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N-Heterocyclic carbene-catalyzed aza-Michael addition†

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Aza-Michael addition of amines, including aromatic and aliphatic amines, with α , β -unsaturated ketones was realized employing N-Heterocyclic Carbene (NHC) as organocatalyst, yielding β -amino ketones with up to 98% yield.

Introduction

β -Aminocarbonyl compounds have been used as building blocks for nitrogen-containing natural products and biologically active drugs.¹ Aza-Michael addition² is one of the most direct approaches for construction of these prevalent structure motifs. It represents a valuable synthetic alternative to the established Mannich reaction. Most aza-Michael reaction protocols are often promoted by Lewis acidic catalysts or Brønsted acids. However, the latter have suffered some drawbacks such as metal contaminations, harsh reaction conditions as well as oligomerization of Michael acceptors.³ Therefore, developing new efficient and robust catalytic system for aza-Michael addition is important for their broad application in organic synthesis. Recently, N-heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts which realized numerous *Umpolung* reactions⁴ via “Breslow intermediate”⁵ or the homoenolate equivalent species.⁶ However, the reaction catalyzed by NHCs employing other substrates, except aldehydes,^{5,8–10} was quite limited.⁷ As part of our effort focused on application of NHCs as organocatalysts,¹¹ herein we report an alternative protocol for aza-Michael addition of amines to α , β -unsaturated ketones catalyzed by N-heterocyclic carbenes.

Results and discussion

The initial investigation was carried out between aniline **2a** and α , β -unsaturated ketone **3a** in the presence of 10 mol% imidazolium salt **1a**, which afforded the desired addition product **4a** in moderate yield (42%, Table 1, entry 1). The yield could be significantly improved by introducing 10 mol% KO^tBu (75% yield, Table 1, entry 2) into the reaction system. It should be noted that without imidazolium salt ketone **3a** undergoes quick oligomerization and polymerization in the presence of a catalytic amount of KO^tBu (Table 1, entry 3). Catalyst optimization using different imidazolium and imidazolinium salts indicated that sterically

Table 1 Catalyst Screening^a

1a: R = Mes, X = Cl 1b: R = 2,6-(ⁱ Pr) ₂ -C ₆ H ₃ , X = Cl 1c: R = 1-adamantyl, X = BF ₄ [−] 1d: R = ^t Bu, X = BF ₄ [−]				
Entry	Catalyst	Base	Time	Yield (%) ^b
1	1a	—	20 h	42
2	1a	KO ^t Bu	20 h	75
3	—	KO ^t Bu	10 min	0 ^c
4	1b	KO ^t Bu	20 h	44
5	1c	KO ^t Bu	20 h	Trace
6	1d	KO ^t Bu	20 h	Trace
7	1e	KO ^t Bu	20 h	69
8	1f	KO ^t Bu	20 h	37

^a Reaction conditions: 10 mol% of **1**, 10 mol% of KO^tBu, 1.2 equiv of **3a**, 0.25 mol L^{−1} of **2a** at 23 °C. ^b Yield of isolated product. ^c **3a** decomposed. Mes = 2,4,6-trimethylphenyl.

more demanding imidazolium salt **1b** provided the lower yield of **4a** (44% yield, Table 1, entry 4) and alkyl substituted imidazolium salts **1c** and **1d** only gave trace amounts of desired product (Table 1, entries 5 and 6). The reaction catalyzed by **1e** went smoothly to afford **4a** in 69% yield (Table 1, entry 7). Compared to imidazolium salt **1a**, imidazolinium salt **1f** gave much lower yield (37%, Table 1, entry 8).

Investigations with respect to the effect of bases indicated that bases which were examined generally had no significant effect on reaction yield (Table 2, entries 1–4). The reaction time was shortened as *n*-butyl lithium (ⁿBuLi) was used. The byproduct, oligomer of Michael acceptor **3a**, could be minimized in the reaction system by using 10 mol% of potassium bis(trimethylsilyl)amide (KHMDS) as the base.

