Supplementary Material (ESI) for Chemical Communications

Gold(I)-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes with Carboxamides

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Supporting Information

Experimental procedures, and analytical and spectroscopic data for substrates and products of catalytic reactions (16 pages).

Experimental

General Methods. Reactions were performed under a nitrogen atmosphere utilizing standard Schlenk and drybox techniques unless specified otherwise. NMR were obtained on a Varian spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR in $CDCl_3$ at 25 °C unless stated otherwise. IR spectra were obtained on a Nicolet Avatar 360-FT IR spectrometer. Gas chromatography was performed on a HP 5890 gas chromatography equipped with a 25 m polydimethylsiloxane capillary column. Column chromatography was performed employing 230-450 mesh silica gel (Sorbent Technologies). Elemental analyses were performed by Complete Analysis Laboratories (Parsippany, NJ). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254}.

1,4-Dioxane (anhydrous Acros), P(*t*-Bu)$_2$*o*-biphenyl (Strem), and $NaAuCl_4 \cdot 2\, H_2O$ (Aldrich) were used as received. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under N_2, dichloromethane was distilled from CaH under N_2, and $CDCl_3$ was distilled from CaH_2 under N_2. All other reagents were purchased from major chemical suppliers and were used as received. 2,2-Diphenyl-4-pentenylamine (**S1**),[S1] *C*-(1-allyl-cyclohexyl)methylamine (**S2**),[S1] *C*-[1-(2-methylallyl)-cyclohexyl]methylamine (**S3**),[S1] *C*-(1-but-3-enyl-cyclohexyl)methylamine (**S4**),[S1] 2-isopropyl-4-pentenylamine (**S5**),[S1] 2,2-dimethyl-4-pentenenitrile (**S6**),[S1] 2-allyl-phenylamine (**S7**),[S2] *cis*-2-allyl-cyclohexylamine (**S8**),[S3] and AuCl[P(*t*-Bu)$_2$*o*-biphenyl] (**2**)[S4] were synthesized employing publisher procedures.

Substrates

***N*-(2,2-Diphenyl-4-pentenyl)acetamide (4).**[S5] Acetyl chloride (0.31 mL, 4.4 mmol) was added slowly to a solution of **S1** (1.0 g, 4.3 mmol) and pyridine (0.51 mL, 6.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C, warmed, and stirred overnight at room temperature. The resulting solution was diluted with CH_2Cl_2 (30 mL), washed with 1 M HCl (3 × 20 mL), 1 M NaOH (20 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated. The resulting oily residue was chromatographed (EtOAc–CH_2Cl_2 = 1:2) to give **4** (0.95 g, 80%) as a white solid. mp 87-88 °C. TLC (ether–CH_2Cl_2 = 1:2): R_f= 0.64. ^{1}H NMR: δ 7.14-7.33 (m, 10 H), 5.43 (tdd, J = 7.2, 10.6, 16.6 Hz, 1 H), 5.01 (br s, 1 H), 4.95-4.99 (m, 2 H), 3.96 (d, J = 5.8 Hz, 2 H), 2.85 (d, J = 7.0 Hz, 2 H), 1.83 (s, 3 H). $^{13}C\{^1H\}$ NMR: δ 169.9, 145.3, 133.7, 128.4, 128.1, 126.6, 118.7, 50.2, 46.1, 42.2, 23.5.

1-(2,2-Diphenyl-4-pentenyl)-3-phenylurea (S9). Phenylisocyanate (0.31 mL, 2.8 mmol) was added dropwise to a solution of **S1** (0.66 g, 2.8 mmol) in THF (10 mL) at 0 °C and the reaction was stirred overnight. The resulting solution was diluted with ether (50 mL), washed with 1 M HCl (25 mL), sat. $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated. The resulting white solid was chromatographed (ether–CH_2Cl_2 = 1:9) to give **S9** (0.79 g, 80%) as a white solid. TLC (ether–CH_2Cl_2 = 1:9): R_f= 0.64. ^{1}H NMR: δ 6.99-7.24 (m, 15 H), 6.56 (br s, 1 H), 5.40 (tdd, J = 7.2, 10.1, 17.1 Hz, 1 H), 4.89-4.96 (m, 2 H), 4.55 (t, J = 5.6 Hz, 1 H), 3.90 (d, J = 5.6 Hz, 2 H), 2.92 (d, J = 7.0 Hz, 2 H). $^{13}C\{^1H\}$ NMR: δ 155.9, 145.5, 138.4, 133.9, 129.3, 128.1, 126.5, 124.0, 121.5, 118.7, 50.3, 47.1, 42.0. IR (neat, cm^{-1}): 3324, 2360, 1642, 1550, 1232, 694. mp 171-172.5 °C. HRMS calcd (found) for $C_{24}H_{25}N_2O$ (MH^+): 357.1967 (357.1966).

N-(1-Allyl-cyclohexylmethyl)-1-propylamide (**6**), *N*-(1-allyl-cyclohexylmethyl)cyclohexylamide (**8**), *N*-(1-allyl-cyclohexylmethyl)benzamide (**S10**), methyl-4-[(1-allyl-cyclohexylmethyl)carbamoyl]butyrate (**S113**), *N*-[1-(2-methyl-allyl)cyclohexylmethyl]acetamide (**S12**), *N*-(1-but-3-enyl-cyclohexylmethyl)acetamide (**S13**), *N*-(2-isopropyl-4-pentenyl)-3-phenylpropionamide (**S14**), *cis*-*N*-(2-allylcyclohexyl)acetamide (**S15)**, and *N*-(2-allyl-phenyl)acetamide **(10)** were synthesized employing a procedure similar to that used to synthesize **4**.

