Development of a Generic Activation Mode: Nucleophilic α-Substitution of Ketones via Oxy-Allyl Cations.

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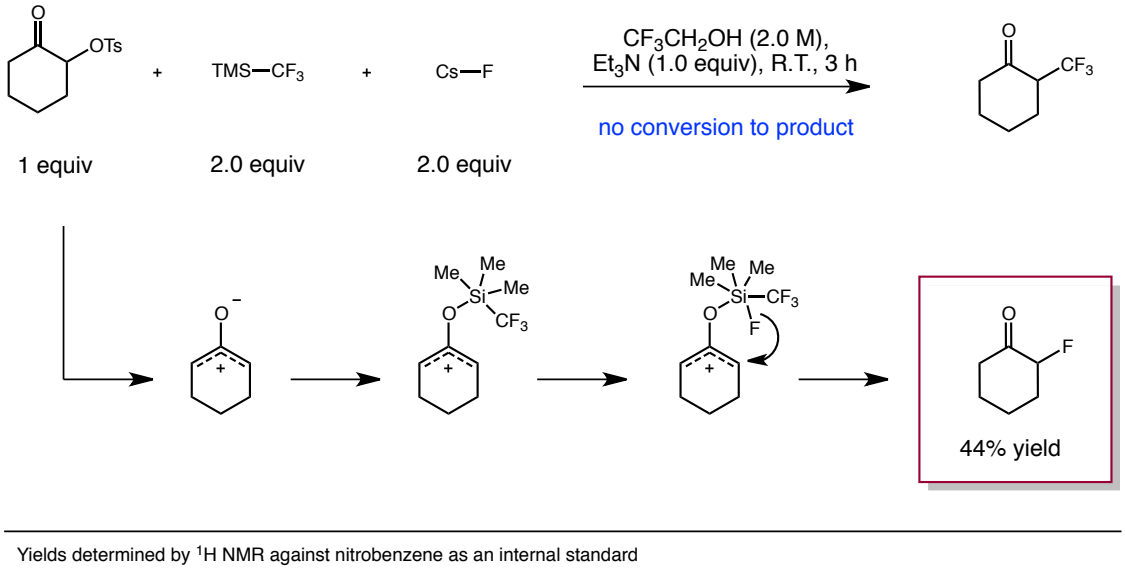
Supporting Information

Supporting Information Figure 1.



Yields determined by ^{1}H NMR against nitrobenzene as an internal standard

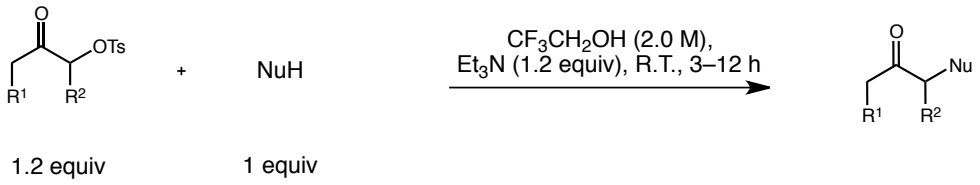
I. General Information. Commercial reagents were used as received from supplier. All solvents were used as received from supplier. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using a Biotage™ purification system using high-pressure columns of specified SiO_2 mass and specified solvent gradients. Thin-layer chromatography (TLC) was performed on

Silicycle 250 mm silica gel F-254 plates. Visualization of the developed plates was performed by fluorescence quenching or by $KMnO_4$, anisaldehyde, ceric ammonium molybdate, or ninhydrin stain.

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 (500 MHz or 125 MHz) and are internally referenced to residual protio solvent signals (note: $CDCl_3$ referenced at d 7.27 ppm for ^1H and d 77.0 ppm for ^{13}C). Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass spectra were obtained from the Princeton Mass Spectrometry Laboratory. High Performance Liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series chromatographs using a chiral column (25 cm) and guard column (5 cm) as noted for each compound. Optical rotations were measured on a Jasco P-1010 polarimeter with $[a]_D$ values reported in degrees; concentration (c) is in g/100 mL.

II. Racemic Nucleophilic Substitution of α-Tosyloxy Ketones

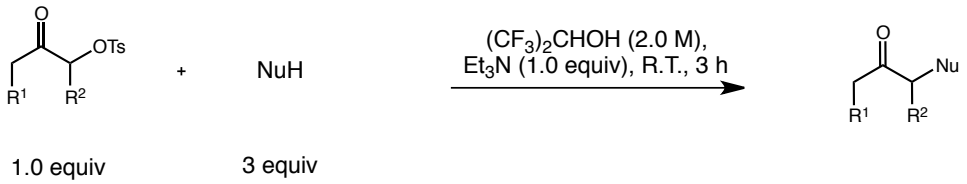
General Method A: Generic Procedure for Most Substrates



To an 8 mL vial equipped with a magnetic stir bar and screw-top PIFE septa was added nucleophile (1.0 mmol, 1.0 equiv) and 2,2,2-trifluoroethanol (0.5 mL, 2 M). To this mixture was

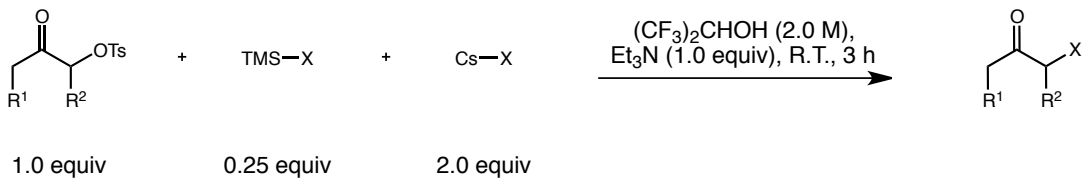
added ketone (1.2 mmol, 1.2 equiv) followed by Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The reaction mixture was then stirred for the required time at room temperature (usually 3 hours, if longer time required it will be noted). The crude reaction mixture was loaded directly onto a 10 g Biotage™ column with DCM as a rinsing solvent. The 10 g column was then fit on top of a pre-equilibrated 50 g Biotage™ column and the specified solvent gradient was initiated. The product containing fractions were combined and concentrated to yield pure product.

General Method B: Generic Procedure for Alkyl Alcohols and Amines

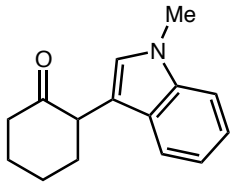


To an 8 mL vial equipped with a magnetic stir bar and screw-top PIFE septa was added nucleophile (3.0 mmol, 3.0 equiv) and 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M). To this mixture was added ketone (1.0 mmol, 1.0 equiv) followed by Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The reaction mixture was then stirred for three hours at room temperature. The crude reaction mixture was loaded directly onto a 10 g Biotage™ column with DCM as a rinsing solvent. The 10 g column was then fit on top of a pre-equilibrated 50 g Biotage™ column and the specified solvent gradient was initiated. The product containing fractions were combined and concentrated to yield pure product.

