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Practical Catalytic Method for Synthesis of Sterically Hindered Anilines

Melrose Mailig, Richard P. Rucker, and Gojko Lalic*

Department of Chemistry, University of Washington, Seattle, WA 98195, USA

Supporting information

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1. General

All reactions were performed under a nitrogen atmosphere with flame-dried glassware, using standard Schlenk techniques, or in a glove box (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 μm, 230-400 mesh). Ion Exchange Chromatography was performed using analytical grade cation exchange resin from sulfonic acid functionalized styrene (Bio-Rad Laboratories, 200-400 mesh, 5.2 meq/g). General method for purification by ion exchange chromatography is as follows: crude product was adsorbed on the cation exchange resin (200 mg resin/mmol product) using MeOH, and the resin was subsequently washed with 10% dichloromethane in MeOH over 4 CV, then 10% Et_3N in MeOH over 4 CV to elute the product. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual proteated solvent peak ($CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), or CD_2Cl_2 (5.32 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm, CD_2Cl_2: δ 54.0 ppm, CD_3CN: δ 1.3 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet), integration, and coupling constants in Hertz (Hz). Mass spectra were collected on a JEOL HX-110 mass spectrometer. GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 μm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

Materials

THF, CH_2Cl_2, diethyl ether, and toluene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled from purple Na/benzophenone ketyl and stored over 4Å molecular sieves. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. Deuterated solvents were degassed and dried over 4Å molecular sieves before use. Commercial reagents were purchased from Sigma-Aldrich Co., VWR International, LLC., or STREM Chemicals, Inc., and were used as received. Cesium fluoride was purchased from Sigma-Aldrich and used as recieved, unless otherwise noted. Aryl boronic esters were prepared according to a literature procedure.[1]

2. Reaction optimization

A. General:

All optimization reactions were performed in a glove box. A dram vial was charged with a stir bar. To the vial was added copper catalyst (0.025 equiv), ligand (0.035 equiv), cesium fluoride (3.00 equiv), aryl boronic ester (1.20 equiv), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv), 1,3,5-trimethoxybenzene (0.50 equiv), and solvent (0.2 M). The reaction vial was capped and stirred for 6 h with heating at the indicated temperature. Product yield was determined by GC comparison against 1,3,5-trimethoxybenzene as an internal standard. . Cesium fluoride used for the optimization was dried rigorously by flame-drying under vacuum followed by griding with mortar and pestle in a glovebox.

B. Optimization of the catalyst (Entries 2 – 5, Table S1):

Reactions were conducted according to the General Procedure using the indicated copper catalyst (0.025 equiv, 0.006 mmol), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 0.009 mmol), cesium fluoride (3.00 equiv, 0.750 mmol), aryl boronic ester (1.20 equiv, 0.300 mmol), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (1.00 equiv, 0.250 mmol), 1,3,5-trimethoxybenzene (0.50 equiv, 0.125 mmol) and THF as solvent (1.25 mL). For entries 4-5, sodium ascorbate (1.5 equiv, 0.375 mmol) was added. Reactions were heated at 66 °C with stirring for 6 h.

C. Optimization of the Ligand (Entries 6 – 7, Table S1):

Reactions were conducted according to the General Procedure using copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 0.006 mmol), the indicated ligand (0.035 equiv, 0.009 mmol), cesium fluoride (3.00 equiv, 0.750 mmol), 5,5-dimethyl-2-(2-methylphenyl)-1,3,2-dioxaborinane (1.20 equiv, 0.300 mmol), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (1.00 equiv, 0.250 mmol), 1,3,5-trimethoxybenzene (0.50 equiv, 0.125 mmol) and THF as solvent (1.25 mL). Reactions were heated at 66 °C with stirring for 6 h.

D. Optimization of the turnover reagent (Entry 8, Table S1):

Reactions were conducted according to the General Procedure using copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 0.006 mmol), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 0.009 mmol), potassium fluoride (3.00 equiv, 0.750 mmol), 5,5-dimethyl-2-(2-methylphenyl)-1,3,2-dioxaborinane (1.20 equiv, 0.300 mmol), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (1.00 equiv, 0.250 mmol), 1,3,5-trimethoxybenzene (0.50 equiv, 0.125 mmol) and THF as solvent (1.25 mL). Reaction was heated at 66 °C with stirring for 6 h.

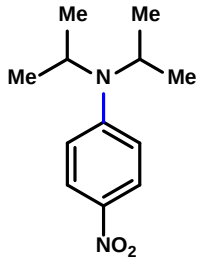
E. Optimization of the solvent (Entries 9 – 12, Table S1):

Reactions were conducted according to the General Procedure using copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 0.006 mmol), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 0.009 mmol), cesium fluoride (3.00 equiv, 0.750 mmol), 5,5-dimethyl-2-(2-methylphenyl)-1,3,2-dioxaborinane (1.20 equiv, 0.300 mmol), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (1.00 equiv, 0.250 mmol), 1,3,5-trimethoxybenzene (0.50 equiv, 0.125 mmol) and either 2-methyl THF, 1,4-dioxane, acetonitrile, or toluene as solvent (1.25 mL). Reactions were heated at 66 °C with stirring for 6 h.

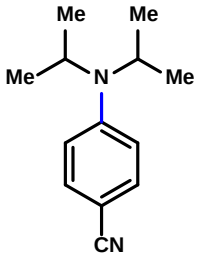
3. Amination of aryl boronic ester

A. General procedure for the synthesis of tertiary aniline:

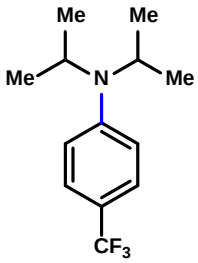
An air-free reaction flask charged with a stir bar was flame dried under vacuum, allowed to cool under nitrogen. To the flask was added CsF (3.00 equiv, 227.9 mg, 1.500 mmols), boronic ester (1.20 equiv, 0.600 mmol), *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (1.00 equiv, 0.500 mmol), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 9.8 mg, 0.018 mmol), copper(I) trifluoromethanesulfonate benzene complex (0.025 equiv, 3.1 mg, 0.013 mmol), and THF (2.5 mL). The mixture was allowed to stir at 66 °C until complete conversion of the hydroxylamine by TLC (all reactions were complete in less than 12 h). The mixture was then filtered through a plug of silica using dichloromethane (10 mL) followed by diethyl ether (10 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography.



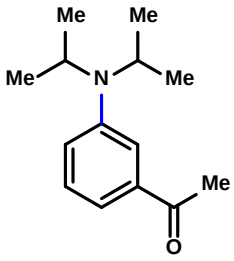
4-nitro-*N*,*N*-bis(propan-2-yl)aniline (7): Compound was isolated as an orange powder (102.4 mg, 92% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 8.14 – 7.99 (m, 2H), 6.30 – 6.19 (m, 2H), 3.28 (hept, J = 6.8 Hz, 2H), 0.80 (d, J = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 152.8, 137.3, 125.7, 113.4, 47.8, 20.4. GCMS (EI) calculated for $[M]^+$ 222.14, found 222.10. HRMS calculated for $[M+H]^+$ 222.14, found xxx.xx. FTIR (neat, cm-1): 2976(w), 1598(s), 1310(s), 1294(s).



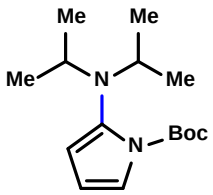
4-[bis(propan-2-yl)amino]benzonitrile (8): Compound was isolated as a white powder (95.2 mg, 94% yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 6.82 – 6.71 (m, 2H), 3.93 (hept, J = 13.8, 6.9 Hz, 2H), 1.30 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 151.0, 133.0, 120.6, 115.0, 98.1, 47.4, 20.5. GCMS (EI) calculated for [M]+ 202.15, found 202.10 FTIR (neat, cm-1): 3436(s), 2218(w),1636(s), 1516(s), 1265(s). The spectral data match the literature values.[2]



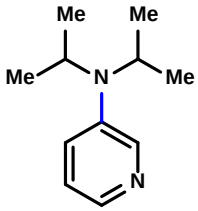
***N,N*-bis(propan-2-yl)-4-(trifluoromethyl)aniline (12):** Compound was isolated as a colorless oil (108 mg, 89% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.61 – 7.28 (m, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.39 (hept, J = 6.9 Hz, 2H), 0.92 (d, J = 6.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 126.0 (q, J = 3.7 Hz), 125.4 (q, J = 269.9 Hz), 117.5 (q, J = 32.5 Hz), 115.0, 47.5, 21.1. GCMS (EI) calculated for [M]+ 245.14, found 245.10. HRMS calculated for $[M+H]^+$ 245.14, found xxx.xx. FTIR (neat, cm-1): 2962(m), 2877(m), 1618(s), 1524(s), 1321(s), 1109(s).



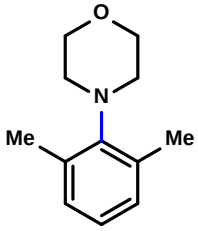
1-{3-[bis(propan-2-yl)amino]phenyl}ethan-1-one (14): Compound was isolated as a yellow oil (105.2 mg, 96% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.77 (dd, J = 2.7, 1.6 Hz, 1H), 7.23 (dt, J = 7.5, 1.3 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.93 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 3.51 (hept, J = 6.8 Hz, 2H), 2.23 (s, 3H), 1.01 (d, J = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 197.2, 148.8, 138.3, 128.8, 123.1, 118.6, 117.7, 47.7, 26.4, 21.3. GCMS (EI) calculated for [M]+ 219.16, found 219.20. HRMS calculated for $[M+H]^+$ 219.16, found xxx.xx. FTIR (neat, cm-1): 3054(w), 2973(w), 1680(m),1593(m), 1491(m), 1265(s).



