Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Material

Catalytic Methoxylation of Aryl Halides Using ^{13}C and ^{14}C-Labeled CO_2

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I. General Information

All reactions were carried out under argon in an mBraun LabMaster dp glovebox and on a Schlenk line. Glassware was dried overnight at 110 °C before use. Unless otherwise stated, reagents were purchased from commercial suppliers. Liquids were stored over 4 Å molecular sieves, which were activated at 200 °C under dynamic vacuum prior to use. Tetrahydrofuran (THF), d_8-THF and C_6D_6 were dried over sodium/benzophenone and distilled before use. CD_3CN was dried over CaH_2 and distilled before use. Carbon dioxide was purchased from Messner in a 5.5 purity gas bottle.

^1H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz spectrometer. Chemical shifts (δ) are expressed in parts per million. Coupling constants (*J*) were reported in Hertz (Hz). ^1H and ^{13}C chemical shifts are referenced to residual solvent signals. The following abbreviations are used: s, singlet; d, doublet; t, triplet; quint, quintuplet; m, multiplet. ^1H and ^{13}C resonance signals were attributed by means of 2D HSQC and HMBC experiments.

IR spectra were recorded on a Shimadzu IRAffinity-1S spectrometer.

Gas chromatography data were recorded at 100 °C under a stream of argon on a Shimadzu GC-2010 Plus equipped with a Carboxen 1010 fused silica capillary column (30 m × 0,53 mm × 30 µm).

Mass spectra were collected from a Shimadzu GCMS-QP2010 Ultra gas chromatograph mass spectrometer equipped with a Supelco SLB$_{TM}$-ms fused silica capillary column (30 m x 0.25 mm x 0.25 µm), source EI.

High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer by the "Fédération de Recherche" ICOA/CBM (FR2708) platform (University of Orléans).

For Carbon-14 radiolabeling:

Carbon-14 reagents and compounds were handled by experimentalist uniquely trained in working with radioactive materials and operating in specialized laboratories. Carbon-14 radioactivity was either measured with a PerkinElmer Ultra Gold liquid scintillation cocktail or with a PerkinElmer 3110TR liquid scintillation analyzer.

RadioHPLC and HPLC-UV analyses were conducted with a Waters Alliance 2695 connected to a MS detector Waters ZQ 2000 and a Scintillation Analyzer Berthold 514 (column Xbridge BEH C18 100x4.6 mm, 3.5 µm). Alternatively, they were also conducted on a Waters Acquity UPLC® equipped PDA eλ Detector and SQ Detector 2, mobile phase A: H_2O + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid and a Scintillation Analyzer Berthold 509 (Xbridge BEH C18 50x2.1, 1.7).

When using $^{14}CO_2$: $^{14}CO_2$ (2.172 GBq.mmol^{-1}) was generated using a $^{14}CO_2$ manifold system (RC Tritec AG).

https://www.rctritec.com/en/tritium-handling-technology/c-14-manifold-system.html

Mass spectra (ESI) for the calculation of specific activities were obtained using a Waters Micromass ZQ spectrometer. Radiochemical purities were determined by Thin Layer Chromatography on TLC silica gel 60F254 glass plates (Merck) using a RITA scanner (Raytest) for the radioactive detection.

II. CO_2 Reduction into BBN-OCH_3

A. General Procedure for CO_2 Reduction into BBN-OCH_3 [1]

A 2.0 mL J. Young NMR tube was charged with $(9\text{-BBN})_2$ dimer **1** (56.8 mg, 2.4×10^{-4} mol, 1.0 eq.), Verkade's base VB^{Me} (2.6 mg, 1.2×10^{-5} mol, 0.050 eq.) and 0.30 mL of d_8-THF. The reaction mixture was freeze-pump-thaw degassed twice and exposed to 1 bar of CO_2. The reaction was stirred at RT and the formation of BBN-OCH_3 **2** was followed by ^{1}H NMR in d_8-THF using mesitylene as internal standard. Full conversion was reached after 2 h. at RT. [1]

Characterization of **BBN-OCH_3** (selected data): **^{1}H NMR** (400 MHz, d_8-THF): 3.70 (s, 3H, BBN-O*C*H_3) ppm, **^{13}C{^{1}H} NMR** (100 MHz, d_8-THF): 53.4 (BBN-O*C*H_3) ppm and **^{11}B NMR** (128.4 MHz, d_8-THF): 56.7 ppm.

B. Evidence for Stoichiometric Conversion of $^{13}CO_2$ into BBN-O$^{13}CH_3$

A J. Young NMR tube was charged with $(9\text{-BBN})_2$ dimer **1** (36.6 mg, 1.5×10^{-4} mol, 1.5 eq.), Verkade's base VB^{Me} (1.6 mg, 7.5×10^{-6} mol, 0.075 eq. = 5 mol% *vs.* $(9\text{-BBN})_2$) and 0.4 mL of d_8-THF. The tube was connected to the Tritec, frozen, vacuum pumped and loaded with $^{13}CO_2$ (1.0×10^{-4} mol, 1 eq.). The reaction was stirred for 3 h at RT and monitored by NMR spectroscopy using mesitylene as internal standard.