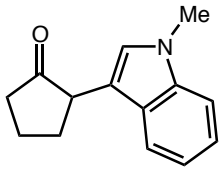
General Method C: Generic Procedure for Halide Nucleophiles



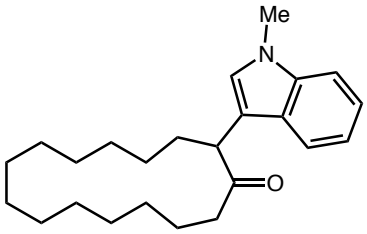
To an 8 mL vial equipped with a magnetic stir bar and screw-top PIFE septa was added CsX (2.0 mmol, 2.0 equiv) and 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M). To this mixture was added ketone (1.0 mmol, 1.0 equiv) followed by TMSX (0.25 mmol, 0.25 equiv) and finally Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The reaction mixture was then stirred for three hours at room temperature. The crude reaction mixture was loaded directly onto a 10 g Biotage™ column with DCM as a rinsing solvent. The 10 g column was then fit on top of a pre-equilibrated 50 g Biotage™ column and the specified solvent gradient was initiated. The product containing fractions were combined and concentrated to yield pure product.



2-(1-methyl-1*H*-indol-3-yl)cyclohexanone (Table 2, Entry 1). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (322 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–30% EtOAc in hexanes gradient to give pure title compound (207.1 mg, 91% yield) as a clear oil. IR (thin film) 2931, 2858, 1707, 1474, 1327, 1124, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.47 (d, J = 7.7 Hz, 1H, Ar**H**), 7.31 (d, J = 8.1 Hz, 1H, Ar**H**), 7.23 (t, J = 7.2 Hz, 1H, Ar**H**), 7.10 (t, J = 7.1 Hz, 1H, Ar**H**), 7.04 (s, 1H, Ar**H**), 3.94 (dd, J = 11.5, 5.4 Hz, 1H, COC**H**Ar), 3.78 (s, 3H, N**Me**), 2.66 – 2.45 (m, 2H, COC$\mathbf{H_2}$), 2.46 – 2.33 (m, 1H, (C$\mathbf{H_2}$)$_3$), 2.25 – 1.98 (m, 3H, (C$\mathbf{H_2}$)$_3$), 1.97 – 1.80 (m, 2H, (C$\mathbf{H_2}$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 210.8, 136.7, 127.3, 126.6, 121.5, 119.1, 118.8, 112.1, 109.3, 48.6, 42.0, 35.2, 32.7, 28.1, 25.3; HRMS (ESI-TOF) calculated for $C_{15}H_{18}NO$ $[M+H]^+$ m/z 228.1383, found 228.1385.

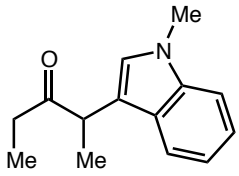


2-(1-methyl-1*H*-indol-3-yl)cyclopentanone (Table 2, Entry 2). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclopentanone (305 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–30% EtOAc in hexanes gradient to give pure title compound (160.5 mg, 75% yield) as a clear oil. IR (thin film) 2960, 2877, 1737, 1474, 1331, 1145, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.57 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.33 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.26 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.14 (t, *J* = 7.5 Hz, 1H, Ar**H**), 6.98 (s, 1H, Ar**H**), 3.76 (s, 1H, N**Me**), 3.64 (t, J = 9.8 Hz, 1H, COC**H**Ar), 2.68 – 2.48 (m, 2H, COC$\mathbf{H_2}$), 2.47 – 2.35 (m, 1H, (C$\mathbf{H_2}$)$_2$), 2.28 – 2.12 (m, 2H, (C$\mathbf{H_2}$)$_2$), 2.07 – 1.94 (m, 1H, (C$\mathbf{H_2}$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 219.1, 137.1, 127.0, 126.4, 121.7, 119.3, 118.9, 111.3, 109.3, 47.1, 38.1, 32.6, 31.7, 21.0; HRMS (ESI-TOF) calculated for $C_{14}H_{16}NO$ $[M+H]^+$ m/z 214.1226, found 214.1227.

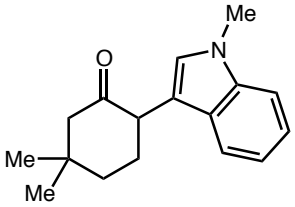


2-(1-methyl-1*H*-indol-3-yl)cyclopentadecanone (Table 2, Entry 3). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclopentadecanone (474 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–30%

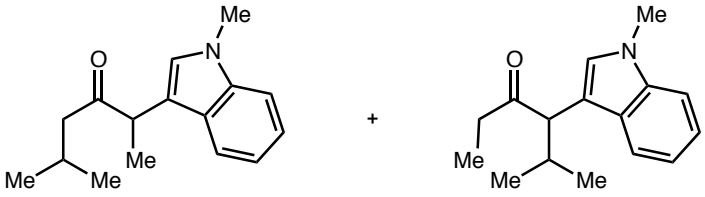
EtOAc in hexanes gradient to give pure title compound (317.8 mg, 90% yield) as a clear oil. IR (thin film) 2925, 2855, 1705, 1459, 1329, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.64 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.31 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.24 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.14 (t, *J* = 7.4 Hz, 1H, Ar**H**), 6.96 (s, 1H, Ar**H**), 4.05 (dd, *J* = 9.5, 5.7 Hz, 1H, COC**H**Ar), 3.77 (s, 3H, N**Me**), 2.56 – 2.44 (m, 1H, (C**H₂**)$_{13}$), 2.36 (ddd, *J* = 15.5, 7.6, 5.7, 1H, (C**H₂**)$_{13}$), 2.25 (ddt, *J* = 13.6, 9.7, 6.9, 1H, (C**H₂**)$_{13}$), 1.84 – 1.65 (m, 2H, (C**H₂**)$_{13}$), 1.62 – 1.22 (m, 21H, (C**H₂**)$_{13}$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 212.5, 136.9, 127.1, 126.8, 121.7, 119.1, 118.9, 112.7, 109.3, 49.0, 40.6, 32.8, 31.7, 27.5, 27.1, 26.9, 26.8, 26.7, 26.3, 26.3, 26.3, 26.3, 23.5; HRMS (ESI-TOF) calculated for $C_{24}H_{36}NO$ $[M+H]^+$ m/z 354.2791, found 354.2788.



