

C-C Bond Formation via Copper-Catalyzed Conjugate Addition Reactions to Enones in Water at Room Temperature

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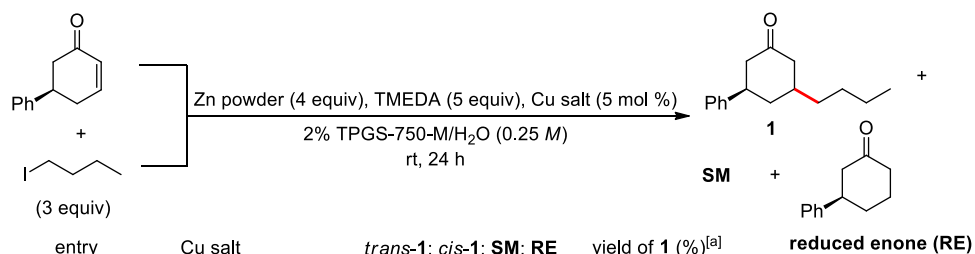
WWW: <http://www.chem.ucsb.edu/~lipshutzgroup/>

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Additional Results

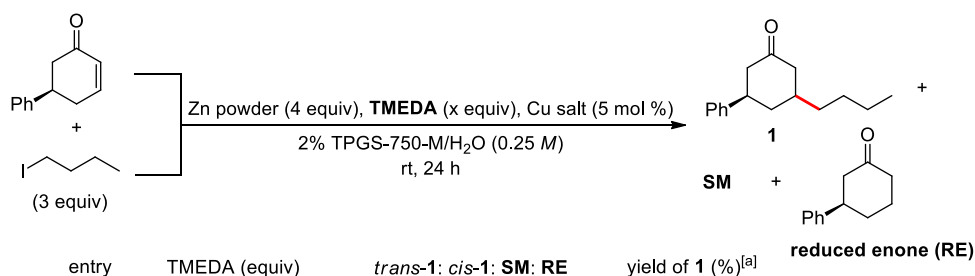
Table S1. Survey of Cu salts



entry	Cu salt	<i>trans</i> -1: <i>cis</i> -1: SM: RE	yield of 1 (%) ^[a]
1	Cu(OAc) ₂ ·H ₂ O	46: 8: 41: 5	54
2	CuBr ₂ ·SMe ₂	2.2: 0.3: 97.5: 0	2.5
3	Cu(NO ₃) ₂ ·2H ₂ O	2: 0: 98: 0	2
4	Cu(TMHD) ₂	40: 7: 43: 10	47
5	Cu(CH ₃ CN) ₄ PF ₆	18: 3: 79: 0	21
6	Cu(CH ₃ CN) ₄ NTf ₂	46: 8: 38: 8	54
7	(CuOTf) ₂ ·PhCH ₃	46: 8: 38: 8	54

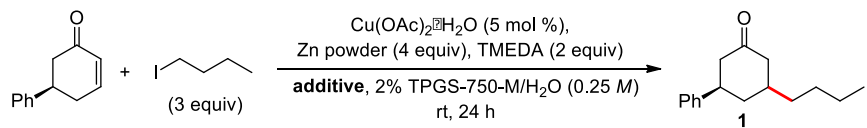
[a] Determined by GC on crude material.

Table S2. Screening of TMEDA loading



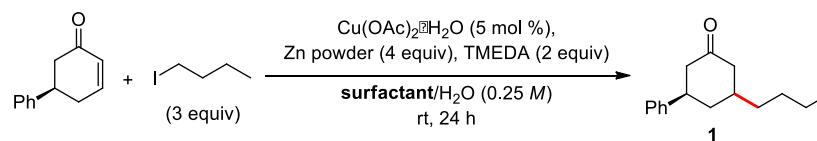
entry	TMEDA (equiv)	<i>trans</i> -1: <i>cis</i> -1: SM: RE	yield of 1 (%) ^[a]
1	5	46: 8: 41: 5	54
2	2	57: 10: 32: 1	67
3	0.5	50: 9: 40: 1	59
4	0.05	33: 6: 61: 0	39

[a] Determined by GC on crude material.

Table S3. Survey of additives


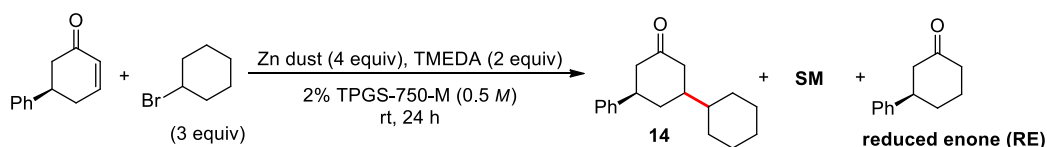
entry	additive (equiv)	yield of 1 (%) ^[a]	entry	additive (equiv)	yield of 1 (%) ^[a]
1	LiClO ₄ (0.05)	78	12	Ni(dppf)Cl ₂ (0.05)	79
2	LiBr (1.0)	85	13	Ni(acac) ₂ (0.05)	70
3	LiCl (1.0)	58	14	Sc(OTf) ₃ (0.03)	47
4	LiI (1.0)	48	15	AuBr ₃ (0.05)	71
5	LiOTf (1.0)	87	16	KAuCl ₄ (0.05)	31
6	LiOH (1.5)	43	17	IPrAuNTf ₂ (0.05)	61
7	LiOH (1.5), TIPSOH (1.5)	83	18	Ph ₃ PAuNTf ₂ (0.05)	73
8	KOH (1.5), TIPSOH (1.5)	82	19	AuCl ₃ (0.05)	87
9	NiCl ₂ (0.05)	45	20	AuCl ₃ (0.03)	64
10	Ni(PPh ₃) ₂ Cl ₂ (0.05)	62	21 ^b	AuCl ₃ (0.05)	93
11	Ni(dppp)Cl ₂ (0.05)	54	22 ^b	AuCl (0.05)	92

[a] Determined by GC on crude material. [b] Iodobutane was added in two portions: t = 0 h, 1.5 equiv; t = 6 h, 1.5 equiv

Table S4. Screening of the surfactant


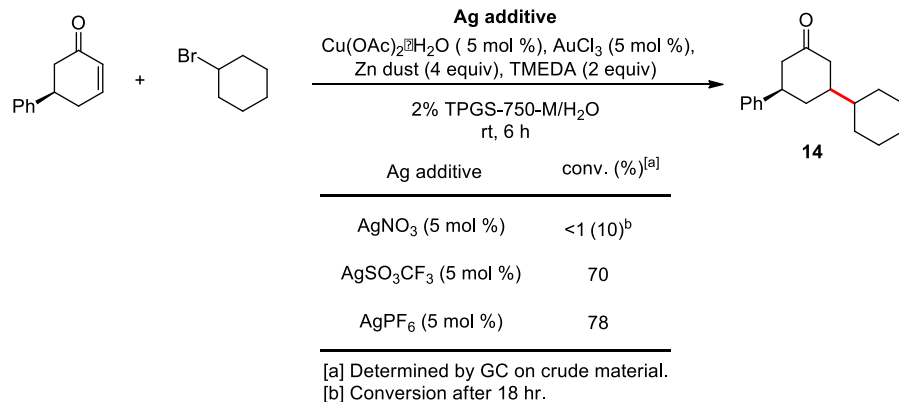
entry	surfactant	yield of 1 (%) ^[a]
1	TPGS-750-M	93
2	Brij 30	52
3	Brij 35	61
4	Solutol HS	72
5	Triton X-100	68
6	Cremonophor EL	58

[a] Determined by GC on crude material.