For 6. Colorless oil, 66%. TLC (ether–CH_2Cl_2 = 1:9): R_f = 0.53. ^{1}H NMR: δ 5.78-5.89 (m, 1 H), 5.57 (br s, 1 H), 5.01-5.07 (m, 2 H), 3.16 (d, *J* = 6.2 Hz, 2 H), 2.14 (t, *J* = 7.5 Hz, 2 H), 2.02 (d, *J* = 7.7 Hz, 2 H), 1.63 (sextet, *J* = 7.3 Hz, 2 H), 1.22-1.51 (m, 10 H), 0.92 (t, *J* = 7.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR: δ 173.1, 135.0, 117.4, 45.7, 41.2, 39.0, 37.0, 33.6, 26.2, 21.5, 19.4, 13.9. IR (neat, cm^{-1}): 3304, 2925, 1643, 1550, 1453, 911. Anal. calcd (found) for $C_{14}H_{25}NO$: H, 11.28 (11.24); C, 75.28 (75.24).

For 8. White solid, 62%. TLC (ether–hexanes = 1:19): R_f = 0.44. ^{1}H NMR: δ 5.75-5.86 (m, 1 H), 5.61 (br t, *J* = 6.2 Hz, 1 H), 4.99-5.04 (m, 2 H), 3.12 (d, *J* = 6.3 Hz, 2 H), 2.04 (tt, *J* = 3.4, 8.2 Hz, 1 H), 1.99 (d, *J* = 7.7 Hz, 2 H), 1.13-1.82 (m, 20 H). $^{13}C\{^1H\}$ NMR: δ 176.0, 135.0, 117.3, 45.8, 45.4, 41.1, 37.0, 33.5, 29.9, 26.2, 25.8, 25.8, 21.4. IR (neat, cm^{-1}): 3311, 2925, 2853, 1637, 1549, 1447. mp 68.5-69.0 °C. Anal. calcd (found) for $C_{17}H_{29}NO$: H, 11.10 (11.34); C, 77.51 (77.47).

For S10. White solid, 65%. TLC (ether–hexanes = 1:19): R_f = 0.44. ^{1}H NMR: δ 5.75-5.86 (m, 1 H), 5.61 (br t, *J* = 6.2 Hz, 1 H), 4.99-5.04 (m, 2 H), 3.12 (d, *J* = 6.3 Hz, 2 H), 2.04 (tt, *J* = 3.4, 8.2 Hz, 1 H), 1.99 (d, *J* = 7.7 Hz, 2 H), 1.13-1.82 (m, 20 H). $^{13}C\{^1H\}$ NMR: δ 176.0, 135.0, 117.3, 45.8, 45.4, 41.1, 37.0, 33.5, 29.9, 26.2, 25.8, 25.8, 21.4. IR (neat, cm^{-1}): 3311, 2925, 2853, 1637, 1549, 1447. mp 68.5-69 °C. Anal. calcd (found) for $C_{17}H_{29}NO$: H, 11.10 (11.34); C, 77.51 (77.47).

For S11. Colorless oil, 76%. TLC (EtOAc-CH_2Cl_2 = 1:4): R_f = 0.42. ^{1}H NMR: δ 5.81 (tdd, *J* = 7.5, 9.4, 17.8 Hz, 1 H), 5.64 (br s, 1 H), 5.01-5.06 (m, 2 H), 3.64 (s, 3 H), 3.15 (d, *J* = 6.3 Hz, 2 H), 2.35 (t, *J* = 7.2 Hz, 2 H), 2.21 (t, *J* = 7.5 Hz, 2 H), 2.01 (d, *J* = 7.5 Hz, 2 H), 1.93 (quintet, *J* = 7.2 Hz, 2 H), 1.20-1.52 (m, 10 H). ^{13}C{^{1}H} NMR: δ 173.8, 172.2, 134.9, 117.5, 51.6, 45.7, 41.1, 36.9, 35.7, 33.6, 33.1, 26.2, 21.5, 21.1. IR (neat, cm^{-1}): 3311, 2925, 1737, 1645, 1547, 1441. Anal. calcd (found) for $C_{16}H_{27}NO_3$: H, 9.67 (9.59); C, 68.29 (67.96).

For S12. White solid, 79%. mp 79.5-80.0 °C. TLC (ether–CH_2Cl_2 = 1:1): R_f = 0.55. ^{1}H NMR: δ 5.77 (br s, 1 H), 4.85 (s, 1 H), 4.66 (s, 1 H), 3.19 (d, *J* = 6.2 Hz, 2 H), 2.00 (s, 2 H), 1.94 (s, 3 H), 1.76 (s, 3 H), 1.28-1.49 (m, 10 H). ^{13}C{^{1}H} NMR: δ 170.1, 143.6, 114.9, 45.7, 45.3, 37.5, 34.1, 26.1, 25.4, 23.5, 21.7. IR (neat, cm^{-1}): 3295, 2916, 2855, 1643, 1561, 1448. Anal. calcd (found) for $C_{13}H_{23}NO$: H, 11.07 (11.29); C, 74.59 (74.55).