2-(1-methyl-1*H*-indol-3-yl)pentan-3-one (Table 2, Entry 4). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxy-3-pentanone (308 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–30% EtOAc in hexanes gradient to give pure title compound (155.2 mg, 72% yield) as a clear oil. IR (thin film) 2973, 2934, 1708, 1472, 1370, 1329, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.64 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.36 (d, *J* = 8.0 Hz, 1H, Ar**H**), 7.29 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.18 (t, *J* = 7.5 Hz, 1H, Ar**H**), 6.97 (s, 1H, Ar**H**), 4.08 (q, *J* = 7.0 Hz, 1H, COC**H**Ar), 3.81 (s, 3H, N**Me**), 2.63 – 2.38 (m, 2H, COC**H₂**), 1.54 (d, *J* = 7.1, 3H, CHAr**Me**), 1.01 (t, *J* = 7.3, 3H, CH_2C**H₃**); ^{13}C NMR (125 MHz, $CDCl_3$) d: 212.5, 136.9, 126.8, 126.5, 121.8, 119.2, 118.9, 114.1, 109.3, 43.6, 33.4, 32.7, 17.0, 8.0; HRMS (ESI-TOF) calculated for $C_{14}H_{18}NO$ $[M+H]^+$ m/z 216.1383, found 216.1381.

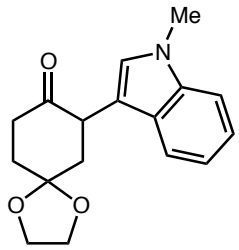


5,5-dimethyl-2-(1-methyl-1*H*-indol-3-yl)cyclohexanone (Table 2, Entry 5). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxy-5,5-dimethylcyclohexanone (356 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–30% EtOAc in hexanes gradient to give pure title compound (222.5 mg, 87% yield) as a clear oil. IR (thin film) 2953, 2869, 1708, 1473, 1157, 909, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.46 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.31 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.22 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.09 (t, *J* = 7.8 Hz, 1H, Ar**H**), 7.04 (s, 1H, Ar**H**), 3.85 (dd, *J* = 11.3, 6.1 Hz, 1H, COC**H**Ar), 3.78 (s, 3H, N**Me**), 2.48 – 2.38 (m, 1H, COC**H$_2$**CMe$_2$), 2.36 – 2.26 (m, 2H, COC**H$_2$**CMe$_2$ and CMe$_2$(C**H$_2$**)$_2$CHAr), 2.20 (dtd, *J* = 13.8, 11.4, 4.1 Hz, 1H, CMe$_2$(C**H$_2$**)$_2$CHAr), 1.93 – 1.72 (m, 2H, CMe$_2$(C**H$_2$**)$_2$CHAr), 1.14 (s, 3H, C**Me$_2$**), 1.04 (s, 3H, C**Me$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) d: 210.4, 136.8, 127.3, 126.6, 121.5, 119.2, 118.9, 111.9, 109.3, 54.7, 47.6, 38.3, 37.2, 32.8, 31.1, 30.7, 26.3; HRMS (ESI-TOF) calculated for $C_{17}H_{22}NO$ $[M+H]^+$ m/z 256.1696, found 256.1697.



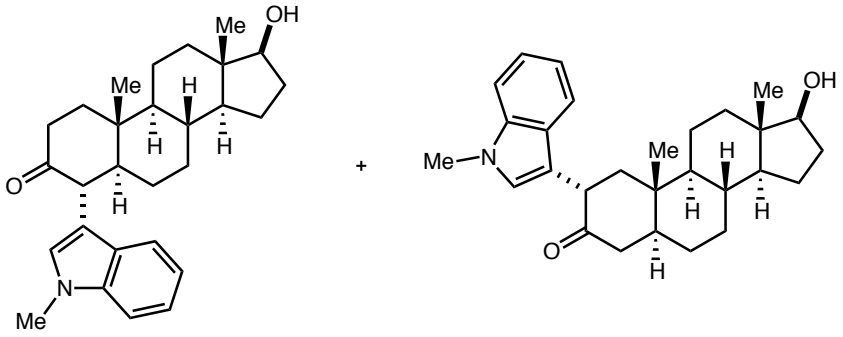
5-methyl-2-(1-methyl-1*H*-indol-3-yl)hexan-3-one and 5-methyl-4-(1-methyl-1*H*-indol-3-yl)hexan-3-one (Table 2, Entry 6). General method A was used using 1-methylindole (125 μL,

1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxy-5-methyl-3-hexanone (341 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–25% EtOAc in hexanes gradient to give a pure mixture of the title compounds in a 2.5:1 ratio by NMR of the 2-substituted product to the 5-substituted product (200.1 mg, 82% yield) as a clear oil. IR (thin film) 2956, 2934, 2871, 1707, 1468, 1368, 1329, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.68 (d, *J* = 8.0 Hz, 1H, Ar**H** minor), 7.60 (d, *J* = 8.1 Hz, 1H, Ar**H** major), 7.36 – 7.29 (m, 1H, Ar**H** major and minor), 7.29 – 7.22 (m, 1H, Ar**H** major and minor), 7.19 – 7.12 (m, 1H, Ar**H** major and minor), 6.95 (s, 1H, Ar**H** minor), 6.94 (s, 1H, Ar**H** major), 4.01 (q, *J* = 7.0 Hz, 1H, COC**H**Ar major), 3.78 (s, 3H, N**Me** major), 3.77 (s, 3H, N**Me** minor), 3.65 (d, *J* = 9.9 Hz, 1H, COC**H**Ar minor), 2.71 – 2.26 (m, 2H major, 3H minor, COC$\mathbf{H_2}$ major, COC$\mathbf{H_2}$ and C**H**Me_2 minor), 2.14 (tt, *J* = 13.4, 6.7 Hz, 1H, C**H**Me_2 major), 1.49 (d, *J* = 7.1 Hz, 3H, CHAr**Me** major), 1.03 (d, *J* = 6.5 Hz, 3H, CH$\mathbf{Me_2}$ minor), 0.98 (t, *J* = 7.3 Hz, 3H, $CH_2C\mathbf{H_3}$ minor), 0.86 (d, *J* = 6.6 Hz, 3H, CH$\mathbf{Me_2}$ major), 0.82 – 0.77 (m, 3H, CH$\mathbf{Me_2}$ major and minor); ^{13}C NMR (125 MHz, $CDCl_3$) d: 211.9, 211.5, 137.0, 127.9, 127.4, 126.9, 126.5, 121.7, 121.6, 119.2, 119.1, 119.1, 118.9, 113.8, 111.4, 109.3, 109.2, 56.9, 49.2, 44.2, 35.8, 32.8, 32.7, 30.6, 24.4, 22.6, 22.3, 21.8, 20.6, 16.9, 7.9; HRMS (ESI-TOF) calculated for $C_{16}H_{22}NO$ $[M+H]^+$ m/z 244.1696, found 244.1698.