Scheme S1. Control Experiment (no Cu and Au)

The desired product **14** was obtained in low yields (11%), with a majority of the crude mixture being unreacted starting material **SM** (51%) and reduced enone **RE** (38%).

Scheme S2. Screening of other silver salts

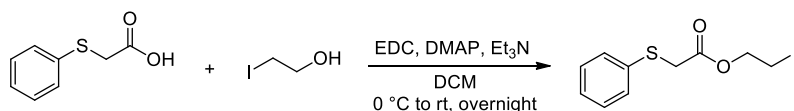


General information

Unless otherwise noted, all reactions were performed under an atmosphere of argon. All commercially available reagents were used without further purification. Zinc dust (LOT#: A019970201), AgBF₄ (LOT#: A0296087), 1-iodobutane, 1-iodooctane, and 4-phenoxybutylbromide (LOT#: A004983601) were purchased from Acros Organics. *N,N,N',N'*-tetramethylethylenediamine and *N,N,N',N'*-tetraethylethylenediamine were purchased from Sigma-Aldrich[®]. Zinc powder (LOT#: A7637038) and AuCl₃ (LOT#: A2180108) were purchased from Strem Chemicals. (*R*)-1-(tert-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one was purchased from Merck Research Laboratories (LOT#: L-701,997-0008). Ethyl 5-bromovalerate (LOT#: 10121073), bromocyclohexane, and 2-iodobutane were purchased from Alfa Aesar[®]. 5-bromo-1-pentene was purchased from TCI America (LOT#: WRE4E). α,β -Unsaturated ketones 5-phenyl-2-cyclohexenone;¹ 5,5-dimethylcyclohex-2-enone and 3-methylenebicyclo[2.2.1]heptan-2-one;² 1-(4-methoxyphenyl)prop-2-en-1-one, (*E*)-6-(benzyloxy)hex-3-en-2-one and (*E*)-12-((tert-butyldimethylsilyloxy)dodec-3-en-2-one;³ (*E*)-13-((tert-butyldimethylsilyloxy)tridec-3-en-2-one;⁴ and alkyl halides 1-chloro-6-iodohexane;⁵ 5-bromopentanenitrile;⁶ and 2-iodopropane;⁷ were prepared according to literature procedures. 4-iodobutylphenone was synthesized via a Finkelstein reaction of 4-chlorobutylphenone which was purchased from Alfa Aesar[®]. A 2 wt % TPGS-750-M/H₂O solution was prepared by dissolving 4 g TPGS-750-M in 196 g water (HPLC grade), followed by degassing with argon. TPGS-750-M was made as previously described,⁸ and is available from Sigma-Aldrich (catalog #733857). Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F₂₅₄ plates (Merck, 0.25 mm thick). The developed chromatograms were analyzed by UV (lamp, 254 nm). Non-UV active compounds were developed using aqueous potassium permanganate (KMnO₄) or vanillin stain. Flash chromatography was performed in glass columns using Silica Flash[®] P60 (SiliCycle, 40-63 μ m). GCMS data was recorded on a 5975C Mass Selective Detector

coupled with a 7890A Gas Chromatograph (Agilent Technologies). A capillary column (HP-5MS cross-linked 5% phenylmethylpolysiloxanediphenyl, 30 m x 0.250 mm, 0.25 micron, Agilent Technologies) was employed. Helium was used as carrier gas at a constant flow of 1 mL/min. Retention times (t_R) refer to the following temperature program: 50 °C for 5 min; heating rate 20 °C/min; 300 °C for 20 min; injection temperature 250 °C; detection temperature 280 °C. ^1H and ^{13}C NMR were recorded at 22 °C on a Varian UNITY INOVA Avance at 400, 500, or 600 MHz. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sep = septet, m = multiplet, br = broad), coupling constant in Hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of CDCl_3 (77.23 ppm) on the δ scale. Chiral HPLC data were collected using a Shimadzu SPD-m20a Prominence diode array detector. Chiral GC analysis was performed using a Restek RT-*beta*DEXest column (30 m x 0.250 mm, 0.25 micron). Retention times (t_R) are from compound dependent temperature programs; split-inlet at 200 °C at 11.60 psi (H_2 , constant pressure) with 20:1 split, FID 290 °C. High resolution mass analyses were obtained using an APE Sciex QStar Pulsar quadrupole/TOF instrument (API) for ESI, or a GCT Premier TOF MS (Waters Corp) for FI.

II. Experimental Procedures



Synthesis of alkyl iodides. To a 100 mL round-bottom flask (oven-dried and under Ar) equipped with a Teflon[®] stir bar 1-iodoethane (258 mg, 1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) hydrochloride (600 mg, 3 mmol) and DMAP (91 mg, 0.0075 mmol) were added. The solids were dissolved in DCM (15 mL). The reaction mixture was cooled to 0 °C with an ice-bath. In an additional 25 mL round-bottom (oven-dried and under Ar) equipped with a Teflon[®] stir bar, 2-(phenylthio)acetic acid (328 mg, 1.95 mmol) was dissolved in DCM (12 mL). This solution was added semi-drop wise via syringe to the cooled solution. The 25 mL round-bottom flask was rinsed with DCM (3 mL), and transferred to the cooled solution via syringe. Lastly, triethylamine (0.32 mL 2.25 mmol) was added to the cooled mixture. The mixture was allowed to warm to rt with stirring overnight. TLC analysis: 25% EtOAc/hex confirmed completion: $R_f = 0.60$ for the product. The reaction was worked up with HCl (1 M) and extracted with DCM (x3), washed with brine, and dried over anhydrous Na_2SO_4 . Flash column chromatography provided the desired compound as a yellow oil (340 mg, 70% yield). ^1H NMR (500

MHz, CDCl₃) δ 7.45-7.42 (m, 2H), 7.34-7.31 (m, 2H) 7.27-7.24 (m, 1H), 4.37 (t, *J* = 6.5 Hz, 2H), 3.82 (s, 2H), 3.23 (t, *J* = 7.5 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 169.3, 134.8, 130.3, 129.3, 127.4, 120.7, 65.6, 36.7; HRESIMS (*m/z*): [M+Na]⁺ calcd. for C₁₀H₁₁IO₂SNa, 344.9422; found 344.9424.

Procedure for Cu-Catalyzed conjugate additions in water:

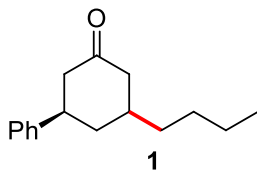
Note: Stirring is a very important parameter in this chemistry, as is the nature of the reaction vessel. Common vials, or more frequently, microwave vials, should be used for small-scale reactions.

General procedure. A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc powder (66 mg, 1 mmol), Cu(OAc)₂•H₂O (3.0 mg, 5 mol %), AuCl₃ (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (42 μL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 42 μL of 1-iodobutane was added and the reaction was continued for an additional 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography using EtOAc/hexanes provided 3-butyl-5-phenylcyclohex-anone (*trans* : *cis* = 85 : 15, 50 mg, 87%) as a colorless oil.