For S13. Colorless oil, 81%. TLC (ether–CH_2Cl_2 = 1:1): R_f = 0.38. ^{1}H NMR: δ 5.76 (tdd, *J* = 6.5, 10.3, 16.9 Hz, 1 H), 5.57 (br s, 1 H), 4.86 (m, 2 H), 3.12 (d, *J* = 6.2 Hz, 2 H), 1.94 (s, 3 H), 1.91-1.98 (m, 2 H), 1.18-1.47 (m, 12 H). ^{13}C{^{1}H} NMR: δ 170.2, 139.3, 114.2, 45.4, 36.1, 34.9, 33.6, 27.4, 26.2, 23.4, 21.4. IR (neat, cm^{-1}): 3300, 3080, 2924, 1645, 1555, 1288. Anal. calcd (found) for $C_{13}H_{23}NO$: H, 11.07 (11.01); C, 74.59 (74.70).

For S14. Colorless oil, 24%. TLC (EtOAc–CH_2Cl_2 = 1:19): R_f = 0.31. ^{1}H NMR: δ 7.17-7.29 (m, 5 H), 5.71 (tdd, *J* = 6.7, 10.3, 17.8 Hz, 1 H), 5.42 (br s, 1 H), 4.97-5.03 (m, 2 H), 3.26 (td, *J* = 6.0, 13.7 Hz, 1 H), 3.10 (ddd, *J* = 6.0, 7.2, 13.3 Hz, 1 H), 2.95 (t, *J* = 7.7 Hz, 2 H), 2.45 (t, *J* = 7.5 Hz, 2 H), 2.04-2.11 (m, 1 H), 1.82-1.89 (m, 1 H), 1.61 (doublet of sextets, *J* = 4.6, 6.8 Hz, 1 H), 1.32-1.40 (m, 1 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR: δ 172.0, 141.0, 137.8, 128.6, 128.4, 126.3, 116.2, 44.0, 40.8, 38.7, 33.9, 31.8, 28.6, 19.6, 19.1. IR (neat, cm^{-1}): 3295, 2958, 1641, 1551, 1450, 698. Anal. calcd (found) for $C_{17}H_{25}NO$: H, 9.71 (9.79); C, 78.72 (78.80).

For S15.[S6] White solid, 60%. mp 80-81 °C. TLC (ether–CH_2Cl_2 = 1:1): R_f = 0.52. ^1H NMR: δ 5.70-5.81 (m, 1 H), 5.64 (br s, 1 H), 4.95-5.01 (m, 2 H), 4.12-4.17 (m, 1 H), 2.03-2.10 (m, 1 H), 1.99 (s, 3 H), 1.85-1.92 (m, 1 H), 1.11-1.73 (m, 9 H). $^{13}C\{^1H\}$ NMR: δ 169.4, 137.2, 116.0, 48.3, 39.2, 36.1, 30.4, 27.6, 24.1, 23.7, 22.0. IR (neat, cm^{-1}): 3315, 2930, 1638, 1543, 1368, 912. HRMS calcd (found) for $C_{11}H_{19}NO$ (M^+): 181.1467 (181.1468).

For 10.[S7] White solid, 86%. mp 95.5-96.5 °C (Lit 87-89 °C).[S7] TLC (EtOAc-CH_2Cl_2 = 1:4): R_f = 0.39. ^1H NMR: δ 7.83 (d, *J* = 8.0 Hz, 1 H), 7.09-7.27 (m, 4 H), 5.97 (tdd, *J* = 6.0, 10.4, 16.5 Hz, 1 H), 5.08-5.19 (m, 2 H), 3.38 (d, *J* = 6.2 Hz, 2 H), 2.15 (s, 3 H). $^{13}C\{^1H\}$ NMR: δ 168.4, 136.5, 136.2, 130.3, 130.0, 127.6, 125.4, 123.9, 116.7, 37.1, 24.4.

***N*-(1-Allyl-cyclohexylmethyl)-5-hydroxypentamide (S16).** A solution of **S11** (2.44 g, 8.67 mmol) in ether (10 mL) was added dropwise to a suspension of $LiAlH_4$ (660 mg, 17.4 mmol) in ether (10 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 2 h and then treated sequentially with water (0.9 mL), 15% NaOH (0.9 mL), and water (0.9 mL). The resulting suspension was filtered through Celite, extracted with ether (100 mL), and concentrated. The resulting oily residue was chromatographed (EtOAc) to give **S19** (1.43 g, 65%) as a pale yellow oil. TLC (EtOAc): $R_f = 0.33$. ^{1}H NMR: δ 5.74-5.87 (m, 2 H), 5.02-5.06 (m, 2 H), 3.59-3.63 (m, 2 H), 3.15 (d, $J = 6.3$ Hz, 2 H), 2.79 (br s, 1 H), 2.21 (t, $J = 7.3$ Hz, 2 H), 2.02 (d, $J = 7.5$ Hz, 2 H), 1.71 (quintet, $J = 7.5$ Hz, 2 H), 1.21-1.60 (m, 12 H). ^{13}C{^{1}H} NMR: δ 173.4, 134.9, 117.5, 62.0, 45.8, 41.1, 36.9, 36.3, 33.6, 32.1, 26.2, 22.0, 21.5. IR (neat, cm^{-1}): 3300, 2923, 2858, 1643, 1549, 1450. Anal. calcd (found) for $C_{15}H_{27}NO_2$: H, 10.74 (10.84); C, 71.10 (71.06).