7-(1-methyl-1*H*-indol-3-yl)-1,4-dioxaspiro[4.5]decan-8-one (Table 2, Entry 7). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol

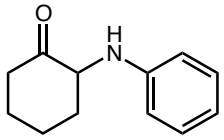
(0.5 mL, 2 M), 8-oxo-1,4-dioxaspiro[4.5]decan-7-yl tosylate (392 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 0–40% EtOAc in hexanes gradient to give pure title compound (268.8 mg, 94% yield) as a clear oil. IR (thin film) 2955, 2884, 1716, 1474, 1114, 1031, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.45 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.32 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.24 (t, *J* = 7.6 Hz, 1H, Ar**H**), 7.12 (t, *J* = 7.5 Hz, 1H, Ar**H**), 7.01 (s, 1H, Ar**H**), 4.32 (t, *J* = 9.7 Hz, 1H, COC**H**Ar), 4.18 – 4.01 (m, 4H, O**CH$_2$CH$_2$**O), 3.77 (s, 3H, N**Me**), 2.99 – 2.84 (m, 1H, COC**H$_2$**), 2.58 (dt, *J* = 14.3, 4.0 Hz, 1H, COC**H$_2$**), 2.45 – 2.36 (m, 2H, CO(C**H$_2$**)$_2$CO$_2$), 2.27 – 2.15 (m, 2H, CO(C**H$_2$**)$_2$CO$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 209.1, 136.8, 127.1, 126.7, 121.6, 119.0, 118.9, 111.0, 109.3, 107.3, 64.8, 64.6, 44.5, 41.7, 38.2, 34.8, 32.7; HRMS (ESI-TOF) calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$ m/z 286.1438, found 286.1436.



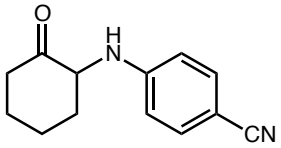
(4*R*,5*S*,8*R*,9*S*,10*R*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethyl-4-(1-methyl-1*H*-indol-3-yl)tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one and (2*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethyl-2-(1-methyl-1*H*-indol-3-yl)tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (Table 4, Entry 8). General method A was used using 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), (2*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-2-yl tosylate (553 mg, 1.2 mmol, 1.2 equiv),

and Et_3N (167 μL, 1.2 mmol, 1.2 equiv) for 12 hours. The crude reaction mixture was subjected to column chromatography using a 0–60% EtOAc in hexanes gradient to give the faster eluting minor 2-substituted product (101.3 mg, 24% yield) and the slower eluting major 4-substituted product (143.6 mg, 34%) both as white solids. Minor slower eluting 2-substituted product: IR (thin film) 3417, 2931, 2868, 1710, 1472, 1446, 1190, 1177, 911, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.40 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.30 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.22 (t, *J* = 7.7 Hz, 1H, Ar**H**), 7.09 (t, *J* = 7.4 Hz, 1H, Ar**H**), 7.02 (s, 1H, Ar**H**), 4.01 (dd, *J* = 13.4, 5.6 Hz, 1H, COC**H**Ar), 3.77 (s, 3H, N**Me**), 3.64 (t, *J* = 8.4 Hz, 1H, C**H**OH), 2.57 (t, *J* = 14.1 Hz, 1H, steroid methine), 2.37 (dd, *J* = 13.2, 6.0 Hz, 1H, steroid methine), 2.29 (dd, *J* = 14.1, 3.7 Hz, 1H, steroid methine), 2.14 – 2.02 (m, 1H, steroid methine), 1.87 – 1.65 (m, 3H, steroid methylene), 1.68 – 1.18 (m, 12H, steroid methylene and methyl), 1.15 – 0.89 (m, 3H, steroid methylene), 0.88 – 0.69 (m, 5H, steroid methylene and methyl); ^{13}C NMR (125 MHz, $CDCl_3$) d: 210.0, 136.8, 127.2, 126.8, 121.5, 119.0, 118.8, 112.0, 109.4, 81.8, 54.0, 50.8, 48.1, 48.1, 45.1, 44.5, 43.0, 36.8, 36.5, 35.3, 32.7, 31.3, 30.4, 28.6, 23.4, 21.1, 12.4, 11.2; HRMS (ESI-TOF) calculated for $C_{28}H_{38}NO_2$ $[M+H]^+$ m/z 420.2897, found 420.2898. Major faster eluting 4-substituted product: IR (thin film) 3205, 2919, 2856, 1705, 1329, 1064, 907, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.40 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.29 (d, *J* = 8.2 Hz, 1H, Ar**H**), 7.20 (t, *J* = 7.8 Hz, 1H, Ar**H**), 7.06 (t, *J* = 7.4 Hz, 1H, Ar**H**), 6.88 (s, 1H, Ar**H**), 3.77 (s, 3H, N**Me**), 3.73 (d, *J* = 12.7 Hz, 1H, COC**H**Ar), 3.63 (t, *J* = 8.6 Hz, 1H, C**H**OH), 2.64 (dt, *J* = 14.2, 7.3 Hz, 1H, steroid methine), 2.60 – 2.52 (m, 1H, steroid methine), 2.18 (dt, *J* = 10.6, 3.9 Hz, 1H, steroid methine), 2.04 (td, *J* = 9.4, 4.7 Hz, 1H, steroid methine), 1.90 – 1.79 (m, 2H, steroid methylene), 1.69 (d, *J* = 16.9 Hz, 1H, steroid methylene), 1.66 – 1.57 (m, 1H, steroid methylene), 1.58 – 1.34 (m, 6H, steroid methylene), 1.29 – 1.18 (m, 4H, steroid methylene and methyl), 1.17 – 1.05 (m, 3H, steroid methylene), 0.92 (ddd,

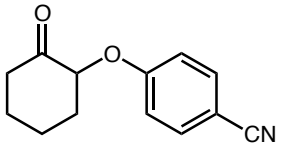
J = 12.7, 10.8, 7.3 Hz, 1H, steroid methylene), 0.86 – 0.73 (m, 4H, steroid methylene and methyl), 0.67 (ddt, *J* = 17.9, 12.4, 8.9 Hz, 1H, steroid methylene); ^{13}C NMR (125 MHz, $CDCl_3$) d: 210.6, 137.0, 128.0, 127.7, 121.3, 119.4, 118.7, 110.1, 109.4, 81.8, 54.3, 52.9, 50.8, 50.0, 39.0, 38.3, 36.8, 36.7, 35.1, 32.8, 31.4, 30.5, 26.6, 23.3, 21.0, 12.5, 11.1; HRMS (ESI-TOF) calculated for $C_{28}H_{38}NO_2$ $[M+H]^+$ m/z 420.2897, found 420.2897.



