 mmol) and $InCl_3$ (0.2 mmol) in the same manner were stirred for half an hour in D_2O (5 mL) before the addition of silyl enol ether (0.5 mmol) (Fig. 1). After mixing all the reactants for 7 h, the ratio of benzaldehyde/imine/Mannich-product was 62:33:5. After 22 h, the ratio changed to 47:20:33. Again, no aldol product was observed. For comparison purposes, the ^{1}H NMR spectra of pure aldol product, Mannich product and aldimine are presented (Fig. 2). Therefore, these results demonstrated the significance of $InCl_3$ as a catalyst in the Mannich type reaction of aldimine over the aldol reaction of benzaldehyde with silyl enol ether.

Aldimine vs 2-pyridine carboxaldehyde

Next, we employed 2-PyCHO (2-pyridine carboxaldehyde), a more reactive aldehyde for our studies in the reaction of the imine (derived from 2-PyCHO and aniline) with silyl ketene acetal in D_2O. The reactions were carried out as

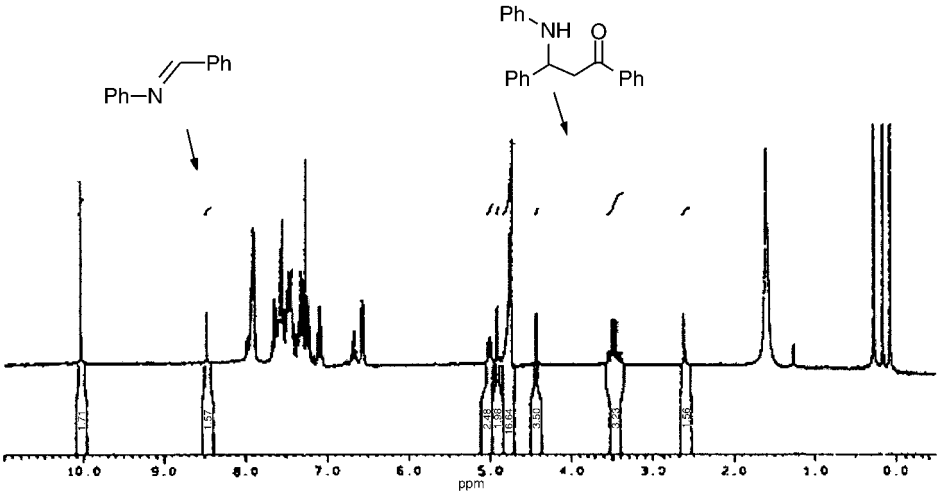


Figure 1. 22 h after mixing benzaldehyde and aniline (extracted into $CDCl_3$ and monitored by ^{1}H NMR).

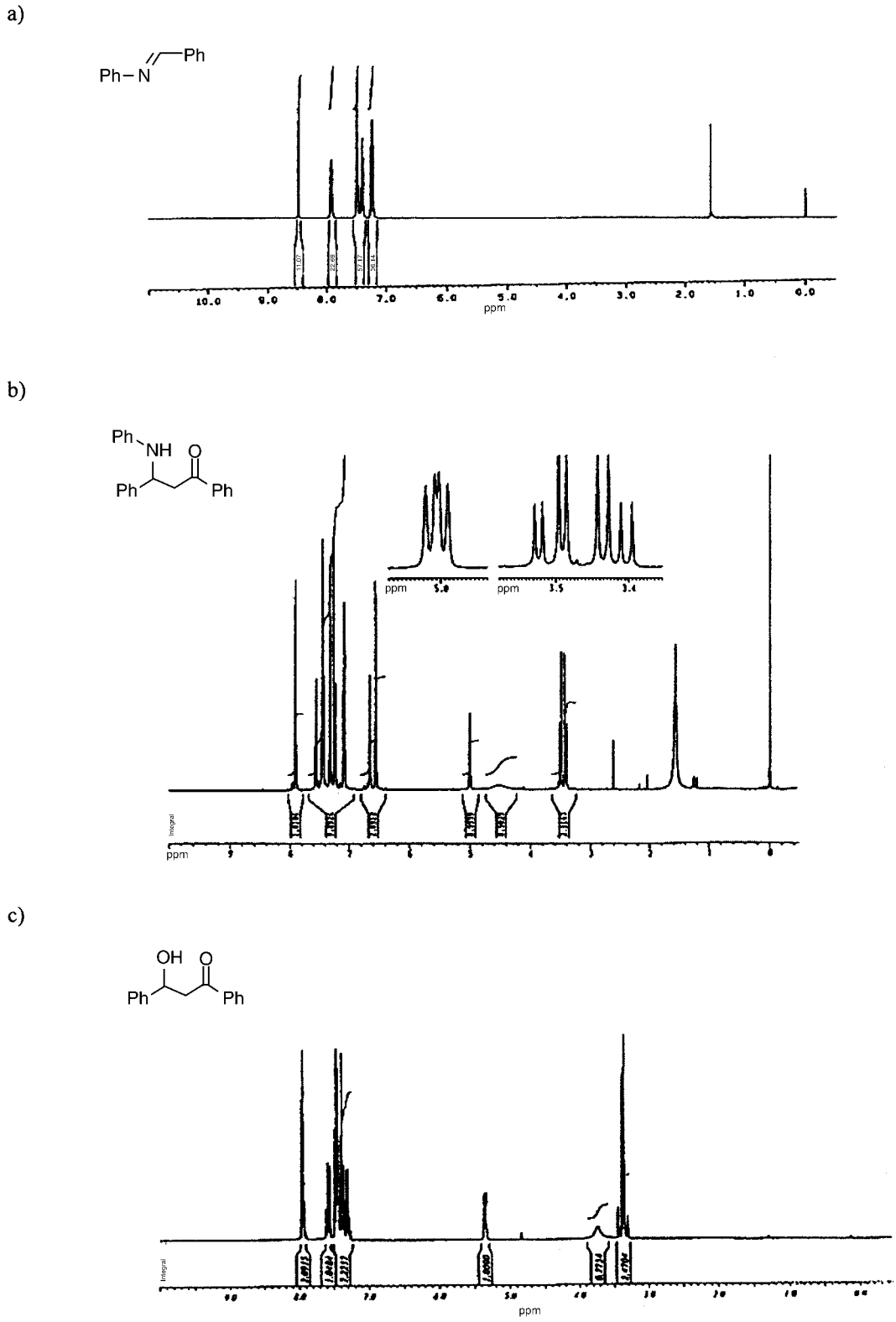
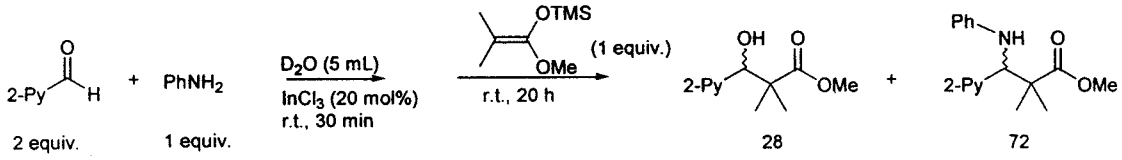


Figure 2. ^{1}H NMR of the pure products (a), (b) and (c)

follows: 2-PyCHO (0.5 mmol), aniline (0.6 mmol) were mixed for half an hour in D_2O (5 mL) before the addition of silyl ketene acetal (1 mmol).

In the absence of $InCl_3$, the imine, the aldol product, aniline and traces of 2-PyCHO were in the reaction mixture after 17 h of mixing. The ratio of imine and aldol-product was 58:42 and no Mannich product was observed. Nevertheless, addition of $InCl_3$ (20 mol%) into the reaction mixture largely converted the 2-PyCHO into the Mannich product together with a trace amount of the aldol-product in a 95:5 ratio after 17 h of mixing.



Scheme 5.