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Table 2 Condition optimization^a

Entry	Base	Solvent	Time/h	Yield (%) ^b
1	KO ^t Bu	THF	20	75
2	KHMDS	THF	24	76 (0 ^c)
3	LiHMDS	THF	24	67
4	ⁿ BuLi	THF	4	59
5	KHMDS	CH ₂ Cl ₂	24	35
6	KHMDS	Toluene	20	92
7	KHMDS	Et ₂ O	18	84
8	KHMDS	MeCN	20	33
9 ^d	KHMDS	Toluene	40	72
10 ^e	KHMDS	Toluene	48	67

^a Reaction conditions: 10 mol % of **1a**, 10 mol% of base, 1.2 equiv of **3a**, 0.25 mol L⁻¹ of **2a** at 23 °C. ^b Yield of isolated product. ^c Without **1a**. ^d 5 mol% of **1a** was used. ^e 2 mol% of **1a** was used. KHMDS = Potassium bis(trimethylsilyl)amide. LiHMDS = lithium bis(trimethylsilyl)amide.

Several solvents were examined for the reaction by employing 10 mol% of imidazonium salt **1a** and 10 mol% KHMDS at 23 °C. Aza-Michael reaction went smoothly in several common solvents such as THF (76%), CH₂Cl₂ (35%), toluene (92%), Et₂O (84%), MeCN (33%). The reaction performed better in less polar solvents as compared to that in polar solvents. Toluene was chosen as the optimal solvent since the reaction in toluene led to complete conversion in 20 h and did not afford oligomerization byproduct. Further studies on the catalyst loading disclosed that less catalyst loading (5 mol% and 2 mol%, respectively) afforded lower yields (72% and 67%, Table 2, entries 9 and 10), even when the reaction time was prolonged to 40 or 48 h.

A wide range of amines, including aromatic and aliphatic amines, were screened under optimized reaction conditions (1.0 equiv of amine, 1.2 equiv of **3a**, 10 mol% of **1a** and 10 mol% of KHMDS in toluene at 23 °C). The results were summarized in Table 3. Several substituted aromatic amines were examined in the reaction with enone **3a**. For aromatic amines with an electron-donating group, such as **2b** and **2f**, the reaction went smoothly, affording the desired products with high yields (98% yield for **2b**, 84% yield for **2f**, Table 3, entries 2 and 6). For an aromatic amine with electron-withdrawing group, the reaction needed a longer time (41 h) to achieve a good yield (69%, Table 3, entry 3). In the case of **2d** (4-ethynylaniline) and **2e** (3,5-dimethylaniline), products **4d** (92%) and **4e** (88%) were obtained in good yields (Table 3, entries 4 and 5). Hetero-aromatic amine **2g** was also examined and a high yield was obtained (83%, entry 7).

Aliphatic amines such as benzylamine **2h**, cyclohexylamine **2i**, allylamine **2j** and propargylamine **2k** were readily tolerated in this reaction and good yields were obtained (82–87% yield, Table 3, entries 8–11). Addition of phenylethylamine **2l** to enone **3a** is also successful but with low diastereoselectivity (1.4 : 1 *dr*, Table 3, entry 12).

The possible utilization of various conjugate enones was investigated, as shown in Table 4. Alkyl ketones such as methyl vinyl ketone (entry 1), and hexene ethyl ketone (entry 2) are well tolerated under optimized conditions. Michael acceptors without substituted group in the β-position afforded the desired product

Table 3 Amine scope^a

Entry	RNH ₂	Time/h	Product	Yield (%) ^b
1	C ₆ H ₅ NH ₂ (2a)	20	4a	92
2	4-OMe-C ₆ H ₄ NH ₂ (2b)	22	4b	98
3	4-Cl-C ₆ H ₄ NH ₂ (2c)	41	4c	69
4	4-ethynyl-C ₆ H ₄ NH ₂ (2d)	20	4d	92
5	3,5-(Me) ₂ -C ₆ H ₃ NH ₂ (2e)	18	4e	88
6	(2f)	18	4f	84
7	(2g)	22	4g	83
8	Benzylamine (2h)	5	4h	87
9	Cyclohexylamine (2i)	5	4i	82
10	Allylamine (2j)	5	4j	83
11	Propargylamine (2k)	5	4k	84
12	(2l)	4	4l	91

