Non-Cryogenic $CeCl_3$-Promoted Double Additions of Methyllithium and *n*-Butyllithium to Unsaturated Nitriles

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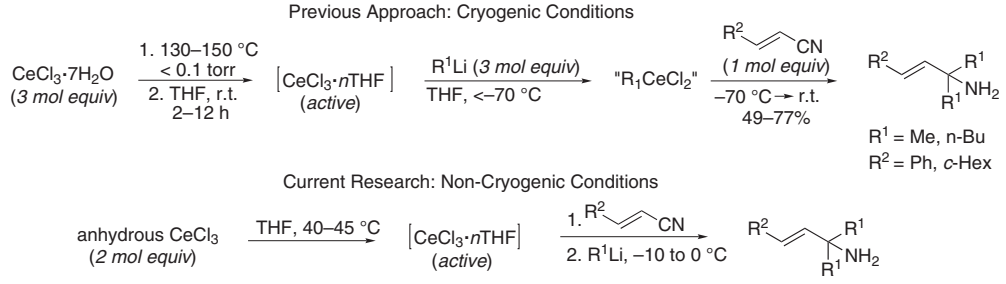
Abstract: Subjection of methyl or *n*-butyllithium to a mixture of nitriles and activated cerium chloride in THF at –10 to 0 °C afforded the corresponding carbinamines, which were isolated as either the hydrochloride salts or acetamide or benzamide derivatives in 30–91% yields.

Key words: carbinamines, carbinamides, organocerium reagents, non-cryogenic conditions, reaction optimization

Addition of organolithium or Grignard reagents to nitriles generally concludes at the ketimines (ketones) stage.[1] Subsequent addition to the initially generated metal ketimines usually requires the use of highly nucleophilic organocerium reagent to afford the corresponding tertiary carbinamines.[2] In few isolated cases, however, double additions of Grignard or organolithium reagents have been observed with α-alkoxy nitriles[3] or when allylmagnesium halide was used as the nucleophile.[4] In the case of α,β-unsaturated nitriles, reaction with an organolithium or Grignard reagent at low temperature could result in either 1,2-addition or 1,4-conjugated addition.[5]

1,2-Double additions of pre-formed methylcerium reagent to *various saturated* nitriles and to a *small set* of α,β-unsaturated nitriles, have been reported by Ciganek.[6] The general procedure for the preparation of organocerium reagents was initially developed by Imamoto et al.,[7] involving pre-drying solid $CeCl_3 \cdot 7H_2O$ under vacuum at elevated temperature,[8] followed by stirring the dried solid in THF at room temperature for 2–12 hours[9] and subjecting the suspension to the organolithium reagent at low temperatures (≤ –70 °C). The presumed generated organocerium reagent ('$RCeCl_2$') was then treated with the nitriles followed by warming to 0 °C to room temperature (Scheme 1). Even though good yields of carbinamines could be obtained using Ciganek's procedure, *the use of cryogenic conditions* and *excess amount* of $CeCl_3$ (≥ 3 mol equiv) are not feasible for large-scale processes. While other ways for generating *gem*-dimethyl carbinamines are available,[10] we recently required access to this class of compounds from their α,β-unsaturated nitrile precursors. In this regard, we investigated the possibility of effecting the same transformation by subjecting a mixture of activated $CeCl_3$ and various nitriles to MeLi at higher temperature, based on the notion that the potentially unstable nucleophiles ('$RCeCl_2$') would react with the substrate, as soon as they are being formed (Scheme 1).[11]

Considering the availability and low price of anhydrous $CeCl_3$ in bulk quantity,[12] our studies were conducted with commercial reagent, which typically contains ≤0.15 wt% of water. While activation of $CeCl_3$ in THF could be carried out at room temperature for 2–12 hours as mentioned above, a more reproducible process involves heating the solid (2 mol equiv) in 5–6 mL/g of THF at 40–45 °C for three hours to afford active, crystalline, rod-shaped $CeCl_3 \cdot THF$ complex.[13] Gratifyingly, subsequent addition of *p*-dimethylaminocinnamonitrile (**1**) (1 mol equiv) to the slurry of the activated species, followed by subjecting the resulting mixture to MeLi·LiBr (2.5 mol equiv) in Et_2O at –10 to 0 °C, afforded the corresponding carbinamine **2** in 90% HPLC assay yield (Table 1). Upon benzoylation (BzCl, CH_2Cl_2/H_2O, K_2CO_3), the allylic benzamide derivative **3** was isolated by crystallization in 75% yield.



Scheme 1 Preparation of allylic carbinamines

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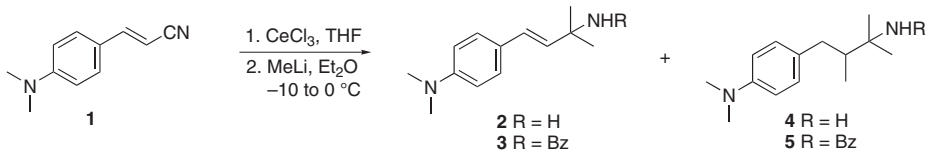
Table 1 Reaction Profiling for $CeCl_3$-Promoted Double Additions of MeLi to Nitrile **1**



Entry	$CeCl_3$ (mol equiv)	MeLi (mol equiv)	Observed product[a]	Yield (%) HPLC	Isolated product[b]	Yield (%)[c]
1	2	2.5	**2**	90	**3**	75
2	2	2.0	**2**	83	ND[d]	ND
3	0	2.5	complex mixture	–	–	–
4	2[e]	2.5	complex mixture	trace	–	–
5	0.3	2.5	**2**	20	ND	ND
6	1	2.5	**2**:**4** = 5:1	70	**3**	51
7	3	2.5	**2**	90	**3**	73
8	2	1.2	**2**:**1** = 1:1.2	40	ND	ND

[a] Ratio determined by ^1H NMR spectroscopy.
[b] BzCl, K_2CO_3, MTBE–CH_2Cl_2/H_2O.
[c] Yield of isolated product **3**, crystallized from CH_2Cl_2–MTBE.
[d] Not determined.
[e] No activation of commercial anhyd $CeCl_3$.