***N*-(2,2-Dimethyl-1-phenyl-4-pentenyl)acetamide (S17).** A solution of phenyl magnesium bromide (1 M in THF, 17 mL, 17 mmol) and **S6** (1.26 g, 11.5 mmol) in ether (70 mL) was refluxed for 21 h. The resulting suspension was cooled to -15 °C, treated with methanol (20 mL), stirred for 5 min, cooled to –78 °C, and treated with $NaBH_4$ (1.08 g, 28.5 mmol) in one portion. The reaction mixture was warmed slowly to room temperature and stirred for an additional 2 h. The resulting suspension was treated with 1 M NaOH (50 mL) and extracted with ether (3 × 50 mL). The combined ether extracts were washed aqueous sodium hydroxide (1 M, 5 mL) and brine (45 mL), dried ($MgSO_4$), and concentrated. Acetyl chloride (0.31 mL, 4.4 mmol) and pyridine (0.51 mL, 6.3 mmol) were added drop-wise to a solution of the resulting residue in CH_2Cl_2 (15mL) at 0 °C, the reaction mixture was warmed to room temperature and stirred overnight. The resulting solution was diluted with CH_2Cl_2 (25 mL), washed with 1 M HCl (3 × 15 mL), 1 N NaOH (15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated. The resulting oily residue was chromatographed (CH_2Cl_2–EtOAc = 6:1) to give **S17** (0.58 g, 22% from **S6**) as a colorless oil that solidified over several weeks. mp 114-115 °C. TLC (CH_2Cl_2–EtOAc = 6:1): $R_f = 0.37$. ^{1}H NMR: δ 7.16-7.32 (m, 5 H), 6.36 (br d, $J = 9.4$ Hz, 1 H), 5.86 (tdd, *J* = 7.5, 9.9, 16.9 Hz, 1 H), 5.01-5.10 (m, 2 H), 4.88 (d, *J* = 9.7 Hz, 1 H), 1.96-2.07 (m, 2 H), 1.98 (s, 3 H), 0.89 (s, 3 H), 0.86 (s, 3 H). $^{13}C\{^1H\}$ NMR: δ 169.2, 140.0, 134.9, 128.5, 127.9, 127.1, 118.0, 60.9, 44.0, 37.7, 24.0, 23.8, 23.6. IR (neat, cm^{-1}): 3301, 2969, 1639, 1542, 1371, 739. Anal. calcd (found) for $C_{15}H_{21}NO$: H, 9.15 (9.27); C, 77.88 (77.96).

Heterocyclic Carboxamides

1-(2-Methyl-4,4-diphenyl-pyrrolidin-1-yl)-ethanone (5). Dioxane (0.5 mL) was added to a mixture of **4** (0.14 g, 0.50 mmol), **2** (13 mg, 2.5×10^{-2} mmol), and AgOTf (6.6 mg, 2.6×10^{-2} mmol) and the resulting suspension was stirred at 80 °C for 21 h, cooled to room temperature, and concentrated. The resulting residue was chromatographed (ether–CH_2Cl_2 = 1:2) to give **5** (139 mg, 99%) as a colorless oil. TLC (ether–CH_2Cl_2 = 1:2): R_f = 0.57. ^1H NMR (1:1 mixture of rotomers): δ 7.13-7.33 (m, 10 H), [4.99 (dd, *J* = 2.4, 12.1 Hz), 4.29 (dd, *J* = 1.9, 10.8 Hz), 1:1, 1 H], [4.04 (qdd, *J* = 6.5, 6.5, 8.9 Hz), 3.77 (qdd, *J* = 6.2, 6.2, 12.6 Hz), 1:1, 1 H], [3.94 (d, *J* = 10.9 Hz), 3.58 (d, *J* = 12.1 Hz), 1:1, 1 H], [3.00 (ddd, *J* = 2.6, 6.8, 12.6 Hz), 2.93 (ddd, *J* = 1.9, 7.0, 12.8), 1:1, 1 H], [2.40 (dd, *J* = 8.7, 12.5 Hz), 2.23 (dd, *J* = 9.1, 12.8 Hz), 1:1, 1 H], [2.11 (s), 2.02 (s), 1:1, 3 H], [1.33 (d, *J* = 6.2 Hz), 1.32 (d, *J* = 6.2 Hz), 1:1, 3 H]. $^{13}C\{^1H\}$ NMR (1:1 mixture of rotomers): δ 169.9, 168.9, 145.8, 145.7, 145.2, 145.0, 128.8, 128.7, 128.7, 128.7, 126.8, 126.7, 126.7, 126.5, 126.5, 126.4, 58.1, 54.6, 53.1, 52.8, 52.5, 52.3, 47.4, 45.7, 23.5, 22.1, 21.6, 20.2. IR (neat, cm^{-1}): 2969, 2876, 1637, 1412, 1347, 699. Anal. calcd (found) for $C_{19}H_{21}NO$: H, 7.58 (7.38); C, 81.68 (81.80).

The remaining nitrogen heterocycles were synthesized employing a procedure analogous to that used to synthesize **5**. Reaction times and yields are given in Table 1.