^a Reaction conditions: 10 mol % of **1a**, 10 mol% of KHMDS, 1.2 equiv of **3a**, 0.25 mol L⁻¹ of **2** in toluene at 23 °C. ^b Yield of isolated product.

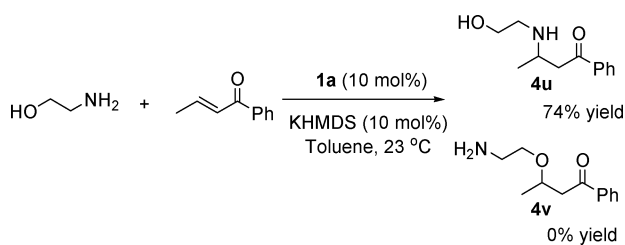
Table 4 Conjugate acceptor scope^a

Entry	R ¹	R ²	R ³	product	Yield (%) ^b
1	H	H	Me	4m	49
2	H	CH ₃ (CH ₂) ₃	Et	4n	56
3	H	H	C ₆ H ₅	4o	72
4	H	CH ₃ (CH ₂) ₃	C ₆ H ₅	4p	69
5	H	CO ₂ Et	C ₆ H ₅	4q	75
6	Me	Me	C ₆ H ₅	4r	0
7	H	C ₆ H ₅	C ₆ H ₅	4s	29
8	H	Me	OBn	4t	0

^a Reaction conditions: 10 mol % of **1a**, 1.2 equiv of **3**, 10 mol% of KHMDS, 0.25 mol L⁻¹ of **2a** in toluene at 23 °C. ^b Yield of isolated product.

in good yield (entry 3), whereas Michael acceptors with an alkyl (entry 4) or ester group (entry 5) in the β-position gave acceptable yields. β,β-Disubstituted enone employed could not afford the desired addition product (entry 6). However, the reaction was sluggish when an enone with aryl substituted in the β-position was employed, affording a yield of 29% (entry 7). Unfortunately, efforts for aza-Michael addition of aniline **2a** to an α,β-unsaturated ester (entry 8), cyclohexenone and cyclopentenone have not been proven successful so far.

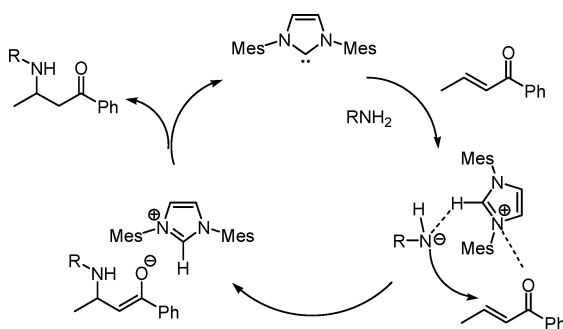
As shown in Scheme 1, the addition of 2-aminoethanol to α,β-unsaturated ketones was examined in the presence of 10 mol% NHC catalyst and 10 mol% KHMDS in toluene. In contrast to K. A. Scheidt's conjugate addition of alcohols to activated alkene reaction,^{7f} only nitrogen attached addition product **4u** was



Scheme 1

detected in 74% yield and product in which the oxygen side acted as nucleophile was not observed at all.

Based on the results we obtained, the mechanism of this reaction is speculated as shown in Scheme 2. N-heterocyclic carbene, generated from imidazolium salt upon treatment with base, reacts with amine to form an NHC-amine complex. This complex might activate the enone and expedite the 1,4-addition of amine to enone, affording β -amino ketone and regenerating the N-heterocyclic carbene.¹²



Scheme 2 Proposed mechanism.

