Development of the Direct Suzuki-Miyaura Cross-Coupling of Primary *B*-Alkyl MIDA-Boronates and Aryl Bromides

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General Information:

Tetrahydrofuran (THF) was purified by distillation from sodium/benzophenone ketyl radical under an atmosphere of nitrogen. Acetonitrile (MeCN) was purified by distillation from 3Å molecular sieves (3Å MS). Dichloromethane, methanol (MeOH) and triethylamine (Et_3N) were purified by distillation from CaH_2 respectively. Diethyl ether (Et_2O), toluene, dimethyl formamide (DMF), was purified through a solvent purification system.[1] All other reagents were purchased from commercial sources used as received.

Chromatography:

Flash column chromatography was carried out using Silicycle 230-400 mesh silica gel. Thin-layer chromatography (TLC) was performed on Macherey Nagel pre-coated glass backed TLC plates (SIL G/UV254, 0.25 mm) and visualized using a UV lamp (254 nm) $KMnO_4$, ninhydrin, or I_2 stain in case of no UV activity.

Nuclear Magnetic Resonance Spectroscopy:

Proton (^{1}H-NMR), carbon (^{13}C-NMR) and 2D NMR experiments were performed on Bruker 400 MHz or Varian 300, 400, or 500 MHz spectrometers. NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (CDCl3, δ = 7.26, DMSO-d6, δ = 2.49, acetone-d6 δ = 2.05). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd= doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) were referenced to carbon resonances in the NMR solvent (CDCl3, δ = 77.0; DMSO-*d6*, δ = 39.5, center line, acetone-*d6*= 206.2 centre line, 29.8). High-Resolution Mass Spectra was obtained at the University of Toronto mass spectrometry centre.

Mass Spectrometry

[1] Pangborn, A.B., Giardello, M.A., Grubbs, R.H. *Organometallics* **1996**, *5*, 1518-1520; Alaimo, Peter J.; Peters, David W.; Arnold, John; Bergman, Robert G.; *J. Chem. Ed.* **2001**, *78*, 64-66

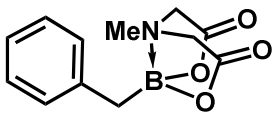
High resolution mass spectra were obtained on a VG 70- 250S (double focusing) mass spectrometer at 70 eV or on an ABI/Sciex Qstar mass spectrometer with ESI source, MS/MS and accurate mass capabilities.

Gas Chromatography

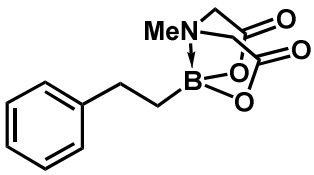
Gas-phase chromatography (GC) was performed on a Hewlett Packard HP-6890 series instrument using a DB-35 column (crosslinked 35% phenyl methylsiloxane, 30 m x 0.32 mm x 0.25 μm film thickness). Oven was heated at 160 °C for 3 min followed by a temperature gradient of 60 °C/min to 240 °C followed by being held at 240 °C for 5 min. Inlet temperature and pressure were 250 °C and 4.88 psi respectively, with a split ratio of 50:1. Hydrogen was the carrier gas.

Internal standard was napthalene (T = 3.08 min).

Commerically Available Primary Alkyl MIDA Boronates Used



1
Benzyl MIDA Boronate



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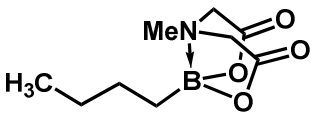
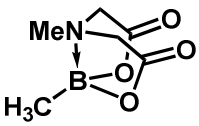
Phenethyl MIDA Boronate



16
Butyl MIDA Boronate



17
Methyl MIDA Boronate

Synthesis of Primary Alkyl MIDA Boronates

Procedure A

To an oven dried, stir bar quipped vial was added alkene followed by the dropwise addition of neat catechol borane. The reaction flask was then warmed to 65 °C for 24 hrs. Upon complete consumption of starting alkene the reaction was removed from the reaction block and allowed to cool to room temperature. Then distilled water (10 mL) was added to the reaction mixture and allowed to stir for 2-3 hrs at which time the solid precipitate was filtered to yield the crude boronic acid.

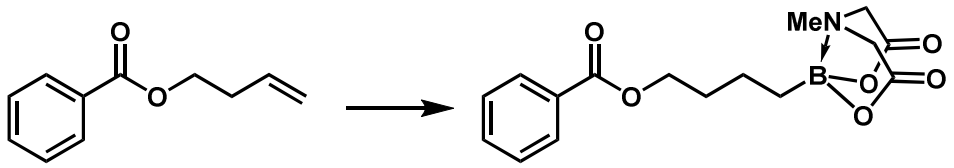
The crude boronic acid was then dissolved in DMF (0.3 M) and *N*-methyliminodiacetic acid (1.0 equiv) was added. The mixture was warmed to 80 °C for 24 hours. The reaction was then removed from heat and concentrated *in vacuo*. To the residue was added 50 mL H_2O, 50 mL sat. $NaHCO_3$ and 100 mL EtOAc and the organic was the separated. The aqueous layer was the extracted 5 x 75 mL EtOAc. The combined organics were washed with brine, dried over $NaSO_4$ and concentrated to yield crude MIDA boronate. The crude MIDA boronate was then purified via SiO_2 using hexanes:acetone to yield pure primary alkyl MIDA boronate as a white solid.[2]

Procedure B

[2] Grob, J. E.; Nunez, J.; Dechantsreiter, M. A; Hamann, L. G. *J. Org. Chem.* **2011**, *76*, 4930–40.

A reaction flask was equipped with a magnetic stir-bar and reflux condenser and to it was added terminal alkene (10 mmol, 1.0 equiv) and DCM (10 mL). HBBr2·SMe2 (20 mmol, 1.0 M in DCM, 2.0 equiv) was then added dropwise along the wall of the flask and upon complete addition the mixture was warmed to reflux for 24 hours. The reaction was then removed from heat and cooled to 0 °C in an ice-water bath. The cooled reaction mixture was then transferred to a pre-cooled 0 °C mixture of Et_2O (25 mL) and H_2O (5 mL). The resulting mixture was allowed to stir for 30 minutes and then the organic layer was separated. The aqueous layer was subsequently extracted with 5 x 25 mL of Et_2O. The combined organics were then washed with H_2O (50 mL). The organics were then dried ($MgSO_4$), filtered and concentrated to yield crude boronic acid.[3]

The crude boronic acid was then dissolved in DMF (0.3 M) and *N*-methyliminodiacetic acid (1.0 equiv) was added. The mixture was warmed to 80 °C for 24 hours. The reaction was then removed from heat and concentrated *in vacuo*. To the residue was added 50 mL H_2O, 50 mL sat. $NaHCO_3$ and 100 mL EtOAc and the organic was the separated. The aqueous layer was the extracted 5 x 75 mL EtOAc. The combined organics were washed with brine, dried over $NaSO_4$ and concentrated to yield crude MIDA boronate. The crude MIDA boronate was then purified via SiO_2 using hexanes:acetone to yield pure primary alkyl MIDA boronate as a white solid.