PCy_2*o*-biphenyl was an effective supporting ligand and toluene and diglyme were effective solvents for gold-catalyzed hydroamination. As examples, reaction of *N*-[1-(2-methallyl)cyclohexylmethyl]acetamide (**S18**; Table 1, entry 11) under our standard conditions [**2** (5 mol%) and AgOTf (5 mol%) in dioxane at 80 °C for 15 h] led to complete consumption of **S18** to form the corresponding bicyclic carboxamide **S19** in quantitative yield by ^{1}H NMR analysis. In comparison, treatment of **S18** with a catalytic 1:1 mixture of Au[PCy_2(*o*-biphenyl)]Cl (5 mol%) and AgOTf (5 mol%) in dioxane at 80 °C for 19 h led to formation of **S19** in 89% yield (^{1}H NMR). Reaction of **S18** with a catalytic 1:1 mixture of **2** (5 mol%) and AgOTf (5 mol%) in either toluene or diglyme at 80 °C for 19 h led to formation of **S19** in quantitative yield (^{1}H NMR).

2-Methyl-4,4-diphenyl-pyrrolidine-1-carboxylic acid phenylamide (Table 1, entry 4). White microcrystals. mp 184.5-186 °C. TLC (ether–CH_2Cl_2 = 1:30): R_f = 0.41. ^{1}H NMR: δ 7.44 (d, *J* = 7.7 Hz, 2 H), 7,13-7.30 (m, 12 H), 7.01 (tt, *J* = 1.2, 7.3 Hz, 1 H), 6.54 (br s, 1 H), 4.60 (d, *J* = 10.6 Hz, 1 H), 3.79-3.87 (m, 1 H), 3.75 (d, *J* = 10.8 Hz, 1 H), 2.84 (ddd, *J* = 1.4, 6.3, 12.3 Hz, 1 H), 2.35 (dd, *J* = 9.2, 12.3 Hz, 1 H), 1.34 (d, 3 H). $^{13}C\{^1H\}$ NMR: δ 154.2, 145.6, 145.2, 139.2, 128.9, 128.7, 128.5, 126.8, 126.6, 126.4, 122.9, 119.8, 56.2, 52.8, 52.1, 46.6, 20.8. IR (neat, cm^{-1}): 3267, 1645, 1538, 1443, 1388, 695. HRMS calcd (found) for $C_{24}H_{25}N_2O$ (MH^+): 357.1967 (357.1969).

1-(3-Methyl-2-aza-spiro[4.5]dec-2-yl)-1-butanone (7). Colorless oil. TLC (EtOAc-CH_2Cl_2 = 1:4): R_f = 0.46. ^{1}H NMR (2.5:1 mixture of rotomers): δ [3.90-4.08

(m), 3.86-3.96 (m), 2.5:1, 1 H], [3.88 (d, *J* = 11.8 Hz), 3.36 (d, *J* = 10.4 Hz), 1:2.5, 1 H], [3.05 (d, *J* = 10.4 Hz), 2.87 (d, *J* = 12.0 Hz), 2.5:1, 1 H], 2.13-2.28 (m, 2 H), [2.08 (dd, *J* = 8.0, 12.6 Hz), 2.01 (dd, *J* = 7.7, 12.6 Hz), 2.5:1, 1 H], 1.58-1.71 (m, 2 H), 1.18-1.47 (m, 14 H), 0.90-0.94 (m, 3 H). $^{13}C\{^1H\}$ NMR (both rotomers): δ 172.2, 171.8, 57.5, 55.2, 52.2, 51.9, 46.6, 45.0, 41.7, 40.6, 37.4, 37.0, 36.6, 35.5, 35.2, 34.6, 26.2, 23.8, 23.0, 23.0, 22.9, 20.7, 19.1, 18.7, 14.1, 14.0. IR (neat, cm^{-1}): 2924, 2855, 1639, 1419, 1345, 1209. Anal. calcd (found) for $C_{14}H_{25}NO$: H, 11.28 (11.38); C, 75.28 (75.05).

Cyclohexyl-(3-methyl-2-aza-spiro[4.5]dec-2-yl)-methanone (9). Colorless oil. TLC (EtOAc–CH_2Cl_2 = 1:8): R_f = 0.49. ^1H NMR (2.5:1 mixture of rotomers): δ 3.89-4.03 (m, 1 H), [3.82 (d, *J* = 12.0 Hz), 3.37 (d, *J* = 10.4 Hz), 1:2.5, 1 H], [3.02 (d, *J* = 10.4 Hz), 2.80 (d, *J* = 11.8 Hz), 2.5:1, 1 H], [2.32 (tt, *J* = 3.6, 11.1 Hz), 2.22 (tt, *J* = 3.4, 11.4 Hz), 1:2.5, 1 H], [2.06 (dd, *J* = 8.0, 12.8 Hz), 1.98 (dd, *J* = 7.7, 12.8 Hz), 1:2.5, 1 H], 1.12-1.73 (m, 24 H). $^{13}C\{^1H\}$ NMR (both rotomers): δ 175.4, 174.8, 57.1, 55.0, 51.8, 51.7, 46.2, 44.5, 43.0, 41.9, 41.6, 40.6, 36.9, 36.5, 35.0, 34.3, 30.0, 29.3, 29.2, 28.8, 26.1, 26.1, 26.0, 25.9, 25.9, 25.8, 25.7, 25.7, 23.7, 23.6, 22.9, 22.8, 20.6. IR (neat, cm^{-1}): 2923, 2853, 1636, 1421, 1349, 1207. Anal. calcd (found) for $C_{17}H_{29}NO$: H, 11.10 (11.10); C, 77.51 (77.40).