Conclusions

In summary, we have identified an N-heterocyclic carbene as catalyst for aza-Michael addition of amines with α,β -unsaturated ketones to afford β -amino ketones. The reaction features a metal-free approach, high yields, mild reaction conditions, as well as an operationally simple and environmentally benign procedure. These features, together with the tolerability of both aromatic and aliphatic amines, warrant the wide application of the current methodology for the synthesis of β -amino ketones. Further investigation of the mechanism of this reaction and potential application of the catalytic system is ongoing in our group.

Experimental

General method

Reactions were carried out under nitrogen or argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, methylene chloride (CH_2Cl_2) and acetonitrile (MeCN) were purchased in anhydrous form and used without further purification. Ethyl acetate (EtOAc), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), and hexanes were purchased at the highest commercial quality and used without further purification, unless otherwise

stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate and anisaldehyde and heat as developing agents. E. Merck silica gel was used for flash column chromatography. NMR spectra were recorded on a Bruker AV-400 instrument. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad.

General procedure

To a solution of imidazolium salt (0.05 mmol) in toluene (1 mL) was added KHMDS (75 μ L, 15% w/w solution in toluene, 0.05 mmol) at 23 °C under Ar atmosphere. The resulting mixture was stirred at that temperature for 1 h before the solution of α,β -unsaturated ketone (0.6 mmol) and amine (0.5 mmol) in toluene (1 mL) was added. The reaction was stirred at 23 °C (monitored by TLC) before it was quenched with NH_4Cl (4 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in *vacuo*. Flash column chromatography (silica gel, hexanes : EtOAc = 30 : 1 ~ 2 : 1) afforded β -amino ketone.

1-Phenyl-3-(phenylamino)butan-1-one (4a). 92% yield as colorless oil. IR (film) ν_{max} 3390, 1676, 1597, 1495, 1001, 688 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2 H), 7.59–7.55 (m, 1 H), 7.49–7.44 (m, 2 H), 7.20–7.16 (m, 2 H), 6.73–6.69 (m, 1 H), 6.65–6.63 (m, 2 H), 4.19–4.14 (m, 1 H), 3.82 (br, 1 H), 3.33 (dd, J = 4.0, 16.4 Hz, 1 H), 3.07 (dd, J = 7.6, 16.4 Hz, 1 H), 1.33 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 146.7, 137.0, 133.2, 129.3, 128.6, 128.0, 117.5, 113.4, 45.5, 44.3, 20.9 ppm; HRMS (ESI): calcd for $C_{16}H_{18}NO^+$ [$M + H^+$] 240.1383, found 240.1374.

3-(4-Methoxyphenylamino)-1-phenylbutan-1-one (4b). 98% yield as colorless oil. IR (film) ν_{max} 1677, 1508, 1448, 1232, 1035, 819, 689 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2 H), 7.60–7.55 (m, 1 H), 7.48–7.45 (m, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.64 (d, J = 8.8 Hz, 2 H), 4.12–4.04 (m, 1 H), 3.75 (s, 3 H), 3.57 (br, 1 H), 3.31 (dd, J = 4.0, 16.4 Hz, 1 H), 3.05 (dd, J = 7.6, 16.4 Hz, 1 H), 1.31 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 152.2, 140.8, 137.0, 133.1, 128.5, 127.9, 115.3, 114.8, 55.6, 46.7, 44.3, 20.9 ppm; HRMS (ESI): calcd for $C_{17}H_{20}NO_2^+$ [$M + H^+$] 270.1489, found 270.1485.