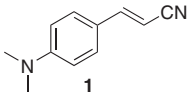
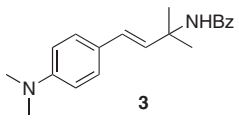
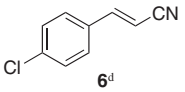
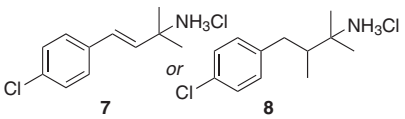
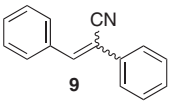
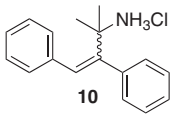
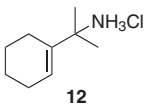
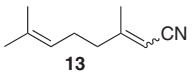
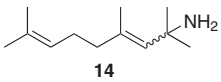
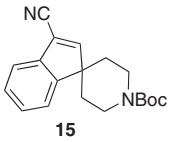
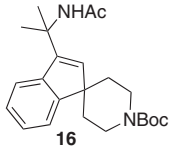
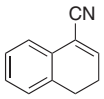
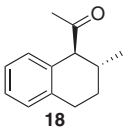
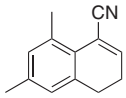
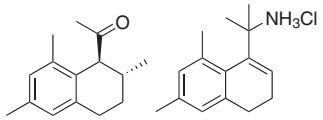
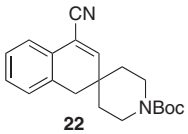
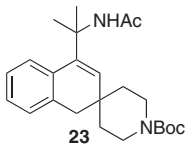
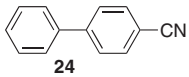
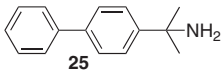
Investigation of reaction stoichiometry was subsequently performed, while keeping the reaction temperature between –10 to 0 °C. A slightly lower assay yield of product was obtained when 2 molar equivalents of MeLi were used (Table 1, entry 2). In the absence of $CeCl_3$ (entry 3) or when commercial anhydrous reagent was used without activation (entry 4), a complex mixture of products was obtained, and only a trace amount of desired carbinamine was detected in the latter case. While reducing the amount of $CeCl_3$ to 30 mol% afforded **2** in only 20% assay yield (entry 5), performing the same reaction using equimolar amount of $CeCl_3$ gave a 5:1 mixture of **2** and over-alkylated product **4** in 70% combined yield (entry 6). On the other hand, increasing the amount of $CeCl_3$ to 300 mol%, while keeping the amount of MeLi constant, did not appear to favor the formation of amine **4** nor did it improve formation of the desired carbinamine (entry 7). Using MeLi as a limiting reagent (entry 8) afforded a 1:1.2 mixture of product and unreacted starting material with no trace of ketimine intermediate, suggesting that the rate of the second addition is considerably faster.

The experimental results in Table 1 indicate that an effective reaction could be realized using 2 molar equivalents of activated $CeCl_3$ and 2.5 molar equivalents of MeLi. To probe the scope and limitation of this non-cryogenic transformation, further investigations were carried out using other α,β-unsaturated nitriles and the results are summarized in Table 2. The carbinamine products were isolated as either the hydrochloride salt, acetamide or benzamide derivatives. Under the conditions described above, *p*-chlorocinnamonitrile afforded carbinamine **7**, which was isolated as its HCl salt in 68% yield (entry 2). Employing excess amount of $CeCl_3$ and MeLi (3 and 4 mol equiv, respectively) resulted predominantly in the formation of over-alkylated product **8** (entry 2). Sterically encumbered substrate, such as α-phenylcinnamonitrile (**9**), also underwent double addition to afford the carbinamine HCl salt **10**, albeit in only 42% yield (entry 3).

The studies were further extended to include cyclic and/or aliphatic α,β-unsaturated nitriles. An example of the latter class of substrates includes cyclohexenecarbonitrile **11**, which underwent the transformation smoothly to give the corresponding amine HCl salt **12** in 74% yield (entry 4). Additionally, the non-conjugated diene-nitrile **13** afforded the corresponding amine-HCl **14** in 40% yield (entry 5). In terms of cyclic unsaturated nitriles, subjection of an *N*-Boc-piperidine-indene **15** to the standard reaction conditions also cleanly afforded the desired allylic carbinamine, which was isolated as its acetamide **16** in 73% yield (entry 6).