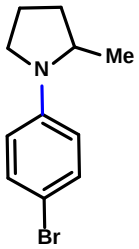
***tert*-butyl 2-[bis(propan-2-yl)amino]-1H-pyrrole-1-carboxylate (24):** Compound was isolated as a colorless oil (125.9 mg, 95% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.29 (dd, J = 3.7, 1.9 Hz, 1H), 6.06 (t, J = 3.6 Hz, 1H), 5.89 (dd, J = 3.4, 1.9 Hz, 1H), 3.35 (hept, J = 6.4 Hz, 2H), 1.37 (s, 9H), 1.05 (d, J = 6.4 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 149.3, 138.1, 119.0, 112.0, 108.8, 81.9, 50.8, 28.0, 21.6. GCMS (EI) calculated for [M]+ 266.20, found 266.10. HRMS calculated for $[M+H]^+$ 266.20, found xxx.xx. FTIR (neat, cm-1): 3106(w), 2970(s), 2871(m), 1729(s), 1330(s).



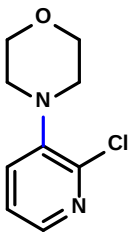
***N,N*-bis(propan-2-yl)pyridin-3-amine (21):** Compound was isolated as a colorless oil (117.9 mg, 94%) ^{1}H NMR (500 MHz,C_6D_6) δ 8.48 (d, J = 2.8 Hz, 1H), 8.21 (dd, J = 4.5, 1.6 Hz, 1H), 6.92 – 6.75 (m, 2H), 3.39 (hept, J = 6.7 Hz, 2H), 0.92 (d, J = 6.8 Hz, 12H). ^{13}C NMR (126 MHz, C_6D_6) δ 144.3, 142.2, 140.1, 124.9, 123.1, 47.6, 21.2. GCMS (EI) calculated for [M]+ 178.15, found 178.20. FTIR (neat, cm-1): 3046(m), 2972(s), 2875(m), 1583(s), 1265(s). The spectral data match the literature values.[3]



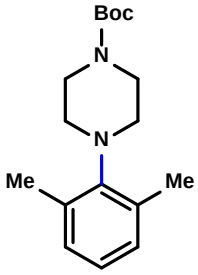
4-(2,6-dimethylphenyl)morpholine (17): Compound was isolated as a white powder (121.3 mg, 91% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 6.95 (s, 3H), 3.58 (t, 4H), 2.78 (t, 4H), 2.22 (s, 6H). ^{13}C NMR (126 MHz, C_6D_6) δ 148.4, 137.0, 129.5, 125.7, 68.2, 50.4, 19.7. GCMS (EI) calculated for [M]+ 191.13, found 191.20. FTIR (neat, cm-1): 3053(s), 1631(s), 1264(s), 1111(w). The spectral data match the literature values.[4]



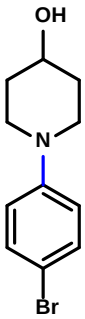
1-(4-bromophenyl)-2-methylpyrrolidine (15): Compound was isolated as a white powder (114.8 mg, 96% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.44 – 7.23 (m, 2H), 6.37 – 6.02 (m, 2H), 3.35 (tt, J = 6.4, 3.2 Hz, 1H), 2.87 (ddd, J = 9.5, 7.6, 2.5 Hz, 1H), 2.69 – 2.54 (m, 1H), 1.70 – 1.33 (m, 3H), 1.29 – 1.05 (m, 1H), 0.81 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 131.8, 113.4, 106.9, 53.8, 48.3, 33.2, 23.4, 19.1. GCMS (EI) calculated for [M]+ 239.03, found 239.10. FTIR (neat, cm-1): 3053(w), 2986(w), 1593(w), 1422(w), 1265(s). This compound is commercially available.



4-(2-chloropyridin-3-yl)morpholine (20): Compound was isolated as a yellow oil (129.9 mg, 94% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.88 (t, J = 3.1 Hz, 1H), 6.53 (d, J = 3.2 Hz, 2H), 4.02 – 3.10 (m, 4H), 3.02 – 2.05 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 145.7, 143.0, 128.0, 123.0, 66.9, 51.2. GCMS (EI) calculated for [M]+ 198.06, found 198.10. FTIR (neat, cm-1): 3053(m), 2860(m), 1447(s), 1409(s), 1267(s), 1375(s). This compound is commercially available.



***tert*-butyl 4-(2,6-dimethylphenyl)piperazine-1-carboxylate (16):** Compound was isolated as a white powder (190.2 mg, 94% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 6.91 (s, 3H), 3.40 (s, 4H), 2.98 – 2.41 (m, 4H), 2.10 (s, 6H), 1.50 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 154.8, 148.6, 136.9, 129.4, 125.7, 79.1, 49.9, 28.6, 19.7. GCMS (EI) calculated for [M]+ 290.20, found 290.20. FTIR (neat, cm-1): 3053(s), 2985(w), 1675(s), 1642(s), 1266(s). This compound is commercially available.



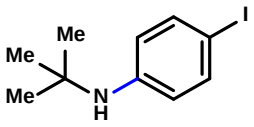
1-(4-bromophenyl)piperidin-4-ol (18): Compound was isolated as a yellow powder (117.3 mg, 92% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.30 – 7.21 (m, 2H), 6.42 – 6.33 (m, 2H), 3.28 (s, 1H), 3.13 – 2.94 (m, 2H), 2.38 (ddd, J = 12.7, 9.5, 3.3 Hz, 2H), 1.48 (dddt, J = 12.9, 5.3, 3.7, 2.0 Hz, 2H), 1.27 (dtd, J = 12.8, 9.0, 3.9 Hz, 2H), 0.63 (s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 150.9, 132.3, 118.4, 111.4, 68.0, 47.5, 34.5. GCMS (EI) calculated for [M]+ 255.03, found 255.10. FTIR (neat, cm-1): 3287(b), 3054(w), 2818(w), 1589(s), 1494(s), 1265(s). This compound is commercially available.

Synthesis of secondary anilines.

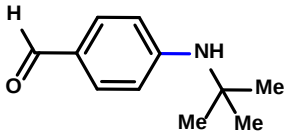
Synthesis of secondary anilines can be performed without use of a glove box as all of the materials used in the reaction are sufficiently stable in air. CsF is highly hygroscopic and should be used either from a freshly opened bottle of dried CsF or should be flame dried under vacuum for several minutes in the reaction flask before the use. Copper(I) trifluoromethanesulfonate benzene complex does slowly oxidize in air and should be manipulated quickly when exposed to air. We found that with older bottles of copper(I) trifluoromethanesulfonate benzene complex we had to use higher catalyst loadings to achieve the same rate of the reaction. For convenience, we have performed the majority of the reactions described in table 3 using a glove box. However, as the results shown below demonstrate there is no significant difference in yields obtained in reactions that are setup using a glovebox and those set up outside of a glovebox.

B. General procedure for secondary aniline:

An air-free reaction flask charged with a stir bar was flame dried under vacuum, allowed to cool under nitrogen. To the flask was added CsF (3.00 equiv, 227.9 mg, 1.500 mmols), boronic ester (1.20 equiv, 0.600 mmol), bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 9.8 mg, 0.018 mmol), copper(I) trifluoromethanesulfonate benzene complex (0.025 equiv, 3.1 mg, 0.013 mmol), and THF (1.5 mL). The mixture was allowed to stir vigorously at 66 °C. Solution of *O*-benzoyl-*N*-alkyl hydroxylamine (1.00 equiv, 0.250 mmol, 0.5 M) in THF was added using a syringe pump over three hours under inert atmosphere. After 30 minutes, the reaction was filtered through a plug of silica using dichloromethane (10 mL) followed by diethyl ether (10 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified using ion exchange chromatography.



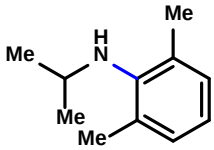
***N*-*tert*-butyl-4-iodoaniline (30):** Compound was isolated as a white solid (124.8 mg, 90% yield)



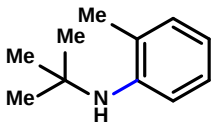
4-(*tert*-butylamino)benzaldehyde (32): Compound was isolated as an orange oil (111.2 mg, 88% yield)

C. General procedure for secondary aniline using glove box:

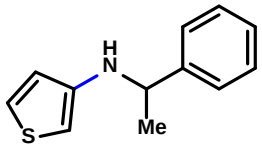
In a glove box, a 5 mL Schlenk flask was charged with a stir bar, copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 3.1 mg, 0.013 mmol), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 9.8 mg, 0.018 mmol), cesium fluoride (3.00 equiv, 1.500 mmol), 5,5-dimethyl-2-(2-methylphenyl)-1,3,2-dioxaborinane (1.20 equiv, 0.300 mmol) and THF (1.5 mL). The reaction flask was then brought outside of the glove box and vigorously stirred in an oil bath at 66 °C. Solution of *O*-benzoyl-*N*-alkyl hydroxylamine (1.00 equiv, 0.250 mmol, 0.5 M) in THF was added using a syringe pump over three hours under inert atmosphere. After 30 minutes, the reaction was filtered through a plug of silica using dichloromethane (10 mL) followed by diethyl ether (10 mL) as an eluent. The solvent was removed under reduced pressure, and the crude product was purified using ion exchange chromatography.