Next, the competitive experiment of imine (derived from 2-PyCHO and aniline) using excess 2-PyCHO was carried out as follows: 2-PyCHO (1 mmol), aniline (0.5 mmol) and $InCl_3$ (0.2 mmol) were stirred in D_2O (5 mL) before adding silyl ketene acetal (0.5 mmol). Based on NMR studies, the conversion of aniline to imine was at least 95% complete in the presence of $InCl_3$ after half an hour of mixing. Therefore, the ratio of 2-PyCHO and imine was about 50:50 in the reaction system when silyl ketene acetal (1 equiv.) was added. From ^1H NMR spectra, the ratio of aldol-product and Mannich product was 28:72 after 20 h of mixing (Scheme 5).

This result indicates that even in the presence of excess aldehyde, the Mannich product is still obtained as the major product.

It is therefore clear that $InCl_3$ plays an important role in Mannich type reactions in water. As we have presented above, in the presence of $InCl_3$, the reaction using an excess of benzaldehyde preferentially reacts with the silyl enol ether to give the expected Mannich product without a trace of the competing aldol product. When a more reactive aldehyde is used in excess, for example, 2-pyridine carboxaldehyde, $InCl_3$ promotes the formation of the Mannich product preferentially over the aldol product, but without $InCl_3$ only the aldol product is observed.

Conclusions

In summary, the synthesis of β-amino ketones from aldehydes has been achieved in water using indium trichloride as catalyst. The catalyst could be recovered after the reaction was complete and could be reused for a repeat reaction without any significant drop in reactivity. Commercially available formaldehyde solution and glyoxylic acid monohydrate were used directly to give the corresponding β-amino ketones in good yields, whilst glyoxylic acid monohydrate yielded the α-amino acids, which provides a convenient method of preparing α-amino acids. However, this methodology is limited to non-enolizable imines. In the conventional Mannich reaction, deamination of Mannich bases to produce α,β-unsaturated derivatives resulted in undesirable side reactions, no deamination occurred with this reaction. The main side-reactions in this methodology is the aldol reaction between aldehydes and the silyl enol ethers and further alkylation of Mannich products but they were only observed occasionally. The high efficiency using simple starting materials and a catalytic amount of a reusable catalyst in water is especially noteworthy.

NMR studies indicated that $InCl_3$ is essential for this Mannich-type reaction in water. Without $InCl_3$, only imines and aldol products were obtained. In the presence of $InCl_3$, however, the Mannich reaction proceeded smoothly in water. The results of competitive experiments show that the use of $InCl_3$ changed the reactivities of imine and aldehydes. *Thus, $InCl_3$ catalyzes the Mannich reaction of imines preferentially over the aldol reaction of aldehydes.*

β-Amino carbonyl compounds are useful intermediates for the synthesis of various biologically active compounds. Therefore the development of new synthetic strategies for combinatorial synthesis, which will lead to large libraries of these compounds, is of much interest. In this article, we have developed a new method for the preparation of β-amino carbonyl compounds using a Lewis acid-catalyzed reaction in water. We envisage that these three component organic reactions in water, where the catalyst remains in the aqueous layer after the reaction, will be useful for combinatorial library construction. According to this method, large quantities of β-amino ketones and ester can be prepared (quantities greater than 100 mg).

Further studies to apply this reaction to the synthesis of natural products as well as to develop new synthetic reactions using indium trichloride in conjunction with a water-soluble ligand as a chiral catalyst are now in progress.

Experimental

General methods and materials

NMR spectra were recorded on a Bruker ACF 300 NMR or AMX 500 NMR. MS spectra were obtained with a Hewlett–Packard 5890A gas chromatograph. HR-mass spectra (EI) were obtained with V.G. Micromass 7035. IR spectra were measured with a Perkin–Elmer 1600 FTIR spectrometer. Column chromatography was performed on silica gel, Merck grade 60 (40–63 μm particle size). All the solvents were distilled before use. Silyl enol ethers were prepared according to the references or purchased from Fluka. Aniline, benzaldehyde and 2-PyCHO were distilled before used. Formaldehyde, glyoxylic acid monohydrate, amines and indium trichloride were purchased (Aldrich) and used directly.

Formaldehyde (46 μL, 0.5 mmol, 37% in water) and indium trichloride (22.6 mg, 0.1 mmol, 98%) were mixed and stirred at room temperature in water (5 mL) for 10 min before the addition of aniline (distilled, 46.6 mg, 0.6 mmol). The resulting mixture was stirred at room temperature for 30 min. 1-Methoxy-1-trimethylsilyloxypropene **A** (183 mg, 1 mmol, 95%) was then added. The suspension was stirred at room temperature for 1 day and then extracted with ethyl acetate (25 mL) three times. The organic layers were

combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The corresponding products **1A** and **1A′** (see Table 2, footnote d) were obtained in 30% (31 mg, based on aniline) and 8% yield (13 mg, based on aniline) separately after silica gel column chromatography.

Methyl 2,2-dimethyl-3-(phenylamino)propanoate 1A (Table 2, Entry 1, product of **A**). Yellowish, wet-solid; R_f 0.61 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.19–7.13 (m, 2H), 6.71–6.61 (m, 3H), 3.68 (s, 3H), 3.23 (s, 2H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 177.40, 148.41, 129.12, 117.29, 112.84, 64.49, 52.60, 51.92, 43.56, 23.45; FTIR (thin film) 1717.1 cm^{-1}; MS (*m/z*, relative intensity) 207 (61), 106 (100), 101 (2), 77 (64), 59 (13), 29 (7); HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1244.

Methyl 3-{[2-(methoxycarbonyl)-2-methylpropyl]phenylamino}-2,2-dimethylpropanoate 1A′. Dark brown, wet-solid; mp 48–50°C; R_f 0.55 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.16–7.11 (m, 2H), 6.94–6.91 (m, 2H), 6.70–6.66 (m, 1H), 3.60 (s, 4H), 3.40 (s, 6H), 1.10 (s, 12H); ^{13}C NMR ($CDCl_3$): δ 177.50, 148.87, 128.57, 118.52, 118.42, 60.74, 51.47, 45.00, 23.82; FTIR (thin film) 1730.6 cm^{-1}; MS (*m/z*, relative intensity) 321 (35), 290 (10), 262 (5), 220 (92), 115 (50), 77 (60), 59 (100); HRMS calcd for $C_{18}H_{27}NO_4$ 321.1940, found 321.1928.

Methyl 2,2-dimethyl-3-phenyl-3-(phenylamino)propanoate 2A. Known[19a–d] (Table 2, Entry 2, product of **A**). Benzaldehyde (53 mg, 51 μL, 0.5 mmol, distilled) and indium trichloride (22.6 mg, 0.1 mmol, 98%) were stirred in water (5 mL) at room temperature for 10 min before aniline (distilled, 55.9 mg, 0.6 mmol) was added. The resulting mixture was stirred at room temperature for 30 min before the addition of 1-methoxy-1-trimethylsilyloxypropene **A** (183 mg, 1 mmol, 95%). The suspension was stirred at room temperature for 1 day and then extracted with ethyl acetate (25 mL×3). The organic layers were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The corresponding product was obtained in 54% yield (76 mg) after silica gel chromatography. Yellowish wet-solid; R_f 0.61 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.31–7.23 (m, 5H), 7.10–7.03 (m, 2H), 6.65–6.50 (m, 3H), 4.53 (s, 1H), 3.67 (s, 3H), 1.30 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.97, 146.86, 139.17, 128.95, 128.21, 127.93, 127.38, 117.22, 113.34, 64.30, 52.01, 46.95, 24.48, 20.65; FTIR (thin film) 1715.8 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1568.