On the other hand, the six-membered-ring variants, such as dihydronaphthalene **17** or **19** gave predominantly [1,4-1,2] adducts **18** and **20**, each as a single diastereomer, in 68% and 79% yields, respectively (entries 7,8). Reaction involving substrate **19** also afforded the desired carbinamine **21**, which could be isolated as its HCl salt **21** in 13% yield. Incorporation of substituents at the γ-position, such as in substrate **22**, strongly favored the [1,2]-double addition, affording the carbinamide **23** in 83% yield (entry 9). Not surprisingly, the current non-cryogenic

Table 2 $CeCl_3$-Promoted Double Additions of MeLi to α,β-Unsaturated Nitriles[a]

Entry	Substrate	Product(s)[b]	Yield (%)[c]
1	 **1**	 **3**	75
2	 **6**[d]	 **7** *or* **8**	**7** 68[e] **8** 42[f]
3	 **9**	 **10**	42
4	 **11**	 **12**	74
5	 **13**	 **14**	40[g]
6	 **15**	 **16**	73
7	 **17**	 **18**	68[g]
8	 **19**	 **20** **21**	**20**[g]:**21** = 79:13
9	 **22**	 **23**	83[g]
10	 **24**	 **25**	80

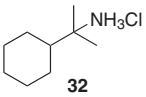
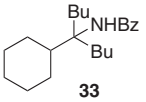
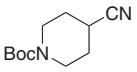
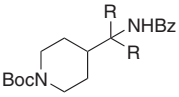
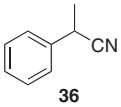
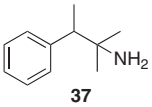
[a] Typical conditions: activated [$CeCl_3$] (2 mol equiv) = 6–8 mL/g THF, MeLi·LiBr (2.5 mol equiv), –10 to 0 °C, 1 h.
[b] Amide or HCl salt formation was carried out using standard procedure. Unless otherwise noted, products were isolated by crystallization.
[c] Overall isolated yields for the addition and amidation or salt formation.
[d] Exists as an 85:15 *E*/*Z* mixture.
[e] Three mol equiv of $CeCl_3$ was used; 85:15 *E*/*Z* product mixture was isolated.
[f] Four mol equiv of MeLi was used.
[g] Isolated by SiO_2 gel flash column chromatography.

conditions could also be applied to aromatic nitriles, such as 4-phenylbenzonitrile (**24**), to generate the corresponding benzylic carbinamine HCl salt **25** in 80% isolated yield (entry 10).

While reactions between MeLi and α,β-unsaturated nitriles generate the corresponding carbinamines in moderate to good yields as illustrated in Table 2, *n*-butyllithium, on the other hand, adds to unsaturated nitriles less efficiently as shown in Table 3. For example, under typical reaction conditions, the γ-disubstituted dihydronaphthalene **22** afforded the corresponding benzamide derivative **26** in only 46% yield (vs. 83% for MeLi addition, entry 9, Table 2) (entry 1). Interestingly, a decyanation process also took place to generate dihydronaphthalene **27** in 26% yield (entry 1). Furthermore, the cinnamonitrile substrate **1** reacted with *n*-BuLi in the presence of $CeCl_3$ to give predominantly the [1,4-1,2]-adduct **28** in 58% yield, in addition to the desired carbinamine, isolated as its benzamide derivative **29** in 22% yield (entry 2). On the other hand, a cyclic aliphatic nitrile, such as substrate **11**, underwent the double addition smoothly to generate the desired carbinamine, which was benzoylated and isolated by crystallization to give **30** in 78% overall yield (entry 3).

Additional substrate probing was carried out using saturated nitriles and the results are summarized in Table 4. Under standard conditions, cyclohexanecarbonitrile (**31**) underwent smooth double-additions with either MeLi or *n*-BuLi to afford HCl salt **32** or benzamide derivative **33** in 91% or 94% yields, respectively (entries 1,2). Furthermore, similar treatment of *N*-Boc piperidine carbonitrile **34** with the organolithium reagents and $CeCl_3$ also afforded the corresponding carbinamine benzamides **35a** and **35b** in 68% and 78%, respectively. Substrates bearing a more acidic α-proton,[14] such as α-phenylpropionitrile (entry 4), however, underwent only a 50% conversion, suggesting that the α-deprotonation was a competing event.

Table 4 $CeCl_3$-Promoted Double Addition of RLi to Saturated Nitriles

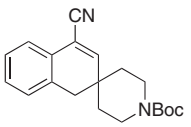
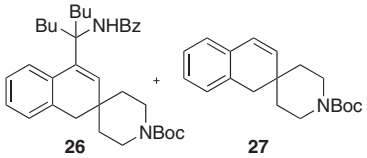
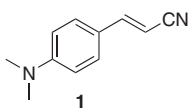
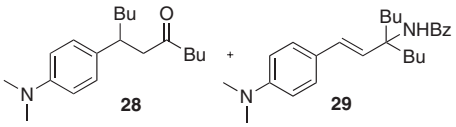
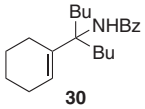
Entry	Substrate	Products[a]	Yield (%)[b]
1	 **31**	 **32**	91
2	 **31**	 **33**	94
3	 **34**	 **35a** R = Me **35b** R = *n*-Bu	**35a** 68 **35b** 78
4	 **36**	 **37**	47 (85)[c]

[a] Isolated by either SiO_2 gel chromatography or crystallization.
[b] Overall two-step yields.
[c] Yield under cryogenic conditions.

Nonetheless, the desired carbinamide **37** could be isolated in 47% yield. When the same substrate was subjected to a preformed methylcerium reagent ('$MeCeCl_2$') at –70 °C, the transformation occurred smoothly to give carbinamide **37** after acetylation in 85% isolated yield.