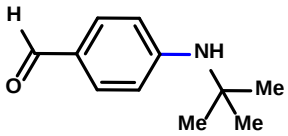
2,6-dimethyl-*N*-(propan-2-yl)aniline (26): Compound was isolated as a colorless oil (102.5 mg, 90% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.00 (d, J = 7.3 Hz, 2H), 6.87 (dd, J = 8.0, 6.8 Hz, 1H), 3.26 (hept, J = 6.3 Hz, 1H), 2.57 (s, 1H), 2.13 (s, 6H), 0.93 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.4, 129.3, 128.9, 121.4, 48.6, 24.0, 19.1. GCMS (EI) calculated for [M]+ 163.14, found163.15. FTIR (neat, cm-1); 3370(s), 2965(s), 1595(m), 1475(s), 1380(m). The spectral data match the literature values.[5]



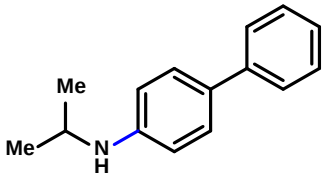
***N*-*tert*-butyl-2-methylaniline (28):** Compound was isolated as an orange solid (101.2 mg, 89% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.12 (d, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 7.3 Hz, 1H), 3.23 (s, 1H), 1.90 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.1, 130.6, 126.7, 123.7, 117.2, 114.3, 51.3, 30.3, 18.3. GCMS (EI) calculated for [M]+ 163.14, found 163.10. FTIR (neat, cm-1): 3440(m), 3050(s), 2975(s), 1586(S), 1482(S), 1320(s). The spectral data match the literature values.[6]



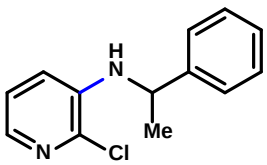
***N*-(1-phenylethyl)thiophen-3-amine (29):** Compound was isolated as a brown oil (89.0 mg, 88% yield) ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.52 – 7.17 (m, 5H), 7.08 (dd, J = 5.1, 3.0 Hz, 1H), 6.61 (dd, J = 5.1, 1.5 Hz, 1H), 5.66 (dd, J = 3.0, 1.5 Hz, 1H), 4.36 (q, J = 6.7 Hz, 1H), 4.14 (s, 1H), 1.48 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz,CD_2Cl_2) δ 148.1, 146.1, 129.1, 129.0, 127.5, 125.0, 121.0, 97.9, 56.3, 25.3. GCMS (EI) calculated for [M]+ 203.08, found 203.00. FTIR (neat, cm-1): 3402(w), 3050(w) 2977(w), 2867(w), 1558(s), 1261(s). This compound is commercially available.



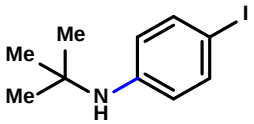
4-(*tert*-butylamino)benzaldehyde (32): Compound was isolated as an orange oil (111.2 mg, 90% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 9.80 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 8.8 Hz, 2H), 3.62 (s, 1H), 0.97 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.2, 152.5, 132.1, 125.7, 113.8, 51.4, 29.5. GCMS (EI) calculated for [M]+ 177.12, found 177.15. HRMS calculated for $[M+H]^+$ 177.12, found xxx.xx. FTIR (neat, cm-1): 3357(w), 2978(m), 2812(m), 1670(s), 1598(s), 1310(m), 1208(m), 1164(s).



4-phenyl-*N*-(propan-2-yl)aniline (31): compound was isolated as a yellow solid (100.4 mg, 95% yield) ^{1}H NMR (300 MHz,C_6D_6) δ 7.74 – 7.53 (m, 2H), 7.53 – 7.45 (m, 2H), 7.27 (t, J = 7.6 Hz, 2H), 6.45 (d, J = 8.6 Hz, 2H), 3.49 – 3.20 (m, 1H), 3.01 (s, 1H), 0.90 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 147.9, 141.9, 130.0, 129.3, 128.4, 126.7, 126.6, 114.0, 44.9, 23.4. GCMS (EI) calculated for [M]+ 211.14, found 211.20. FTIR (neat, cm-1): 3412(s), 2097(m), 1645(m), 1264(m). The spectral data match the literature values.[7]



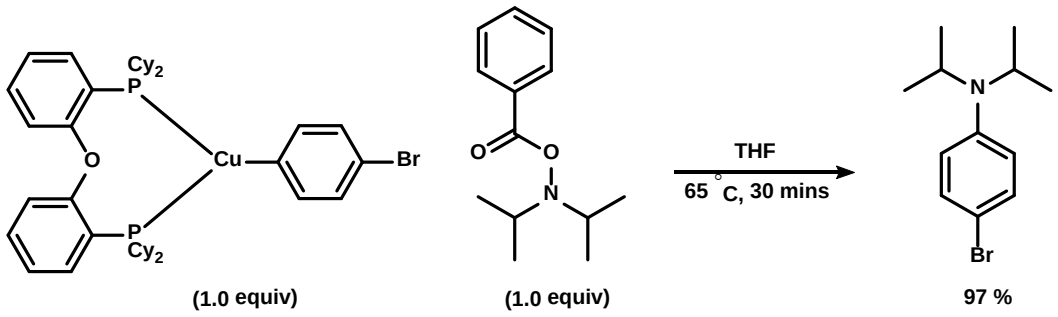
2-chloro-*N*-(1-phenylethyl)pyridin-3-amine (27): Compound was isolated as a yellow solid (103.0 mg, 89% yield) ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.61 (dd, J = 4.6, 1.6 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.18 (m, 1H), 6.92 (dd, J = 8.0, 4.6 Hz, 1H), 6.64 (dd, J = 8.1, 1.6 Hz, 1H), 4.79 (s, 1H), 4.64 – 4.34 (m, 1H), 1.58 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 139.9, 137.1, 136.6, 129.0, 127.5, 125.7, 123.3, 118.9, 77.2, 53.4, 25.2. GCMS (EI) calculated for [M]+ 232.08, found 232.20. FTIR (neat, cm-1): 350 (s), 1652(m), 149(w). This compound is commercially available.

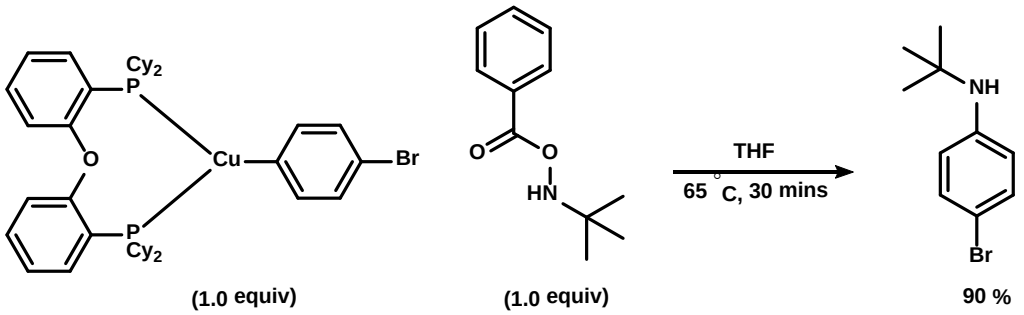


***N-tert*-butyl-4-iodoaniline (30):** Compound was isolated as a white solid (124.8 mg, 91% yield) ^{1}H NMR (300 MHz, C_6D_6) δ 7.53 – 7.20 (m, 2H), 6.29 – 5.93 (m, 2H), 3.01 (s, 1H), 0.99 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.5, 137.5, 118.8, 78.8, 51.4, 29.9. GCMS (EI) calculated for [M]+ 275.02, found 275.00. FTIR (neat, cm-1): 3416(s), 2978(w), 1636(m), 1458(m), 1219(m). This compound is commercially available.

4. Stoichiometric reactions of organocopper complexes

All reactions were performed in a glove box. To a dram vial charged with a stir bar was added Cy_4DPE-Phos-Cu-(4-bromo)Ph (1.00 equiv, 0.250 mmol), either, *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (1.00 equiv, 0.250 mmol), or *O*-benzoyl-*N*-tertbutyl hydroxylamine (1.00 equiv, 0.250 mmol), and THF (1.25 mL) as a solvent. The reaction vial was capped and stirred at 65 °C. Yields of 4-bromo-*N*,*N*-bis(propan-2-yl)aniline and 4-bromo-*N*-*tert*-butylaniline were determined by GC analysis of a reaction aliquot, using 1,3,5-trimethoxybenzene as an internal standard.





5. Kinetics experiments

A. Order in Boronic ester:

All reactions were performed in a glove box. To a dram vial charged with a stir bar was added CsF (3.00 equiv, 113.95 mg, 0.750 mmol), copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 250 uL of a 0.025 M stock solution), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 250 uL of a 0.035 M stock solution), varying amounts of 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**a**: 1.50 equiv, **b**: 3.0 equiv, **c**: 4.5 equiv), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (1.00 equiv), dodecane (0.25 equiv, 10.6 mg, 0.063 mmol), and THF (0.2 M). The reaction vial was capped and stirred with heating at 80 °C. At each desired timepoint, a 30 µL aliquot of the reaction mixture was removed and diluted in 500 µL DCM. The solution was removed from the glovebox, filtered through silica and cotton. Product yield was determined by GC comparison against dodecane as an internal standard.