(3-Methyl-2-aza-spiro[4.5]dec-2-yl)-phenyl-methanone (Table 1, entry 8). Colorless oil. TLC (EtOAc–hexanes = 1:8): R_f = 0.43. ^1H NMR (55 °C): δ 7.47-7.50 (m, 2 H), 7.35-7.42 (m, 3 H), 4.29 (br s, 1 H), 3.31 (br s, 1 H), 3.17 (d, J = 10.8 Hz, 1 H), 2.13 (dd, *J* = 7.5, 12.6 Hz, 1 H), 1.24-1.44 (m, 14 H). $^{13}C\{^1H\}$ NMR (55 °C): δ 170.2, 137.6, 129.7, 128.2, 127.3, 60.2, 52.1, 44.9, 42.3, 36.4, 33.8, 26.1, 23.8, 22.6, 20.5. IR (neat, cm^{-1}): 2923, 2854, 1627, 1405, 1221, 715. Anal. calcd (found) for $C_{17}H_{23}NO$: H, 9.01 (8.91); C, 79.33 (79.16).

Methyl-5-(3-methyl-2-aza-spiro[4.5]dec-2-yl)-5-oxo-pentanoate (Table 1, entry 9). Colorless oil. TLC (EtOAc–CH_2Cl_2 = 1:4): R_f = 0.28. ^{1}H NMR (2.7:1 mixture of rotomers): δ [4.01 (qdd, J = 6.3, 6.3, 7.6 Hz), 3.90 (qdd, J = 6.3, 7.0, 7.0 Hz), 2.7:1, 1 H], [3.86 (d, J = 12.6 Hz), 3.34 (d, J = 10.4 Hz), 1:2.7, 1 H], [3.63 (s), 3.62 (s), 2.7:1, 3 H], [3.04 (d, J = 10.4 Hz), 2.86 (d, J = 12.0 Hz), 2.7:1, 1 H], 2.19-2.38 (m, 4 H), 1.88-2.10 (m, 3 H), 1.26-1.45 (m, 11 H), [1.22 (d, J = 6.2 Hz), 1.21 (d, J =6.2 Hz), 2.7:1, 3 H]. $^{13}C\{^1H\}$ NMR (both rotomers): δ 173.9, 173.9, 171.2, 170.8, 57.4, 55.3, 52.1, 52.0, 51.5, 51.5, 46.6, 44.9, 41.7, 40.6, 37.0, 36.6, 35.2, 34.6, 34.3, 33.3, 33.3, 32.3, 26.1, 26.1, 23.8, 23.8, 23.0, 22.9, 22.9, 20.7, 20.7, 20.3. IR (neat, cm^{-1}): 2924, 2854, 1736, 1638, 1423, 1163. HRMS calcd for $C_{16}H_{27}NO_3$ 281.1991, found 281.1992.

5-Hydroxy-1-(3-methyl-2-aza-spiro[4.5]dec-2-yl)-1-pentanone (Table 1, entry 10). Yellow oil. TLC (EtOAc): R_f = 0.17. ^{1}H NMR (2.5:1 mixture of rotomers): δ [4.04 (qdd, J = 6.4, 6.4, 7.6 Hz), 3.92 (qdd, J = 6.4, 6.8, 7.2 Hz), 2.5:1, 1 H], [3.87 (d, J = 12.0 Hz), 3.36 (d, J = 10.6 Hz), 1:2.5, 1 H], 3.50-3.61 (m, 2 H), [3.07 (d, J = 10.6 Hz), 2.88 (d, J = 12.0 Hz), 2.5:1, 1 H], [2.53 (br s), 2.44 (br s), 2.5:1, 1 H], 2.19-2.36 (m, 2 H), [2.10 (dd, J = 7.9, 13.0 Hz), 2.02 (dd, J = 7.7, 12.8 Hz), 1:2.5, 1 H], 1.20-1.79 (m, 18 H). $^{13}C\{^1H\}$ NMR (both rotomers): δ 172.5, 172.0, 62.0, 61.9, 57.6, 55.5, 52.3, 52.2, 46.7, 44.9, 41.8, 40.7, 37.1, 36.7, 35.3, 34.7, 34.7, 32.9, 32.6, 32.6, 26.2, 26.2, 23.9, 23.9, 23.1, 23.0, 23.0, 21.0, 20.7, 20.5. IR (neat, cm^{-1}): 3404, 2922, 2854, 1618, 1427, 1062. Anal. calcd (found) for $C_{15}H_{27}NO_2$: H, 10.74 (10.42); C, 71.10 (71.07).

1-(3,3-Dimethyl-2-aza-spiro[4.5]dec-2-yl)-ethanone (S19; Table 1, entry 11). Colorless oil. TLC (ether–CH_2Cl_2 = 1:2): R_f = 0.55. ^1H NMR (10:1 mixture of rotomers): δ [3.49 (s), 3.28 (s), 1:10, 2 H], [2.14 (s), 1.99 (s), 1:10, 3 H], [1.88 (s), 1.73 (s), 1:10, 2 H], 1.40-1.48 (m, 16 H). $^{13}C\{^1H\}$ NMR (both rotomers): 169.3, 164.0, 61.8, 60.2, 53.9, 40.0, 37.4, 37.1, 30.5, 28.1, 26.0, 25.0, 23.5, 23.0. IR (neat, cm^{-1}): 2925, 2853, 1645, 1405, 1354, 1191. Anal. calcd (found) for $C_{13}H_{23}NO$: H, 11.07 (10.81); C, 74.59 (74.40).