(4-(benzoyloxy)butyl)MIDA boronate (**32**)

26% over two steps, white solid

^{1}H NMR (400 MHz, Acetonitrile-d_3)

δ 8.14 – 7.99 (m, 2H), 7.71 – 7.62 (m, 1H), 7.59 – 7.47 (m, 2H), 4.35 (t, *J* = 6.6 Hz, 2H), 3.96 (d, *J* = 16.9 Hz, 2H), 3.80 (d, *J* = 16.9 Hz, 2H), 2.88 (s, 3H), 1.89 – 1.76 (m, 2H), 1.52 (dtd, *J* = 9.1, 7.8, 5.7 Hz, 2H), 0.76 – 0.63 (m, 2H)

[3] Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626–31.

^{13}C NMR (101 MHz, Acetonitrile-d_3)

δ 167.8, 165.9, 132.5, 130.3, 128.8, 128.2, 64.3, 61.4, 45.2, 31.0, 20.1

^{11}B NMR (128 MHz, Acetonitrile-d_3)

δ 13.1

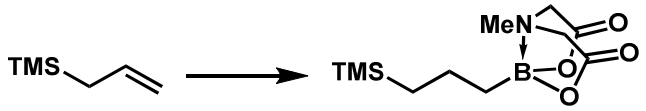
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{16}H_{20}BNO_6$= 334.1461

m/z found = 334.1462

TLC (Hexanes:acetone 1:1)

R_f = 0.28



(3-(trimethylsilyl)propyl)MIDA boronate (**33**)

60% yield over two steps, white solid

^{1}H NMR (400 MHz, Acetonitrile-d_3)

δ 3.93 (d, *J* = 16.9 Hz, 2H), 3.77 (d, *J* = 16.9 Hz, 2H), 2.85 (s, 3H), 1.51 – 1.28 (m, 2H), 0.72 – 0.51 (m, 4H), 0.00 (s, 9H)

^{13}C NMR (101 MHz, Acetonitrile-d_3)

δ 168.1, 61.5, 45.4, 19.9, 18.4, -2.6

^{11}B NMR (128 MHz, Acetonitrile-d_3)

δ 13.0

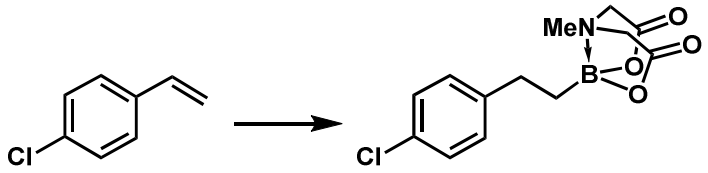
HRMS [DART] ($M+Na^+$)

m/z calculated for $C_{11}H_{22}BNO_4NaSi$ = 294.103

m/z found = 294.1309

TLC (Hexanes:acetone 3:4)

R_f = 0.46



(4-chlorophenethyl)MIDA boronate (**34**)

66% over two steps, white solid

^{1}H NMR (400 MHz, Acetonitrile-d_3)

δ 7.31 – 7.14 (m, 2H), 6.96 – 6.82 (m, 2H), 3.98 (d, *J* = 16.9 Hz, 2H), 3.82 (d, *J* = 16.9 Hz, 2H), 3.78 (s, 3H), 2.89 (s, 3H), 2.81 – 2.53 (m, 2H), 1.07 – 0.78 (m, 2H)

^{13}C NMR (101 MHz, Acetonitrile-d_3)

δ 168.7, 158.2, 137.9, 129.3, 114.2, 62.3, 55.3, 46.2, 29.7

^{11}B NMR (128 MHz, Acetonitrile-d_3)

δ 13.0

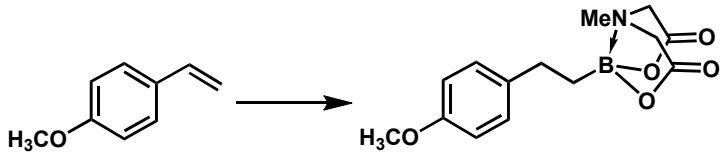
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{14}H_{22}BN_2O_5$= 295.0892

m/z found = 295.0893

TLC (Hexanes:acetone 4:3)

R_f = 0.29



(4-methoxyphenethyl) MIDA boronate (**35**)

^{1}H NMR (400 MHz, Acetonitrile-d_3)

δ 7.26 – 7.10 (m, 2H), 6.98 – 6.80 (m, 2H), 3.98 (d, J = 16.9 Hz, 2H), 3.82 (d, J = 16.9 Hz, 2H), 3.78 (s, 3H), 2.89 (s, 3H), 2.65 – 2.56 (m, 2H), 0.99 – 0.86 (m, 2H)

^{13}C NMR (101 MHz, Acetonitrile-d_3)

δ 169.1, 158.6, 138.3, 129.7, 114.6, 62.8, 55.8, 46.6, 30.2

^{11}B NMR (128 MHz, Acetonitrile-d_3)

δ 13.0

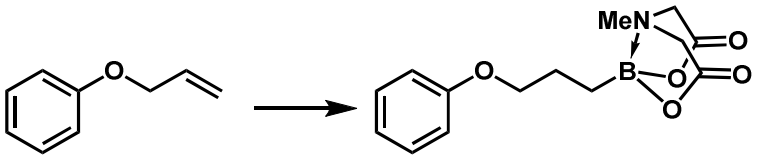
HRMS [DART] ($M+NH_4^+$)

m/z calculated for $C_{14}H_{22}BN_2O_5$= 309.1621

m/z found = 309.1627

TLC (Hexanes:acetone 1:1)

R_f = 0.54



(3-phenoxypropyl)MIDA boronate (**36**)