Representative procedure for recycling of the aqueous reaction medium. A 5 mL round-bottom flask (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc dust (135 mg, 2 mmol), Cu(OAc)₂•H₂O (6.0 mg, 6 mol %), AuCl₃ (7.6 mg, 5 mol %), 5-phenyl-2-cyclohexenone (86 mg, 0.50 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150 μL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 1.0 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of bromocyclohexane (92 μL, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 92 μL bromocyclohexane was added and the reaction was stirred continuously for 18 h. The product was extracted using hexanes (3 x 2 mL). The hexane layer was then removed via syringe. The combined extracts were filtrated through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by GC-MS to determine conversion. A small aliquot was removed using a pipette from the reaction mixture after the final extraction to ensure the product and any starting materials were completely removed. The small aliquot taken was

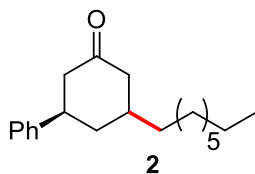
filtrated through a pad of silica gel using EtOAc as the mobile phase and analyzed by TLC and GC-MS. The reaction vessel was purged with a high flow of Ar with a vent needle for 15 min to ensure removal of all hexanes from the reaction medium. The remaining aqueous solution was then charged with zinc dust (135 mg, 2 mmol), 5-phenyl-2-cyclohexenone (86 mg, 0.50 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 113 μ L, 0.75 mmol). The mixture was stirred for several minutes before adding bromocyclohexane (92 μ L, 0.75 mmol) via syringe. The resulting mixture was stirred vigorously at rt for 6 h. Another 92 μ L of bromocyclohexane were added and the reaction was stirred continuously for 18 h. The aforementioned procedure was repeated for the extraction. *Note: The same procedure above was used regardless of the enone/halide combination.*

Representative Procedure associated with the use of AgBF_4 . A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc dust (33 mg, 0.5 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3.0 mg, 6 mol %), AgBF_4 (1.2 mg, 2.5 mol %), AuCl_3 (2.0 mg, 2.5 mol %), 5-phenyl-2-cyclohexenone (43 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of bromocyclohexane (46 μ L, 0.38 mmol). The resulting mixture was stirred vigorously at rt for 6 h. After filtration through a pad of silica gel with EtOAc, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography using EtOAc/hexanes provided (51 mg, 88%) of 3-butyl-5-phenylcyclohexanone as a colorless oil. *Note: The same procedure above was used regardless of the halide combination with only 5-phenyl-2-cyclohexenone.*



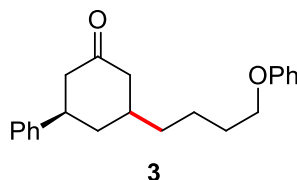
3-Butyl-5-phenylcyclohexanone. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (42 μ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 42 μ L of 1-

iodobutane was added and stirring was continued for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*, and the crude reaction mixture analyzed by NMR, GC, and GC/MS. Flash column chromatography provided 3-butyl-5-phenylcyclohexanone (*trans* : *cis* = 85 : 15, 50 mg, 87%). The *trans* and *cis* products were isolated by multiple preparative TLC; *trans*-product: ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.31 (m, 2H), 7.27-7.21 (m, 3H), 3.33 (m, 1H), 2.60 (m, 2H), 2.55 (dd, $J = 14.4, 4.8$ Hz, 1H), 2.40 (dd, $J = 14, 6$ Hz, 1H), 2.07 (m, 1H), 2.04 (dd, $J = 13.6, 4$ Hz, 1H), 1.94 (dd, $J = 13.6, 8$ Hz, 1H), 1.34-1.27 (m, 6H), 0.87 (t, $J = 8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.7, 144.5, 128.7, 127.0, 126.6, 47.6, 46.8, 39.6, 37.4, 34.5, 33.9, 29.3, 22.8, 14.1; HREI-MS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{O}$, 230.1671; found 230.1676. *cis*-product: ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.30 (m, 2H), 7.26-7.20 (m, 3H), 2.95 (tt, $J = 12.8, 4$ Hz 1H), 2.61-2.45 (m, 2H), 2.13-2.04 (m, 2H), 1.90-1.82 (m, 1H), 1.60-1.43 (m, 2H), 1.41-1.24 (m, 6H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.2, 144.6, 128.9, 126.9, 126.7, 49.0, 48.0, 44.0, 40.0, 38.5, 37.0, 29.0, 22.9, 14.2; HREIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{16}\text{H}_{22}\text{O}$, 230.1671; found 230.1677.

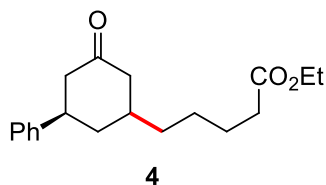


3-Octyl-5-phenylcyclohexanone. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL , 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodooctane (42 μL , 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6h. Another 42 μL of 1-iodooctane was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*, and the crude reaction mixture analyzed by NMR, GC, and GC/MS. Flash column chromatography provided 3-octyl-5-phenylcyclohexanone (*trans* : *cis* = 83 : 17, 63.7 mg, 89%). The *trans*- and *cis*-products were isolated by multiple preparative TLC. *trans*-Product: ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H), 3.33 (m, 1H), 2.61-2.48 (m, 3H), 2.23 (dd, $J = 14.4, 6$ Hz, 1H), 2.08-2.02 (m, 2H), 2.01-1.91 (m, 1H), 1.30-1.24 (m, 14H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.9, 144.6, 128.8, 127.1, 126.7, 47.7, 47.0, 39.7, 37.5, 34.6, 34.3, 32.1, 29.8, 29.7, 29.5, 27.2, 22.9, 14.3; HREIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{20}\text{H}_{30}\text{O}$, 286.2297; found 286.2301. *cis*-Product: ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.28 (m, 2H), 7.25-7.21 (m, 3H), 2.95 (tt, J

= 13.2, 3.6 Hz 1H), 2.59-2.46 (m, 3H), 2.12-2.05 (m, 3H), 1.89-1.83 (m, 1H), 1.42-1.26 (m, 14H), 0.88 (t, $J = 7.2$ Hz, 3H); HREIMS (m/z): $[M]^+$ calcd. $C_{20}H_{30}O$, 286.2297; found 286.2308.

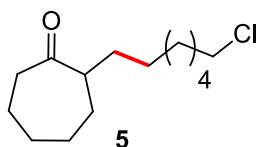


3-(4-Phenoxybutyl)-5-phenylcyclohexanone. A 5 mL microwave vial containing a stir bar was charged with zinc dust (33 mg, 0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 3 mol %), $AuCl_3$ (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and N,N,N',N' -tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 4-bromobutyl phenyl ether (85 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 85 mg of 1-(3-bromopropoxy)benzene and 33 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 3-(4-phenoxybutyl)-5-phenylcyclohexanone (70 mg, 87%). 1H NMR (400 MHz, $CDCl_3$) of two isomers: δ 7.28-7.12 (m, 7H), 6.87-6.79 (m, 3H), 3.92-3.84 (m, 2H), 3.28-3.22 (m, 1H), 2.97-2.88 (m, 1H), 2.58-2.30 (m, 3H), 2.17 (dd, $J = 17.5, 7.5$ Hz, 1H), 2.11-1.96 (m, 2H), 1.90-1.62 (m, 2H), 1.48-1.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) of two isomers: δ 211.7, 159.2, 144.5, 144.4, 129.6, 128.9, 128.88, 128.81, 127.1, 126.9, 126.88, 126.76, 126.74, 120.8, 114.6, 67.7, 49.1, 48.9, 47.8, 47.6, 46.9, 44.9, 44.0, 41.4, 39.9, 39.7, 38.4, 37.4, 36.9, 34.5, 34.1, 33.0, 29.5, 29.4, 25.7, 23.8, 23.4; HREIMS (m/z): $[M]^+$ calcd. for $C_{22}H_{26}O_2$, 322.1933; found 322.1939.