2-(phenylamino)cyclohexanone (Table 3, Entry 1). General method A was used using aniline (91 μL, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (322 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 10–60% EtOAc in hexanes gradient to give pure title compound (134.4 mg, 71% yield) as a clear oil. IR (thin film) 3384, 2938, 2862, 1711, 1599, 1504, 1297, 1124, 746, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 7.19 (td, *J* = 7.2, 1.8 Hz, 1H, Ar**H**), 6.72 (t, *J* = 7.3 Hz, 1H, Ar**H**), 6.62 (d, *J* = 8.1 Hz, 1H, Ar**H**), 4.91 (bs, 1H, N**H**), 4.02 (dd, *J* = 12.3, 5.8 Hz, 1H, COC**H**Ar), 2.69 (ddd, *J* = 13.1, 5.8, 3.0 Hz, 1H, COC**H$_2$**), 2.60 (ddt, *J* = 13.4, 4.5, 2.3 Hz, 1H, CO**CH$_2$**), 2.44 (tdd, *J* = 13.4, 6.2, 1.5 Hz, 1H, $COCH_2(C$**H$_2$**$)_3$CHAr), 2.18 (ddt, *J* = 12.7, 6.2, 3.0 Hz, 1H, $COCH_2(C$**H$_2$**$)_3$CHAr), 1.99 – 1.90 (m, 1H, $COCH_2(C$**H$_2$**$)_3$CHAr), 1.90 – 1.66 (m, 2H, $COCH_2(C$**H$_2$**$)_3$CHAr), 1.45 (qd, *J* = 12.8, 3.6 Hz, 1H, $COCH_2(C$**H$_2$**$)_3$CHAr); ^{13}C NMR (125 MHz, $CDCl_3$) d: 208.4, 146.4, 129.3, 117.4, 112.9, 61.7, 41.1, 35.7, 28.1, 24.0; HRMS (ESI-TOF) calculated for $C_{12}H_{16}NO$ $[M+H]^+$ m/z 190.1226, found 190.1228.

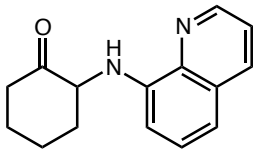


4-((2-oxocyclohexyl)amino)benzonitrile (Table 3, Entry 2). General method A was used using 4-cyanoaniline (118 mg, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (322 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 10–60% EtOAc in hexanes gradient to give pure title compound (163.0 mg, 76% yield) as a clear oil. IR (thin film) 3373, 2941, 2864, 2212, 1715, 1606, 1522, 1174, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.42 (d, *J* = 8.8 Hz, 2H, Ar**H**), 6.56 (d, *J* = 8.8 Hz, 2H, Ar**H**), 5.41 (d, *J* = 5.5 Hz, 1H, N**H**), 4.05 (dtd, *J* = 12.4, 5.6, 1.3 Hz, 1H, COC**H**Ar), 2.71 – 2.57 (m, 2H, COC**H$_2$**), 2.46 (tdd, *J* = 13.5, 6.4, 1.4 Hz, 1H, $COCH_2(CH_2)_3CHAr$), 2.27 – 2.15 (m, 1H, $COCH_2(CH_2)_3CHAr$), 2.02 – 1.91 (m, 1H, $COCH_2(CH_2)_3CHAr$), 1.91 – 1.66 (m, 1H, $COCH_2(CH_2)_3CHAr$), 1.43 (qd, *J* = 12.9, 3.5 Hz, 1H, $COCH_2(CH_2)_3CHAr$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 207.2, 149.4, 133.8, 120.3, 112.5, 98.9, 60.6, 41.0, 34.9, 28.0, 23.8; HRMS (ESI-TOF) calculated for $C_{13}H_{15}N_2O$ $[M+H]^+$ m/z 215.1179, found 215.1177.



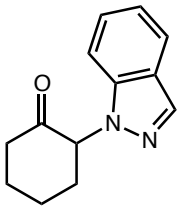
4-((2-oxocyclohexyl)oxy)benzonitrile (Table 3, Entry 4). General method A was used using 4-hydroxyaniline (119 mg, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (322 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 10–50% EtOAc in

hexanes gradient to give pure title compound (157.4 mg, 73% yield) as a clear oil. IR (thin film) 3016, 2970, 2867, 1738, 1601, 1505, 1366, 1217, 1066, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.54 (d, *J* = 8.8 Hz, 2H, Ar**H**), 6.87 (d, *J* = 8.9 Hz, 2H, Ar**H**), 4.73 (dd, *J* = 10.2, 5.3 Hz, 1H, COC**H**Ar), 2.66 – 2.53 (m, 1H, CO(C**H₂**)$_4$CHAr), 2.48 – 2.34 (m, 2H, CO(C**H₂**)$_4$CHAr), 2.14 – 1.95 (m, 3H, CO(C**H₂**)$_4$CHAr), 1.86 – 1.72 (m, 2H, CO(C**H₂**)$_4$CHAr); ^{13}C NMR (125 MHz, $CDCl_3$) d: 206.6, 160.8, 133.9, 119.0, 115.8, 104.3, 80.3, 40.6, 34.2, 27.5, 23.0; HRMS (ESI-TOF) calculated for $C_{13}H_{14}NO_2$ $[M+H]^+$ m/z 216.1019, found 216.1020.