1-(4-Isopropyl-2-methyl-pyrrolidin-1-yl)-3-phenyl-1-propanone (S20; Table 1, entry 12). Dioxane (0.5 mL) was added to a mixture of **S14** (131 mg, 0.505 mmol), **2** (13.3 mg, 0.025 mmol), and AgOTf (6.5 mg, 0.025 mmol) and the resulting suspension was stirred at 80 °C for 22 h, cooled to room temperature, and concentrated. The resulting residue was chromatographed (EtOAc–CH_2Cl_2 = 1:8) to give two fraction of pure **S20**. One fraction (33 mg, 25%) was composed of an 8:1 mixture of the major and minor diastereomers and the second fraction (93 mg, 71%) was composed of a 1:1 mixture of the two diastereomers. NMR spectroscopy of the fractions allowed full identification of the ^1H NMR resonances of the major diastereomer and full identification of the ^{13}C NMR resonances of both diastereomers. Colorless oil. TLC (EtOAc–CH_2Cl_2 = 1:8): R_f = 0.43. ^1H NMR (major diastereomer, 2.7:1 mixture of rotomers): δ 7.15-7.27 (m, 5 H), [4.13 (dd, J = 7.0, 11.8 Hz), 3.44 (dd, J = 7.2, 9.9 Hz), 1:2.7, 1 H], [3.92-4.01 (m), 3.72-3.81 (m), 2.7:1, 1 H], 2.88-3.02 (m, 2 H), [2.82 (t, J = 10.4 Hz), 2.72 (t, J = 11.1 Hz), 2.7:1, 1 H], 2.45-2.60 (m, 2 H), 2.17-2.31 (m, 1 H), 1.50-1.61 (m, 1 H), 1.32-1.44 (m, 1 H), [1.25 (d, J = 6.2 Hz), 1.16 (d, J = 6.3 Hz), 2.7:1, 3 H], 1.04-1.12 (m, 1 H), [0.89 (d, J = 7.0 Hz), 0.87 (d, J = 6.8 Hz), 1:2.7, 3 H], [0.88 (d, J = 6.5 Hz), 0.82 (d, J =

6.5 Hz) (1:2.7) 3 H]. ^{1}H NMR (minor diastereomer, 1.5:1 mixture of rotomers, partial assignment): δ [4.20-4.27 (m), 3.79-3.86 (m), 1.5:1, 1 H], 3.62 (dd, *J* = 8.2, 12.1, 0.4 H), 1.89-2.00 (m, 1 H), [1.65 (dd, *J* = 6.3, 11.4 Hz), 1.62 (dd, *J* = 6.2, 11.1 Hz), 1:1.5, 1 H], [1.14 (d, *J* = 6.5 Hz), 1.07 (d, *J* = 6.7 Hz), 1.5:1, 3 H]. ^{13}C{^{1}H} NMR (major diastereomer, both rotomers): δ 171.0, 170.6, 141.7, 141.7, 128.6, 128.5, 126.2, 53.9, 53.4, 51.8, 49.8, 45.8, 45.1, 40.2, 39.0, 37.5, 35.6, 32.3, 32.0, 31.8, 31.5, 23.1, 21.6, 21.6, 21.3, 21.2, 20.7. ^{13}C{^{1}H} NMR (minor diastereomer, both rotomers): δ 170.5, 141.8, 141.6, 128.6, 128.6, 128.5, 126.1, 53.9, 53.3, 51.6, 50.4, 44.5, 42.5, 38.0, 37.0, 36.7, 36.1, 32.7, 32.4, 31.9, 31.3, 21.5, 21.5, 21.3, 21.2, 19.9. IR (neat, cm^{-1}): 2960, 2871, 1639, 1420, 1203, 701. Anal. calcd (found) for $C_{17}H_{25}NO$: H, 9.71 (9.53); C, 78.72 (78.57).

1-(3,3,5-Trimethyl-2-phenyl-pyrrolidin-1-yl)-ethanone (S21; Table 1, entry 13). Pure **S21** (1.8 mixture of diastereomers) was chromatographed a second time to yield a fraction composed of a ~10:1 mixture of the major and minor diastereomer and one fraction consisting of 1.5:1 mixture of major and minor diastereomers. Spectroscopic analysis of these fractions allowed full identification of the ^{1}H NMR resonances for the major rotomers of both diastereomers. Colorless oil. TLC (EtOAc–CH_2Cl_2 = 1:6): R_f= 0.26. ^{1}H NMR (major diastereomer, major rotomer): δ 7.25-7.36 (m, 3 H), 7.18 (d, *J* = 7.3 Hz, 2 H), 4.34 (s, 1 H), 4.11-4.20 (m, 1 H), 1.81 (s, 3 H), 1.78 (dd, *J* = 6.8, 12.8 Hz, 1 H), 1.58 (d, *J* = 6.2 Hz, 3 H), 1.51-1.56 (m, 1 H), 1.19 (s, 3 H), 0.62 (s, 3 H). ^{1}H NMR (minor diastereomer, major rotomer): δ 7.15-7.30 (m, 3 H), 6.99 (d, *J* = 7.2 Hz, 2 H), 4.40 (s, 1 H), 4.36-4.43 (m,1 H), 2.10 (dd, *J* = 10.6, 13.0 Hz, 1 H), 1.70 (s, 3 H), 1.49 (d, *J* = 6.5 Hz, 3 H), 1.40-1.44 (m, 1 H), 1.36 (s, 3 H), 0.56 (s, 3 H). ^{13}C{^{1}H} NMR (major diastereomer, major rotomer): δ 171.5, 140.9, 128.5, 127.5, 127.2, 75.1, 53.1, 45.3, 41.9, 29.4, 25.2, 23.6, 20.0. $^{13}C\{^1H\}$ NMR (minor diastereomer, major rotomer): δ 171.4, 141.8, 128.5, 127.4, 127.2, 75.1, 54.6, 43.8, 42.5, 31.2, 26.4, 23.9, 21.5. IR (neat, cm^{-1}): 2960, 1642, 1397, 1342, 1188, 701. Anal. calcd (found) for $C_{15}H_{21}NO$: H, 9.15 (9.17); C, 77.88 (77.49).