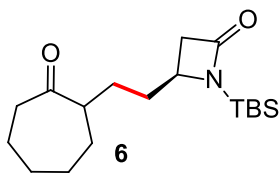


Ethyl 5-(3-oxo-5-phenylcyclohexyl)pentanoate. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 mg, 3 mol %), $AuCl_3$ (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and N,N,N',N' -tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by

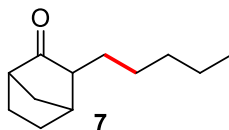
the addition of ethyl 5-bromopentanoate (59 μ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 59 μ L of ethyl 5-bromopentanoate was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*, and the crude reaction mixture analyzed by NMR, GC, and GC/MS. Flash column chromatography provided ethyl 5-(3-oxo-5-phenylcyclohexyl)pentanoate (*trans* : *cis* = 80 : 20, 60.5 mg, 80%). *trans*-Product: ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.30 (m, 2H), 7.25-7.20 (m, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.50-3.29 (m, 1H), 2.63-2.53 (m, 3H), 2.27 (t, $J = 7.2$ Hz, 2H), 2.22 (dd, $J = 15, 6$ Hz, 1H), 2.11-2.03 (m, 2H), 1.94-1.90 (m, 1H), 1.63-1.54 (m, 2H), 1.41-1.27 (m, 4H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.7, 144.5, 128.7, 127.0, 126.6, 47.6, 46.8, 39.6, 37.4, 34.5, 33.9, 29.3, 22.8, 14.1; HRESI-MS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_3\text{Na}$, 325.1780; found 325.1771.



2-(7-Chloroheptyl)cycloheptanone. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), 2-methylenecycloheptanone (31 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-chloro-6-iodohexane (55 μ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 55 μ L of 1-chloro-6-iodohexane was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 2-(7-chloroheptyl)cycloheptanone (50 mg, 82%). ^1H NMR (400 MHz, CDCl_3) δ 3.52 (t, $J = 7.2$ Hz, 2H), 2.53-2.38 (m, 3H), 1.87-1.83 (m, 4H), 1.78-1.71 (m, 2H), 1.68-1.57 (m, 2H), 1.42-1.27 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 216.8, 52.6, 45.4, 42.9, 32.8, 32.5, 31.5, 29.8, 29.7, 28.9, 28.7, 27.3, 27.0, 24.9; HREIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{14}\text{H}_{25}\text{OCl}$, 244.1594; found 244.1618.

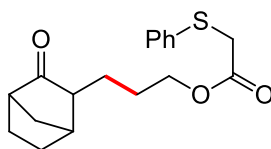


1-(*tert*-Butyldimethylsilyl)-4-(2-(2-oxocycloheptyl)ethyl)azetid-2-one. A 5 mL microwave vial containing a stir bar was charged with zinc dust (66 mg, 1.0 mmol), Cu(OAc)₂•H₂O (5.0 mg, 5 mol %), AuCl₃ (7.6 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (31 μL, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetid-2-one (244 mg, 0.38 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 244 mg of 1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetid-2-one and 66 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided 1-(*tert*-butyldimethylsilyl)-4-(2-(2-oxocycloheptyl)ethyl)azetid-2-one (134 mg, 83% yield). ¹H NMR (500 MHz, CDCl₃) of both isomers: δ 3.46-3.44 (m, 1H), 3.09 (dd, *J* = 15, 5.5 Hz, 1H), 2.57 (t, *J* = 16.5 Hz, 1H), 2.49- 2.43 (m, 3H), 1.88- 1.76 (m, 5H), 1.63- 1.56 (m, 2H), 1.42- 1.19 (m, 5H), 0.92 (s, 9H), 0.19 (d, *J* = 8 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) of both isomers: δ 215.7, 215.6, 172.8, 51.9, 51.7, 50.1, 49.5, 49.47, 46.5, 44.0, 43.9, 43.94, 43.2, 43.1, 34.1, 33.8, 31.9, 31.6, 29.5, 28.8, 28.3, 28.2, 26.4, 26.35, 24.5, 24.45, 18.6, 18.5, 9.9, -5.14, -5.15, -5.5; HRESIMS (*m/z*): [M+Na]⁺ calcd. for C₁₈H₃₃NO₂SiNa, 346.2178; found 346.2179.



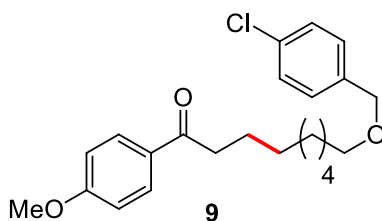
3-Pentylbicyclo[2.2.1]heptan-2-one. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1.0 mmol), Cu(OAc)₂•H₂O (3.0 mg, 3 mol %), AuCl₃ (7.6 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (59 μL, 0.50 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150 μL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (84 μL, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 84 μL 1-iodobutane and 66 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 3-pentylbicyclo[2.2.1]heptan-2-one (78 mg, 86%). The *endo* isomer was exclusively observed by comparison of the ¹H-NMR spectrum to an analogous reaction with 3-alkylsubstituted-2-norbornanones previously reported.⁹ ¹H NMR (400 MHz, CDCl₃) of two isomers: δ 2.53 (t, *J* = 4.5 Hz, 2H), 1.95-1.91

(m, 1H), 1.79-1.72 (m, 1H), 1.66-1.60 (m, 2H), 1.55-1.49 (m, 4H), 1.39-1.07 (m, 7H), 0.88-0.78 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) of two isomers: δ 220.2, 53.69, 53.67, 50.64, 50.61, 38.28, 38.26, 37.1, 31.8, 27.8, 26.3, 25.4, 22.6, 21.2, 14.1; HREIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{12}\text{H}_{20}\text{O}$, 180.1514; found 180.1504.