Methyl 2,2-dimethyl-3-(phenylamino)-3-(2-pyridyl)propanoate 3A (Table 2, Entry 3, product of **A**). 2-Pyridinecarboxaldehyde (54 mg, 48 μL, 0.5 mmol, 99%) and indium trichloride (22.6 mg, 0.1 mmol, 98%) were stirred in water (5 mL) at room temperature for 10 min before aniline (distilled, 55.9 mg, 0.6 mmol) was added. The resulting mixture was stirred at room temperature for 30 min before the addition of 1-methoxy-1-trimethylsilyloxypropene **A** (183 mg, 1 mmol, 95%). The suspension was stirred at room temperature for 1 day and then extracted with ethyl acetate (25 mL×3). The organic layers were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The corresponding product was obtained in 92% yield (131 mg) after silica gel chromatography. Yellowish oil; mp 105–107°C; R_f 0.55 (hexane/ethyl acetate=2:1); ^1H NMR ($CDCl_3$): δ 8.57–8.54 (m, 1H), 7.59–6.61 (m, 8H), 4.76 (s, 1H), 3.67 (s, 3H), 1.254 (s, 3H), 1.249 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 177.05, 159.22, 148.76, 136.10, 129.09, 123.12, 122.41, 117.73, 113.99, 64.93, 51.98, 47.55, 23.34, 21.59; FTIR (thin film) 1730.8 cm^{-1}; MS (*m/z*, relative intensity) 284 (24), 183 (99), 101 (2), 78 (45), 42 (8); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1514.

3-(Methoxycarbonyl)-3-methyl-2-(phenylamino) butanoic acid 1 (Table 3, Entry 1, product of **A**). Glyoxylic acid monohydrate (46 mg, 0.5 mmol) and indium trichloride (22.6 mg, 0.1 mmol, 98%) were stirred in water (5 mL) at room temperature for 10 min before aniline (distilled, 93.1 mg, 1.0 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. 1-Methoxy-1-trimethylsilyloxypropene **A** (183 mg, 1 mmol, 95%) was then added. The suspension was stirred at room temperature for 1 day. The corresponding product was obtained after the usual acid–base workup in 10% yield (13 mg). Yellowish, wet-solid; R_f 0.47 (hexane/ethyl acetate/ HOAc=1:2:0.1; ^1H NMR ($CDCl_3$): δ 7.22–7.17 (m, 2H), 6.81–6.71 (m, 3H), 4.35 (s, 1H), 3.71 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (Acetone-d_6): δ 177.21, 149.69, 130.57, 119.62, 115.49, 64.17, 53.00, 47.18, 23.25, 22.88; FTIR (thin film) 1735.1, 1713.6 cm^{-1}; MS (*m/z*, relative intensity) 207 (4), 206 [(M−COOH)+, 7], 160 (52), 102 (36), 77 (59); HRMS calcd for M $C_{13}H_{17}NO_4$ 251.1158, $(M-COOH)^+$ 206.1181, found $(M-COOH)^+$ 206.1165.

Methyl 3-[(4-chlorophenyl) amino]-2,2-dimethylpropanoate 4A (Table 2, Entry 4, product of **A**). Yield 21%; colorless wet-solid, mp 113–115°C; R_f 0.55 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.10–7.07 (m, 2H), 6.55–6.52 (m, 2H), 3.67 (s, 3H), 3.19 (d, J=6.0 Hz, 2H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 177.42, 147.08, 129.01, 121.85, 113.99, 52.79, 52.08, 43.68, 23.54; FTIR (thin film) 1713.4 cm^{-1}; MS (*m/z*, relative intensity) 241 (13), 140 [$(M-C_6H_4NHCH_2^+)$, 99], 59 (15); HRMS calcd for $C_{12}H_{16}{}^{35}ClNO_2$ 241.0870, found 241.0855.

Methyl 3-[(4-chlorophenyl)amino]-2,2-dimethyl-3-phenylpropanoate 5A (Table 2, Entry 5, product of **A**). Yield 23%; yellowish wet-solid; R_f 0.58 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.28–7.25 (m, 5H), 6.99–6.96 (m, 2H), 6.43–6.40 (m, 2H), 4.42 (br, 1H), 3.65 (s, 3H), 1.28 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.86, 145.42, 138.69, 128.75, 128.13, 128.00, 127.54, 121.82, 114.39, 64.54, 52.02, 46.85, 24.56, 20.62; FTIR (thin film) 1716.1 cm^{-1}; MS (*m/z*, relative intensity) 317 (8), 216 (100), 111 (22), 105 (4), 101 (2), 77 (12); HRMS calcd for $C_{18}H_{20}{}^{35}ClNO_2$ 317.1183, found 317.1200.

Methyl 3-[(4-chlorophenyl)amino]-2,2-dimethyl-3-(2-pyridyl) propanoate 6A (Table 2, Entry 6, product of **A**). Yield 90%; yellowish wet-solid: mp 92–94°C; R_f 0.53 (hexane/ethyl acetate=2:1); ^1H NMR ($CDCl_3$): δ 8.56–8.54 (m, 1H), 7.60–7.55 (m, 1H), 7.26–7.00 (m, 4H), 6.61–6.55 (m, 2H), 4.69 (s, 1H), 3.66 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.98, 158.73, 148.87, 148.21, 136.21,

128.93, 123.16, 122.59, 115.16, 65.16, 52.08, 47.48, 23.55, 21.37; FTIR (thin film) 1723.2 cm^{-1}; MS (*m/z*, relative intensity) 318 (10), 217 (21), HRMS calcd for $C_{17}H_{19}{}^{35}ClN_2O_2$ 318.1135, found 318.1140.

2-[(4-Chlorophenyl)amino]-3-(methoxycarbonyl)-3-methylbutanoic acid *2* (Table 3, Entry 2, product of **A**). Yield 31%; yellowish wet-solid; R_f 0.32 (hexane/ethyl acetate/HOAc=1:2:0.1); ^1H NMR ($CDCl_3$) δ 7.13–7.10 (m, 2H), 6.65–6.62 (m, 2H), 4.28 (s, 1H), 3.69 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.02, 175.96, 145.53, 129.09, 123.60, 115.22, 63.28, 52.35, 45.82, 22.43, 21.80; FTIR (thin film) 1715.9 cm^{-1}; MS (*m/z*, relative intensity) 285 (1), 241 (40), 240 (12), HRMS $C_{13}H_{16}{}^{35}ClNO_4$, calcd for $(M-CO_2H)^+$ $C_{12}H_{15}{}^{35}ClNO_2$ 240.0791, found 240.0788.

Methyl 3-[4-methoxyphenyl)amino]-2,2-dimethylpropanoate 7A (Table 2, Entry 7, product of **A**). Yield 35%; dark brown wet-solid; R_f 0.47 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 6.79–6.57 (m, 4H), 3.74 (s, 3H), 3.67 (s, 3H), 3.18 (s, 2H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 177.42, 152.04, 142.72, 114.77, 114.28, 55.72, 53.95, 51.84, 43.51, 23.46; FTIR (thin film) 1724.7 cm^{-1}; MS (*m/z*, relative intensity) 237 (84), 206 (8), 136 (100), 122 (65), 108 (59); HRMS calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1376.

Methyl 3-{[2-(methoxycarbonyl)-2-methylpropyl](4-methoxyphenyl) amino}-2,2-dimethylpropanoate 7A′ (Table 2, Entry 7, see Table footnote h). Yield 17%; dark brown wet-solid; R_f 0.47 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 6.96–6.71 (m, 4H), 3.73 (s, 3H), 3.43 (s, 4H), 3.36 (s, 6H), 1.09 (s, 12H); ^{13}C NMR ($CDCl_3$): δ 177.45, 153.69, 143.26, 123.24, 113.79, 63.77, 55.33, 51.34, 44.81, 23.80; FTIR (thin film) 1731.5 cm^{-1}; MS (*m/z*, relative intensity) 351 (40), 320 (5), 250 (99), 115 (33), 59 (90); HRMS calcd for $C_{19}H_{29}NO_5$ 351.2046, found 351.2061.