1-(2-Methyl-octahydro-1-indolyl)-ethanone (**Table 1, entry 14**). Colorless oil. TLC (ether-CH_2Cl_2 = 2:1): $R_f = 0.36$. ^1H NMR (major diastereomer, 2.8:1 mixture of rotomers): δ [4.13-4.19 (m), 3.60 (td, *J* = 6.2, 11.3 Hz), 1:2.8, 1 H], [3.95-4.04 (m), 3.79-3.88 (m), 2.8:1, 1 H], 1.08-2.27 (m, 11 H), [2.05 (s), 2.03 (s), 2.8:1, 3 H], [1.36 (d, *J* = 6.0 Hz), 1.35 (d, *J* = 6.2 Hz), 1:2.8, 3 H]. ^1H NMR (minor diastereomer, 2.1:1 mixture of rotomers): δ [4.12-4.19 (m), 3.95-4.00 (m), 2.1:1, 1 H], [3.94 (td, *J* = 6.7, 14.0 Hz), 3.65 (td, *J* = 6.0, 10.8 Hz), 1:2.1, 1 H], 0.83-2.58 (m, 11 H), [2.05 (s), 2.04 (s), 2.1:1, 3 H], [1.23 (d, *J* = 6.3 Hz), 1.22 (d, *J* = 6.3 Hz), 2.1:1, 3 H] $^{13}C\{^1H\}$ NMR (major diastereomer, both rotomers): δ 169.2, 168.7, 59.5, 57.3, 53.9, 53.2, 36.8, 36.8, 35.8, 35.1, 29.6, 28.5, 26.0, 25.9, 24.3, 24.3, 24.2, 22.6, 22.2, 21.7, 20.6, 20.3. $^{13}C\{^1H\}$ NMR (minor diastereomer, both rotomers): δ 169.0, 168.9, 59.1, 57.1, 53.4, 52.2, 35.3, 34.9, 33.5, 33.2, 30.4, 28.8, 26.8, 26.0, 24.1, 23.9, 22.7, 22.7, 22.7, 21.0, 20.4, 20.4. IR (neat, cm^{-1}): 2928, 2860, 1632, 1409, 1345, 642. HRMS calcd for $C_{11}H_{19}NO$ 181.1467, found 181.1473.

1-(3-methyl-2-aza-spiro[5.5]undec-2-yl)-ethanone (Table 1, entry 15). Colorless oil. TLC (ether–CH_2Cl_2 = 1:1): $R_f = 0.50$. ^1H NMR (1:1 mixture of rotomers): δ [4.78-4.86 (m), 3.97-4.04 (m), 1:1, 1 H], [4.45 (d, *J* = 13.3 Hz), 3.32 (d, *J* = 13.5 Hz), 1:1, 1 H], [2.82 (d, *J* = 13.7 Hz), 2.27 (d, *J* = 13.5 Hz), 1:1, 1 H], [2.06 (s), 2.03 (s), 1:1, 3 H], [1.81-1.91 (m), 1.70-1.79 (m), 1:1, 1 H], 1.12-1.52 (m, 13 H), [1.16 (d, *J* = 6.9 Hz), 1.06 (d, *J* = 7.0 Hz), 1:1, 3 H]. ^{13}C{^{1}H} NMR (both rotomers): δ 169.4, 169.2, 50.8, 49.1, 44.1, 43.8, 38.3, 38.0, 33.8, 33.3, 31.3, 30.9, 30.6, 29.5, 26.7, 26.6, 26.0, 25.1, 22.0, 21.9, 21.7, 21.6, 21.5, 16.7, 15.7. IR (neat, cm^{-1}): 2925, 2855, 1635, 1427, 1365, 1024. Anal. calcd (found) for $C_{13}H_{23}NO$: H, 11.07 (11.25); C, 74.59 (74.23).

1-(2-Methyl-2,3-dihydro-indol-1-yl)-ethanone (11). Pale yellow oil. TLC (EtOAc–CH_2Cl_2 = 1:4): R_f = 0.45. ^{1}H NMR (major rotomer): δ 8.15 (d, *J* = 7.5 Hz, 1 H), 6.99-7.21 (m, 3 H), 4.40-4.47 (m, 1 H), 3.40 (dd, *J* = 8.7, 14.9 Hz, 1 H), 2.65 (d, *J* = 15.5 Hz, 1 H), 2.27 (s, 3 H), 1.29 (d, *J* = 6.0 Hz, 3 H). ^{13}C{^{1}H} NMR (both rotomers): δ 168.2, 141.6, 132.9, 130.3, 127.5, 126.2, 124.9, 123.8, 123.4, 117.9, 115.1, 56.3, 55.7, 36.5, 35.1, 24.5, 23.3, 21.7, 20.2. IR (neat, cm^{-1}): 2975, 1651, 1480, 1392, 1285, 755. Anal. calcd (found) for $C_{11}H_{13}NO$: H, 7.48 (7.59); C, 75.40 (75.22).

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