31% yield over two steps, white solid

^{1}H NMR (400 MHz, Acetonitrile-d_3)

δ 7.36 – 7.27 (m, 2H), 6.99 – 6.92 (m, 3H), 4.04 – 3.94 (m, 4H), 3.83 (d, J = 17.0 Hz, 2H), 2.91 (s, 3H), 1.86 – 1.76 (m, 3H), 0.86 – 0.67 (m, 2H)

^{13}C NMR (101 MHz, Acetone)

δ 168.76, 130.20, 121.0, 115.3, 70.7, 62.7, 46.3, 25.0

^{11}B NMR (128 MHz, Acetonitrile-d_3)

δ 12.9

HRMS [DART] ($M+H^+$)

m/z calculated for $C_{14}H_{19}BNO_5$= 292.1356

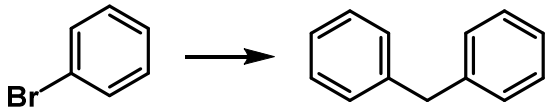
m/z found = 292.1357

TLC (Hexanes:acetone 1:1)

R_f = 0.62

General Method for the Suzuki-Miyaura Cross Coupling between *B*-alkyl-MIDA-boronates and Aryl Bromides

To a Teflon lined 2 dram screw-top vial equipped with a magnetic stir bar was added *B*-alkyl-MIDA-boronate (4.5 mmol, 1.1 equiv.) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (**3**) (0.4 mmol, 10 mol%). The vial was evacuated under vacuum and a nitrogen atmosphere was introduced. Freshly distilled THF (4.0 mL, 0.1 M) was added followed by aryl bromide (4.0 mmol, 1.0 equiv.) and nitrogen (N_2)-sparged and distilled H_2O (0.8 mL). The reaction was stirred at room temperature for approximately 5 minutes followed by addition of K_2CO_3 (12.0 mmol, 6.0 equiv). The reaction was sealed with a screw-cap and placed in an 80 °C reaction block for the required time as judged by GC analysis (24-72 h). Upon starting material consumption the reaction vial was cooled to room temperature and 2 mL H_2O was added. The aqueous mixture was extracted 3x with Et_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The coupled products were purified via silica gel chromatography using pentanes:Et_2O as eluent.



Diphenylmethane (**2**)

GC retention time **bromobenzene**: 2.08 min

77% yield, clear oil

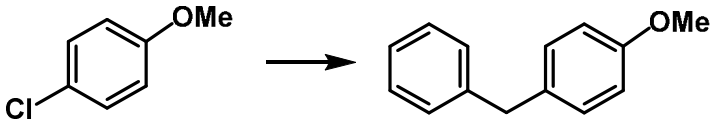
Spectra matched literature reports

^{1}H NMR (399 MHz, Chloroform-*d*)

δ 7.35 – 7.29 (m, 4H), 7.27 – 7.20 (m, 6H), 4.02 (s, 4H)

^{13}C NMR (100 MHz, Chloroform-*d*)

δ 141.1, 128.9, 128.4, 126.0, 41.9



1-benzyl-4-methoxybenzene (**4**)

GC retention time of **4-bromoanisole**: 3.07 min

Spectra matched literature reports:

Amatore, M.; Gosmini, C. *Chem. Commun.* **2008**, 5019-5021

74% yield (95% pure), clear oil

^{1}H NMR (399 MHz, Chloroform-*d*)

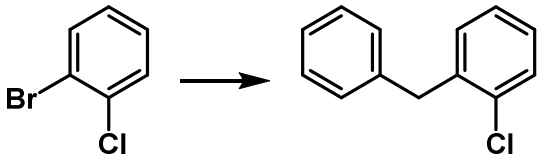
δ 7.31 – 7.24 (m, 3H), 7.22 – 7.15 (m, 3H), 7.13 – 7.08 (m, 2H), 6.92 – 6.75 (m, 2H), 3.93 (s, 2H), 3.78 (s, 3H)

^{13}C NMR (75 MHz, Chloroform-*d*)

δ 133.2, 129.8, 128.9, 128.7, 128.4, 125.9, 113.8, 109.9, 55.2, 41.0

TLC (Hexanes:Et_2O 1:1)

R_f = 0.51



1-benzyl-2-chlorobenzene (**5**)

GC retention time of **2-chloro-bromobenezene**: 2.75 min

85% yield, clear oil

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 7.41 – 7.34 (m, 1H), 7.34 – 7.22 (m, 2H), 7.24 – 7.11 (m, 5H), 4.11 (s, 2H)

^{13}C NMR (75 MHz, Chloroform-*d*)

δ 139.4, 138.6, 134.2, 130.9, 129.5, 128.9, 128.4, 127.6, 126.7, 126.2, 39.1

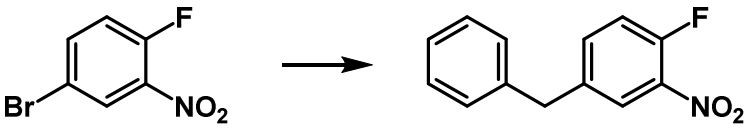
HRMS [DART] (M^+)

m/z calculated for $C_{13}H_{11}Cl$= 202.0549

m/z found = 202.0549

TLC (Hexanes:Et_2O 1:1)

R_f = 0.47



4-benzyl-1-fluoro-2-nitrobenzene (**6**)

84%, yellow oil

GC retention time of **4-bromo-1-fluoro-2-nitrobenzene**: 3.89 min

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.87 (ddt, *J* = 7.1, 2.3, 0.7 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.36 – 7.31 (m, 2H), 7.28 – 7.24 (m, 1H), 7.22 – 7.15 (m, 3H), 4.03 (d, *J* = 1.0 Hz, 2H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 157.0, 154.5 (d, $^{1}J_{CF}$= 263.3 Hz), 139.0, 138.2 (d, $^{1}J_{CF}$= 4.3 Hz), 135.7 (d, $^{1}J_{CF}$= 8.3 Hz), 128.8, 128.6, 126.8, 125.9, (d, $^{1}J_{CF}$= 2.9 Hz), 118.4 (d, $^{1}J_{CF}$= 20.8 Hz), 40.7

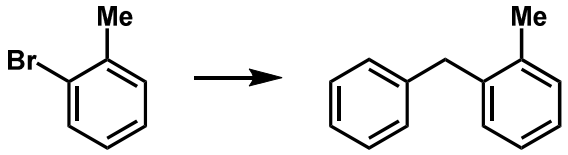
HRMS [TOF] (M^{+})

m/z calculated for = 231.0696

m/z found = 231.0695

TLC (Hexanes:Et_2O 1:1)

R_f = 0.32



1-benzyl-2-methylbenzene (**7**)

GC retention time of **2-bromotoluene**: 2.28 min

Spectra matched literature reports:

Krueger, T.; Vorndran, K.; Linker, T. *Chem. Eur. J.* **2009**, *15*, 12082-12091.