Methyl 3-[(4-methoxyphenyl)amino]-2,2-dimethyl-3-phenylpropanoate 8A (Table 2, Entry 8, product of **A**). Yield 30%; dark brown wet-solid; mp 92–94°C; R_f 0.50 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.28–7.24 (m, 5H), 6.66–6.44 (m, 4H), 4.46 (br, 1H), 3.66 (s, 6H), 1.25 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 177.03, 151.84, 141.15, 139.28, 128.26, 127.85, 127.27, 114.62, 114.59, 65.12, 55.57, 51.93, 47.04, 24.37, 20.36; FTIR (thin film) 1719.2 cm^{-1}; MS (*m/z*, relative intensity) 313 (73), 250 (75), 212 (100), 77 (65); HRMS calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1673.

Methyl 3-[(methoxyphenyl)amino]-2,2-dimethyl-3-(2-pyridyl) propanoate 9A (Table 2, Entry 9, product of **A**). Yield 90%; dark brown wet-solid; R_f 0.47 (hexane/ethyl acetate=2:1); ^1H NMR ($CDCl_3$): δ 8.56–8.54 (m, 1H), 7.55–7.52 (m, 1H), 7.19–7.10 (m, 2H), 6.75–6.59 (m, 4H), 4.67 (s, 1H), 3.67 (s, 6H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 177.20, 159.27, 152.36, 148.82, 141.87, 135.97, 122.85, 122.36, 115.72, 114.68, 66.23, 55.69, 52.00, 47.63, 23.42, 21.18; FTIR (thin film) 1729.4 cm^{-1}; MS (*m/z*, relative intensity) 314 (64), 283 (40), 182 (38), 91 (36), 59 (28); HRMS calcd for $C_{18}H_{22}N_2O_3$ 314.1631, found 314.1648.

3-(Methoxycarbonyl)-2-[(4-methoxyphenyl)amino]-3-methylbutanoic acid *3* (Table 3, Entry 3, product of **A**). Yield 10%; dark brown oil; R_f 0.26 (hexane/ethyl acetate/HOAc=1/2/0.1); ^1H NMR ($CDCl_3$): δ 6.78–6.58 (m, 4H), 3.74 (s, 3H), 3.67 (s, 3H), 3.18 (s, 1H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 177.46, 152.03, 142.71, 114.77, 114.28, 55.76, 53.96, 51.89, 43.52, 23.49; FTIR (thin film) 1713.4 cm^{-1}; MS (*m/z*, relative intensity) 237 (55), 205 (12), 77 (32); HRMS calcd for $(M-CO_2H)^+$ $C_{13}H_{18}NO_3$ 236.1287, found 236.1282; calcd for $(M-CO_2)^+$ $C_{13}H_{19}NO_3$ 237.1365, found 237.1352.

1-Phenyl-3-(phenylamino)propan-1-one 1B (Table 2, Entry 1, product of **B**). Yield 91%; yellowish oil; mp 11–113°C; R_f 0.29 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.96–7.94 (m, 2H), 7.58–7.44 (m, 3H), 7.19–7.16 (m, 2H), 6.72–6.64 (m, 3H), 3.62 (t, J=6.1 Hz, 2H), 3.29 (t, J=6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 199.34, 147.74, 136.78, 133.36, 129.36, 128.69, 128.06, 117.64, 113.09, 38.77, 37.71; FTIR (thin film) 1681.5 cm^{-1}; MS (*m/z*, relative intensity) 225 (90), 148 (12), 133 (51), 120 (80), 119 (54), 105 (98), 92 (60); HRMS calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1166.

1,2-Diphenyl-3-(phenylamino)propan-1-one 2B. Known[19a–d] (Table 2, Entry 2, product of **B**). Yield 75%; yellowish oil; mp 168–170°C; R_f 0.52 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.91–7.90 (m, 2H), 7.57–7.07 (m, 10H), 6.67–6.55 (m, 3H), 5.00 (dd, J=5.2, 7.5 Hz, 1H), 4.55 (br, 1H), 3.50 (dd, J=5.2, 16.1 Hz, 1H), 3.42 (dd, J=7.5, 16.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.29, 147.00, 142.99, 136.73, 133.42, 129.11, 128.83, 128.70, 128.21, 127.36, 126.38, 117.80, 113.84, 54.83, 46.31; FTIR (thin film) 1670.6 cm^{-1}; HRMS calcd for $C_{21}H_{19}NO$ 301.1467, found 301.1471.

1-Phenyl-3-(phenylamino)-3-(2-pyridyl)propan-1-one 3B (Table 2, Entry 3, product of **B**). Yellowish oil; yield 94%; mp 110–112°C; R_f 0.40 (hexane/ethyl acetate/HOAc=1:2:0.1); ^1H NMR ($CDCl_3$): δ 8.56–8.55 (m, 1H), 7.92–7.91 (m, 2H), 7.60–7.40 (m, 5H), 7.15–7.12 (m, 3H), 6.71–6.65 (m, 3H), 5.20 (br, 1H), 4.88 (br, 1H), 3.70 (dd, J=6.5, 16.6 Hz, 1H), 3.60 (dd, J=5.7, 16.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.89, 161.25, 149.36, 146.73, 136.75, 136.70, 133.29, 129.30, 128.59, 128.22, 122.32, 122.22, 117.90, 113.81, 55.35, 43.95; FTIR (thin film) 1679.9 cm^{-1}; MS (*m/z*, relative intensity) 302 (6), 208 [$(M-PhNH)^+$, 40], 181 (90), 105 (95), 78 (90), 77 (76); HRMS calcd for $C_{20}H_{18}N_2O$ 302.1419, found 302.1413.

3-[(4-Chlorophenyl) amino]-1-phenylpropan-1-one 4B (Table 2, Entry 4, product of **B**). Yield 85%; colorless oil; mp 133–135°C; R_f 0.26 (hexane/ethyl acetate=4:1); ^1H NMR ($CDCl_3$): δ 7.95–7.94 (m, 2H), 7.59–7.45 (m, 3H), 7.12–7.11 (m, 2H), 6.58–6.55 (m, 2H), 3.58 (t, J=6.0 Hz, 2H), 3.27 (t, J=6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 199.17, 146.34, 136.68, 133.47, 129.17, 128.73, 128.05, 122.19, 114.15, 38.89, 37.46; FTIR (thin film) 1670.2 cm^{-1}; MS (*m/z*, relative intensity) 259 (85), 154 [$(M-C_6H_4CO)^+$, 23], 111 (51), 105 (100), 77 (96), 43 (10); HRMS calcd for $C_{15}H_{14}{}^{35}ClNO$ 259.0764, found 259.0766.

3-[(4-Chlorophenyl)amino]-1,3-diphenylpropan-1-one 5B (Table 2, Entry 5, product of **B**). Yield 60%; yellowish wet-solid; R_f 0.48 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.90–7.89 (m, 2H), 7.58–7.22 (m, 8H), 7.03–7.00 (m, 2H), 6.48–6.45 (m, 2H), 4.94 (dd, J=5.0, 7.7 Hz, 1H), 3.49 (dd, J=5.0, 16.2 Hz, 1H), 3.40 (dd, J=7.7, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.17, 145.59, 142.51, 136.65, 133.52, 128.93, 128.91, 128.74, 128.20, 127.51, 126.29, 122.48, 114.98, 54.95, 46.22; FTIR (thin film) 1665.2 cm^{-1}; MS (*m/z*, relative intensity) 335 (45), 258 [$(M-C_6H_5)^+$, 2)], 216 (86), 111 (77), 105 (78), 77 (88); HRMS calcd for $C_{21}H_{18}{}^{35}ClNO$ 335.1077, found 335.1058.