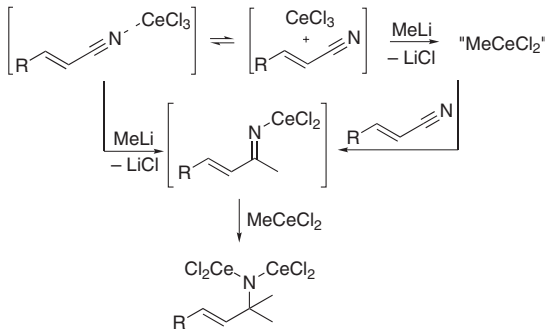
Mechanistically, based on the original report by Ciganek,[6] it is likely that the current protocol also involves in situ generation of methylcerium reagents ('$MeCeCl_2$'), which immediately add to nitriles, affording the corresponding carbinamines (Scheme 2). On the other hand, while the

Table 3 $CeCl_3$-Promoted Additions of *n*-BuLi to α,β-Unsaturated Nitriles

Entry	Substrate	Product(s)[a]	Yield (%)[b]
1	 **22**	 **26** **27**	**26**:**27** = 46:26
2	 **1**	 **28** **29**	**28**:**29** = 58:22
3	 **11**	 **30**	78

[a] Products were purified and isolated by either silica gel chromatography or crystallization.
[b] Obtained for the two-step process.

second addition certainly requires the use of an organocerium reagent,[2b,6] the initial addition might involve direct attack of MeLi to activated RCN–$CeCl_3$ complex, similar to the previously reported reactions between Grignard reagents and ketone–$CeCl_3$ complexes.[3a] In any events, while in the absence of $CeCl_3$, reactions between MeLi and α,β-unsaturated nitriles at –10 °C give a complex mixture of products (Table 1, entry 3),[15] reactions involving saturated nitriles bearing acidic α-protons result in partial conversions, due to competing deprotonation under our reaction conditions.



Scheme 2 Possible transformation pathways

In summary, we have developed a *non-cryogenic* method for accessing carbinamines via double additions of MeLi and to some extent, *n*-BuLi, to various α,β-unsaturated and saturated nitriles in the presence of activated $CeCl_3$ at –10 to 0 °C. The desired carbinamines are generally isolated as either their HCl salts or amide derivatives in moderated to good yields (40–94%). While the use of anhydrous $CeCl_3$ eliminates the tedious pre-drying process for the commonly used $CeCl_3$ heptahydrate salt, pregeneration of the organocerium reagent at low temperature (–70 °C) was no longer necessary. The current improved protocol certainly offers major practicality and convenience in both academic and large-scale industrial set-ups.

All reactions were conducted under N_2. Commercial reagents and the following commercial solvents were used without further purification: anhyd THF (<100 ppm H_2O), HPLC-grade hexanes and MTBE. HPLC analysis was performed using ACE 3C-18 (150 × 3 mm i.d.) column under the following assay conditions: 95% solvent A (99% H_2O, 1% buffer of 0.2 M NH_4CO_2H:0.2 M HCO_2H in H_2O) and 5% solvent B (90% MeCN, 9% H_2O, 1% buffer), ramped to 100% solvent B at 1 mL/min flow rate over 9.5 min and aged for 5 additional min, measured at 210 nm and 35 °C column temperature. ^{1}H NMR spectra were measured on either a 400 MHz or 500 MHz instrument and ^{13}C NMR spectra on the corresponding 100 MHz or 125 MHz instrument. IR spectra were reported in wavenumbers and measured with an FT-IR or ATR-IR spectrometer on either a KBr salt or PTFE IR card. Melting points are uncorrected. HRMS measurements were performed at Merck Research Laboratory, Rahway, NJ.

Double Additions of MeLi to α,β-Unsaturated Nitriles; Allylic Acetamide 23; Typical Procedure

A suspension of commercial, anhyd $CeCl_3$ (4.5 g, 18.25 mmol, 2 equiv) in anhyd THF (27 mL) was heated to 45 °C for 3 h and checked under microscope to ensure complete formation of rod-shaped crystalline materials. The slurry was cooled to r.t. and treated with solid nitrile **22** (2.96 g, 9.13 mmol, 1 equiv). After further cooling to –10 °C, a 1.5 M solution of MeLi·LiBr in Et_2O (14.9 mL, 22.38 mmol, 2.5 equiv) was added dropwise over 30 min to give a brown slurry, which was aged for an additional 30 min. The reaction was quenched by addition of concd NH_4OH (6 mL) over 30 min. The yellow suspension obtained was allowed to warm to r.t., stirred for 1 h, and then filtered. The wet cake was rinsed several times with THF and the combined filtrates were then concentrated to almost dryness, diluted with MTBE (50 mL) and washed with H_2O (2 × 15 mL). To the crude carbinamine solution was added H_2O (15 mL) and K_2CO_3 (3.78 g, 27.39 mmol, 3 equiv). The resulting biphasic layers were cooled to 0 °C, treated with neat acetyl chloride (1.95 mL, 27.39 mmol, 3 equiv) and aged for 30 min at r.t. The organic layer was then separated, washed with brine (15 mL) and concentrated in vacuo. The crude oil was purified by SiO_2 gel flash column chromatography (8:1 to 1:1 hexanes–MTBE) to give pure allylic acetamide **23** in 83% isolated yield; colorless foam.