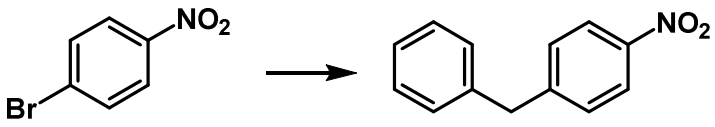
77% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 7.16 – 7.09 (m, 4H), 4.00 (s, 2H), 2.26 (s, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 140.3, 138.9, 136.6, 130.2, 129.9, 128.7, 128.3, 126.4, 125.9, 125.8, 39.4, 19.6



1-benzyl-4-nitrobenzene (**8**)

GC retention time **4-nitrobromobenzene**: 4.05 min

68 % yield, yellow oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 8.21 – 8.05 (m, 2H), 7.37 – 7.29 (m, 4H), 7.28 – 7.23 (m, 1H), 7.20 – 7.15 (m, 2H), 4.08 (s, 2H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 148.8, 146.5, 139.1, 129.6, 128.9, 128.8, 126.7, 123.7, 41.7

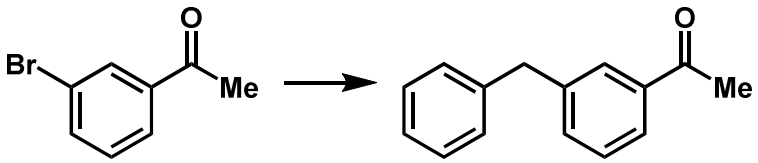
HRMS [DART] (M^+)

m/z calculated for $C_{13}H_{12}NO_2$= 214.0868

m/z found = 214.0865

TLC (Hexanes:Et_2O 1:1)

R_f = 0.5



1-(3-benzylphenyl)ethan-1-one (**9**)

GC retention time of **3-bromoacetophenone:** 3.35 min

90% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.84 – 7.79 (m, 2H), 7.42 – 7.38 (m, 2H), 7.34 – 7.29 (m, 2H), 7.25 – 7.22 (m, 1H), 7.22 – 7.17 (m, 2H), 4.06 (s, 2H), 2.59 (s, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 198.2, 141.6, 140.3, 137.3, 133.7, 128.8, 128.8, 128.7, 128.6, 128.6, 126.3, 41.7, 26.7

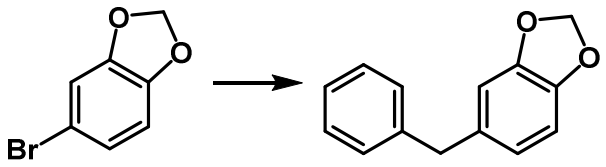
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{15}H_{15}O$= 211.1122

m/z found = 211.1125

TLC (Hexanes:Et_2O 5:1)

R_f = 0.21



5-benzylbenzo[d][1,3]dioxole (**10**)

GC retention time of **5-bromobenzo[d][1,3]dioxole**: 3.71 min

72% yield, clear oil

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 7.29 (tt, *J* = 6.8, 1.2 Hz, 2H), 7.24 – 7.15 (m, 3H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.67 (dddt, *J* = 3.8, 2.1, 1.4, 0.7 Hz, 2H), 5.91 (d, *J* = 0.6 Hz, 2H), 3.90 (d, *J* = 0.9 Hz, 2H)

^{13}C NMR (100 MHz, Chloroform-*d*)

δ 147.6, 145.8, 141.2, 134.9, 128.7, 128.4, 126.0, 121.7, 109.4, 108.1, 100.8, 41.6

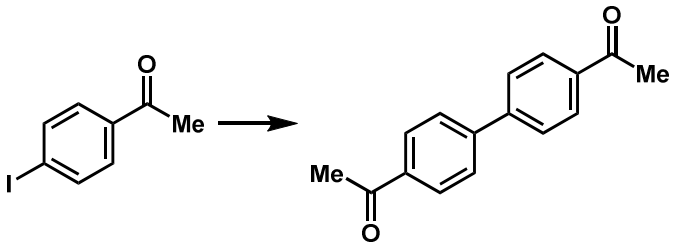
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{14}H_{13}O_2$ = 213.09155

m/z found = 213.0909

TLC (Hexanes:Et_2O 2:1)

R_f = 0.29



1,1'-([1,1'-biphenyl]-4,4'-diyl)bis(ethan-1-one) (**11**)

GC retention time of **4-iodoacetophenone**: 4.78 min

41% yield, opaque residue

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 8.15 – 7.96 (m, 4H), 7.77 – 7.68 (m, 4H), 2.65 (s, 6H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 197.5, 144.3, 136.5, 128.9, 127.4, 26.7

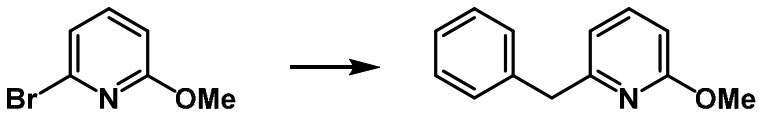
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{16}H_{15}O_2$= 239.1072

m/z found = 239.1067

TLC (Hexanes:Et_2O 1:1)

R_f = 0.19



2-benzyl-6-methoxypyridine (**12**)

GC retention time of **2-bromo-6-methoxypyridine** =2.824 min

52% yield, clear residue

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 7.44 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.25 – 7.18 (m, 1H), 6.68 – 6.61 (m, 1H), 6.54 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.03 (s, 2H), 3.92 (s, 3H)

^{13}C NMR (101 MHz, Chloroform-*d*)

δ 163.6, 158.7, 139.7, 138.9, 129.2, 128.3, 126.2, 115.4, 107.7, 53.2, 44.3

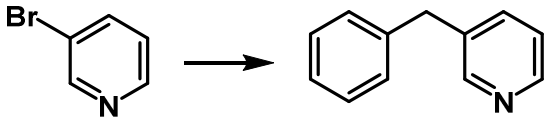
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{13}H_{14}NO$ = 200.1062

m/z found = 200.1065

TLC (Hexanes:EtOAc 5:1)