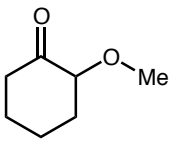


2-(quinolin-8-ylamino)cyclohexanone (Table 3, Entry 3). General method A was used using 8-aminoquinoline (144 mg, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (322 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 20–70% EtOAc in hexanes gradient to give pure title compound (160.3 mg, 67% yield) as a white solid. IR (thin film) 3380, 2938, 2861, 1714, 1574, 1512, 1378, 1124, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H, Ar**H**), 8.04 (dd, *J* = 8.2, 1.7 Hz, 1H, Ar**H**), 7.41 – 7.31 (m, 2H, Ar**H**), 7.11 (d, *J* = 5.9 Hz, 1H, N**H**), 7.06 (d, *J* = 8.2 Hz, 1H, Ar**H**), 6.58 (d, *J* = 7.8 Hz, 1H, Ar**H**), 4.20 (dt, *J* = 11.5, 5.6 Hz, 1H, COC**H**Ar), 2.75 (dt, *J* = 12.5, 3.0 Hz, 1H, CO(C**H₂**)$_4$CHAr), 2.70 – 2.61 (m, 1H, CO(C**H₂**)$_4$CHAr), 2.47 (tdd, *J* = 13.3, 6.1, 1.3 Hz, 1H, CO(C**H₂**)$_4$CHAr), 2.17 (ddt, *J* = 12.8, 6.2, 3.0 Hz, 1H, CO(C**H₂**)$_4$CHAr), 2.05 – 1.94 (m, 1H, CO(C**H₂**)$_4$CHAr), 1.95 – 1.71 (m, 2H, CO(C**H₂**)$_4$CHAr), 1.72 – 1.58 (m, 1H, CO(C**H₂**)$_4$CHAr); ^{13}C NMR (125 MHz, $CDCl_3$) d: 208.0, 147.1, 143.1, 138.3, 135.8, 128.7, 127.4, 121.4, 114.3, 104.6, 61.3, 41.1,

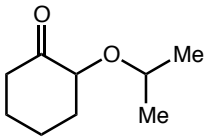
34.9, 28.1, 24.0; HRMS (ESI-TOF) calculated for $C_{15}H_{17}N_2O$ $[M+H]^+$ m/z 241.1335, found 241.1334.



2-(1*H*-indazol-1-yl)cyclohexanone (Table 3, Entry 5). General method A was used using 1*H*-indazol (118 mg, 1.0 mmol, 1.0 equiv), 2,2,2-trifluoroethanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (322 mg, 1.2 mmol, 1.2 equiv), and Et_3N (167 μL, 1.2 mmol, 1.2 equiv). The crude reaction mixture was subjected to column chromatography using a 20–100% EtOAc in hexanes gradient to give pure title compound (132.5 mg, 62% yield) as a white solid. IR (thin film) 2943, 2867, 1725, 1516, 1450, 1125, 756, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d: 7.95 (s, 1H, Ar**H**), 7.71 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.68 (d, *J* = 8.5 Hz, 1H, Ar**H**), 7.29 (t, *J* = 8.0 Hz, 1H, Ar**H**), 7.08 (t, *J* = 8.0 Hz, 1H, Ar**H**), 5.31 (dd, *J* = 13.1, 5.7 Hz, 1H, COC**H**Ar), 2.73 – 2.58 (m, 2H, CO(C**H₂**)$_4$CHAr), 2.53 (td, *J* = 13.6, 6.1 Hz, 1H, CO(C**H₂**)$_4$CHAr), 2.42 (qd, *J* = 12.8, 3.7 Hz, 1H, CO(C**H₂**)$_4$CHAr), 2.20 (dq, *J* = 9.4, 3.0 Hz, 1H, CO(C**H₂**)$_4$CHAr), 2.16 – 2.10 (m, 1H, CO(C**H₂**)$_4$CHAr), 1.99 – 1.76 (m, 2H, CO(C**H₂**)$_4$CHAr); ^{13}C NMR (125 MHz, $CDCl_3$) d: 203.9, 148.2, 126.1, 122.7, 121.7, 121.7, 120.4, 117.4, 70.5, 41.2, 34.6, 27.0, 24.6; HRMS (ESI-TOF) calculated for $C_{13}H_{15}N_2O$ $[M+H]^+$ m/z 215.1179, found 215.1177.

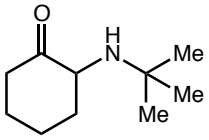


2-methoxycyclohexanone (Table 3, Entry 6). General method B was used using MeOH (122 μL, 3.0 mmol, 3.0 equiv), 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (268 mg, 1.0 mmol, 1.0 equiv), and Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 20–60% Et_2O in pentanes gradient to give pure title compound (91.3 mg, 71% yield) as a clear oil. Spectra match those known for the title compound.[1]

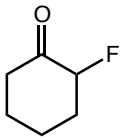


2-*iso*-propoxycyclohexanone (Table 3, Entry 7). General method B was used using ^{i}PrOH (230 μL, 3.0 mmol, 3.0 equiv), 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (268 mg, 1.0 mmol, 1.0 equiv), and Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 20–40% Et_2O in pentanes gradient to give pure title compound (127.7 mg, 82% yield) as a clear oil. IR (thin film) 2937, 2866, 1721, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 3.88 (ddd, J = 9.8, 5.3, 1.3 Hz, 1H, COC**H**OR), 3.64 (hept, J = 6.1 Hz, 1H, C**H**Me_2), 2.61 – 2.49 (m, 1H, CO(C**H$_2$**)$_4$CHOR), 2.32 – 2.21 (m, 1H, CO(C**H$_2$**)$_4$CHOR), 2.17 – 2.05 (m, 1H, CO(C**H$_2$**)$_4$CHOR), 1.99 – 1.87 (m, 2H, CO(C**H$_2$**)$_4$CHOR), 1.84 – 1.58 (m, 3H, CO(C**H$_2$**)$_4$CHOR), 1.20 (d, J = 6.3 Hz, 3H, CH**Me$_2$**), 1.13 (d, J = 6.2 Hz, 3H, CH**Me$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) d: 210.8, 80.2, 71.0, 40.5, 35.1, 27.7, 23.0, 22.8, 21.6; HRMS (ESI-TOF) calculated for $C_9H_{16}NaO_2$ $[M+Na]^+$ m/z 179.1043, found 179.1043.

[1] Winkler, C. K.; Stueckler, C.; Mueller, N. J.; Pressnitz, D.; Faber, K. *Euro. J. Org. Chem.* **2010**, *33*, 6354.

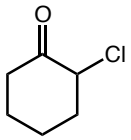


2-*tert*-butylaminocyclohexanone (Table 3, Entry 8). General method B was used using $^{t}BuNH_2$ (315 μL, 3.0 mmol, 3.0 equiv), 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (268 mg, 1.0 mmol, 1.0 equiv), and Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 50–100% EtOAc containing 1% Et_3N in hexanes gradient to give pure title compound (118.7 mg, 70% yield) as a clear oil. IR (thin film) 3309, 2956, 2864, 1707, 1363, 1231, 1121, 714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 3.27 (ddd, *J* = 12.3, 6.0, 1.4 Hz, 1H, COC**H**NHR), 2.98 (bs, 1H, N**H**), 2.57 – 2.46 (m, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 2.32 (tdd, *J* = 13.4, 6.2, 1.4 Hz, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 2.18 (ddd, *J* = 13.0, 6.1, 3.1 Hz, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 2.05 (ddt, *J* = 12.7, 6.3, 3.1 Hz, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 1.92 – 1.79 (m, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 1.70 (qt, *J* = 13.1, 3.4 Hz, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 1.64 – 1.52 (m, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 1.45 (qd, *J* = 12.8, 3.7 Hz, 1H, CO(C$\mathbf{H_2}$)$_4$CHNHR), 1.02 (s, 9H, C$\mathbf{Me_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 211.4, 60.9, 50.6, 41.4, 39.5, 29.2, 27.9, 24.8; HRMS (ESI-TOF) calculated for $C_{10}H_{20}NO$ $[M+H]^+$ m/z 170.1539, found 170.1538.