3-[(4-Chlorophenyl)amino]-1-phenyl-3-(2-pyridyl)propan-1-one 6B (Table 2, Entry 6, product of **B**). Yield 91%; yellowish oil; mp 115–117°C; R_f 0.43 (hexane/ethyl acetate=2:1); ^{1}H NMR ($CDCl_3$): δ 8.56–8.55 (m, 1H), 7.92–7.90 (m, 2H), 7.61–7.41 (m, 5H), 7.16–7.06 (m, 3H), 6.61–6.57 (m, 2H), 5.14 (br, 1H), 4.95 (br, 1H), 3.66 (dd, J=6.3, 16.7 Hz, 1H), 3.59 (dd, J=5.8, 16.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.71, 160.83, 149.43, 145.32, 136.79, 136.66, 133.40, 129.13, 128.63, 128.21, 122.47, 122.13, 114.95, 55.53, 43.88; FTIR (thin film) 1686.3 cm^{-1}; MS (*m/z*, relative intensity) 336 (18), 231 (48), 217 (80), 216 (88), 210 (67), 120 (65), 105 (96), 77 (97); HRMS calcd for $C_{20}H_{17}{}^{35}ClN_2O$ 336.1029, found 336.1043.

3-[(4-Methoxyphenyl)amino]-1-phenylpropan-1-one 7B. Known[19a–d] (Table 2, Entry 7, product of **B**). Yield 86%; brownish wet-solid; mp 110–112°C; R_f 0.19 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.95–7.93 (m, 2H), 7.58–7.44 (m, 3H), 6.80–6.63 (m, 4H), 3.74 (s, 3H), 3.56 (t, J=6.1 Hz, 2H), 3.27 (t, J=6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 199.43, 152.55, 141.68, 136.79, 133.34, 128.68, 128.05, 115.02, 114.87, 55.83, 40.13, 37.66; FTIR (thin film) 1674.2 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_2$ 255.1259, found 255.1266.

3-[(4-Methoxyphenyl)amino]-1,3-diphenylpropan-1-one 8B. Known[19a–d] (Table 2, Entry 8, product of **B**). Yield 40%; brownish wet-solid; mp 140–142°C; R_f 0.39 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.92–7.90 (m, 2H), 7.57–7.21 (m, 8H), 6.69–6.52 (m, 4H), 4.92 (dd, J=5.1, 7.7 Hz, 1H), 3.68 (s, 3H), 3.48 (dd, J=5.1, 16.2 Hz, 1H), 3.42 (dd, J=7.7, 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.44, 152.50, 143.19, 141.12, 136.82, 133.42, 128.84, 128.72, 128.24, 127.37, 126.51, 115.51, 114.77, 55.88, 55.74, 46.44; FTIR (thin film) 1666.3 cm^{-1}; HRMS calcd for $C_{22}H_{21}NO_2$ 331.1572, found 331.1588.

3-[(4-Methoxyphenyl)amino]-1-phenyl-3-(2-pyridyl)-propan-1-one 9B. Known[19a–d] (Table 2, Entry 8, product of **B**). Yield 90%; dark brown wet-solid; mp 82–84°C; R_f 0.29 (hexane/ethyl acetate=1:2); ^{1}H NMR ($CDCl_3$): δ 8.55–8.54 (m, 1H), 7.92–7.90 (m, 2H), 7.60–7.40 (m, 5H), 7.13–7.11 (m, 1H), 6.74–6.62 (m, 4H), 5.11 (t, J=6.2 Hz, 1H), 4.80 (br, 1H), 3.70 (s, 3H), 3.67 (dd, J=6.4, 16.5 Hz, 1H), 3.57 (dd, J=6.0, 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 198.94, 161.51, 152.51, 149.35, 140.90, 136.81, 136.65, 133.25, 128.58, 128.21, 122.32, 122.28, 115.50, 114.88, 56.53, 55.71, 44.07; FTIR (thin film) 1673.7 cm^{-1}; HRMS calcd for $C_{21}H_{20}N_2O_2$ 332.1525, found 332.1511.

2-[(4-Chlorophenyl)amino]-4-oxo-4-phenylbutanoic acid *4* (Table 3, Entry 2, product of **B**). Yield 63%; yellowish wet-solid; R_f 0.38 (hexane/ethyl acetate/HOAc=1:2:0.1); ^{1}H NMR (D_2O): δ 8.06–8.03 (m, 2H), 7.76–7.62 (m, 3H), 7.27–7.24 (m, 2H), 6.76–6.73 (m, 2H), 4.41 (br, 1H), 3.57 (m, 2H); ^{13}C NMR (D_2O): δ 205.14, 182.62, 148.92, 139.09, 136.85, 131.77, 131.64, 131.09, 125.24, 118.38, 59.14, 44.47; FTIR (thin film) 1634.4 cm^{-1}; MS (*m/z*, relative intensity) 254 (32), 176 (42), 105 (70), 77 (64); HRMS $C_{16}H_{14}{}^{35}ClNO_3$, calcd for $(M-CO_2-H_2)^+$ $C_{15}H_{12}{}^{35}ClNO$ 257.0607, found 257.0610.

2-Methyl-1-phenyl-3-(phenylamino)propan-1-one 1C (Table 2, Entry 1, product of **C**). Yield 58%; colorless wet-solid; R_f 0.53 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.93–7.91 (m, 2H), 7.57–7.43 (m, 3H), 7.17–7.14 (m, 2H), 6.70–6.59 (m, 3H), 3.88–3.84 (m, 1H), 3.60 (dd, J=7.7, 13.4 Hz, 1H), 3.32 (dd, J=5.2, 13.4 Hz, 1H), 1.27 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 203.47, 147.78, 136.30, 133.16, 129.26, 128.65, 128.30, 117.34, 112.76, 46.47, 40.25, 15.94; FTIR (thin film) 1677.2 cm^{-1}; MS (*m/z*, relative intensity) 239 (28), 133 (7), 106 (100), 105 (74), 77 (71), 27 (5); HRMS calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1324.

2-Methyl-1,3-diphenyl-3-(phenylamino)propan-1-one 2C (Table 2, Entry 2, product of **C**). Yield 80% (*syn*/*anti*=57:43); yellowish oil; mp 108–110°C; R_f 0.55 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): (*syn*+*anti*) δ 7.99–7.04 (m, 12H), 6.68–6.49 (m, 3H), 4.81 (d, J=5.1 Hz, 1H×0.57), 4.77 (d, J=6.0 Hz, 1H×0.43), 4.07–3.89 (m, 1H), 1.34 (d, J=7.0 Hz, 3H×0.43), 1.27 (d, J=6.9 Hz, 3H×0.57); ^{13}C NMR ($CDCl_3$): major δ 202.60, 147.20, 141.51, 136.23, 133.22, 128.89, 128.72, 128.21, 127.20, 126.80, 117.55, 113.77, 59.21, 46.90, 11.52; minor δ 204.03, 147.12, 141.80, 137.15, 133.08, 129.01, 128.59, 128.49, 128.11, 126.73, 117.22, 113.42, 61.13, 46.44, 16.65; FTIR (thin film) 1671.9 cm^{-1}; MS (*m/z*, relative intensity) 315 (6), 182 (87), 133 (19), 105 (99), 77 (100), 27 (37); HRMS calcd for $C_{22}H_{21}NO$ 315.1623, found 315.1631.