IR (PTFE IR card): 3309, 3058, 2993, 2930, 2870, 1692, 1664, 1647, 1531, 1425, 1366, 1097, 975, 769, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (1 H, dm, *J* = 7.5 Hz), 7.67 (2 H, dm, *J* = 8.3 Hz), 7.45 (1 H, ddt, *J* = 8.3, 6.4, 1.2 Hz), 7.40–7.36 (2 H, m), 7.20–7.13 (3 H, m), 6.31 (1 H, s), 6.16 (1 H, s), 3.54 (2 H, br m), 3.41 (2 H, ddd, *J* = 13.5, 8.4, 3.6 Hz), 2.73 (2 H, s), 1.86 (6 H, s), 1.58 (2 H, m), 1.48 (9 H, s), 1.47 (1 H, m), 1.30 (1 H, m).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 155.1, 140.3, 136.6, 136.0, 133.2, 132.3, 131.2, 129.3, 128.7, 127.1, 126.8, 126.2, 125.3, 79.5, 56.6, 40.7, 40.5 (br), 39.5 (br), 34.8, 33.0, 29.2, 28.2.

HRMS: *m/z* calcd for $C_{29}H_{37}N_2O_3$ (MH^+): 461.2804; found: 461.2811.

HCl Salts; General Procedure

For formation of an HCl salt, the crude carbinamine solution in MTBE was cooled to 0 °C and treated with a 5 N solution of HCl in propan-2-ol, followed by aging for 1 h and filtration. When necessary, recrystallization can be carried out in either MeCN–H_2O or *i*-PrOH–H_2O solvent system.

Benzamide 3

Colorless solid; mp 147–149 °C.

IR (KBr thin film): 3283 (br), 2967, 1636, 1610, 1524, 1489, 1359, 1312, 1187, 1169, 966, 949, 806, 711, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (2 H, d, *J* = 7.6 Hz), 7.45 (3 H, m), 7.33 (2 H, d, *J* = 8.2 Hz), 6.70 (2 H, d, *J* = 8.2 Hz), 6.51 (1 H, d, *J* = 16.2 Hz), 6.40 (1 H, d, *J* = 16.2 Hz), 6.27 (1 H, br s), 2.96 (6 H, s), 1.71 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 150.1 135.8, 131.4, 131.1, 128.5, 127.4, 127.3, 126.9, 125.3, 112.5, 54.7, 40.5, 27.5.

HRMS: *m/z* calcd for $C_{20}H_{25}N_2O$ (MH^+): 309.1961; found: 309.1966.

Hydrochloride Salt 7

Colorless solid; mp 168–178 °C (85% *trans*- and 15% *cis*-isomeric mixture).

IR (PTFE IR card): 3419, 2971, 2678, 2577, 2510, 2086, 1620, 1522, 1491, 1392, 1376, 1306, 1296, 1088, 1012, 976, 858, 802, 757 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*trans*-isomer) = 7.30 (2 H, d, *J* = 8.3 Hz), 7.23 (2 H, d, *J* = 8.3 Hz), 6.08 (1 H, d, *J* = 16.3 Hz), 6.36 (1 H, d, *J* = 16.3 Hz), 1.62 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*trans*-isomer) = 134.3, 134.2, 130.9, 130.3, 128.9, 128.2.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*cis*-isomer) = 7.30 (2 H, d, *J* = 8.3 Hz), 7.13 (2 H, d, *J* = 8.3 Hz), 6.49 (1 H, d, *J* = 12.7 Hz), 5.90 (1 H, d, *J* = 12.7 Hz), 1.35 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ (*cis*-isomer) = 135.3, 133.5, 133.3, 131.4, 129.9, 128.5.

HRMS: *m*/*z* calcd for $C_{11}H_{15}ClN$ (M^+ – Cl): 196.0893; found: 196.0896.

Hydrochloride Salt 8
Colorless solid; mp 223–224 °C.

IR (ATR IR): 2972, 2875, 2048, 1626, 1506, 1395, 1277, 1173, 1094, 1013, 851, 805, 661 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (3 H, br s), 7.18 (2 H, d, *J* = 8.4 Hz), 7.12 (2 H, d, *J* = 8.4 Hz), 3.12 (1 H, d, *J* = 12.6 Hz), 2.17 (1 H, t, *J* = 12.4 Hz), 2.07 (1 H, m), 1.44 (3 H, s), 1.43 (3 H, s), 0.82 (3 H, d, *J* = 6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 131.9, 130.4, 128.3, 58.3, 43.4, 36.6, 24.4, 22.2, 13.4.

HRMS: *m*/*z* calcd for $C_{12}H_{19}ClN$ (M^+ – Cl): 212.1206; found: 212.1198.

Hydrochloride Salt 10
Colorless solid; mp 236–241.

IR (ATR IR): 2971, 2921, 2877, 2567, 1741, 1595, 1520, 1443, 1374, 1175, 978, 767, 743, 665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (3 H, br s), 7.35 (10 H, m), 6.68 (1 H, s), 1.52 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 140.5, 136.9, 132.9, 129.1, 128.9, 128.3, 127.8, 127.6, 58.4, 28.1.

HRMS: *m*/*z* calcd for $C_{17}H_{20}N$ (M^+ – Cl): 238.1596; found: 238.1597.

Hydrochloride Salt 12
Colorless solid; mp 203–206 °C.

IR (KBr thin film): 3395 (br), 2937 (br), 2773, 2565, 2505, 2051 (br), 1597, 1511, 1446, 1394, 1372, 1295, 1169, 923, 845, 802, 737, 556 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 5.79 (1 H, m), 2.11 (4 H, m), 1.70 (2 H, m), 1.60 (2 H, m), 1.46 (6 H, s).