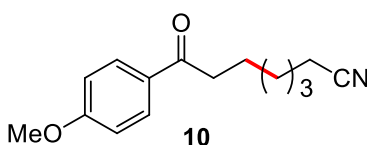


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3-(3-Oxobicyclo[2.2.1]heptan-2-yl)propyl 2-(phenylthio)acetate. A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc powder (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (31 μL , 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL , 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodoethyl 2-(phenylthio)acetate (120 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 120 mg of 2-iodoethyl 2-(phenylthio)acetate was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture was analyzed by NMR, GC, and GC/MS. Flash column chromatography (EtOAc/hexanes) provided 3-(3-oxobicyclo[2.2.1]heptan-2-yl)propyl 2-(phenylthio)acetate (62 mg, 75%). The *endo* isomer was exclusively observed by comparison of the ^1H NMR spectrum to an analogous reaction with 3-alkylsubstituted-2-norbornanones previously reported.⁹ Note: Not all coupling constants could be identified due to overlap/resolution issues. ^1H NMR (600 MHz, CDCl_3) δ 7.40 (d, $J = 7.2$ Hz, 2H), 7.30 (m, $J = 7.2$ Hz, 2H) 7.22 (m, $J = 7.2$ Hz, 1H), 4.11 (m, $J = 6.6$ Hz, 2H), 3.64 (s, 2H), 2.60 (br d, $J = 4.8$ Hz, 1H), 2.56 (s br, 1H), 1.98-1.95 (m, $J = 4.8$ and 10.2 Hz, 1H), 1.84-1.78 (m, $J = 4.8$ and 12.6 Hz, 1H), 1.73-1.65 (m, 4H), 1.64-1.50 (m, 3H), 1.40-1.36 (m, 1H), 1.26-1.17 (m, $J = 6.0$ and 10.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 219.5, 169.8, 135.1, 130.0, 129.2, 127.1, 65.4, 53.1, 50.6, 38.4, 37.1, 36.7, 27.2, 25.5, 23.0, 21.2; HRESIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_3\text{SNa}$, 341.1187; $[\text{M}+\text{Na}]^+$ found 341.1194.

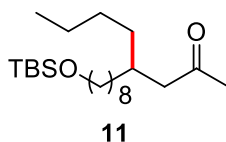


9-(4-Chlorobenzoyloxy)-1-(4-methoxyphenyl)nonan-1-one. A 5 mL microwave vial containing a stir bar was charged with zinc powder (33 mg, 0.5 mmol), Cu(OAc)₂•H₂O (1.5 mg, 3 mol %), AuCl₃ (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (41 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-chloro-4-(6-iodohexyloxymethyl)benzene (132 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 132 mg of 1-((6-iodohexyloxy)methyl)-4-chlorobenzene and 33 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided 9-(4-chlorobenzoyloxy)-1-(4-methoxyphenyl)nonan-1-one (78 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 8.9 Hz, 2H), 7.35-7.20 (m, 4H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.45 (s, 2H), 3.86 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 1.77- 1.61 (m, 2H), 1.68-1.47 (m, 4H), 1.44-1.16 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 199.4, 163.5, 137.5, 133.4, 130.5, 130.4, 130.4, 129.1, 128.7, 113.9, 72.3, 70.8, 55.7, 38.5, 29.9, 29.6, 29.6, 29.5, 26.3, 24.8; HREIMS (*m/z*): [M]⁺ calcd. for C₂₃H₂₉ClO₃, 388.1805; found 388.1812.

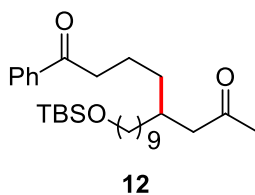


8-(4-Methoxyphenyl)-8-oxooctanenitrile. A 5 mL microwave vial containing a stir bar was charged with zinc dust (66 mg, 1 mmol), Cu(OAc)₂•H₂O (1.5 mg, 3 mol %), AuCl₃ (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (40 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 5-bromovaleronitrile (44 μL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 44 μL of 5-bromovaleronitrile was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column

chromatography provided 8-(4-methoxyphenyl)-8-oxooctanenitrile (53 mg, 86%). ^1H NMR (600 MHz, CDCl_3) δ 7.94 (d, $J = 8.4$ Hz, 2H), 6.94 (d, $J = 8.4$ Hz, 2H), 3.87 (s, 3H), 2.93 (t, $J = 7.2$ Hz, 2H), 3.35 (t, $J = 7.2$ Hz, 2H), 1.75 (m, 2H), 1.69 (m, 2H), 1.54-1.49 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.9, 163.6, 130.5, 130.3, 120.0, 113.9, 55.7, 38.1, 28.72, 28.66, 25.4, 24.2, 17.3; HRESIMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{Na}$, 268.1313; found 268.1305.

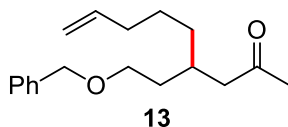


4-Butyl-12-((*tert*-butyldimethylsilyl)oxy)dodecan-2-one. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), (*E*)-12-((*tert*-butyldimethylsilyl)oxy)dodec-3-en-2-one (78 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL , 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-iodobutane (42 μL , 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 42 μL of 1-iodobutane was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 4-butyl-12-((*tert*-butyldimethylsilyl)oxy)dodecan-2-one (79.5 mg, 86%). ^1H NMR (400 MHz, CDCl_3) δ 3.59 (t, $J = 6.8$ Hz, 2H), 2.33 (d, $J = 6.8$ Hz, 2H), 2.17 (s, 3H), 1.88 (m, 1H), 1.57-1.47 (m, 2H), 1.27-1.24 (m, 18H), 0.89 (s, 9H), 0.88 (t, $J = 6.8$ Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 209.7, 63.5, 49.1, 34.2, 34.1, 33.9, 33.1, 30.6, 30.1, 29.8, 29.6, 29.0, 26.8, 26.2, 26.0, 23.2, 18.6, 14.3, -5.0; HRESIMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{46}\text{O}_2\text{SiNa}$, 393.3165; found 393.3150.

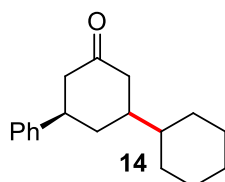


5-(9-((*tert*-Butyldimethylsilyl)oxy)nonyl)-1-phenyloctane-1,7-dione. A 5 mL microwave vial containing a stir bar was charged with zinc powder (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), (*E*)-13-((*tert*-butyldimethylsilyl)oxy)tridec-3-en-2-one (81.6 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL , 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in

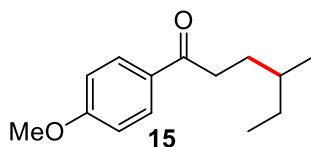
water was added via syringe followed by the addition of 4-iodo-1-phenylbutan-1-one (102.5 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 102.5 mg of 4-iodo-1-phenylbutan-1-one was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 5-(9-((*tert*-butyldimethylsilyl)oxy)nonyl)-1-phenyloctane-1,7-dione (98.5 mg, 83%). ¹H NMR (600 MHz, CDCl₃) δ 7.95 (dd, *J* = 7.2, 4.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 7.2 Hz, 2H), 2.99-2.94 (m, 2H), 2.38 (d, *J* = 6.6 Hz, 2H), 2.13 (s, 3H), 1.96 (m, 1H), 1.77-1.69 (m, 4H), 1.52-1.44 (m, 4H), 1.39-1.24 (m, 12H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 209.4, 200.5, 137.2, 133.2, 128.8, 128.2, 63.6, 48.7, 38.9, 34.1, 33.9, 33.7, 33.1, 30.7, 30.1, 29.8, 29.7, 29.4, 26.9, 26.2, 26.0, 24.4, 21.4, -5.0; HRESIMS (*m/z*): [M+Na]⁺ calcd. for C₂₉H₅₀O₃SiNa, 497.3427; found 497.3405.