^{1}H NMR revealed the formation of 83% of BBN-O$^{13}CH_3$ **[^{13}C]2** along with 7.5% of the acetal $H_2{}^{13}C(OBBN)_2$ (**Figure 1**). ^{13}C{^{1}H} NMR showed one main ^{13}C enriched peak at δ = 53.8 ppm assigned to BBN-O$^{13}CH_3$ **[^{13}C]2** and a minor ^{13}C enriched peak corresponding to $H_2{}^{13}C(OBBN)_2$ at δ = 86.6 ppm. Besides ^{13}C{^{1}H} NMR evidenced the absence of any $^{13}CO_2$ in the solution (no peak at δ = 125.7 ppm) (**Figure 2**). ^{11}B NMR confirmed full consumption of the $(9\text{-BBN})_2$ dimer **1**.

In addition, GC analysis of the J. Young tube's headspace proved the absence of any remaining $^{13}CO_2$ in the gas phase. Tiny amounts of N_2, originating from commercial d_8-THF, and of H_2, arising from the quenching of water traces by 9-BBN, were detected. The chromatogram's peaks could be assigned by comparison of the retention times relative to a standard injection containing a mixture of H_2/CO/CO_2. The chromatograms are presented in **Figure 3**.

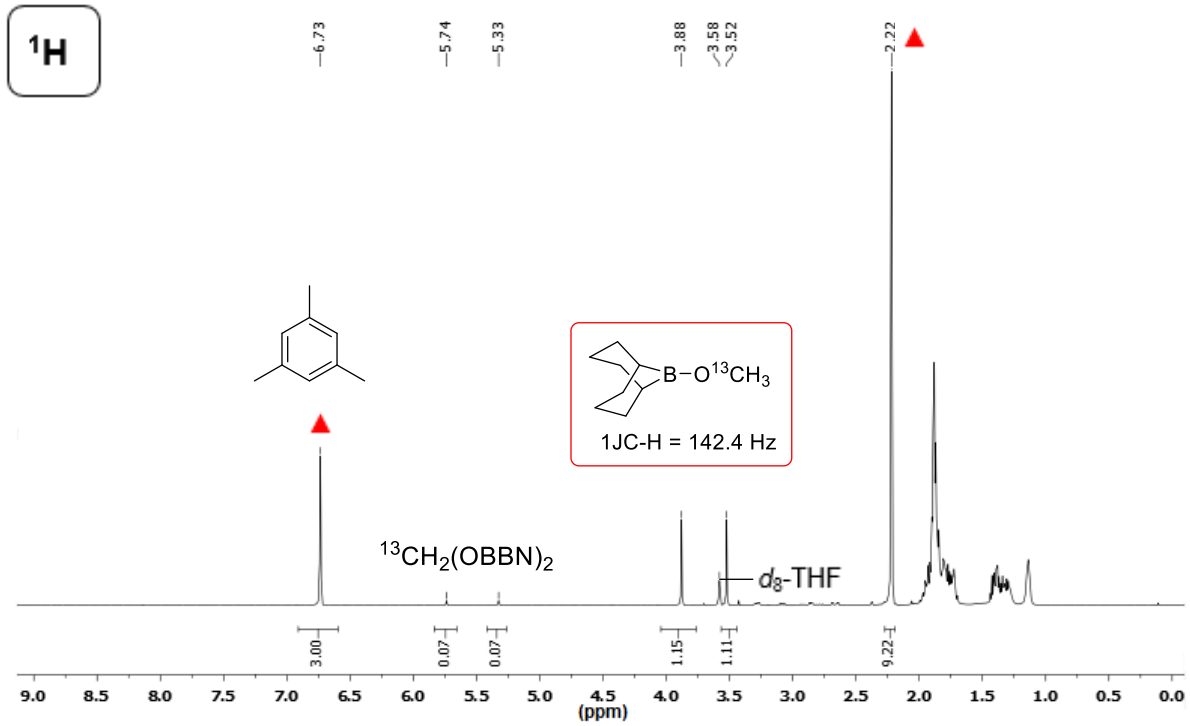


Figure S1: ^{1}H NMR spectrum of the reaction between 1.5 eq. of (9-BBN)$_2$ **1** and 1 eq. of $^{13}CO_2$ in the presence in 5 mol% of VB^{Me} in d_8-THF after 3 h. at RT (D1 = 30). Mesitylene is used as internal standard.