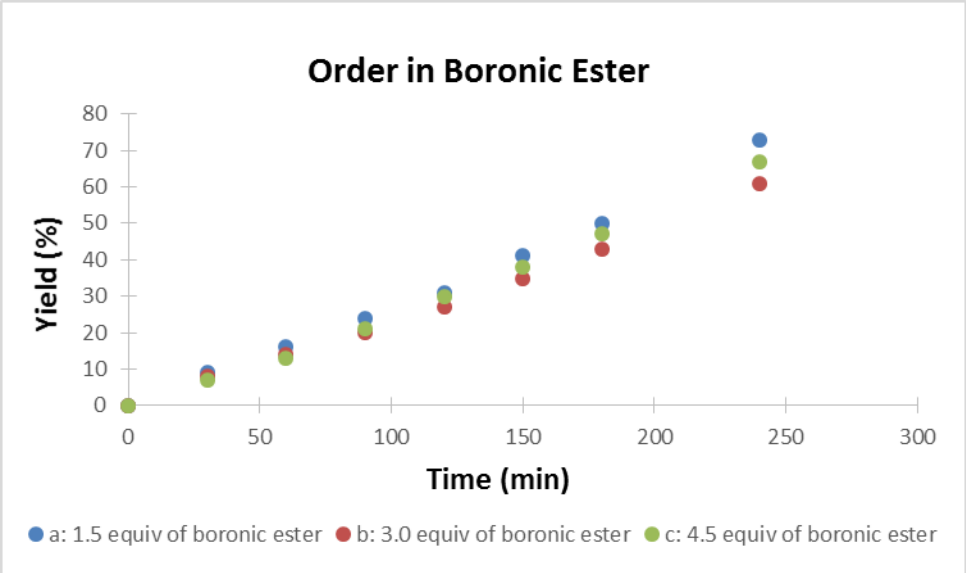


Figure S1. Yield of the aniline product as a function of time. Reaction conditions: 2MeC6H4Bneop (a: 1.5 equiv b: 3.0 equiv c: 4.5 equiv), iPr2NOBz (1.0 equiv), CuOTf 1/2C6H6 (2.5 mol %), Bis(2-dicyclohexylphosphinophenyl)ether (3.5 mol %), CsF (3 equiv), 80 C, THF

B. Order in Amine:

All reactions were performed in a glove box. To a dram vial charged with a stir bar was added CsF (3.00 equiv, 113.95 mg, 0.750 mmol), copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 250 uL of a 0.025 M stock solution), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 250 uL of a 0.035 M stock solution), varying amounts of 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (1.50 equiv), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (**a:**1.00 equiv, **b:** 1.5 equiv, **c:** 2.0 equiv), dodecane (0.25 equiv, 10.6 mg, 0.063 mmol), and THF (0.2 M). The reaction vial was capped and stirred with heating at 80 °C. At each desired timepoint, a 30 µL aliquot of the reaction mixture was removed and diluted in 500 µL DCM. The solution was removed from the glovebox, filtered through silica and cotton. Product yield was determined by GC comparison against dodecane as an internal standard.

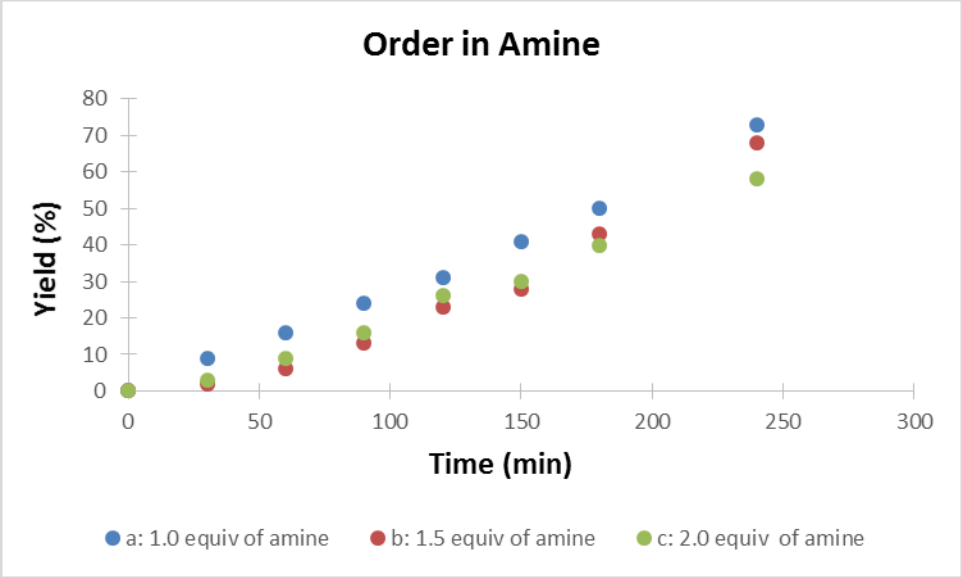


Figure S2. Yield of the aniline product as a function of time. Reaction conditions: 2MeC6H4Bneop (1.5 equiv), iPr2NOBz (1.0 equiv), CuOTf 1/2C6H6 (2.5 mol %), Bis(2-dicyclohexylphosphinophenyl)ether (3.5 mol %), CsF (3 equiv), 80 °C, THF

C. GC analysis of the reaction rate (Figure 1):

All reactions were performed in a glove box. To a dram vial charged with a stir bar was added CsF (3.00 equiv, 113.95 mg, 0.750 mmol), copper (I) trifluoromethanesulfonate benzene complex (0.025 equiv, 250 uL of a 0.025 M stock solution), Bis(2-dicyclohexylphosphinophenyl)ether (0.035 equiv, 250 uL of a 0.035 M stock solution), 2-(4-bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (0.300 mmol, 250 uL of a 1.2 M stock solution), *O*-benzoyl-*N*,*N*-diisopropyl hydroxylamine (0.250 mmol, 250 uL of a 1 M stock solution), dodecane (0.25 equiv, 10.6 mg,

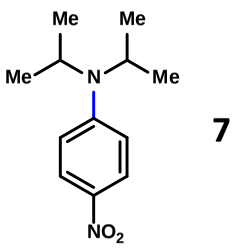
0.063 mmol), and THF (0.2 M). The reaction vial was capped and stirred with heating at 80 °C. At each desired timepoint, a 30 μL aliquot of the reaction mixture was removed and diluted in 500 μL DCM. The solution was removed from the glovebox, filtered through silica and cotton. Product yield was determined by GC comparison against dodecane as an internal standard.

6. References:

1. Schnürch, M.; Holzweber, M.; Mihovilovic, M. D.; Stanetty, P. *Green. Chem.* **2007**, *9*, 139.
2. Vitale, P.; Nunno, D. L.; Scilimati, A. *Tetrahedron* **2011,** *67*, 6944.
3. Samblanet, D. C.; Schmidt, J. A. *J. Organomet. Chem.* **2012,** *720*, 7.
4. Samblanet, D. C.; Schmidt, J. A. *Angew. Chem. Int. Ed.* **2014,** *53*, 6482.
5. Tewaria, A.; Heina, M.; Zapfb, A.; Bellerb, M. *Tetrahedron* **2005,** *61*, 9705.
6. Bacque, E.; Qacemi, M. E.; Zard, S. Z. *Org. Lett.* **2005,** *7*, 3817.
7. Cran, J. W.; Vidhani, D. V.; Krafft, M. E. *Synlett.* **2014,** *25*, 1550.

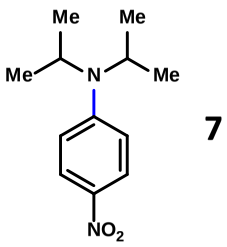
7. Characterizations ^{1}H NMR and ^{13}C NMR

^{1}H NMR (300 MHz, C_6D_6) δ 8.14 – 7.99 (m, 2H), 6.30 – 6.19 (m, 2H), 3.28 (hept, J = 6.8 Hz, 2H), 0.80 (d, J = 6.9 Hz, 12H).



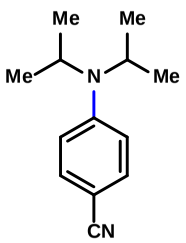
7

^{13}C NMR (126 MHz, C_6D6) δ 152.8, 137.3, 125.7, 113.4, 47.8, 20.4.



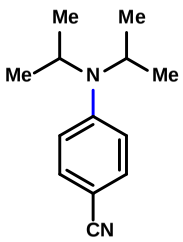
7

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 6.82 – 6.71 (m, 2H), 3.93 (hept, J = 13.8, 6.9 Hz, 2H), 1.30 (d, J = 6.9 Hz, 6H).



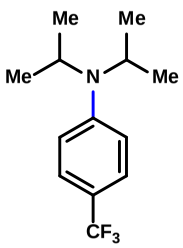
8

^{13}C NMR (126 MHz, C_6D6) δ 151.0, 133.0, 120.6, 115.0, 98.1, 47.4, 20.5.



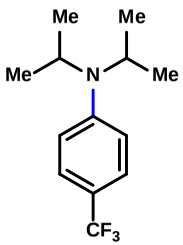
8

^{1}H NMR (300 MHz, Benzene-d_6) δ 7.61 – 7.28 (m, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.39 (hept, J = 6.9 Hz, 2H), 0.92 (d, J = 6.9 Hz, 12H).



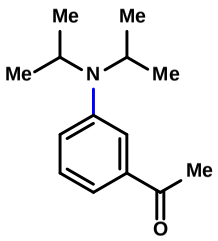
12

^{13}C NMR (126 MHz, Chloroform-*d*) δ 150.7 , 126.0 (q, *J* = 3.7 Hz), 125.4 (q, *J* = 269.9 Hz), 117.5 (q, *J* = 32.5 Hz), 115.0, 47.5 , 21.1.