4-(2-(Benzyloxy)ethyl)non-8-en-2-one. A 10 mL round bottom flask containing a stir bar was charged with zinc dust (66 mg, 1.0 mmol), Cu(OAc)₂•H₂O (5.0 mg, 5 mol %), AuCl₃ (7.6 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (102 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 0.15 mL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 1.0 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 5-bromopent-1-ene (89 μL, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 89 μL of 5-bromopent-1-ene and 66 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*, and the crude reaction mixture was analyzed by NMR. Flash column chromatography provided 4-(2-(benzyloxy)ethyl)non-8-en-2-one (225 mg, 82%). ¹H NMR (500 MHz, CDCl₃): δ 7.29-7.19 (m, 4H), 5.75-5.67 (m, 1H), 4.93-4.86 (m, 2H), 4.39 (s, 2H), 3.41-3.31 (m, 2H), 2.38-2.26 (m, 2H), 2.05- 2.00 (m, 3H), 1.97- 1.93 (m, 2H), 1.63- 1.55 (m, 1H), 1.49- 1.44 (m, 1H), 1.33-1.19 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 209.0, 138.9, 138.7, 128.5, 127.8, 127.7, 114.7, 73.1, 68.6, 48.9, 34.1, 34.0, 33.98, 31.4, 30.5, 26.1; HRESIMS (*m/z*): [M+Na]⁺ calcd. for C₁₈H₂₆O₂Na, 297.1830; found 297.1816.

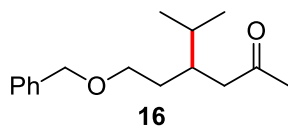


3-Cyclohexyl-5-phenylcyclohexanone. A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc dust (33 mg, 0.5 mmol), Cu(OAc)₂•H₂O (1.5 mg, 3 mol %), AuCl₃ (3.8 mg, 5 mol %), 5-phenyl-2-cyclohexenone (42 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of bromocyclohexane (46 μL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 46 μL of bromocyclohexane and 33 mg zinc dust were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided 3-cyclohexyl-5-phenylcyclohexanone (*trans* : *cis* = 85 : 15, 54 mg, 85%). ¹H NMR (400 MHz, CDCl₃) of major isomer: δ 7.24-7.19 (m, 2H), 7.16-7.12 (m, 3H), 3.32-3.26 (m, 1H), 2.62-2.50 (m, 2H), 2.41-2.28 (m, 2H), 2.07-1.89 (m, 2H), 1.73-1.64 (m, 4H), 1.58-1.52 (m, 2H), 1.18-1.00 (m, 4H), 0.86-0.74 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) of major isomer: δ 212.5, 144.6, 128.8, 127.2, 126.6, 47.0, 44.7, 40.2, 39.7, 39.4, 35.2, 30.5, 30.3, 26.63, 26.60, 26.5; HREIMS (*m/z*): [M]⁺ calcd. for C₁₈H₂₄O, 256.1827; found 256.1828.

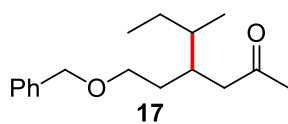


1-(4-Methoxyphenyl)-4-methylhexan-1-one. A 5 mL microwave vial containing a stir bar was charged with zinc powder (33 mg, 0.5 mmol), Cu(OAc)₂•H₂O (2.5 mg, 5 mol %), AuCl₃ (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (41 mg, 0.25 mmol), and *N,N,N',N'*-tetraethylethylenediamine (TEEDA, 110 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodobutane (43 μL, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 43 μL of 2-iodobutane and 33 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided 1-(4-methoxyphenyl)-4-methylhexan-1-one (46 mg, 83%). ¹H NMR (500 MHz, CDCl₃) δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.97-2.85 (m, 2H), 1.79-1.72 (m, 1H), 1.58- 1.49 (m, 1H), 1.46-1.36 (m, 2H), 1.25-1.16 (m, 1H), 0.95- 0.87 (m, 6H); ¹³C NMR

(100 MHz, CDCl₃): δ 199.7, 163.5, 130.5, 130.4, 113.9, 55.7, 36.3, 34.5, 31.5, 29.5, 19.3, 11.6; HRESIMS (m/z): [M+Na]⁺ calcd. for C₁₄H₂₀O₂Na, 243.1361; found 243.1351.

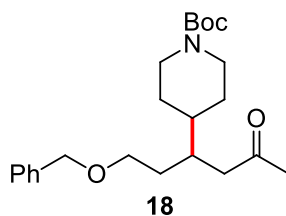


6-(Benzyloxy)-4-isopropylhexan-2-one. A 5 mL microwave vial containing a stir bar was charged with zinc powder (33 mg, 0.5 mmol), Cu(OAc)₂•H₂O (2.5 mg, 5 mol %), AuCl₃ (3.8 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (51 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodopropane (38 μ L, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 38 μ L of 2-iodopropane and 33 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided 6-(benzyloxy)-4-isopropylhexan-2-one (56 mg, 90%). ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.20 (m, 5H), 4.30 (s, 2H), 3.44-3.36 (m, 2H), 2.29 (ddd, J = 22.5, 17.0, 6.0 Hz, 2H), 2.03 (s, 2H), 1.99-1.93 (m, 2H), 1.65-1.57 (m, 2H), 1.43-1.36 (m, 1H), 0.94-0.78 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 209.3, 138.7, 128.5, 127.8, 127.7, 73.1, 69.3, 45.9, 36.8, 31.5, 30.6, 30.4, 19.3, 18.9; HREIMS (m/z): [M]⁺ calcd. for C₁₆H₂₄O₂, 248.1776; found 248.1778.

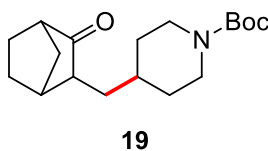


4-(2-(Benzyloxy)ethyl)-5-methylheptan-2-one. A 10 mL round bottom flask containing a stir bar was charged with zinc powder (66 mg, 1.0 mmol), Cu(OAc)₂•H₂O (5.0 mg, 5 mol %), AuCl₃ (7.6 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (102 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 0.15 mL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 1.0 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 2-iodobutane (86 μ L, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 86 μ L of 2-iodobutane and 66 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided 4-(2-

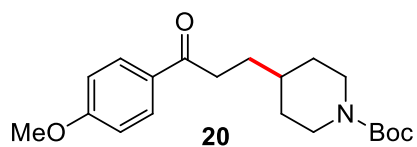
(benzyloxy)ethyl)-5-methylheptan-2-one (121 mg, 85%). ^1H NMR (500 MHz, CDCl_3) of both isomers: δ 7.36-7.26 (m, 4H), 4.46 (s, 2H), 3.50-3.42 (m, 2H), 2.36 (dd, $J=13.5, 7.0$ Hz, 2H), 2.27 (dd, $J=16.5, 8.5$ Hz, 1H), 2.17-2.11 (m, 3H), 1.71-1.59 (m, 1H), 1.55-1.43 (m, 1H), 1.41-1.24 (m, 3H), 1.16-1.06 (m, 1H), 0.88 (t, $J=7.5$ Hz, 3H), 0.81 (q, $J=3.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) of both isomers: δ 209.3, 209.28, 138.7, 128.6, 128.5, 127.9, 127.72, 127.7, 73.1, 73.07, 69.4, 69.2, 46.9, 45.2, 37.8, 37.5, 35.5, 35.3, 32.5, 30.5, 30.4, 27.0, 26.6, 15.3, 15.1, 12.5, 12.4; HRESIMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{Na}$, 285.1831; found 285.1813.