R_f = 0.23



3-benzylpyridine (**13**)

GC retention time **3-bromopyridine**: 2.24 min

78% yield (approx. 85% pure), clear oil

Spectra matched literature reports

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 8.54 – 8.48 (m, 1H), 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.47 (dddd, *J* = 7.8, 2.3, 1.6, 0.7 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.26 – 7.15 (m, 4H), 3.99 (s, 2H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 150.0, 147.5, 139.7, 136.5, 136.3, 128.8, 128.6, 126.4, 123.4, 39.0

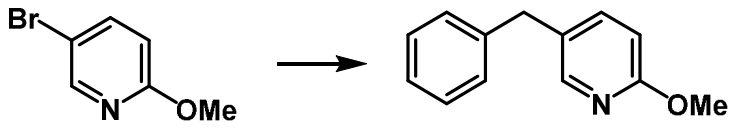
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{12}H_{12}N$= 170.0967

m/z found = 170.0966

TLC (Hexanes:Et_2O 1:4)

R_f = 0.28



5-benzyl-2-methoxypyridine (**14**)

GC retention time of **5-bromo-2-methoxypyridine**: 2.64 min

52%, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 8.03 (dq, *J* = 2.3, 0.7 Hz, 1H), 7.36 (ddt, *J* = 8.4, 2.5, 0.5 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.24 – 7.15 (m, 1H), 6.67 (ddt, *J* = 8.5, 0.3 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 2H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 162.8, 146.3, 140.5, 139.3, 129.1, 128.6, 128.5, 126.2, 110.7, 53.3, 38.1

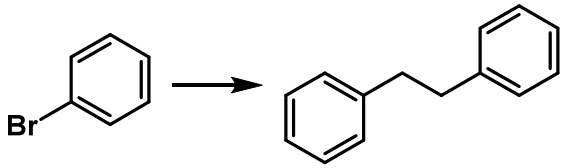
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{13}H_{14}NO$ = 200.1062

m/z found = 200.1065

TLC (Hexanes:EtOAc 4:1)

R_f = 0.44



1,2-diphenylethane (**17**)

GC retention time of **bromobenzene**: 2.08 min

77% yield, clear oil

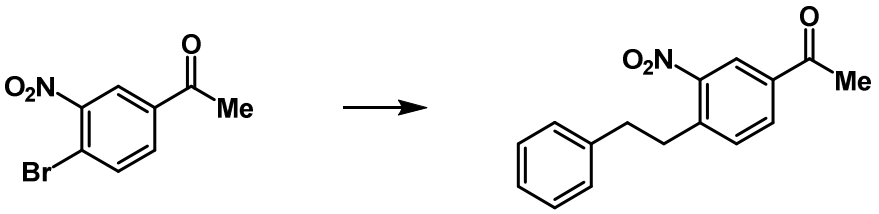
Spectral data were identical to known structure in literature

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 7.32 – 7.24 (m, 4H), 7.24 – 7.13 (m, 6H), 2.93 (s, 4H)

^{13}C NMR (75 MHz, Chloroform-*d*)

δ 141.7, 128.4, 128.3, 125.8, 37.9



1-(3-nitro-4-phenethylphenyl)ethanone (**19**)

GC retention time of **1-(4-bromo-3-nitrophenyl)ethan-1-one**: 6.32 min

78% yield, white solid

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 8.47 (dt, *J* = 1.9, 0.3 Hz, 1H), 8.04 (ddd, *J* = 8.0, 1.8, 0.3 Hz, 1H), 7.35 (dq, *J* = 8.0, 0.4 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 7.20 – 7.16 (m, 2H), 3.28 – 3.21 (m, 2H), 3.01 – 2.95 (m, 2H), 2.64 (d, *J* = 0.3 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 195.4, 141.4, 140.2, 136.1, 132.7, 131.7, 128.5, 128.4, 126.4, 124.7, 36.6, 36.6, 35.4, 26.5

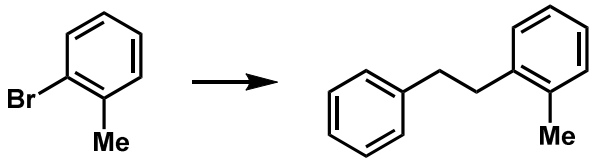
HRMS [DART] ($M+NH_4^+$)

m/z calculated for $C_{16}H_{19}N_2O_3$= 287.1357

m/z found = 287.1394

TLC (Hexanes:Et_2O 1:1)

R_f = 0.2



1-methyl-2-phenethylbenzene (**20**)

GC retention time of 2-chlorotoluene:

GC retention time of **2-bromotoluene**: 2.28 min

Spectra matched literature reports:

Molander, G. A.; Yun, C-S. *Tetrahedron* **2002**, *58*, 1465-1470.

83% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

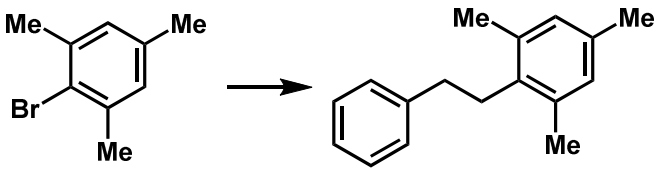
δ 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 7.18 – 7.11 (m, 4H), 3.00 – 2.81 (m, 4H), 2.32 (d, J = 0.6 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 141.9, 139.9, 135.9, 130.1, 128.7, 128.3, 128.3, 126.0, 125.9, 125.9, 36.7, 35.4, 19.2

TLC (Hexanes)

R_f = 0.52



1,3,5-trimethyl-2-phenethylbenzene (**21**)

GC retention time of **2-bromomesitylene:** 3.28 min

Spectra matched literature reports:

Molander, G. A.; Yun, C-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534-5539.