2-Methyl-1-phenyl-3-(phenylamino)-3-(2-pyridyl)propan-1-one 3C (Table 2, Entry 3, product of **C**). Yield 70% (*syn*/*anti*=69:31); yellowish oil; ^{1}H NMR ($CDCl_3$): major δ 8.56–8.54 (m, 1H), 8.02–7.99 (m, 2H), 7.56–7.06 (m, 8H), 6.68–6.55 (m, 3H), 5.94 (d, J=6.2 Hz, 1H), 4.65 (br, 1H), 4.34–4.30 (m, 1H), 1.26 (d, J=7.0 Hz, 3H); minor δ 8.56–8.54 (m, 1H), 7.82–7.80 (m, 2H), 7.52–6.55 (m, 11H), 5.43 (br, 1H), 4.85 (d, J=5.8 Hz, 1H), 4.44–4.35 (m, 1H), 1.28 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): major δ 202.98, 160.62, 149.43, 147.29, 136.27, 136.13, 133.03, 129.02, 128.55, 128.42, 122.56, 122.08, 117.67, 113.71, 60.61, 45.79, 12.70; minor δ 204.25, 160.94, 149.34, 147.32, 136.96, 136.32, 132.95, 129.05, 128.37, 128.20, 122.06, 121.89, 117.43, 113.49, 62.18, 44.56, 16.03; FTIR (thin film) 1672.3 cm^{-1}; MS (*m/z*, relative intensity) 316 (38), 183 (75), 133 (46), 105 (78), 92 (47), 91 (61); HRMS calcd for $C_{21}H_{20}N_2O$ 316.1576, found 316.1579.

3-[(4-Chlorophenyl)amino]-2-methyl-1-phenylpopan-1-one 4C (Table 2, Entry 4, product of **C**). Yield 78%;

yellowish oil; R_f 0.53 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.94–7.90 (m, 2H), 7.59–7.55 (m, 3H), 7.11–7.07 (m, 2H), 6.53–6.48 (m, 2H), 3.90–3.78 (m, 1H), 3.57 (dd, J=7.8, 13.3 Hz, 1H), 3.28 (dd, J=5.0, 13.3 Hz, 1H), 1.26 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 203.28, 146.38, 136.15, 133.25, 129.02, 128.68, 128.24, 121.76, 113.79, 46.47, 40.11, 15.95; FTIR (thin film) 1677.5 cm^{-1}; MS (*m/z*, relative intensity) 273 (49), 140 (28), 133 (28), 111 (40), 105 (19), 77 (68); HRMS calcd for $C_{16}H_{16}{}^{35}ClNO$ 273.0920, found 273.0923.

3-[(4-Chlorophenyl)amino]-2-methyl-1,3-diphenylpropan-1-one 5C (Table 2, Entry 5, product of **C**). Yield 26% (*syn*/*anti*=60:40); yellowish oil; mp 161–163°C; R_f 0.55 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): (*syn*+*anti*) δ 7.95–6.94 (m, 12H), 6.48–6.36 (m, 3H), 4.70 (d, J=4.9 Hz, 1H×0.60), 4.67 (d, J=5.9 Hz, 1H×0.40), 4.00–3.93 (m, 1H), 1.30 (d, J=7.0 Hz, 3H×0.40), 1.22 (d, J=7.0 Hz, 3H×0.60); ^{13}C NMR ($CDCl_3$): δ 202.54, 203.98, 145.75, 145.72, 141.34, 140.95, 137.02, 136.14, 133.25, 133.12, 128.78, 128.72, 128.68, 128.62, 128.53, 128.47, 128.14, 128.05, 127.33, 126.70, 126.61, 122.24, 121.75, 114.85, 114.46, 61.29, 59.31, 46.74, 46.31, 16.67 (minor), 11.39 (major); FTIR (thin film) 1666.3 cm^{-1}; MS (*m/z*, relative intensity) 349 (4), 216 (92), 133 (20), 111 (72), 105 (99), 77 (93); HRMS calcd for $C_{22}H_{20}{}^{35}ClNO$ 349.1234, found 349.1246.

3-[(4-Chlorophenyl)amino]-2-methyl-1-phenyl-3-(2-pyridyl)propan-1-one 6C (Table 2, Entry 6, product of **C**). Yield 55% (*syn*/*anti*=57:43); yellowish oil; mp 129–131°C; R_f 0.51 (major), 0.42 (minor) (hexane/ethyl acetate=2:1); ^{1}H NMR ($CDCl_3$): major δ 8.55–8.53 (m, 1H), 7.99–7.96 (m, 2H), 7.57–6.98 (m, 8H), 6.55–6.45 (m, 3H), 4.87 (d, J=6.1 Hz, 1H), 4.68 (br, 1H), 4.34–4.25 (m, 1H), 1.25 (d, J=7.0 Hz, 3H); minor δ 8.55–8.53 (m, 1H), 7.81–7.78 (m, 2H), 7.52–6.50 (m, 10H), 5.36 (br, 1H), 4.79 (d, J=5.8 Hz, 1H), 4.39–4.30 (m, 1H), 1.25 (d, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): major δ 202.87, 160.14, 149.50, 145.89, 136.33, 136.03, 133.12, 128.84, 128.57, 128.37, 122.49, 122.22, 114.82, 60.76, 45.73, 12.74; minor δ 204.13, 160.48, 149.47, 145.95, 136.82, 136.34, 133.05, 128.88, 128.41, 128.18, 122.20, 121.83, 114.64, 62.44, 44.53, 16.09; FTIR (thin film) 1670.8 cm^{-1}; MS (*m/z*, relative intensity) 350 (33), 217 (83), 133 (51), 111 (72), 105 (84), 77 (77), 27 (30); HRMS calcd for $C_{21}H_{19}{}^{35}ClN_2O$ 350.1186, found 350.1178.

3-[(4-Methoxyphenyl)amino]-2-methyl-1-phenylpropan-1-one 7C (Table 2, Entry 7, product of **C**). Yield 41%; dark brown wet-solid; R_f 0.53 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.94–7.90 (m, 2H), 7.59–7.42 (m, 3H), 6.79–6.54 (m, 4H), 3.74 (s, 3H), 3.89–3.73 (m, 1H), 3.55 (dd, J=7.6, 13.1 Hz, 1H), 3.25 (dd, J=5.2, 13.1 Hz, 1H), 1.26 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 203.53, 152.10, 141.96, 136.33, 133.10, 128.61, 128.24, 114.88, 114.28, 55.70, 47.66, 40.29, 15.90; FTIR (thin film) 1675.2 cm^{-1}; MS (*m/z*, relative intensity) 269 (72), 136 (99), 133 (18), 107 (25), 77 (96), 27 (34); HRMS calcd for $C_{17}H_{19}NO_2$ 269.1416, found 269.1410.

3-[(4-Methoxyphenyl)(2-methyl-3-oxo-3-phenylpropyl)-amino]-2-methyl-1-phenylpropan-1-one 7C′ (Table 2, Entry 7, see Table footnote i). Yield 5%; dark brown oil; R_f 0.42 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.83–7.30 (m, 10H), 6.84–6.67 (m, 4H), 3.78 (s, 3H), 3.87–3.78 (m, 2H), 3.65–3.53 (m, 2H), 3.29–3.14 (m, 2H), 1.11 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 203.97, 203.92, 152.56, 152.34, 142.31, 142.05, 136.62, 136.54, 132.89, 132.78, 128.46, 128.31, 128.18, 128.14, 117.15, 116.69, 114.72, 114.69, 56.65, 55.58, 38.86, 38.61, 15.94; FTIR (thin film) 1679.2 cm^{-1}; MS (*m/z*, relative intensity) 415 (56), 282 (89), 176 (46), 135 (82), 105 (100), 77 (95); HRMS calcd for $C_{27}H_{29}NO_3$ 415.2148, found 415.2142.