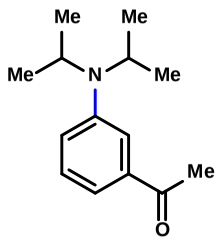
12

^{1}H NMR (300 MHz, Benzene-d_6) δ 7.77 (dd, J = 2.7, 1.6 Hz, 1H), 7.23 (dt, J = 7.5, 1.3 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.93 (ddd, J = 8.2, 2.7, 1.0 Hz, 1H), 3.51 (hept, J = 6.8 Hz, 2H), 2.23 (s, 3H), 1.01 (d, J = 6.8 Hz, 12H).



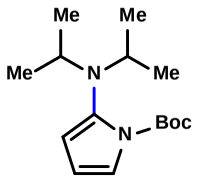
14

^{13}C NMR (126 MHz, C_6D6) δ 197.2, 148.8, 138.3, 128.8, 123.1, 118.6, 117.7, 47.7, 26.4, 21.3.



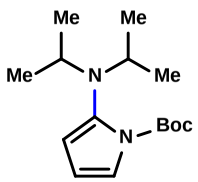
14

^{1}H NMR (300 MHz, Benzene-d_6) δ 7.29 (dd, J = 3.7, 1.9 Hz, 1H), 6.06 (t, J = 3.6 Hz, 1H), 5.89 (dd, J = 3.4, 1.9 Hz, 1H), 3.35 (hept, J = 6.4 Hz, 2H), 1.37 (s, 9H), 1.05 (d, J = 6.4 Hz, 12H).



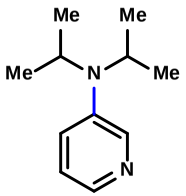
24

^{13}C NMR (126 MHz, C_6D_6) δ 149.3, 138.1, 119.0, 112.0, 108.8, 81.9, 50.8, 28.0, 21.6.



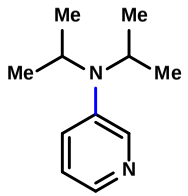
24

^{1}H NMR (500 MHz, Benzene-d_6) δ 8.48 (d, J = 2.8 Hz, 1H), 8.21 (dd, J = 4.5, 1.6 Hz, 1H), 6.92 – 6.75 (m, 2H), 3.39 (hept, J = 6.7 Hz, 2H), 0.92 (d, J = 6.8 Hz, 12H).



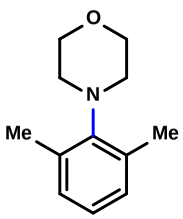
21

^{13}C NMR (126 MHz, C_6D6) δ 144.3, 142.2, 140.1, 124.9, 123.1, 47.6, 21.2.



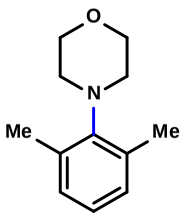
21

^{1}H NMR (300 MHz, C_6D_6) δ 6.95 (s, 3H), 3.58 (t, 4H), 2.78 (t, 4H), 2.22 (s, 6H).



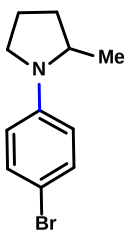
17

^{13}C NMR (126 MHz, C_6D6) δ 148.4, 137.0, 129.5, 125.7, 68.2, 50.4, 19.7.

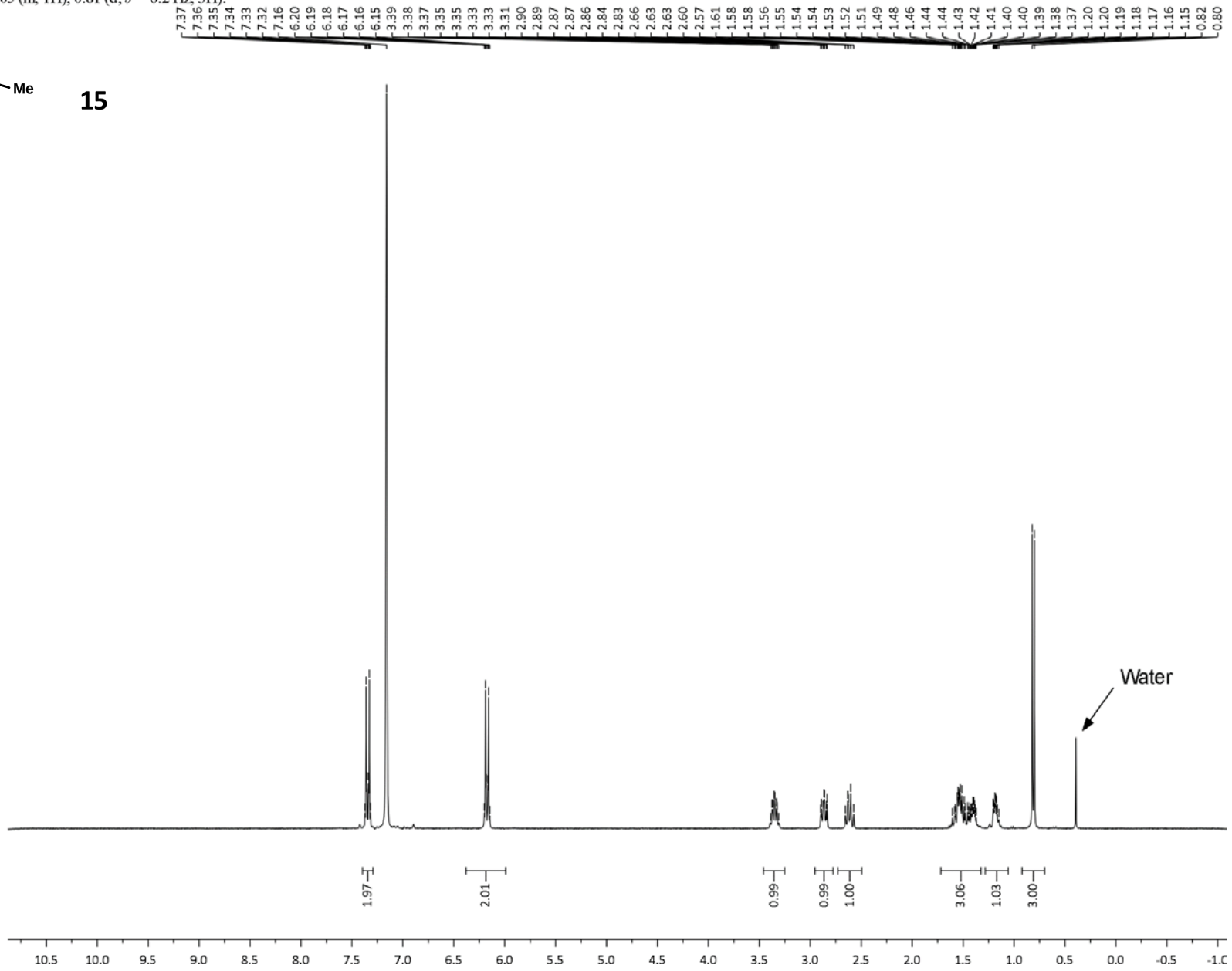


17

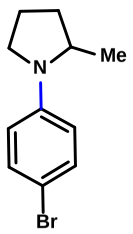
^{1}H NMR (300 MHz, Benzene-d_6) δ 7.44 – 7.23 (m, 2H), 6.37 – 6.02 (m, 2H), 3.35 (tt, J = 6.4, 3.2 Hz, 1H), 2.87 (ddd, J = 9.5, 7.6, 2.5 Hz, 1H), 2.69 – 2.54 (m, 1H), 1.70 – 1.33 (m, 3H), 1.29 – 1.05 (m, 1H), 0.81 (d, J = 6.2 Hz, 3H).