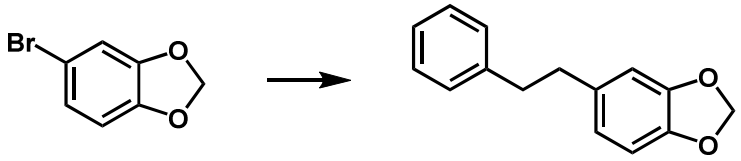
73%, clear residue

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 7.37 – 7.27 (m, 2H), 7.27 – 7.16 (m, 3H), 6.86 (s, 2H), 2.94 – 2.83 (m, 2H), 2.78 – 2.68 (m, 2H), 2.32 (s, 6H), 2.26 (s, 3H)

^{13}C NMR (100 MHz, Chloroform-*d*)

δ 142.3, 135.9, 135.4, 135.1, 128.9, 128.4, 128.2, 125.9, 35.5, 31.7, 20.8, 19.6



5-phenethylbenzo[d][1,3]dioxole (**22**)

GC retention time of **5-bromobenzo[d][1,3]dioxole**: 3.71 min

81% yield, opaque residue

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.31 – 7.25 (m, 7H), 7.22 – 7.15 (m, 4H), 6.74 – 6.66 (m, 2H), 6.64 – 6.59 (m, 1H), 5.92 (d, *J* = 0.4 Hz, 2H), 2.92 – 2.81 (m, 4H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 147.4, 145.6, 141.5, 135.6, 128.4, 128.3, 125.9, 121.1, 108.9, 108.0, 100.7, 38.1, 37.6

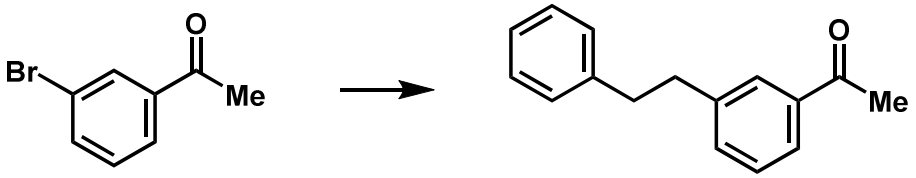
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{15}H_{15}O_2$= 227.1072

m/z found = 227.1064

TLC (Hexanes:Et_2O 4:1)

R_f = 0.61



1-(3-benzylphenyl)ethan-1-one (**23**)

GC retention time of **3-bromoacetophenone:** 3.35 min

92% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.81 – 7.77 (m, 1H), 7.75 (ddq, *J* = 1.7, 1.1, 0.6 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.28 (tq, *J* = 8.0, 1.1 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.15 (m, 2H), 3.02 – 2.96 (m, 2H), 2.96 – 2.92 (m, 2H), 2.57 (s, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 198.3, 142.1, 141.1, 137.1, 133.3, 128.5, 128.4, 128.3, 128.2, 126.1, 126.0, 37.7, 26.6

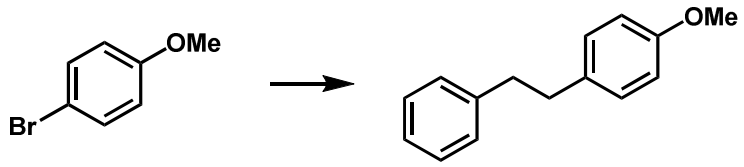
HRMS [DART] (M^+)

m/z calculated for $C_{16}H_{17}O$= 225.1279

m/z found = 225.1271

TLC (Hexanes:Et_2O 6:1)

R_f = 0.23



1-methoxy-4-phenethylbenzene (**24**) (95% pure)

GC retention time of **4-bromoanisole**: 3.07 min

54 % yield, white residue

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.30 – 7.26 (m, 3H), 7.22 – 7.16 (m, 2H), 7.12 – 7.08 (m, 2H), 6.85 – 6.81 (m, 2H), 3.79 (s, 3H), 2.91 – 2.86 (m, 4H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 157.80, 141.8, 133.8, 129.3, 128.4, 128.2, 125.8, 125.8, 113.7, 113.6, 55.2, 38.1, 37.0

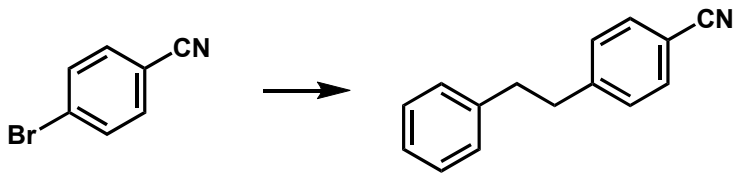
HRMS [DART] ($M+NH_4^+$)

m/z calculated for $C_{15}H_{20}NO$= 230.1544

m/z found = 230.1543

TLC (Hexanes:Et_2O 9:1)

R_f = 0.38



4-phenethylbenzonitrile (**25**)

GC retention time of **4-bromobenzonitrile:** 3.49 min

78% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.57 – 7.53 (m, 1H), 7.50 (dd, *J* = 7.9, 6.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 7.14 – 7.10 (m, 1H), 7.04 – 6.97 (m, 1H), 2.99 (ddt, *J* = 8.1, 6.1, 1.9 Hz, 2H), 2.96 – 2.90 (m, 2H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 147.1, 140.5, 132.1, 129.3, 128.4, 128.3, 126.2, 119.0, 109.8, 37.9, 37.2

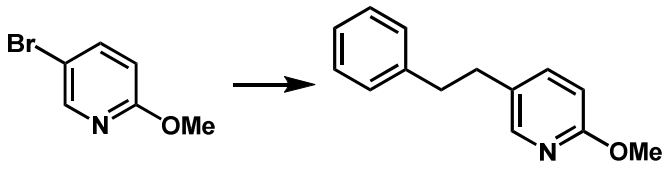
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{15}H_{14}N$= 208.1126

m/z found = 208.1120

TLC (Hexanes:EtOAc 9:1)

R_f = 0.32



2-methoxy-5-phenethylpyridine (**26**)

GC retention time of **5-bromo-2-methoxypyridine**: 2.64 min

54% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.93 (d, *J* = 2.5 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.16 – 7.12 (m, 2H), 6.65 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 2.92 – 2.80 (m, 4H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 146.0, 141.0, 138.9, 129.4, 128.4, 128.3, 127.4, 126.0, 110.3, 53.2, 37.7, 33.9

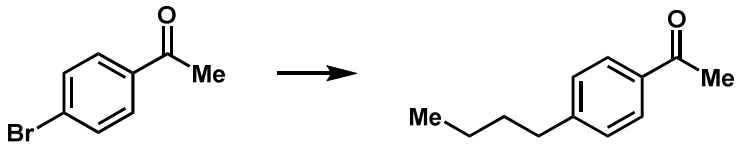
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{14}H_{16}NO$ = 214.1231

m/z found = 214.1227

TLC (Hexanes:EtOAc 9:1)