***tert*-Butyl 4-(1-(benzyloxy)-5-oxohexan-3-yl)piperidine-1-carboxylate.** A 10 mL round bottom flask containing a stir bar was charged with zinc powder (66 mg, 1.0 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (5.0 mg, 5 mol %), AuCl_3 (7.6 mg, 5 mol %), (*E*)-6-(benzyloxy)hex-3-en-2-one (233 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 150 μL , 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 1.0 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-*tert*-butyl 4-iodopiperidine-1-carboxylate (233 mg, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 244 mg of *tert*-butyl 4-iodopiperidine-1-carboxylate and 66 mg zinc powder were added and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography provided *tert*-butyl 4-(1-(benzyloxy)-5-oxohexan-3-yl)piperidine-1-carboxylate (171 mg, 88%). ^1H NMR (500 MHz, CDCl_3): δ 7.28-7.19 (m, 5H), 4.38 (s, 2H), 4.06-4.02 (m, 2H), 3.41-3.37 (m, 2H), 2.52-2.47 (m, 2H), 2.36-2.27 (m, 2H), 2.03-1.97 (m, 4H), 1.77-1.50 (m, 1H), 1.47-1.34 (m, 13H), 1.13-1.05 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 208.6, 154.9, 138.5, 128.5, 127.8, 127.7, 79.4, 73.0, 68.9, 45.8, 39.6, 35.6, 31.5, 30.4, 28.6; HRFIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{23}\text{H}_{35}\text{NO}_4$, 389.2566; found 389.2598.

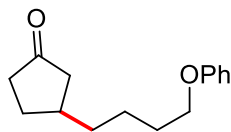


***tert*-Butyl 4-((3-oxobicyclo[2.2.1]heptan-2-yl)methyl)piperidine-1-carboxylate.** A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc dust (65 mg, 1.0 mmol), Cu(OAc)₂•H₂O (1.5 mg, 3 mol %), AuCl₃ (3.8 mg, 5 mol %), 3-methylenebicyclo[2.2.1]heptan-2-one (31 μL, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of *tert*-butyl 4-iodopiperidine-1-carboxylate (117 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 117 mg of *tert*-butyl 4-iodopiperidine-1-carboxylate and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a colorless oil (65 mg, 85%). The *endo* isomer was exclusively observed by comparison of the ¹H-NMR spectrum to an analogous reaction with 3-alkylsubstituted-2-norbornanones previously reported.⁹ Not all coupling constants could be identified due to overlap/resolution issues. ¹H NMR (600 MHz, CDCl₃): δ 4.08 (s br, 2H), 2.69 (m br, 2H), 2.62 (d br, *J* = 4.8 Hz, 1H), 2.59 (s br, 1H), 2.09 (m, *J* = 4.2, 4.8 Hz, 1H), 1.83 (sept, *J* = 5.4 Hz, 1H), 1.70-1.47 (m, 7H), 1.46 (s, 9H), 1.42-1.35 (m, 1H), 1.26 (br m, 1H), 1.22-1.04 (m, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 220.6, 155.2, 79.5, 51.1, 50.6, 38.9, 37.3, 34.5, 33.1, 29.9, 28.6, 28.3, 25.5, 21.5; HRESIMS (*m/z*): [M+Na]⁺ calcd. for C₁₈H₂₉NO₃Na, 330.2045; found 330.2037.



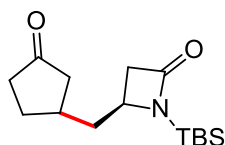
***tert*-Butyl 4-(3-(4-methoxyphenyl)-3-oxopropyl)piperidine-1-carboxylate.** A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc dust (65 mg, 1.0 mmol), Cu(OAc)₂•H₂O (1.5 mg, 3 mol %), AuCl₃ (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (41 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL, 0.5 mmol). The vial was capped with a rubber septum and placed under an Argon atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of *tert*-butyl 4-iodopiperidine-1-carboxylate (117 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 117 mg of *tert*-butyl 4-iodopiperidine-1-carboxylate and the reaction was stirred continuously for 18 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a white solid (70 mg, 81%). ¹H NMR (600 MHz,

CDCl₃): δ 7.94 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 11.4 Hz, 2H), 4.10 (s br, 2H), 3.87 (s, 3H), 2.95 (t, J = 7.2 Hz, 2H), 2.68 (s br, 2H), 1.82 (m, 1H), 1.69 (m, 3H), 1.54-1.48 (m, 2H), 1.56 (s, 9H), 1.26-1.11 (m, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 199.0, 163.6, 155.0, 130.5, 130.2, 113.9, 79.4, 55.6, 35.8, 35.4, 31.1, 28.6; HRESIMS (m/z): [M+Na]⁺ calcd. for C₂₀H₂₉NO₄Na, 370.1994; found 370.1981.



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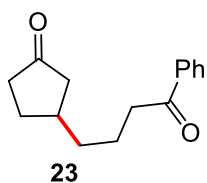
3-(4-Phenoxybutyl)cyclopentanone. A 5 mL round bottom flask containing a Teflon[®] stir bar was charged with zinc dust (33 mg, 0.5 mmol), Cu(OAc)₂•H₂O (3.0 mg, 6 mol %), AgBF₄ (1.8 mg, 2.5 mol %), AuCl₃ (2.0 mg, 2.5 mol %), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The flask was capped with a glass stopper and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of (4-bromobutoxy)benzene (88 mg, 0.38 mmol). The resulting mixture was stirred for 1 min and cyclopentan-2-one (21 μ L, 0.25 mmol) was slowly added over the next 6 h. The resulting mixture was stirred vigorously at rt for 4 h and another addition of (4-bromobutoxy)benzene (43 mg, 0.19 mmol) was added. The reaction mixture was stirred for an additional 8 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a colorless oil (41 mg, 71%). ¹H NMR (600 MHz, CDCl₃): δ 7.31 (m, 2H), 6.95 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 7.8 Hz, 2H), 3.98 (t, J = 6 Hz, 2H), 2.41 (dd, J = 7.8, 18 Hz, 1H), 2.34-2.29 (m, 1H), 2.22-2.14 (m, 3H), 2.13-1.80 (m, 3H), 1.58-1.49 (m, 5H); ¹³C NMR (150 MHz, CDCl₃) δ 220.0, 159.2, 129.6, 120.7, 114.7, 67.7, 45.4, 38.7, 37.4, 35.6, 29.7, 29.5, 24.6; HRFIMS (m/z): [M]⁺ calcd. for C₁₅H₂₀O₂, 232.1463; found 232.1472.