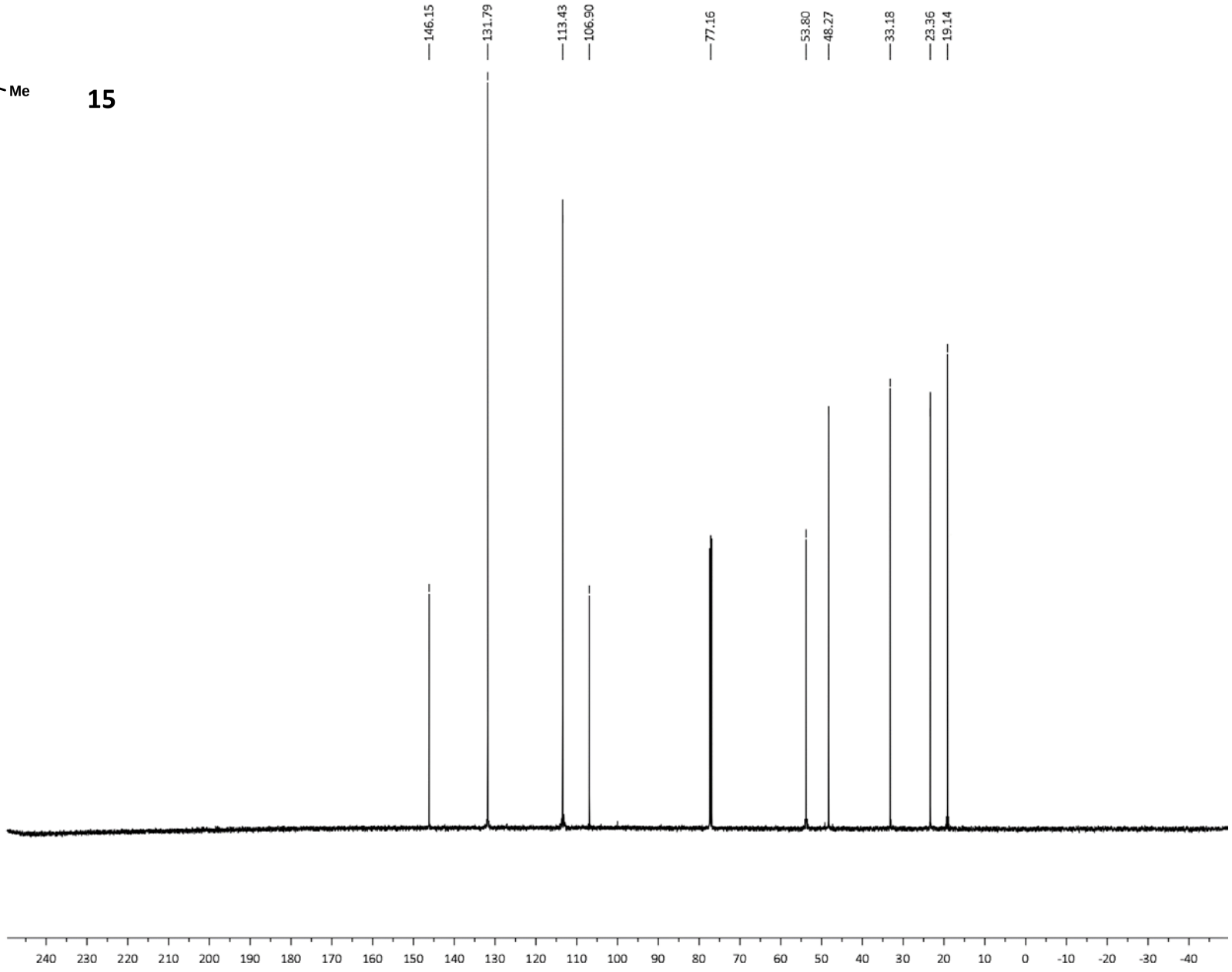
15



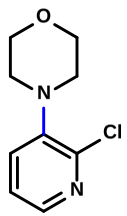
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 131.8, 113.4, 106.9, 53.8, 48.3, 33.2, 23.4, 19.1.



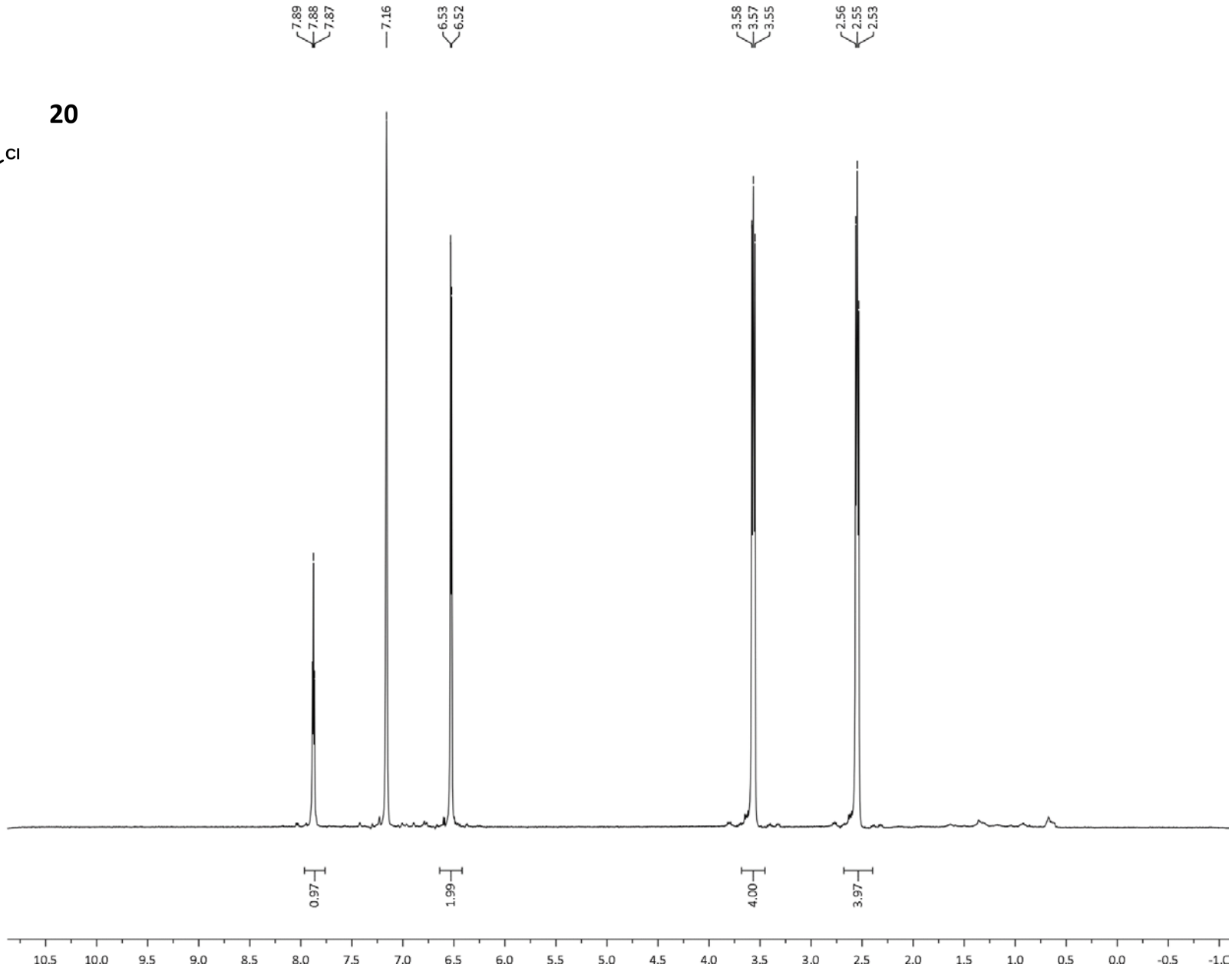
15



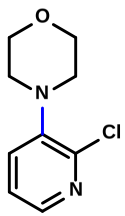
^{1}H NMR (300 MHz, Benzene-d_6) δ 7.88 (t, J = 3.1 Hz, 1H), 6.53 (d, J = 3.2 Hz, 2H), 4.02 – 3.10 (m, 4H), 3.02 – 2.05 (m, 4H).



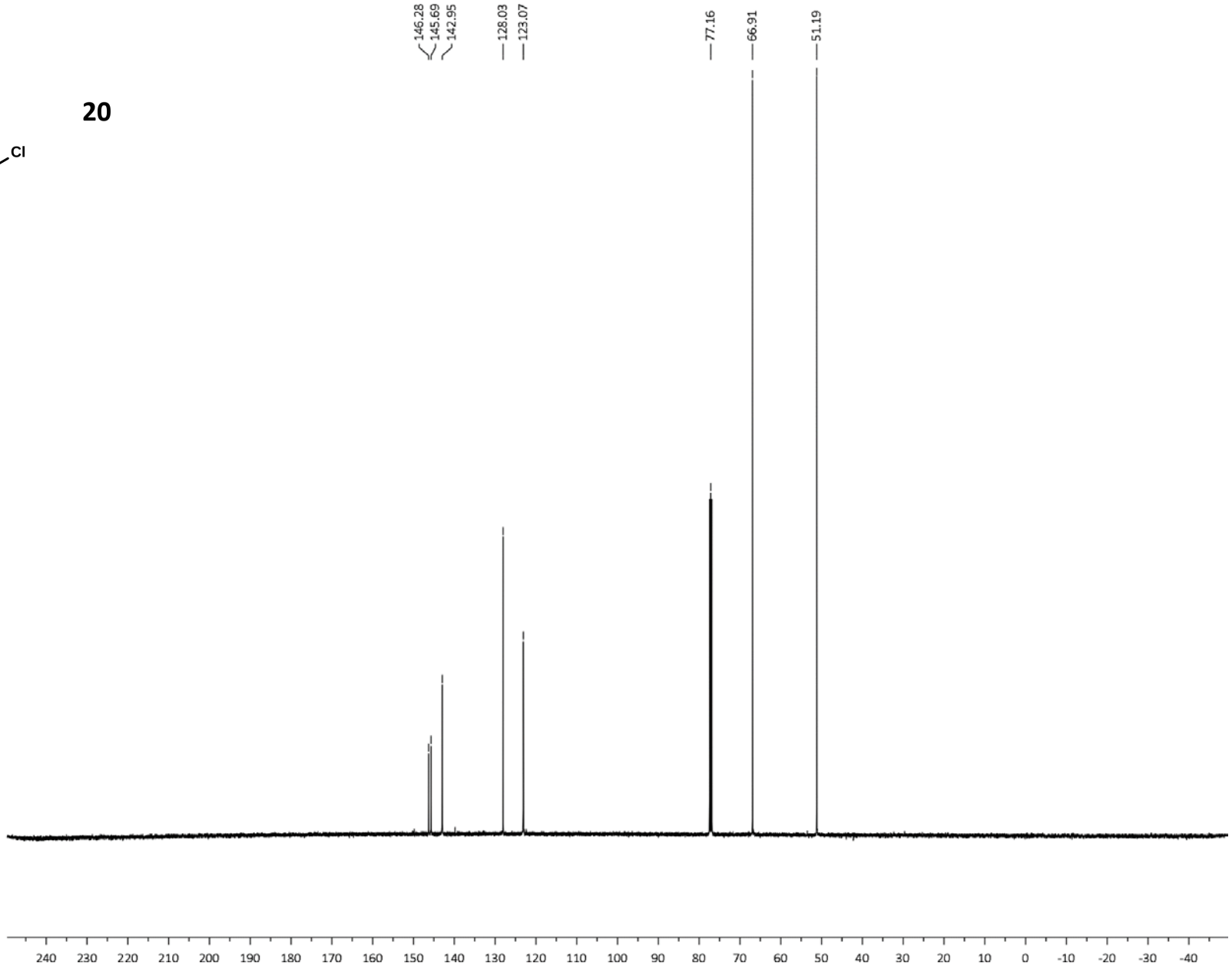
20



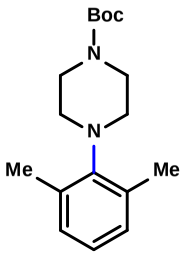
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 145.7, 143.0, 128.0, 123.0, 66.9, 51.2.