R_f = 0.34



1-(4-butylphenyl)ethan-1-one (**27**)

GC retention time of **4-bromoacetophenone**: 3.93 min

61% yield, clear oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.96 – 7.80 (m, 2H), 7.33 – 7.19 (m, 2H), 2.74 – 2.62 (m, 2H), 2.58 (d, *J* = 0.3 Hz, 3H), 1.66 – 1.57 (m, 2H), 1.40 – 1.31 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 197.8, 148.8, 134.8, 128.5, 128.4, 35.6, 33.2, 26.5, 22.3, 13.8

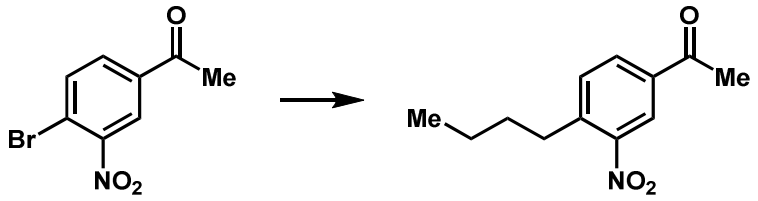
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{12}H_{17}O$ = 177.1279

m/z found = 177.1279

TLC (Hexanes:EtOAc 9:1)

R_f = 0.38



1-(4-butyl-3-nitrophenyl)ethan-1-one (**28**)

GC retention time of **1-(4-bromo-3-nitrophenyl)ethan-1-one**: 6.32 min

91% yield, clear residue

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 8.41 (dd, *J* = 1.8, 0.4 Hz, 1H), 8.07 (ddd, *J* = 8.0, 1.9, 0.3 Hz, 1H), 7.46 (dq, *J* = 8.0, 0.5 Hz, 1H), 2.96 – 2.90 (m, 2H), 2.63 (s, 3H), 1.69 – 1.59 (m, 2H), 1.46 – 1.35 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 195.5, 142.6, 135.8, 132.3, 131.6 (2C), 124.5, 32.7, 32.6, 26.5, 22.6, 13.7

HRMS [DART] ($M+H^+$)

m/z calculated for $C_{12}H_{16}NO_3$= 222.1130

m/z found = 222.1139

TLC (Hexanes:Et_2O 1:2)

R_f = 0.44

4-butylbenzonitrile (**29**)

GC retention time of **4-bromobenzonitrile:** 3.49 min

67% yield (90% conversion), slightly yellow oil

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.64 – 7.49 (m, 2H), 7.30 – 7.24 (m, 2H), 2.72 – 2.59 (m, 2H), 1.67 – 1.55 (m, 2H), 1.41 – 1.30 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 148.5, 132.0, 129.1, 119.1, 109.4, 35.7, 33.0, 22.2, 13.8

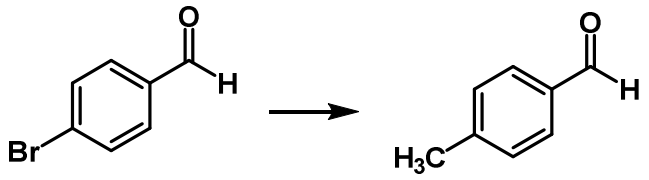
HRMS [DART] ($M+NH_4^+$)

m/z calculated for $C_{11}H_{17}N_2$= 177.1391

m/z found = 177.1404

TLC (Hexanes:Et_2O 1:1)

R_f = 0.41



p-tolylbenzaldehyde (**30**)

79% yield, clear oil

Spectra matched literature reports:

Molander, G. A.; Yun, C-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534-5539.

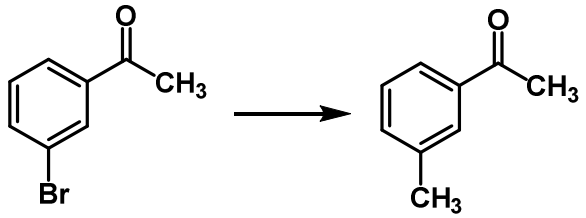
GC retention time of **4-bromobenzaldehdye:** 3.35 min

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 9.96 (s, 1H), 7.93 – 7.63 (m, 2H), 7.45 – 7.19 (m, 2H), 2.44 (s, 3H)

^{13}C NMR (75 MHz, Chloroform-*d*)

δ 192.0, 145.5, 134.1, 129.8, 129.7, 21.8



3-methylacetophenone (**31**)

82% yield, clear oil

Spectra matched literature reports:

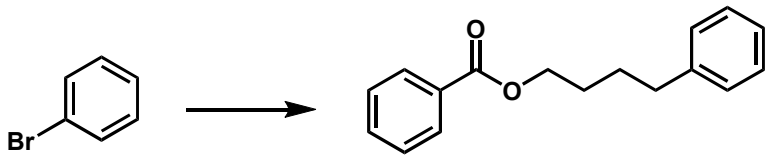
GC retention time of **3-bromoacetophenone:** 3.94 min

^{1}H NMR (300 MHz, Chloroform-*d*)

δ 7.86 – 7.63 (m, 2H), 7.49 – 7.30 (m, 2H), 2.59 (s, 3H), 2.41 (q, J = 0.6 Hz, 4H).

^{13}C NMR (75 MHz, Chloroform-*d*)

δ 198.3, 138.3, 137.1, 133.8, 128.7, 128.4, 125.5, 26.6, 21.3



4-phenylbutyl benzoate (**37**)

58% yield, clear oil

GC retention time **bromobenzene**: 2.08 min

Spectra matched literature reports:

Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626–31.