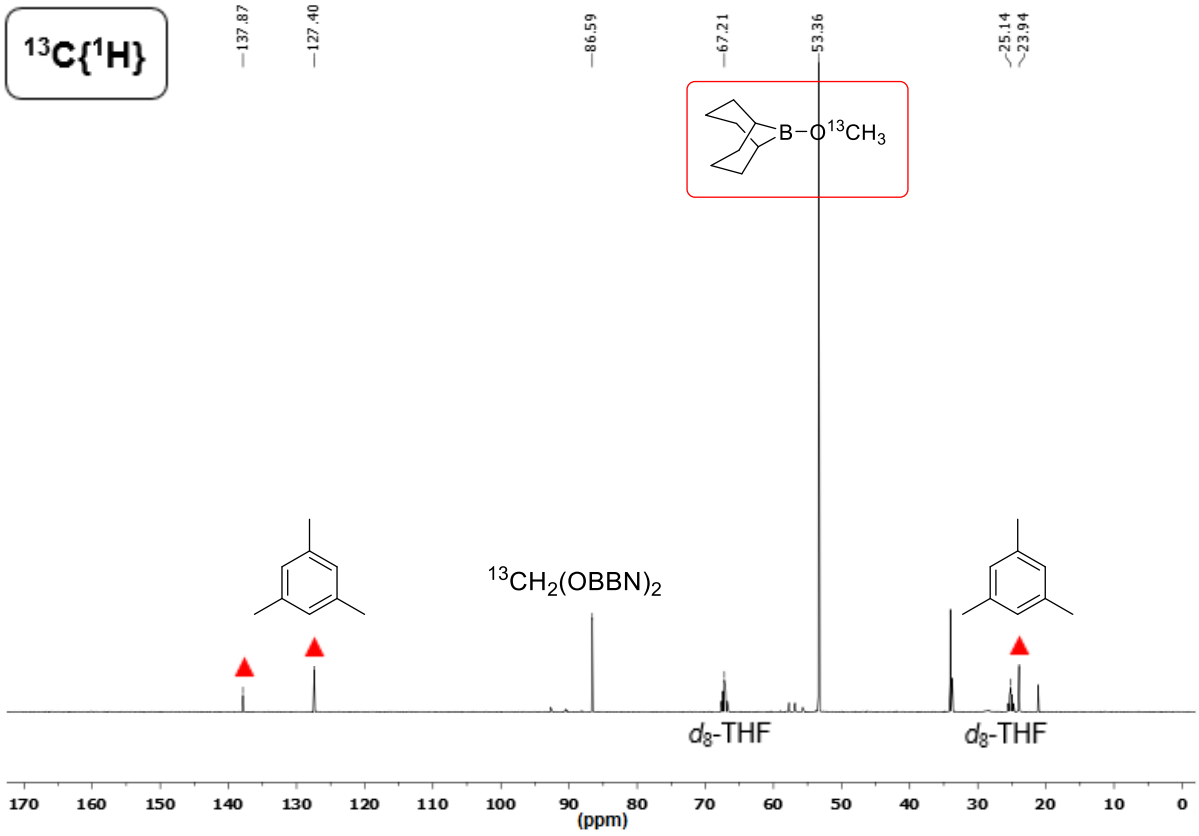


Figure S2: $^{13}C\{^{1}H\}$ NMR spectrum of the reaction between 1.5 eq. of (9-BBN)$_2$ **1** and 1 eq. of $^{13}CO_2$ in the presence in 5 mol% of VB^{Me} in d_8-THF after 3 h. at RT. Generation of BBN-O$^{13}CH_3$ **[^{13}C]2** and minor amounts of acetal $^{13}CH_2(OBBN)_2$. Red triangles mark peaks related to mesitylene.