^{13}C NMR (100 MHz, CD_3OD): δ = 137.6, 122.3, 56.6, 24.7, 24.4, 23.5, 22.3, 21.4.

HRMS: *m*/*z* calcd for $C_9H_{18}N$ (M^+ – Cl): 140.1439; found: 140.1432.

Carbinamine 14
Pale yellow oil; a 1.3:1 mixture of olefin isomers,

IR (PTFE IR card): 3356 (br), 3287 (br), 2964, 2926, 2860, 2725, 1654, 1584, 1448, 1376, 1360, 1201, 1154, 1107, 1056, 985, 832, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.31 (1 H, m), 5.29 (1 H, q, *J* = 1.2 Hz), 5.16 (1 H, tp, *J* = 7.2, 1.6 Hz), 5.10 (1 H, tp, *J* = 7.2, 1.6 Hz), 2.27 (2 H, m), 2.13 (2 H, m), 2.07 (2 H, m), 1.95 (2 H, m), 1.80 (3 H, d, *J* = 1.2 Hz), 1.71 (3 H, d, *J* = 1.6 Hz), 1.70 (3 H, d, *J* = 1.2 Hz), 1.69 (3 H, d, *J* = 1.6 Hz), 1.63 (3 H, d, *J* = 1.2 Hz), 1.62 (3 H, d, *J* = 1.6 Hz), 1.55 (2 H, NH_2, br s), 1.29 (6 H, s), 1.28 (6 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.8, 135.2, 135.0, 134.3, 131.8, 131.6, 124.4, 124.3, 50.7, 50.5, 41.6, 33.0, 32.7, 32.5, 27.1, 26.9, 25.9, 24.8, 17.9, 17.8, 17.2.

HRMS: *m*/*z* calcd for $C_{12}H_{24}N$ (MH^+): 182.1908; found: 182.1909.

Acetamide 16
Colorless solid; mp 177–179 °C (toluene–heptane).

IR (KBr thin film): 3296 (br), 3067, 2980, 2937, 2863, 1692, 1550, 1424, 1364, 1243, 1161, 754, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (1 H, d, *J* = 7.0 Hz), 7.33 (1 H, d, *J* = 6.9 Hz), 7.23 (2 H, m), 6.64 (1 H, s), 5.88 (1 H, s), 4.19 (2 H, br s), 3.11 (2 H, t, *J* = 11.3 Hz), 2.00 (2 H, m), 1.92 (3 H, s), 1.73 (6 H, s), 1.51 (9 H, s), 1.34 (2 H, d, *J* = 12.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 155.0, 153.3, 147.1, 140.6, 133.7, 126.6, 125.3, 122.0, 121.4, 79.5, 53.6, 49.7, 42.3 (br), 33.4, 28.4, 26.8, 24.1.

HRMS: *m*/*z* calcd for $C_{23}H_{33}N_2O_3$ (MH^+): 385.2491; found: 385.2483.

Ketone 18
Colorless oil.

IR (PTFE IR card): 3061, 3017, 2956, 2927, 1707, 1492, 1455, 1435, 1380, 743, 554 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.12 (3 H, m), 6.95 (1 H, d, *J* = 7.6 Hz), 3.44 (1 H, d, *J* = 9.1 Hz), 2.95–2.82 (2 H, m), 2.10 (1 H, m), 2.04 (3 H, s), 1.98 (1 H, ddt, *J* = 13.1, 5.2, 3.4 Hz), 1.47 (1 H, ddt, *J* = 13.1, 10.9, 5.2 Hz), 1.10 (3 H, d, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.9, 137.0, 133.4, 129.7, 128.5, 127.0, 126.3, 62.9, 32.1, 30.1, 29.2, 26.9, 20.6.

HRMS: *m*/*z* calcd for $C_{13}H_{17}O$ (MH^+): 189.1279; found: 189.1281.

Ketone 20
Colorless oil.

IR (PTFE IR card): 2959, 2925, 2876, 1700, 1612, 1578, 1481, 1455, 1380, 1353, 1033, 958, 858, 792, 565, 545, 511 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93 (1 H, s), 6.63 (1 H, s), 3.42 (1 H, d, *J* = 9.5 Hz), 2.77 (1 H, dt, *J* = 17.1, 4.4 Hz), 2.65 (1 H, ddd, *J* = 17.1, 10.7, 5.9 Hz), 2.27 (3 H, s), 2.26 (3 H, s), 2.10–1.99 (2 H, m), 2.05 (3 H, s), 1.48 (1 H, ddt, *J* = 13.1, 10.8, 5.5 Hz), 1.09 (3 H, d, *J* = 6.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.3, 136.8, 135.2, 133.0, 132.1, 129.5, 126.6, 63.1, 31.6, 30.0, 26.8, 26.0, 20.9, 20.3, 19.6.

HRMS: *m*/*z* calcd for $C_{15}H_{21}O$ (MH^+): 217.1592; found: 217.1597.

Hydrochloride Salt 21
Colorless solid; mp 232–235 °C.

IR (KBr thin film): 3408 (br), 2941 (br), 2881 (br), 2561, 1606, 1511, 1476, 1394, 1377, 1286, 1269, 1152, 858, 737, 655 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.94 (3 H, br s), 7.13 (1 H, s), 7.13 (1 H, s), 6.51 (1 H, t, *J* = 4.5 Hz), 2.59 (2 H, t, *J* = 7.4 Hz), 2.35 (3 H, s), 2.27 (3 H, s), 2.18 (2 H, m), 1.89 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 134.8, 134.3, 133.7, 131.6, 129.8, 126.7, 123.1, 58.1, 27.4, 23.5, 23.0, 21.3, 20.1.