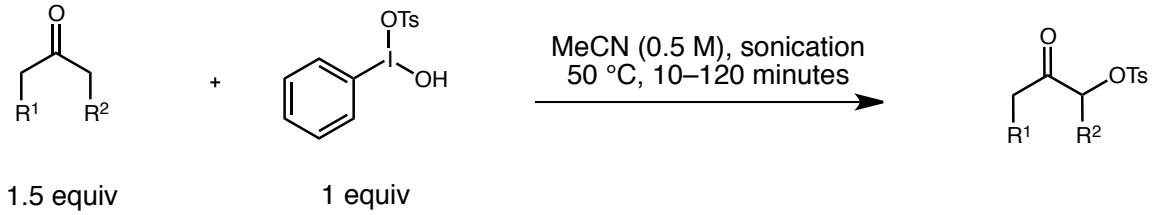
2-fluorocyclohexanone (Table 3, Entry 9). General method C was used using CsF (304 mg, 2.0 mmol, 2.0 equiv), 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (268 mg, 1.0 mmol, 1.0 equiv), fluorotrimethylsilane (23 mg, 0.25 mmol,

0.25 equiv), and Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 20–60% Et_2O in pentanes gradient to give pure title compound (72.3 mg, 62% yield) as a clear oil. Spectra match those known for the title compound.[2]



2-chlorocyclohexanone (Table 3, Entry 10). General method C was used using CsCl (337 mg, 2.0 mmol, 2.0 equiv), 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL, 2 M), 2-tosyloxycyclohexanone (268 mg, 1.0 mmol, 1.0 equiv), chlorotrimethylsilane (32 μL, 0.25 mmol, 0.25 equiv), and Et_3N (139 μL, 1.0 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 20–60% Et_2O in pentanes gradient to give pure title compound (112.7 mg, 85% yield) as a clear oil. Spectra match those known for the title compound.[3]

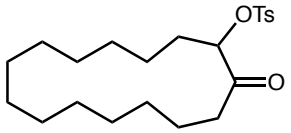
III. Synthesis of Ketone Starting Materials



General Method D for the Synthesis of Unknown α-Tosyloxy Ketones

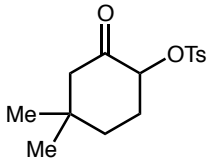
[2] Billings, S. B.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 5171.
[3] Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507.

The following procedure is adapted from the work of Tuncay et al.[4] To the ketone (15.3 mmol, 1.5 equiv) desolved in MeCN (20 mL, 0.5 M) was added [Hydroxy(tosyloxy)iodo]benzene (4 g, 10.2 mmol, 1 equiv) and the heterogeneous suspension was sonicated at 50 °C until a homogeneous solution was noted. The MeCN was removed under reduced pressure and the mixture was immediately subjected to purification on a 100 g Biotage™ column using the noted solvent gradient.

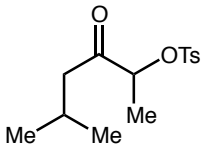


2-tosyloxycyclopentadecanone. General method D was used using cyclopentadecanone (3.43 g, 15.3 mmol, 1.5 equiv), MeCN (20 mL, 0.5 M), and [Hydroxy(tosyloxy)iodo]benzene (4.0 g, 10.2 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 0–60% EtOAc in hexanes gradient to give pure title compound (2.35 g, 58% yield) as a white solid. IR (thin film) 2927, 2857, 1720, 1367, 1190, 1173, 813, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 7.79 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.35 (d, *J* = 8.1 Hz, 2H, Ar**H**), 4.69 (dd, *J* = 6.6, 4.9 Hz, 1H, COC**H**OTs), 2.69 (ddd, *J* = 17.9, 7.9, 6.0 Hz, 1H, (C**H₂**)$_{13}$), 2.45 (s, 3H, Ar**Me**), 2.43 – 2.29 (m, 1H, (C**H₂**)$_{13}$), 1.84 – 1.60 (m, 3H, (C**H₂**)$_{13}$), 1.53 (dt, *J* = 13.5, 6.4 Hz, 1H, (C**H₂**)$_{13}$), 1.40 – 1.14 (m, 10H, (C**H₂**)$_{13}$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 207.5, 145.2, 133.0, 130.0, 127.8, 84.1, 37.6, 31.4, 27.2, 26.9, 26.5, 26.4, 26.4, 26.3, 26.1, 26.0, 25.8, 22.4, 21.7, 21.7; HRMS (ESI-TOF) calculated for $C_{22}H_{35}O_4S$ $[M+H]^+$ m/z 395.2251, found 395.2255.

[4] Tuncay, A.; Dustman, J. A.; Fisher, G.; Tuncay, C. I.; Suslick, K. S. *Tetrahedron Lett.* **1992**, *33*, 7647.

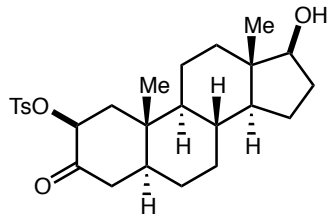


2-tosyloxy-5,5-dimethylcyclohexanone. General method D was used using 3,3-dimethylcyclohexanone (1.9 g, 15.3 mmol, 1.5 equiv), MeCN (20 mL, 0.5 M), and [Hydroxy(tosyloxy)iodo]benzene (4.0 g, 10.2 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 0–60% EtOAc in hexanes gradient to give pure title compound (1.06 g, 35% yield) as a white solid. IR (thin film) 2957, 2872, 1734, 1357, 1173, 1019, 836, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 7.83 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.33 (d, *J* = 8.0 Hz, 2H, Ar**H**), 4.87 (dd, *J* = 10.9, 6.4 Hz, 1H, COC**H**OTs), 2.44 (s, 3H, Ar**Me**), 2.32 – 2.17 (m, 3H, COC$\mathbf{H_2}$, and $CMe_2(C\mathbf{H_2})_2CHOTs$), 2.09 – 1.95 (m, 1H, $CMe_2(C\mathbf{H_2})_2CHOTs$), 1.82 – 1.60 (m, 2H, $CMe_2(C\mathbf{H_2})_2CHOTs$), 1.03 (s, 3H, C$\mathbf{Me_2}$), 0.91 (s, 3H, C$\mathbf{Me_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) d: 202.3, 144.9, 133.5, 129.7, 127.9, 81.3, 53.1, 36.6, 35.9, 30.4, 29.9, 25.8, 21.7; HRMS (ESI-TOF) calculated for $C_{15}H_{21}O_4S$ $[M+H]^+$ m/z 297.1155, found 297.1154.