3-(4-Chlorophenylamino)-1-phenylbutan-1-one (4c). 69% yield as colorless oil. IR (film) ν_{max} 3390, 1676, 1597, 1495, 1290, 1001, 814, 751 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2 H), 7.61–7.56 (m, 1 H), 7.49–7.46 (m, 2 H), 7.12 (d, J = 8.8 Hz, 2 H), 6.56 (d, J = 8.8 Hz, 2 H), 4.15–4.08 (m, 1 H), 3.88 (br, 1 H), 3.28 (dd, J = 4.0, 16.8 Hz, 1 H), 3.09 (dd, J = 7.2, 16.8 Hz, 1 H), 1.33 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 145.4, 137.0, 133.3, 129.2, 128.7, 128.0, 122.0, 114.6, 45.8, 44.1, 20.9 ppm; HRMS (ESI): calcd for $C_{16}H_{17}ClNO^+$ [$M + H^+$] 274.0993, found 274.0982.

3-(4-Ethynylphenylamino)-1-phenylbutan-1-one (4d). 92% yield as colorless oil. IR (film) ν_{\max} 3284, 2098, 1677, 1606, 1513, 1325, 1173, 1001, 823, 688 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.95–7.92 (m, 2 H), 7.60–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 7.33–7.31 (m, 2 H), 6.56–6.53 (m, 2 H), 4.17–4.12 (m, 2 H), 3.28 (dd, J = 6.0, 16.8 Hz, 1 H), 3.09 (dd, J = 7.2, 16.8 Hz, 1 H), 2.99 (s, 1 H), 1.33 ppm (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.0, 147.2, 136.9, 133.6, 133.4, 128.7, 128.0, 112.8, 110.0, 84.7, 74.9, 45.3, 44.1, 20.9 ppm; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{18}\text{NO}^+$ [$\text{M} + \text{H}^+$] 264.1383, found 264.1387.

3-(3,5-Dimethylphenylamino)-1-phenylbutan-1-one (4e). 88% yield as colorless oil. IR (film) ν_{\max} 2970, 1738, 1678, 1597, 1183, 1001, 822, 752 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.98–7.95 (m, 2 H), 7.61–7.57 (m, 1 H), 7.50–7.46 (m, 2 H), 6.40 (s, 1 H), 6.30 (s, 2 H), 4.20–4.13 (m, 1 H), 3.72 (br, 1 H), 3.35 (dd, J = 4.0, 16.4 Hz, 1 H), 3.06 (dd, J = 3.6, 16.4 Hz, 1 H), 2.25 (s, 6 H), 1.33 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.4, 146.8, 139.0, 137.1, 133.2, 128.6, 128.1, 119.6, 111.4, 45.5, 44.6, 21.5, 21.1 ppm; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{22}\text{NO}^+$ [$\text{M} + \text{H}^+$] 268.1696, found 268.1699.

3-(Benzo[d][1,3]dioxol-5-ylamino)-1-phenylbutan-1-one (4f). 84% yield as colorless oil. IR (film) ν_{\max} 2970, 1738, 1503, 1488, 1365, 1202, 1038, 753 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.95–7.93 (m, 2 H), 7.60–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 6.66 (d, J = 8.4 Hz, 1 H), 6.30 (d, J = 2.4 Hz, 1 H), 6.10 (dd, J = 2.4, 8.4 Hz, 1 H), 5.86 (s, 2 H), 4.08–4.00 (m, 1 H), 3.61 (br, 1 H), 3.29 (dd, J = 4.4, 16.4 Hz, 1 H), 3.05 (dd, J = 6.4, 16.4 Hz, 1 H), 1.31 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.3, 148.4, 142.4, 139.8, 137.1, 133.2, 128.6, 128.0, 108.7, 105.7, 100.6, 97.0, 46.8, 44.2, 20.9 ppm; HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_3^+$ [$\text{M} + \text{H}^+$] 284.1281, found 284.1283.