HRMS: *m*/*z* calcd for $C_{15}H_{22}N$ (M^+ – Cl): 216.1752; found: 216.1754.

Biphenylamine 25
Colorless solid; mp 40–41 °C (MTBE–heptane).

IR (NaCl thin film): 3376 (br), 2983, 2938, 1375, 1211, 1154, 1065, 877, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (6 H, m), 7.48 (2 H, t, *J* = 7.6 Hz), 7.38 (1 H, t, *J* = 7.3 Hz), 1.82 (2 H, br s), 1.58 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 140.8, 139.0, 128.7, 127.1, 127.0, 126.9, 125.1, 52.2, 32.8.

HRMS: *m*/*z* calcd for $C_{15}H_{18}N$ (MH^+): 212.1439; found: 212.1434.

Benzamide 26
Colorless foam.

IR (PTFE IR card): 3314, 3058, 2955, 2930, 2870, 1696, 1671, 1650, 1525, 1481, 1425, 1365, 1277, 1176, 1097, 1027, 976, 865, 769, 735, 695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (1 H, dm, *J* = 7.2 Hz), 7.65 (2 H, m), 7.46 (1 H, ddt, *J* = 7.2, 6.8, 1.4 Hz), 7.39 (2 H, m), 7.15 (3 H, m), 6.14 (1 H, s), 6.05 (1 H, s), 3.61 (2 H, br m), 3.36 (2 H, ddd, *J* = 13.5, 9.1, 4.0 Hz), 2.72 (2 H, s), 2.27 (4 H, m), 1.58 (2 H, m), 1.48 (9 H, s), 1.50–1.43 (1 H, m), 1.38–1.13 (9 H, m), 0.88 (6 H, t, *J* = 7.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 155.2, 136.8, 136.7, 136.2, 134.8, 132.8, 131.2, 129.3, 128.7, 127.0, 126.8, 126.1, 124.8, 79.5, 62.5, 41.2, 40.5 (br), 39.8 (br), 35.5, 34.9, 33.5, 32.1, 29.2, 28.7, 26.5, 23.1, 14.3.

HRMS: *m*/*z* calcd for $C_{35}H_{49}N_2O_3$ (MH^+): 545.3743; found: 545.3784.

Dihydronaphthalene 27
Pale yellow oil.

IR (PTFE IR card): 3015, 2975, 2928, 2865, 1700, 1684, 1476, 1452, 1419, 1364, 1246, 1161, 1120, 1092, 1066, 971, 905, 865, 793, 773, 705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20–7.10 (3 H, m), 7.06 (1 H, dd, *J* = 7.2, 1.2 Hz), 6.47 (1 H, d, *J* = 9.9 Hz), 5.97 (1 H, d, *J* = 9.9 Hz), 3.55 (2 H, m), 3.40 (2 H, ddd, *J* = 13.9, 8.3, 3.6 Hz), 2.77 (2 H, s), 1.62–1.54 (2 H, m), 1.52–1.45 (2 H, m), 1.49 (9 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.2, 135.7, 134.1, 133.6, 128.4, 127.4, 127.1, 126.8, 126.1, 79.6, 40.1, 39.8 (br), 35.3, 33.4, 28.7.

HRMS: *m*/*z* calcd for $C_{19}H_{25}NO_2$ + Na (M^+ + Na): 322.1753; found: 322.1826.

Ketone 28
Yellow oil.

IR (PTFE IR card): 2928, 2859, 2799, 1715, 1615, 1520, 1456, 1409, 1347, 1192, 1164, 1129, 1060, 947, 818, 734, 565 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (2 H, d, *J* = 8.7 Hz), 6.71 (2 H, d, *J* = 8.7 Hz), 3.05 (1 H, m), 2.94 (6 H, s), 2.68 (1 H, dd, *J* = 15.5, 7.6 Hz), 2.64 (1 H, dd, *J* = 15.5, 7.2 Hz), 2.31 (1 H, dt, *J* = 16.7, 7.6 Hz), 2.24 (1 H, dt, *J* = 16.7, 7.6 Hz), 1.58 (2 H, m), 1.47 (2 H, m), 1.35–1.10 (6 H, m), 0.86 (6 H, app q, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.9, 149.3, 133.0, 128.2, 113.0, 50.6, 43.4, 40.9, 40.6, 36.4, 29.8, 25.8, 22.8, 22.4, 14.1, 14.0.

HRMS: *m*/*z* calcd for $C_{19}H_{32}NO$ (MH^+): 290.2484; found: 290.2504.

Benzamide 29
Colorless solid; mp 128–130 °C.

IR (KBr thin film): 3339 (br), 2954, 2928, 2868, 1640, 1610, 1524, 1485, 1346, 1286, 1165, 962, 811, 715 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.81 (2 H, d, *J* = 7.1 Hz), 7.47 (3 H, m), 6.72 (2 H, d, *J* = 8.6), 6.40 (1 H, d, *J* = 16.4 Hz), 6.09 (2 H, m), 2.98 (6 H, s), 2.28 (2 H, m), 1.88 (2 H, m), 0.92 (6 H, t, *J* = 6.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 150.1, 136.0, 131.0, 130.5, 128.5, 127.6, 127.2, 126.7, 125.3, 112.4, 60.6, 40.5, 37.4, 26.0, 23.0, 14.1.