20

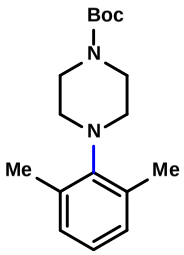


^{1}H NMR (300 MHz, C_6D_6) δ 6.91 (s, 3H), 3.40 (s, 4H), 2.98 – 2.41 (m, 4H), 2.10 (s, 6H), 1.50 (s, 9H).



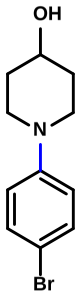
16

^{13}C NMR (126 MHz, C_6D6) δ 154.8, 148.6, 136.9, 129.4, 125.7, 79.1, 49.9, 28.6, 19.7.

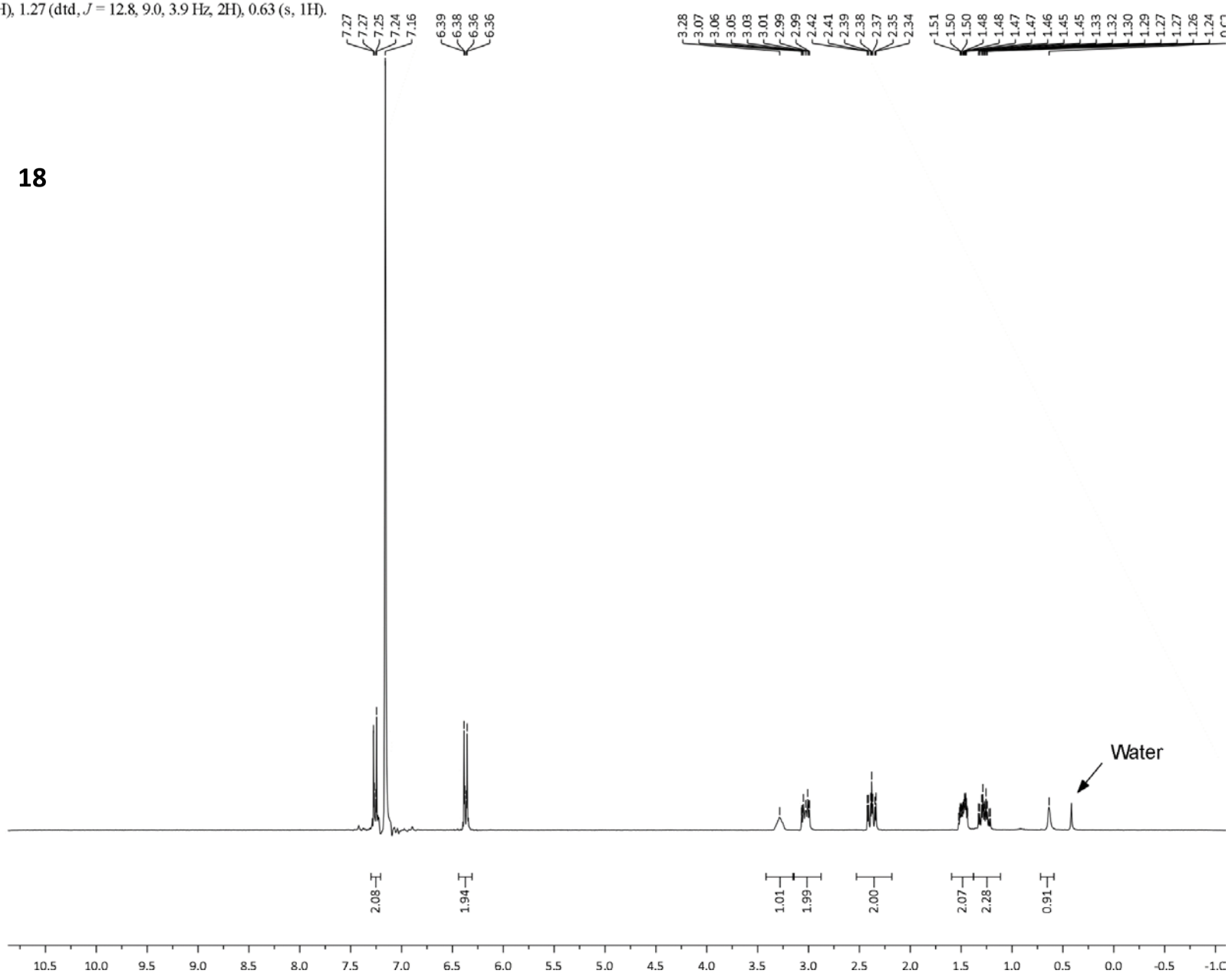


16

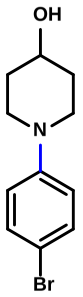
^{1}H NMR (300 MHz, Benzene-d_6) δ 7.30 – 7.21 (m, 2H), 6.42 – 6.33 (m, 2H), 3.28 (s, 1H), 3.13 – 2.94 (m, 2H), 2.38 (ddd, J = 12.7, 9.5, 3.3 Hz, 2H), 1.48 (dddt, J = 12.9, 5.3, 3.7, 2.0 Hz, 2H), 1.27 (dtd, J = 12.8, 9.0, 3.9 Hz, 2H), 0.63 (s, 1H).



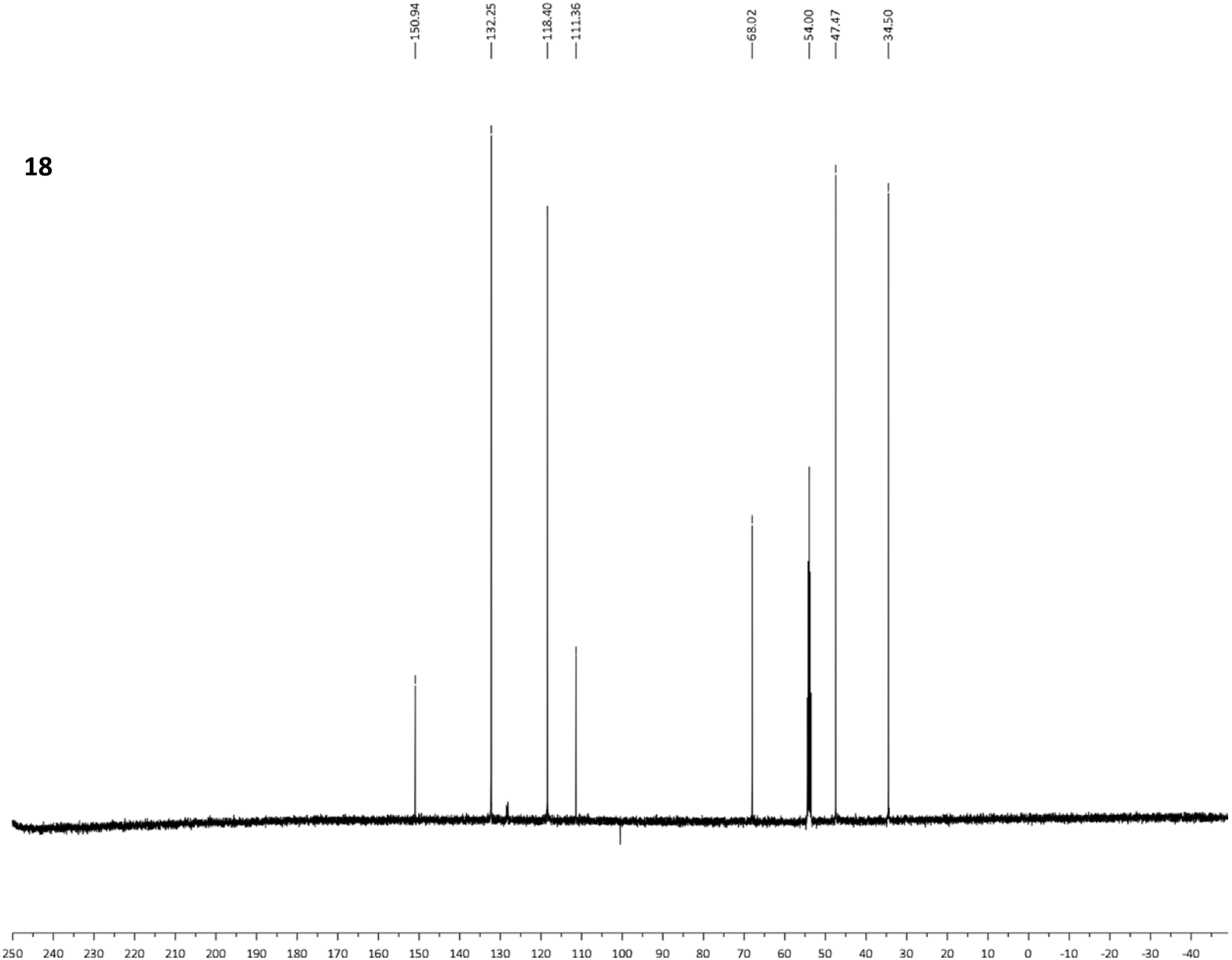
18



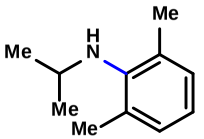
^{13}C NMR (126 MHz, CD_2Cl2) δ 150.9, 132.3, 118.4, 111.4, 68.0, 47.5, 34.5.