1-Phenyl-3-(pyridin-3-ylamino)butan-1-one (4g). 83% yield as pale yellow oil. IR (film) ν_{\max} 3970, 1738, 1681, 1482, 1448, 1216, 1002, 795, 753 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 8.03 (d, J = 2.8 Hz, 1 H), 7.95–7.92 (m, 3 H), 7.60–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 7.09–7.06 (m, 1 H), 6.93–6.90 (m, 1 H), 4.19–4.12 (m, 1 H), 4.01 (br, 1 H), 3.29 (dd, J = 4.4, 16.4 Hz, 1 H), 3.12 (dd, J = 6.8, 16.4 Hz, 1 H), 1.34 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 198.9, 142.9, 138.8, 136.9, 136.7, 133.4, 128.7, 128.0, 123.8, 119.1, 45.4, 44.0, 20.8 ppm; HRMS (ESI): calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}^+$ [$\text{M} + \text{H}^+$] 241.1335, found 241.1342.

3-(Benzylamino)-1-phenylbutan-1-one (4h). 87% yield as colorless oil. IR (film) ν_{\max} 2925, 1677, 1599, 1504, 1291, 1001, 747, 688 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.97–7.94 (m, 2 H), 7.59–7.54 (m, 1 H), 7.48–7.44 (m, 2 H), 7.36–7.30 (m, 4 H), 7.27–7.22 (m, 2 H), 3.88 (d, J = 13.2 Hz, 1 H), 3.80 (d, J = 13.2 Hz, 1 H), 3.44–3.37 (m, 1 H), 3.19 (dd, J = 6.8, 16.8 Hz, 1 H), 3.04 (dd, J = 5.6, 16.8 Hz, 1 H), 1.95 (br, 1 H), 1.23 ppm (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.6, 140.3, 137.1, 133.1, 128.6, 128.4, 128.1, 128.0, 126.9, 51.4, 49.3, 45.7, 20.6 ppm; HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{20}\text{NO}^+$ [$\text{M} + \text{H}^+$] 254.1539, found 254.1535.

3-(Cyclohexylamino)-1-phenylbutan-1-one (4i). 82% yield as colorless oil. IR (film) ν_{\max} 2925, 1680, 1448, 1216, 1002, 752, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.96–7.94 (m, 2 H), 7.58–7.54 (m, 1 H), 7.48–7.44 (m, 2 H), 3.52–3.44 (m, 1 H), 3.12

(dd, J = 6.0, 16.4 Hz, 1 H), 2.97 (dd, J = 6.4, 16.4 Hz, 1 H), 2.56–2.49 (m, 1 H), 1.94–1.85 (m, 2 H), 1.74–1.70 (m, 2 H), 1.62–1.57 (m, 1 H), 1.28–0.98 (m, 5 H), 1.14 ppm (d, J = 6.0 Hz, 3 H), N–H is not observed in ^1H NMR; ^{13}C NMR (100 MHz, CDCl_3): δ = 199.7, 137.2, 133.0, 128.5, 128.0, 53.4, 46.2, 46.0, 34.4, 33.5, 26.1, 25.2, 25.1, 21.2 ppm; HRMS (ESI): calcd for $\text{C}_{16}\text{H}_{24}\text{NO}^+$ [$\text{M} + \text{H}^+$] 246.1852, found 246.1859.

3-(Allylamino)-1-phenylbutan-1-one (4j). 83% yield as pale yellow oil. IR (film) ν_{\max} 2970, 1679, 1448, 1211, 1001, 916, 752, 689 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.97–7.95 (m, 2 H), 7.59–7.55 (m, 1 H), 7.49–7.45 (m, 2 H), 5.97–5.87 (m, 1 H), 5.20 (d, J = 17.2 Hz, 1 H), 5.10 (d, J = 10.4 Hz, 1 H), 3.40–3.14 (m, 3 H), 3.17 (dd, J = 6.4, 16.8 Hz, 1 H), 3.01 (dd, J = 6.0, 16.8 Hz, 1 H), 1.8 (br, 1 H), 1.18 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.6, 137.1, 136.7, 133.2, 128.6, 128.0, 116.0, 49.8, 49.1, 45.6, 20.5 ppm; HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{18}\text{NO}^+$ [$\text{M} + \text{H}^+$] 204.1383, found 204.1377.