3-[(4-Methoxyphenyl)amino]-2-methyl-1,3-diphenylpropan-1-one 8C (Table 2, Entry 8, product of **C**). Yield 45% (*syn*/*anti*=51:49); dark brown wet-solid; R_f 0.45 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): (*syn*+*anti*) δ 7.98–7.15 (m, 10H), 6.70–6.44 (m, 4H), 4.70 (m, 1H), 4.02–3.95 (m, 1H), 3.68 (s, 3H×0.49), 3.67 (s, 3H×0.51), 1.27 (d, J=7.0 Hz, 3H×0.49), 1.26 (d, J=7.0 Hz, 3H×0.51); ^{13}C NMR ($CDCl_3$): δ 202.80 (major), 203.88 (minor), 152.07, 151.96, 141.95, 141.82, 141.44, 141.34, 137.24, 136.29, 133.16, 133.20, 128.69, 128.53, 128.59, 128.53, 128.50, 128.46, 128.40, 128.20, 128.11, 127.17, 127.15, 126.86, 114.97, 114.91, 114.66, 114.55, 62.18, 60.02, 55.61, 55.59, 46.98, 46.66, 16.50, 11.51; FTIR (thin film) 1681.7 cm^{-1}; MS (*m/z*, relative intensity) 345 (6), 212 (83), 133 (44), 122 (5), 105 (97), 77 (92); HRMS calcd for $C_{23}H_{23}NO_2$ 345.1729, found 345.1733.

3-[(4-Methoxyphenyl)amino]-2-methyl-1-phenyl-3-(2-pyridyl)propan-1-one 9C (Table 2, Entry 9, product of **C**). Yield 70% (*syn*/*anti*=66:34); dark brown solid; mp 113–115°C; R_f 0.42 (major), 0.36 (minor) (hexane/ethyl acetate=2:1); ^{1}H NMR ($CDCl_3$): major δ 8.55–8.54 (m, 1H), 8.01–7.98 (m, 2H), 7.54–7.30 (m, 5H), 7.09–7.05 (m, 1H), 6.70–6.48 (m, 4H), 4.83 (d, J=6.2 Hz, 1H), 4.45 (br, 1H), 4.41–4.26 (m, 1H), 3.67 (s, 3H), 1.27 (d, J=7.0 Hz, 3H); minor δ 8.57–8.52 (m, 1H), 7.86–7.83 (m, 2H), 7.53–7.17 (m, 6H), 6.70–6.54 (m, 4H), 4.77 (d, J=6.6 Hz, 1H), 4.36–4.24 (m, 1H), 3.67 (s, 3H), 1.21 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): major δ 203.12, 160.95, 152.22, 149.41, 141.46, 136.19, 132.99, 128.53, 128.41, 122.62, 122.01, 115.14, 114.63, 61.71, 55.58, 45.79, 12.69; minor δ 204.08, 161.02, 152.20, 149.43, 141.53, 136.20, 132.88, 128.37, 128.21, 122.28, 122.08, 115.23, 114.70, 63.50, 55.58, 44.91, 15.91; FTIR (thin film) 1672.4 cm^{-1}; MS (*m/z*, relative intensity) 346 (3), 213 (59), 133 (20), 105 (100), 77 (89); HRMS calcd for $C_{22}H_{22}N_2O_2$ 346.1681, found 346.1676.

2-[(Phenylamino)methyl]cyclopentan-1-one 1D (Table 2, Entry 1, product of **D**). Yield 46%; yellowish oil; R_f 0.38 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.24–7.15 (m, 2H), 6.74–6.63 (m, 3H), 4.19 (br, 1H), 3.34 (dd, J=6.8, 13.0 Hz, 1H), 3.26 (dd, J=6.4, 13.0 Hz, 1H), 2.43–1.62 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 220.74, 147.88, 129.17, 117.65, 113.08, 48.18, 43.90, 38.32, 28.05, 20.67; FTIR (thin film) 1726.4 cm^{-1}; MS (*m/z*, relative intensity) 189 (66), 106 (100), 83 (7), 77 (55); HRMS calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1146.

2-[Phenyl(phenylamino)methyl]cyclopentan-1-one 2D (Table 2, Entry 2, product of **D**). Yield 68% (*syn*/

anti=59:41); yellowish oil; R_f 0.46 (minor), 0.41 (major) (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): major δ 7.56–7.03 (m, 7H), 6.64–6.56 (m, 3H), 5.38 (br, 1H), 4.75 (d, J=4.4 Hz, 1H), 2.75–2.67 (m, 1H), 2.31–1.60 (m, 6H); minor δ 7.54–7.03 (m, 7H), 6.68–6.53 (m, 3H), 5.30 (br, 1H), 4.55 (d, J=7.4 Hz, 1H), 2.75–1.63 (m, 7H); ^{13}C NMR ($CDCl_3$): major δ 220.41, 146.65, 140.77, 128.96, 128.42, 127.35, 127.22, 117.38, 113.58, 57.63, 53.23, 39.65, 25.76, 20.55; minor δ 219.28, 147.48, 141.63, 128.91, 128.55, 127.25, 127.10, 117.76, 114.09, 58.95, 53.98, 39.13, 26.60, 20.39; FTIR (thin film) 1715.7 cm^{-1}; MS (*m*/*z*, relative intensity) 265 (34), 182 (83), 173 (5), 83 (34), 55 (100); HRMS calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1466.

2-[(Phenylamino)-2-pyridylmethyl]cyclopentan-1-one 3D (Table 2, Entry 3, product of **D**). Yield 60% (*syn*/*anti*=52:48); yellowish oil; R_f 0.40 (minor), 0.33 (major) (hexane/ethyl acetate=2:1); ^{1}H NMR ($CDCl_3$): major δ 8.58–8.53 (m, 1H), 7.61–7.55 (m, 1H), 7.29–7.08 (m, 4H), 6.71–6.64 (m, 3H), 5.00 (d, J=3.9 Hz, 1H), 2.76–2.70 (m, 1H), 2.33–1.69 (m, 6H); minor δ 8.58–8.56 (m, 1H), 7.64–7.58 (m, 1H), 7.35–7.33 (m, 1H), 7.19–7.12 (m, 3H), 6.72–6.67 (m, 3H), 5.28 (br, 1H), 5.00 (d, J=5.4 Hz, 1H), 2.92–2.84 (m, 1H), 2.33–1.65 (m, 7H); ^{13}C NMR ($CDCl_3$): major δ 219.93, 160.59, 148.76, 147.09, 136.58, 129.05, 122.15, 121.87, 117.87, 114.13, 58.73, 53.29, 39.18, 25.18, 20.69; minor δ 219.97, 159.62, 148.66, 146.64, 136.62, 129.18, 122.28, 122.19, 117.73, 113.69, 57.91, 52.66, 39.01, 25.08, 20.39; FTIR (thin film) 1731.9 cm^{-1}; MS (*m*/*z*, relative intensity) 266 (47), 174 (67), 146 (38), 118 (80), 83 (30), 55 (100); HRMS calcd for $C_{17}H_{18}N_2O$ 266.1419, found 266.1414.

2-{[4-Chlorophenyl)amino]methyl}cyclopentan-1-one 4D (Table 2, Entry 4, product of **D**). Yield 60%; yellowish wet-solid; R_f 0.35 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 7.12–7.06 (m, 2H), 6.59–6.51 (m, 2H), 3.27 (dd, J=7.0, 13.0 Hz, 1H), 3.20 (dd, J=6.3, 13.0 Hz, 1H), 2.44–1.58 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 220.71, 146.52, 128.95, 122.05, 114.10, 47.98, 43.99, 38.29, 27.99, 20.66; FTIR (thin film) 1726.0 cm^{-1}; MS (*m*/*z*, relative intensity) 223 (78), 140 (96), 126 (88), 111 (58); HRMS calcd for $C_{12}H_{14}{}^{35}ClNO$ 223.0764, found 223.0764.