18

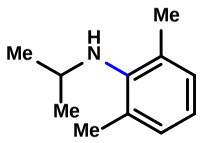


^{1}H NMR (300 MHz, C_6D_6) δ 7.00 (d, J = 7.3 Hz, 2H), 6.87 (dd, J = 8.0, 6.8 Hz, 1H), 3.26 (hept, J = 6.3 Hz, 1H), 2.57 (s, 1H), 2.13 (s, 6H), 0.93 (d, J = 6.3 Hz, 6H).



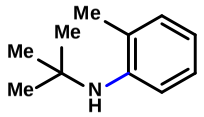
26

^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.4, 129.3, 128.9, 121.4, 48.6, 24.0, 19.1.



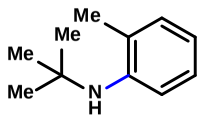
26

^{1}H NMR (300 MHz, C_6D_6) δ 7.12 (d, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 7.3 Hz, 1H), 3.23 (s, 1H), 1.90 (s, 3H), 1.19 (s, 9H).



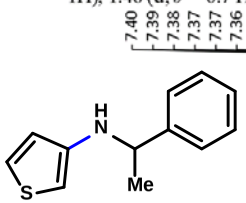
28

^{13}C NMR (126 MHz, $CDCl_3$) δ = 145.1, 130.6, 126.7, 123.7, 117.2, 114.3, 51.3, 30.3, 18.3.



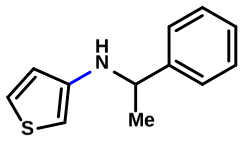
28

^{1}H NMR (300 MHz, Methylene Chloride-d_2) δ 7.52 – 7.17 (m, 5H), 7.08 (dd, J = 5.1, 3.0 Hz, 1H), 6.61 (dd, J = 5.1, 1.5 Hz, 1H), 5.66 (dd, J = 3.0, 1.5 Hz, 1H), 4.36 (q, J = 6.7 Hz, 1H), 4.14 (s, 1H), 1.48 (d, J = 6.7 Hz, 3H).



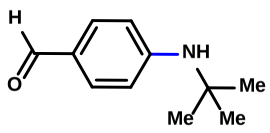
29

^{13}C NMR (126 MHz, Methylene Chloride-d_2) δ 148.1, 146.1, 129.1, 129.0, 127.5, 125.0, 121.0, 97.9, 56.3, 25.3.



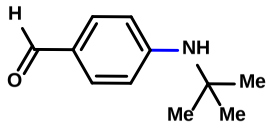
29

^{1}H NMR (300 MHz, C_6D_6) δ 9.80 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 6.26 (d, J = 8.8 Hz, 2H), 3.62 (s, 1H), 0.97 (s, 9H).



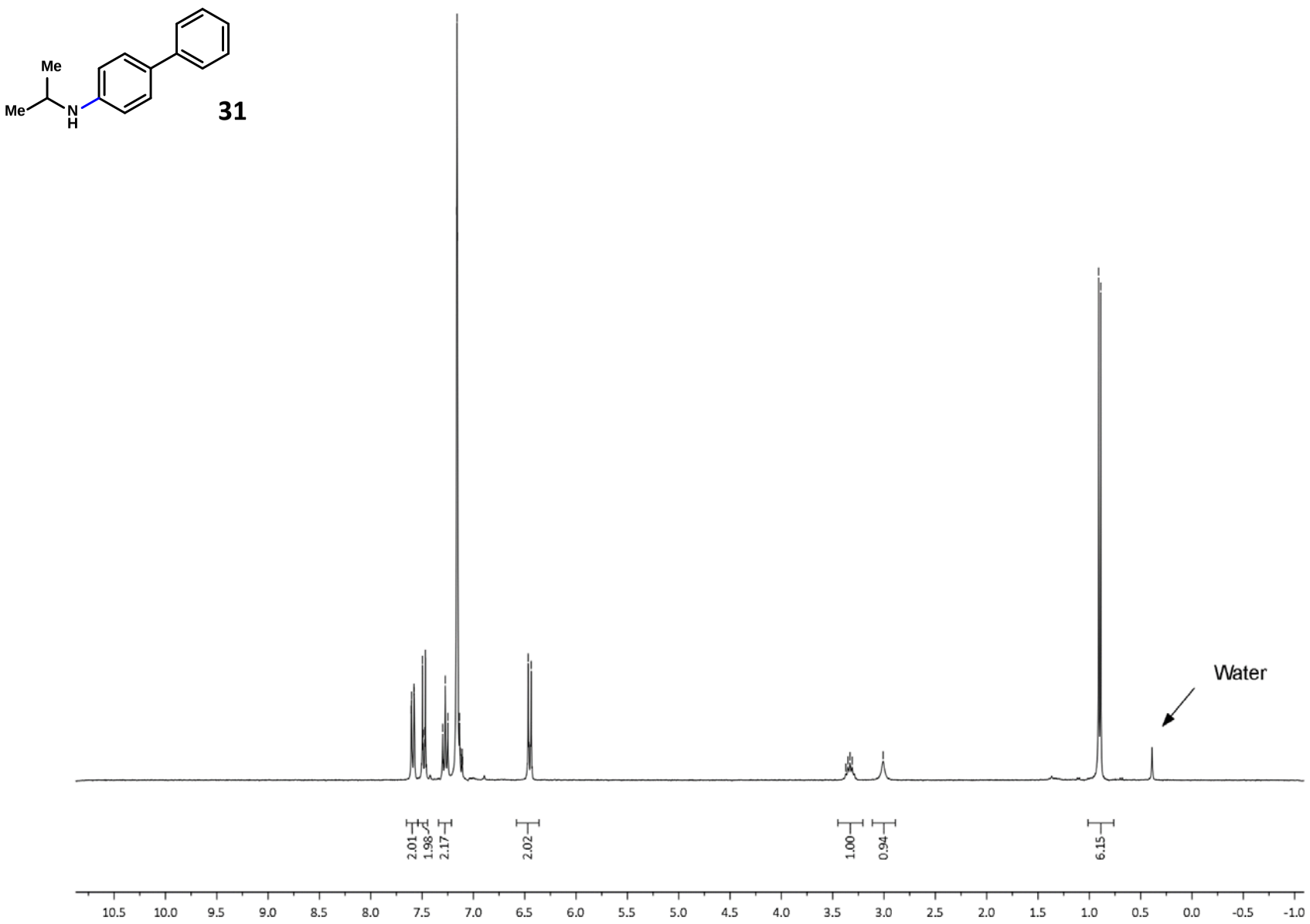
32

^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.2, 152.5, 132.1, 125.7, 113.8, 51.4, 29.5.

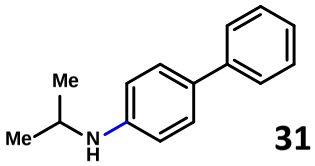


32

^{1}H NMR (300 MHz, Benzene-d_6) δ 7.74 – 7.53 (m, 2H), 7.53 – 7.45 (m, 2H), 7.27 (t, J = 7.6 Hz, 2H), 6.45 (d, J = 8.6 Hz, 2H), 3.49 – 3.20 (m, 1H), 3.01 (s, 1H), 0.90 (d, J = 6.3 Hz, 6H).

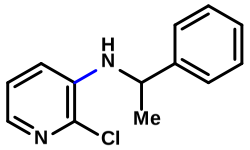


^{13}C NMR (126 MHz, CD_2Cl_2) δ = 147.9, 141.9, 130.0, 129.3, 128.4, 126.7, 126.6, 114.0, 44.9, 23.4



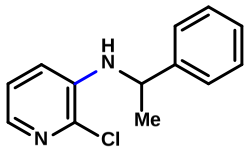
31

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.61 (dd, *J* = 4.6, 1.6 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.18 (m, 1H), 6.92 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.64 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.79 (s, 1H), 4.64 – 4.34 (m, 1H), 1.58 (d, *J* = 6.7 Hz, 3H).



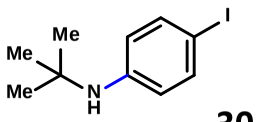
27

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 139.9, 137.1, 136.6, 129.0, 127.5, 125.7, 123.3, 118.9, 77.2, 53.4, 25.2.



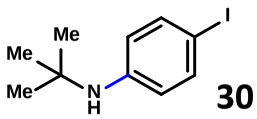
27

^{1}H NMR (300 MHz, C_6D_6) δ 7.53 – 7.20 (m, 2H), 6.29 – 5.93 (m, 2H), 3.01 (s, 1H), 0.99 (s, 9H).



30

^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.5, 137.5, 118.8, 78.8, 51.4, 29.9.



30