1-Phenyl-3-(prop-2-ynylamino)butan-1-one (4k). 84% yield as colorless oil. IR (film) ν_{\max} 2970, 1738, 1679, 1448, 1372, 1215, 1002, 753, 689, 661 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.96–7.93 (m, 2 H), 7.57–7.54 (m, 1 H), 7.47–7.43 (m, 2 H), 3.57–3.49 (m, 1 H), 3.47 (dd, J = 2.4, 8.0 Hz, 2 H), 3.13 (dd, J = 6.8, 16.8 Hz, 1 H), 3.02 (dd, J = 5.6, 16.8 Hz, 1 H), 2.21 (t, J = 2.4 Hz, 1 H), 1.90 (br, 1 H), 1.16 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.3, 136.9, 133.2, 128.6, 128.0, 81.9, 71.4, 48.1, 45.4, 35.5, 20.0 ppm; HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{16}\text{NO}^+$ [$\text{M} + \text{H}^+$] 202.1226, found 202.1229.

3-((R)-1-Phenylethylamino)-1-phenylbutan-1-one (4l). 91% yield (2 diastereomers, dr = 1.4 : 1) as colorless oil. IR (film) ν_{\max} 2970, 1738, 1679, 1448, 1370, 1216, 754, 700, 691 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.91–7.86 (m, 4.8 H), 7.56–7.52 (m, 2.4 H), 7.45–7.40 (m, 4.8 H), 7.34–7.29 (m, 9.6 H), 7.27–7.21 (m, 2.4 H), 3.98–3.92 (m, 2.4 H), 3.27–2.85 (m, 7.2 H), 1.82 (br, 2.4 H), 1.36 (d, J = 6.8 Hz, 3 H), 1.35 (d, J = 6.8 Hz, 4.2 H), 1.13 (d, J = 6.0 Hz, 4.2 H), 1.08 ppm (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 199.9, 199.8, 146.0, 145.2, 137.1, 137.0, 133.0, 128.5, 128.4, 128.1, 128.0, 126.9, 126.8, 126.6, 126.5, 55.3, 55.0, 47.8, 46.6, 46.6, 45.2, 25.3, 24.6, 21.6, 19.9 ppm; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{22}\text{NO}^+$ [$\text{M} + \text{H}^+$] 268.1696, found 268.1706.

4-(Phenylamino)butan-2-one (4m). 49% yield as colorless oil. IR (film) ν_{\max} 3396, 1707, 1601, 1505, 1168, 748, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.26–7.15 (m, 2 H), 6.73–6.71 (m, 1 H), 6.62–6.59 (m, 2 H), 3.96 (br, 1 H), 3.41 (t, J = 6.4 Hz, 2 H), 2.75 (t, J = 6.0 Hz, 2 H), 2.16 ppm (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 208.1, 147.6, 129.2, 117.5, 112.9, 42.5, 38.2, 30.2 ppm; HRMS (ESI): calcd for $\text{C}_{10}\text{H}_{14}\text{NO}^+$ [$\text{M} + \text{H}^+$] 164.1070, found 164.1065.

5-(Phenylamino)nonan-3-one (4n). 56% yield as colorless oil. IR (film) ν_{\max} 2932, 1707, 1602, 1504, 1259, 749, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.17–7.13 (m, 2 H), 6.69–6.66 (m, 1 H), 6.60–6.58 (m, 2 H), 3.85–3.79 (m, 1 H), 3.67 (br, 1 H), 2.67 (dd, J = 4.8, 16.0 Hz, 1 H), 2.56 (dd, J = 6.8, 16.0 Hz, 1 H), 2.41 (q, J = 14.4 Hz, 2 H), 1.57–1.51 (m, 2 H), 1.41–1.27 (m, 4 H), 1.02 (t, J = 7.2 Hz, 3 H), 0.88 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 210.9, 147.2, 129.3, 117.3, 113.2, 49.7,

46.6, 36.8, 34.9, 28.4, 22.5, 14.0, 7.5 ppm; HRMS (ESI): calcd for $C_{15}H_{24}NO^+$ $[M + H]^+$ 234.1852, found 234.1859.