2-tosyloxy-5-methyl-3-hexanone. General method D was used using 5-methyl-3-hexanone (1.74 g, 15.3 mmol, 1.5 equiv), MeCN (20 mL, 0.5 M), and [Hydroxy(tosyloxy)iodo]benzene (4.0 g, 10.2 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 0–40% EtOAc in hexanes gradient to give pure title compound (1.23 g, 42% yield) as a white solid. IR (thin film) 2960, 2873, 1722, 1364, 1176, 910, 814, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 7.80 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.36 (d, *J* = 8.1 Hz, 2H, Ar**H**), 4.76

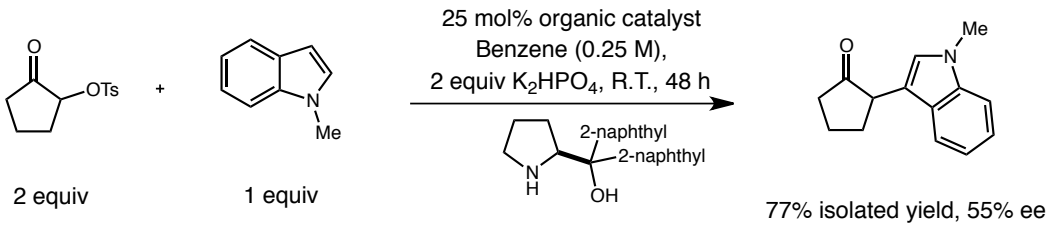
(q, *J* = 7.0 Hz, 1H, COC**H**OTs), 2.50 – 2.40 (m, 4H, Ar**Me** and COC**H₂**), 2.40 – 2.32 (m, 1H, COC**H₂**), 2.10 (dp, *J* = 13.4, 6.7 Hz, 1H, C**H**Me₂), 1.33 (d, *J* = 7.1 Hz, 3H, CHOTs**Me**), 0.86 (dd, *J* = 6.8, 2.1 Hz, 6H, CH**Me₂**); ^{13}C NMR (125 MHz, $CDCl_3$) d: 206.4, 145.3, 133.1, 130.0, 127.8, 80.7, 46.5, 23.5, 22.4, 21.6, 17.3; HRMS (ESI-TOF) calculated for $C_{14}H_{21}O_4S$ $[M+H]^+$ m/z 285.1155, found 285.1153.



(2*S*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethyl-3-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-2-yl 4-methylbenzenesulfonate. General method D was used using (5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (4.44 g, 15.3 mmol, 1.5 equiv), MeCN (20 mL, 0.5 M), and [Hydroxy(tosyloxy)iodo]benzene (4.0 g, 10.2 mmol, 1.0 equiv). The crude reaction mixture was subjected to column chromatography using a 0–60% EtOAc in hexanes gradient to give impure title compound (2.96 g, 63% yield) as a 5:1 mixture of epimers at the OTs position as a white solid. IR (thin film) 3438, 2929, 2870, 1732, 1361, 1175, 908, 726, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d: 7.76 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.32 (d, *J* = 8.1 Hz, 2H, Ar**H**), 4.79 (dd, *J* = 6.7, 5.0 Hz, 1H, COC**H**OTs), 3.60 (t, *J* = 8.4 Hz, 1H, C**H**OH), 2.56 – 2.39 (m, 4H, steroid methine and Ar**Me**), 2.19 – 1.92 (m, 3H, steroid methine), 1.93 – 1.75 (m, 2H, steroid methylene), 1.76 – 1.61 (m, 2H, steroid methylene), 1.62 – 1.25 (m, 7H, steroid methylene), 1.06 – 0.78 (m, 6H, steroid methylene and methyl), 0.79 – 0.64 (m, 5H, steroid methylene and methyl); d: 204.5, 144.9, 132.8, 129.6, 127.7, 81.4, 80.5, 54.4, 53.4, 50.2, 47.1, 44.7, 42.7, 42.7,

41.6, 37.3, 36.2, 36.1, 34.7, 29.6, 23.0, 21.5, 14.0, 11.0; HRMS (ESI-TOF) calculated for $C_{26}H_{37}O_5S$ $[M+H]^+$ m/z 461.2356, found 461.2353.

IV. Enantioselective Synthesis of 2-(1-methyl-1*H*-indol-3-yl)cyclopentanone



To an 8 mL vial equipped with a magnetic stir bar and screw-top PIFE septa was added 1-methylindole (125 μL, 1.0 mmol, 1.0 equiv) and Benzene (4.0 mL, 0.25 M). To this mixture was added 2-tosyloxycyclopentanone (509 mg, 2.0 mmol, 2.0 equiv), potassium hydrogenphosphate (348 mg, 2.0 mmol, 2.0 equiv), and (*S*)-di(naphthalen-2-yl)(pyrrolidin-2-yl)methanol (88 mg, 0.25 mmol, 0.25 equiv). The reaction mixture was then stirred at room temperature for 48 hours. The crude reaction mixture was loaded directly onto a 10 g Biotage™ column with DCM as a rinsing solvent after removal of the solid precipitates by filtration. The 10 g column was then fit on top of a pre-equilibrated 50 g Biotage™ column and eluted with 0–30% EtOAc in hexanes to give pure product (164.9 mg, 77% yield, 55% ee) as a clear oil. Spectra for the title compound match those reported above. The enantiomeric excess was determined using High Performance Liquid Chromatography (HPLC), which was performed on a Hewlett-Packard 1100 Series chromatograph using a chiral OD column (25 cm) and guard column (5 cm). HPLC analysis (OD, 6% EtOH/hexanes, 1.0 mL/min, 254 nm) indicates 55% ee: t_R(major) = 25.90 minutes, t_R(minor) = 20.67 minutes. The optical rotation was measured on a Jasco P-1010 polarimeter with $[a]_D$ value reported in degrees; concentration (c) is in g/100 mL. $[\alpha]_D^{21}$ = –43.8 (c = 1.00, $CHCl_3$).