2-{[(4-Chlorophenyl)amino]phenylmethyl}cyclopentan-1-one 5D (Table 2, Entry 5, product of **D**). Yield 17% (*syn*/*anti*=74:26); yellowish oil; R_f 0.41 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): mixture δ 7.55–6.43 (m, 9H), 4.67 (d, J=4.4 Hz, 1H×0.74), 4.45 (d, J=7.7 Hz, 1H×0.26), 2.73–1.61 (m, 7H); ^{13}C NMR ($CDCl_3$): major δ 220.59, 145.21, 140.16, 128.79, 128.50, 127.35, 127.42, 121.92, 114.64, 57.84, 52.95, 39.68, 25.80, 20.53; minor δ 219.28, 145.97, 141.19, 128.68, 128.63, 127.50, 126.96, 122.42, 115.22, 59.24, 53.79, 39.13, 26.77, 20.33; FTIR (thin film) 1731.8 cm^{-1}; MS (*m*/*z*, relative intensity) 299 (35), 216 (74), 215 (84), 173 (40), 172 (68), 84 (58), 83 (51), 55 (100); HRMS calcd for $C_{18}H_{18}{}^{35}ClNO$ 299.1077, found 299.1054.

2-{[(4-Chlorophenyl)amino]-2-pyridylmethyl}cyclopentan-1-one 6D (Table 2, Entry 6, product of **D**). Yield 35% (*syn*/*anti*=64:36); yellowish wet-solid; R_f 0.38 (minor), 0.28 (major) (hexane/ethyl acetate=2:1); ^{1}H NMR ($CDCl_3$): major δ 8.54–8.52 (m, 1H), 7.62–7.56 (m, 1H), 7.25–7.02 (m, 4H), 6.64–6.58 (m, 2H), 5.40 (d, J=9.0 Hz, 1H), 4.93 (dd, J=4.0, 9.0 Hz, 1H), 2.73–2.65 (m, 1H), 2.33–2.25 (m, 1H), 2.09–1.68 (m, 5H); minor δ 8.58–8.55 (m, 1H), 7.71–7.05 (m, 5H), 6.62–6.56 (m, 2H), 5.36 (d, J=6.5 Hz, 1H), 4.90 (m, 1H), 2.83 (m, 1H), 2.33–1.67 (m, 6H); ^{13}C NMR ($CDCl_3$): major δ 219.98, 160.11, 148.83, 145.69, 136.69, 128.86, 122.31, 121.80, 115.27, 58.87, 53.20, 39.18, 25.09, 20.65; minor δ 219.91, 159.25, 148.74, 145.22, 136.75, 128.99, 122.45, 122.12, 114.81, 58.16, 52.54, 39.01, 25.13, 20.36; FTIR (thin film) 1635.8 cm^{-1}; MS (*m*/*z*, relative intensity) 300 (29), 217 (96), 216 (67), 173 (94), 146 (29), 118 (66), 83 (22), 55 (77); HRMS calcd for $C_{17}H_{17}{}^{35}ClN_2O$ 300.1029, found 300.1033.

2-{[(4-Methoxyphenyl)amino]methyl}cyclopentan-1-one 7D (Table 2, Entry 7, product of **D**). Yield 20%; yellowish oil; R_f 0.22 (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): δ 6.80–6.75 (m, 2H), 6.64–6.61 (m, 2H), 3.75 (s, 3H), 3.30 (dd, J=6.9, 12.8 Hz, 1H), 3.20 (dd, J=6.3, 12.8 Hz, 1H), 2.39–1.65 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 220.91, 152.33, 141.99, 114.79, 114.62, 55.68, 48.03, 45.13, 38.35, 28.06, 20.68; FTIR (thin film) 1731.1 cm^{-1}; MS (*m*/*z*, relative intensity) 219 (60), 136 (87), 122 (19), 108 (88), 97 (8); HRMS calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1240.

2-{[(4-Methoxyphenyl)amino]phenylmethyl}cyclopentan-1-one 8D (Table 2, Entry 8, product of **D**). Yield 11% (*syn*/*anti*=76:24); yellowish oil; R_f 0.32 (major), 0.28 (minor) (hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$): major δ 7.31–7.17 (m, 5H), 6.70–6.53 (m, 4H), 4.71 (d, J=4.2 Hz, 1H), 3.68 (s, 3H), 2.73–2.66 (m, 1H), 2.31–1.64 (m, 6H); minor δ 7.45–7.21 (m, 5H), 6.68–6.48 (m, 4H), 4.45 (d, J=7.5 Hz, 1H), 3.67 (s, 3H), 2.52–1.65 (m, 7H); ^{13}C NMR ($CDCl_3$): major δ 220.38, 152.03, 140.98, 140.83, 128.40, 127.30, 127.15, 115.14, 114.59, 58.53, 55.55, 53.50, 39.62, 25.62, 20.56; minor δ 219.47, 152.30, 141.84, 141.63, 128.48, 127.27, 127.16, 115.56, 114.52, 59.91, 55.58, 53.94, 39.11, 26.71, 20.34; FTIR (thin film) 3418.0, 2955.6, 1622.0, 1557.9, 1511.0, 1455.6, 1239.4, 1177.3, 1034.8, 822.2, 756.0, 696.7, 668.0 cm^{-1}; MS (*m*/*z*, relative intensity) 295 (16), 264 (12), 212 (72), 55 (100); HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1562.

2-{[(4-Methoxyphenyl)amino]-2-pyridylmethyl}cyclopentan-1-one 9D (Table 2, Entry 9, product of **D**). Yield 20% (*syn*/*anti*=76:24); yellowish oil; R_f 0.33 (minor), 0.23 (major) (hexane/ethyl acetate=2:1); ^{1}H NMR ($CDCl_3$): major δ 8.54–8.52 (m, 1H), 7.60–6.62 (m, 7H), 4.91 (d, J=4.0 Hz, 1H), 3.69 (s, 3H), 2.68–2.63 (m, 1H), 2.32–1.65 (m, 6H); minor δ 8.57–8.55 (m, 1H), 7.60–6.62 (m, 7H), 4.87 (d, J=5.7 Hz, 1H), 3.71 (s, 3H), 2.85–1.62 (m, 7H); ^{13}C NMR ($CDCl_3$): major δ 220.01, 160.72, 152.45, 148.77, 147.16, 141.28, 136.50, 122.09, 121.93, 115.98, 114.59, 60.17, 55.55, 53.46, 39.17, 25.01, 20.70; minor δ 220.19, 159.97, 153.00, 149.90, 148.65, 140.81, 136.61, 122.69, 122.25, 115.27, 114.75, 59.12, 55.60, 52.70, 39.03, 25.16, 20.40; FTIR (thin film) 3442.2, 1633.2, 1507.2, 1244.5, 1178.6, 1037.6, 668.1 cm^{-1}; MS (*m*/*z*, relative intensity) 296 (5), 265 (7), 213 (22), 83 (25), 55 (58); HRMS calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found 296.1514.

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20. We conducted an experiment to verify that the Mannich-type reactions are truly catalysed by $InCl_3$ and not through the acidic hydrates of the indium halide complexes that are generated in aqueous solutions. The fact that the Mannich-type reaction can also be carried out under solvent-free conditions as well as in non-protic solvents (Table 1) has affirmed our observations in this article. A brief experimental procedure is described: 2-PyCHO (54 mg, 48 μL, 0.5 mmol, 99%) was stirred with $InCl_3$ (22.6 mg, 0.1 mmol, 98%) at room temperature for 10 min before $PhNH_2$ (55.9 mg, 0.6 mmol) was added. Stirring continued for 30 min before 1-phenyl-1-trimethylsiloxyethylene **B** was added. The reaction mixture was stirred for 1 day and H_2O was added to quench the reaction. Extraction was carried out using ethyl acetate (refer to Experimental). The desired product was obtained in 95% yield after purification by silica gel chromatography.