1-Phenyl-3-(phenylamino)heptan-1-one (4p). 69% yield as colorless oil. IR (film) ν_{\max} 3390, 2955, 1677, 1599, 1505, 1214, 748, 690 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.93 (m, 2 H), 7.59–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 7.20–7.15 (m, 2 H), 6.72–6.63 (m, 3 H), 4.08–4.02 (m, 1 H), 3.79 (br, 1 H), 3.26 (dd, J = 4.8, 16.8 Hz, 1 H), 3.15 (dd, J = 7.2, 16.8 Hz, 1 H), 1.73–0.92 (m, 7 H), 0.92 ppm (t, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 147.2, 137.2, 133.2, 129.4, 128.6, 128.0, 117.3, 113.2, 49.9, 42.7, 35.1, 28.5, 22.6, 14.0 ppm; HRMS (ESI): calcd for $C_{19}H_{24}NO^+$ $[M + H]^+$ 282.1852, found 282.1860.

Ethyl 4-oxo-4-phenyl-2-(phenylamino)butanoate (4q). 75% yield as colorless oil. IR (film) ν_{\max} 2970, 1738, 1602, 1368, 751, 690 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2 H), 7.60–7.56 (m, 1 H), 7.48–7.44 (m, 2 H), 7.21–7.16 (m, 2 H), 6.77–6.73 (m, 1 H), 6.71–6.69 (m, 2 H), 4.65–4.60 (m, 1 H), 4.56–4.54 (m, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 3.59–3.57 (m, 2 H), 1.21 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 172.8, 146.3, 136.3, 133.4, 129.3, 128.6, 128.0, 118.4, 113.6, 61.5, 52.9, 40.7, 14.0 ppm; HRMS (ESI): calcd for $C_{18}H_{20}NO_3^+$ $[M + H]^+$ 298.1438, found 298.1444.

1,3-Diphenyl-3-(phenylamino)propan-1-one (4s). 29% yield as colorless solid. IR (film) ν_{\max} 3385, 1738, 1671, 1600, 1506, 1365, 1291, 1217, 689 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.91 (m, 2 H), 7.60–7.56 (m, 1 H), 7.48–7.44 (m, 4 H), 7.36–7.32 (m, 2 H), 7.27–7.23 (m, 1 H), 7.12–7.08 (m, 2 H), 6.99–6.66 (m, 1 H), 6.59–6.56 (m, 2 H), 5.04–5.00 (m, 1 H), 4.57 (br, 1 H), 3.53 (dd, J = 5.2, 16.0 Hz, 1 H), 3.43 ppm (dd, J = 7.6, 16.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 146.9, 142.9, 136.6, 133.4, 129.1, 128.8, 128.7, 128.2, 127.3, 126.3, 117.7, 113.7, 54.7, 46.3 ppm; HRMS (ESI): calcd for $C_{21}H_{20}NO^+$ $[M + H]^+$ 302.1539, found 302.1539.

3-(2-Hydroxyethylamino)-1-phenylbutan-1-one (4u). 74% yield as colorless oil. IR (film) ν_{\max} 3304, 2928, 1680, 1448, 1359, 1266, 1054, 755, 689, 587 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.95 (m, 2 H), 7.60–7.56 (m, 1 H), 7.49–7.45 (m, 2 H), 3.77–3.69 (m, 4 H), 3.54–3.47 (m, 1 H), 3.34 (dd, J = 6.8, 16.4 Hz, 1 H), 3.17 (dd, J = 6.4, 16.4 Hz, 1 H), 3.01–2.84 (m, 2 H), 1.29 ppm (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9, 136.6, 133.5, 128.7, 128.1, 59.9, 49.8, 48.1, 44.3, 19.5 ppm; HRMS (ESI): calcd for $C_{12}H_{18}NO_2^+$ $[M + H]^+$ 208.1332, found 208.1334.

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