^{1}H NMR (500 MHz, Chloroform-*d*)

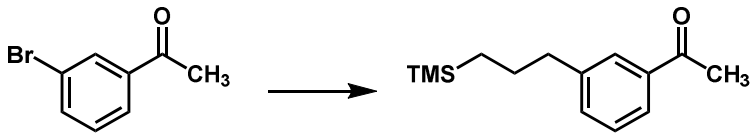
δ 8.07 – 7.99 (m, 2H), 7.58 – 7.48 (m, 1H), 7.47 – 7.38 (m, 2H), 7.32 – 7.27 (m, 2H), 7.22 – 7.16 (m, 3H), 4.41 – 4.29 (m, 2H), 2.73 – 2.66 (m, 2H), 1.86 – 1.77 (m, 4H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 166.3, 142.0, 132.8, 130.4, 129.5, 128.3, 128.3, 128.3, 125.8, 64.8, 35.4, 28.3, 27.8

TLC (Hexanes:Et_2O 4:1)

R_f = 0.58



1-(3-(2-(trimethylsilyl)ethyl)phenyl)ethan-1-one (**38**)

72% yield, clear oil

GC retention time of **3-bromoacetophenone:** 3.94 min

2-conformations observed, major peaks reported

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.82 – 7.68 (m, 2H), 7.42 – 7.31 (m, 2H), 2.70 – 2.66 (m, 3H), 2.60 (s, 3H), 1.67 – 1.58 (m, 2H), 0.58 – 0.50 (m, 2H), -0.02 (s, 9H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 198.4, 143.2, 137.1, 133.3, 128.4, 128.1, 125.9, 39.7, 26.7, 26.0, 16.5, -1.7

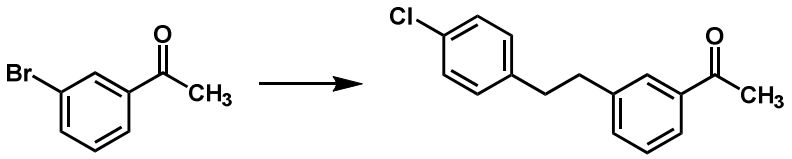
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{16}H_{16}NO$= 235.1582

m/z found = 235.1522

TLC (Hexanes:Et_2O 5:1)

R_f = 0.48



1-(3-(4-chlorophenethyl)phenyl)ethan-1-one (**39**)

76% yield, clear oil

GC retention time of **3-bromoacetophenone:** 3.94 min

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.82 – 7.72 (m, 2H), 7.39 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.10 – 7.04 (m, 2H), 2.99 – 2.93 (m, 2H), 2.91 (ddd, *J* = 8.8, 5.9, 2.2 Hz, 2H), 2.58 (s, 3H)

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 198.2, 141.7, 139.5, 137.2, 133.3, 131.8, 129.8, 128.5, 128.4, 128.1, 126.2, 37.5, 37.02, 26.6

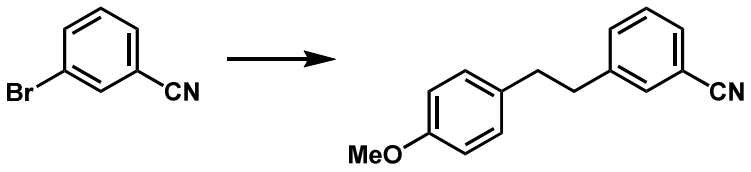
HRMS [DART] ($M+H^+$)

m/z calculated for $C_{16}H_{16}ClO$ = 259.0889

m/z found = 259.0877

TLC (Hexanes:Et_2O 3:1)

R_f = 0.24



3-(4-methoxyphenethyl)benzonitrile (**40**)

52% yield, clear oil

GC retention time of **3-bromobenzonitrile**: 3.36 min

^{1}H NMR (500 MHz, Chloroform-*d*)

δ 7.50 – 7.46 (m, 1H), 7.42 (qd, *J* = 1.0, 0.5 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.06 – 6.99 (m, 2H), 6.84 – 6.79 (m, 2H), 3.79 (s, 3H), 2.95 – 2.88 (m, 2H), 2.89 – 2.83 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*)

δ 158.0, 143.0, 133.1, 132.6, 132.0, 129.7, 129.3, 129.0, 119.0, 113.8, 112.2, 55.2, 37.6, 36.4

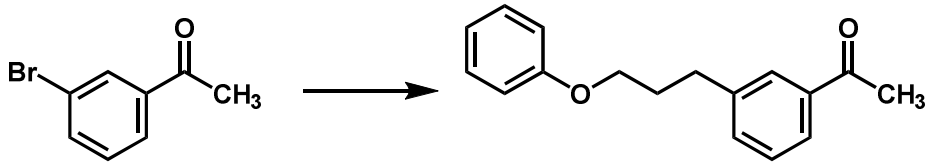
HRMS [ESI-MS] ($M+H^+$)

m/z calculated for $C_{16}H_{16}NO$= 238.1226

m/z found = 238.1227

TLC (Hexanes:Et_2O 4:1)

R_f = 0.36



1-(3-(3-phenoxypropyl)phenyl)ethan-1-one (**41**)

67% yield (84% brsm), clear oil

^{1}H NMR (399 MHz, Chloroform-*d*)

δ 7.83 – 7.75 (m, 2H), 7.45 – 7.36 (m, 2H), 7.31 – 7.26 (m, 2H), 6.94 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.92 – 6.87 (m, 2H), 3.97 (t, *J* = 6.2 Hz, 2H), 2.89 (dd, *J* = 8.5, 6.8 Hz, 2H), 2.57 (s, 3H), 2.19 – 2.07 (m, 2H)

^{13}C NMR (100 MHz, Chloroform-*d*)

δ 198.2, 158.8, 142.0, 137.3, 133.3, 129.4, 128.6, 128.2, 126.1, 120.6, 114.4, 66.5, 32.0, 30.7, 26.6

HRMS [DART] ($M+H^+$)

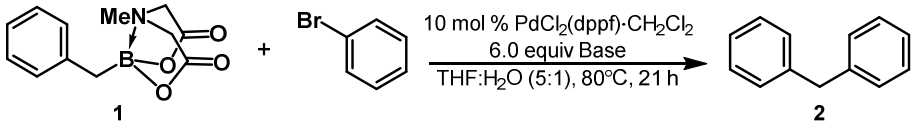
m/z calculated for $C_{16}H_{16}ClO$ = 259.0889

m/z found = 259.0877

TLC (Hexanes:Et_2O 3:1)

R_f = 0.29

Effect of Various Inorganic Bases on Formation of 2



Entry	Base	Conversion %[a]	Yield of **2** %[b]	Selectivity %[c]
1	K_2CO_3	99	89	89
2	K_3PO_4	99	67	67
3	KOH	84	16	19
4	Na_2CO_3	91	69	75
5	$KHCO_3$	82	62	75
6	Cs_2CO_3	96	57	59
7	KF	0	0	0
8	none	0	0	0

Reaction Conditions: 1.1 equiv. **1**, 1.0 equiv. bromobenzene. Reactions stopped at 21 h for comparative purposes [a,b] Determined by calibrated GC analysis against internal standard (naphthalene), [c] Selectivity % = (Yield/ Conversion) x 100