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(4S)-1-(tert-Butyldimethylsilyl)-4-((3-oxocyclopentyl)methyl)azetidin-2-one. A 5 mL round bottom flask containing a Teflon[®] stir bar was charged with zinc powder (33 mg, 0.5 mmol), Cu(OAc)₂•H₂O (3.0 mg, 6 mol %), AgBF₄ (1.8 mg, 2.5 mol %), AuCl₃ (2.0 mg, 2.5 mol %), and *N,N,N',N'*-

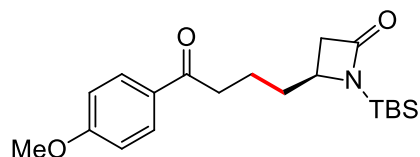
tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The flask was capped with a glass stopper and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of (*R*)-1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one (124 mg, 0.38 mmol). The resulting mixture was stirred for 1 min and cyclopenten-2-one (21 μ L, 0.25 mmol) was slowly added over the next 6 h. The resulting mixture was stirred vigorously at rt for 4 h and another addition of (*R*)-1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one (124 mg, 0.38 mmol) was added. The reaction mixture was stirred for an additional 6 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a colorless oil (53 mg, 75%) as a mixture of diastereomers (47:53): ^1H NMR (600 MHz, CDCl_3): δ 3.75 (m, 1H), 3.6 (0.5H), 3.5 (0.5H), 3.19 (dd, $J = 1.2, 5.4$ Hz, 0.5H), (dd, $J = 0.6, 4.8$ Hz, 0.5H), 2.64 (ddd, $J = 2.4, 10.8, 17.4$ Hz, 1H), 2.44-2.38 (m, 1H), 2.35-2.31 (m, 1H), 2.22-2.10 (m, 2H), 1.99-1.92 (m, 1H), 1.89-1.78 (m, 1H), 1.68-1.52 (m, 2H), 0.97 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 218.2, 172.1, 48.5, 48.2, 45.5, 44.9, 44.4, 42.7, 42.3, 38.5, 38.4, 34.8, 30.3, 29.6, 26.4, -5.0, -5.5; HRESIMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{27}\text{NO}_2\text{SiNa}$, 304.1709; found 304.1718.



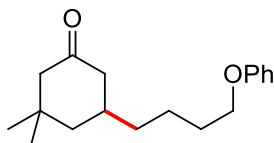
3-(4-Oxo-4-phenylbutyl)cyclopentanone. A 5 mL microwave vial (oven-dried and under Ar) containing a Teflon[®] stir bar was charged with zinc powder (33 mg, 0.5 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3.0 mg, 6 mol %), AgBF_4 (1.8 mg, 2.5 mol %), AuCl_3 (2.0 mg, 2.5 mol %), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μ L, 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 4-iodo-1-phenylbutan-1-one (103 mg, 0.38 mmol). The resulting mixture was stirred for 1 min and cyclopenten-2-one (21 μ L, 0.25 mmol) was slowly added over the next 6 h. Additional 4-iodo-1-phenylbutan-1-one (52 mg, 0.19 mmol) was added after 6 h. The reaction mixture was stirred for an additional 6 h. After filtration through a pad of silica gel using EtOAc as the mobile phase, the solvent was evaporated *in vacuo* and the crude reaction mixture analyzed by NMR. Flash column chromatography (EtOAc/hexanes) provided the desired product as a colorless oil (47 mg, 82%). ^1H NMR (600 MHz, CDCl_3): δ 7.97 (d, $J = 7.2$ Hz, 2H), 7.59-7.56 (m, 1H), 7.49-7.47 (m, 2H), 3.01 (t, $J = 7.2$ Hz, 2H), 2.43 (dd, $J = 7.2$ and 18.6 Hz, 1H), 2.35-2.29 (m, 1H), 2.24-2.14 (m, 3H), 1.88-

1.75 (m, 3H), 1.58-1.50 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 219.8, 200.2, 137.1, 133.2, 128.8, 128.2, 45.4, 38.7, 38.6, 37.4, 35.5, 29.6, 22.6; HRESIMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_2\text{Na}$, 253.1204; found 253.1196.

Additional examples not presented in Tables 2 or 3.



1-(*tert*-Butyldimethylsilyl)-4-(4-(4-methoxyphenyl)-4-oxobutyl)azetidin-2-one. A 5 mL microwave vial containing a stir bar was charged with zinc dust (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 mg, 3 mol %), AuCl_3 (3.8 mg, 5 mol %), 1-(4-methoxyphenyl)prop-2-en-1-one (40 mg, 0.25 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 75 μL , 0.5 mmol). The vial was capped with a rubber septum and placed under an Ar atmosphere, and 0.5 mL of a 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition of 1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one (122 mg, 0.375 mmol). The resulting mixture was stirred vigorously at rt for 6 h. Another 122 mg of 1-(*tert*-butyldimethylsilyl)-4-(iodomethyl)azetidin-2-one was added and the reaction was stirred for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 1-(*tert*-butyldimethylsilyl)-4-(4-(4-methoxyphenyl)-4-oxobutyl)azetidin-2-one (50 mg, 87%). ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H), 3.57-3.51 (m, 1H), 3.17-3.12 (dd, $J = 15.2, 5.6$ Hz, 1H), 2.96 (t, $J = 7.2$ Hz, 2H), 2.67-2.62 (dd, $J = 15.2, 2.4$ Hz, 1H), 1.98-1.89 (m, 1H), 1.75-1.62 (m, 2H), 1.53-1.42 (m, 1H), 0.95 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.2, 172.9, 163.7, 130.5, 130.1, 114.0, 55.7, 49.6, 44.1, 37.9, 36.1, 26.5, 20.6, 18.5, -5.1, -5.5; HRESIMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{20}\text{H}_{31}\text{NO}_3\text{SiNa}$, 384.1971; found 384.1961.



3,3-Dimethyl-5-(3-phenoxypropyl)cyclohexanone. A 10 mL round bottom flask containing a stir bar was charged with zinc dust (66 mg, 1 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3.0 mg, 3 mol %), AuCl_3 (7.6 mg, 5 mol %), 5,5-dimethylcyclohex-2-enone (62 mg, 0.5 mmol), and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 0.15 mL, 1.0 mmol). The vial was capped with a rubber septum and placed under an Argon

atmosphere, and a 1.0 mL 2 wt % TPGS-750-M solution in water was added via syringe followed by the addition (3-bromopropoxy)benzene (0.16g, 0.75 mmol). The resulting mixture was stirred vigorously at rt for 6h. Another 0.16g (3-bromopropoxy)benzene and 66 mg of zinc dust were added and the reaction was continued to stir for 18 h. After filtration through a pad of silica gel, the solvent was evaporated *in vacuo*. Flash column chromatography provided 3,3-dimethyl-5-(3-phenoxypropyl)cyclohexanone (105 mg, 81%). ¹H NMR (600 MHz, CDCl₃) δ 7.29-7.26 (m, 2H), 6.94 (t, *J* = 6 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 2H), 3.95 (t, *J* = 6 Hz, 2H), 2.42 (d, *J* = 12 Hz, 1H), 2.20 (d, *J* = 13.2 Hz, 1H), 2.09 (d, *J* = 13.2 Hz, 1H), 1.97-1.90 (m, 2H), 1.83-1.78 (m, 2H), 1.67 (d, *J* = 13.2 Hz, 1H), 1.56-1.47 (m, 2H), 1.33 (t, *J* = 13.2 Hz, 1H), 1.07 (s, 3H), 0.89 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 212.0, 159.1, 129.7, 120.9, 114.7, 67.9, 54.8, 47.6, 45.5, 35.5, 34.7, 34.0, 32.4, 26.8, 26.0; HREIMS (*m/z*): [M]⁺ calcd. for C₁₇H₂₄O₂, 260.1776; found 260.1870.

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