HRMS: *m*/*z* calcd for $C_{26}H_{37}N_2O$ (MH^+): 393.2906; found: 393.2910.

Benzamide 30
Colorless solid; mp 113–120 °C.

IR (KBr thin film): 3278 (br), 2950, 2924, 2859, 1640, 1541, 1303 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (2 H, d, *J* = 7.1 Hz), 7.44 (3 H, m), 5.94 (1 H, s), 5.62 (1 H, s), 2.14 (2 H, m), 2.00 (4 H, m), 1.81 (2 H, m), 1.61 (4 H, m), 1.30 (4 H, q, *J* = 7.2 Hz), 1.15 (4 H, m), 0.88 (6 H, t, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 138.5, 136.1, 130.9, 128.4, 126.6, 121.4, 62.8, 34.3, 25.8, 25.4, 24.5, 23.1, 22.8, 22.2, 14.1.

HRMS: *m*/*z* calcd for $C_{22}H_{34}NO$ (MH^+): 328.2640; found: 328.2630.

Hydrochloride Salt 32
Colorless solid; mp 259–262 °C.

IR (KBr thin film): 3417 (br), 2933 (br), 2647, 2565, 2500, 2064 (br), 1606, 1511, 1450, 1394, 1377, 1195, 1165, 893, 461 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (3 H, br s), 1.82 (4 H, m), 1.61 (2 H, m), 1.34 (6 H, s), 1.23 (2 H, m), 1.07 (3 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.0, 46.1, 27.2, 26.2, 26.1, 23.5.

HRMS: *m*/*z* calcd for $C_9H_{20}N$ (M^+ – Cl): 142.1596; found: 142.1590.

Benzamide 33
Colorless solid; mp 105–108 °C.

IR (KBr thin film): 3347 (br), 2954, 2928, 2855, 1645, 1532, 1489, 1450, 1290, 711, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (2 H, d, *J* = 7.4 Hz), 7.43 (3 H, m), 5.65 (1 H, bs), 1.82 (10 H, m), 1.21 (14 H, m), 0.92 (6 H, t, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 136.5, 130.7, 128.4, 126.5, 61.7, 45.2, 34.5, 27.9, 27.0, 26.9, 26.6, 26.3, 23.3, 14.1.

HRMS: *m*/*z* calcd for $C_{22}H_{36}NO$ (MH^+): 330.2797; found: 330.2806.

Benzamide 35a
Colorless solid; mp 153–155 °C.

IR (KBr thin film): 3326 (br), 2976, 2942, 2855, 1692, 1537, 1429, 1364, 1295, 1243, 1161, 1040, 715 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.69 (2 H, d, *J* = 7.9 Hz), 7.45 (1 H, t, *J* = 7.3 Hz), 7.38 (2 H, dd, *J* = 7.9, 7.3 Hz), 5.91 (1 H, br s), 4.15 (2 H, d, *J* = 12.7 Hz), 2.65 (2 H, t, *J* = 12.3 Hz), 2.43 (1 H, tt, *J* = 12.3, 3.1 Hz), 1.66 (2 H, d, *J* = 12.6 Hz), 1.43 (9 H, s), 1.37 (6 H, s), 1.20 (2 H, dq, 2 H, t, *J* = 4.2, 12.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 154.6, 135.6, 131.1, 128.4, 126.6, 79.2, 56.5, 44.1, 42.4, 28.4, 26.9, 26.8, 24.3.

HRMS: *m*/*z* calcd for $C_{20}H_{30}N_2O_3$ + Na (M + Na^+): 369.2154; found: 369.2145.

Benzamide 35b
Colorless solid; mp 122–123 °C.

IR (KBr thin film): 2958, 2933, 2863, 1675, 1541, 1424, 1364, 1243, 1165 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.69 (2 H, d, *J* = 7.7 Hz), 7.48 (1 H, t, *J* = 7.2 Hz), 7.42 (2 H, t, *J* = 7.3), 5.62 (1 H, bs), 4.17 (2 H, d, *J* = 12.4 Hz), 2.64 (2 H, t, *J* = 12.4 Hz), 2.19 (1 H, tt, *J* = 12.2 Hz, *J* = 2.8 Hz), 1.97 (2 H, m), 1.67 (4 H, m), 1.44 (9 H, s), 1.32 (10 H, m), 0.92 (6 H, t, *J* = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 154.7, 136.1, 131.0, 128.5, 126.5, 79.2, 61.2, 44.4, 43.6, 34.5, 28.3, 27.2, 26.2, 23.2, 14.0.

HRMS: *m*/*z* calcd for $C_{26}H_{42}N_2O_3$ + Na (M^+ + Na): 453.3093; found: 453.3113.

Acetamide 37

Colorless solid; mp 75–77 °C.

IR (KBr thin film): 3300 (br), 3084, 2971, 1653, 1558, 1459, 1372, 1295, 1187, 1156, 772, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (5 H, m), 5.54 (1 H, bs), 3.68 (1 H, m), 1.83 (3 H, s), 1.37 (3 H, s), 1.26 (3 H, d, *J* = 7.1 Hz), 1.17 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 143.2, 129.0, 127.7, 126.3, 56.7, 44.5, 24.7, 24.3, 24.0, 15.4.

HRMS: *m*/*z* calcd for $C_{13}H_{20}NO$ (MH^+): 206.1545; found: 206.1543.

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