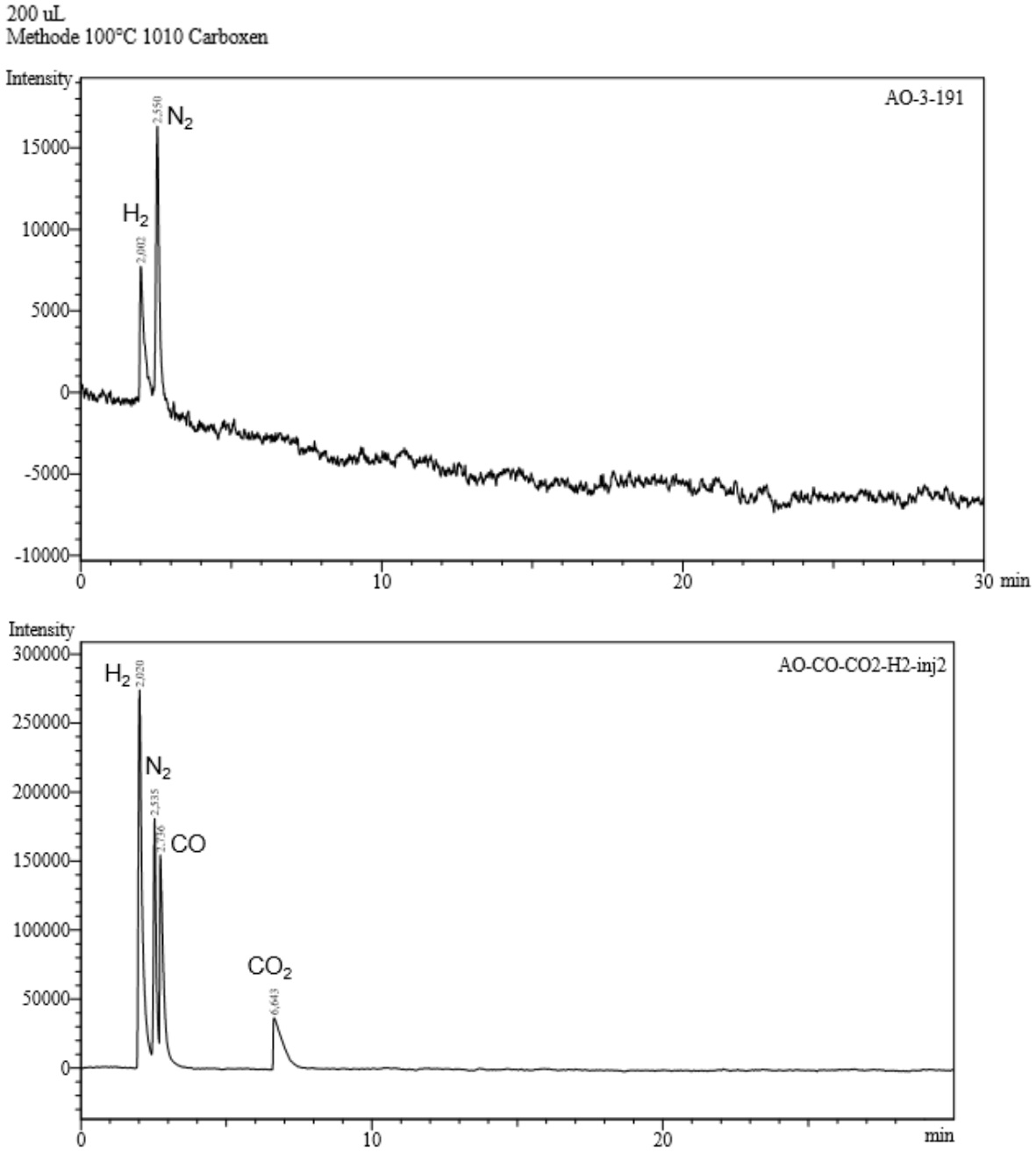


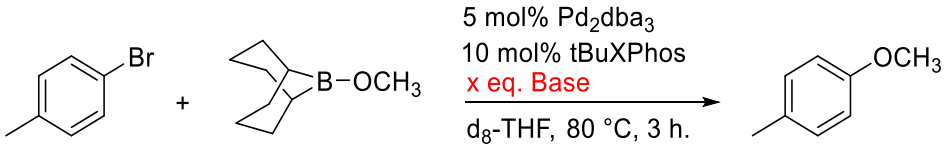
Figure S3: GC analyses carried out at 100 °C under a stream of argon using a Carboxen 1010 capillary column, injected volume 200 µL. **Top** - Chromatogram of the J. Young tube's headspace of the reaction between 1.5 eq. of $(9\text{-BBN})_2$ **1** and 1.0 eq. of $^{13}CO_2$ catalyzed by 5 mol% VB^{Me} after 3 h. at RT. Absence of CO_2. **Bottom** - Chromatogram of a reference sample containing a mixture of $H_2/CO/CO_2$.

III. Optimization of the Palladium Catalyzed Suzuki Cross Coupling

The reaction conditions were optimized on a J. Young tube scale (0.1 mmol).

A J. Young NMR tube was charged with 4-bromotoluene **3a** (17.1 mg, 1.0×10^{-4} mol, 1 eq.), a selected base, 10 mol% ligand (*t*BuXPhos, 4.2 mg, 1.0×10^{-5} mol, 0.10 eq.), 5 mol% Pd catalyst (Pd_2dba_3, 4.6 mg, 5.0×10^{-6} mol, 0.050 eq.) and 0.3 mL of d_8-THF. Finally, BBN-OMe **2** (1.0 M in hexanes) (100 µL, 1.0×10^{-4} mol, 1 eq.) was added to the reaction mixture. Mesitylene or diphenylmethane were used as internal standards. The reactions were kept at 80 °C and monitored by ^{1}H NMR spectroscopy.

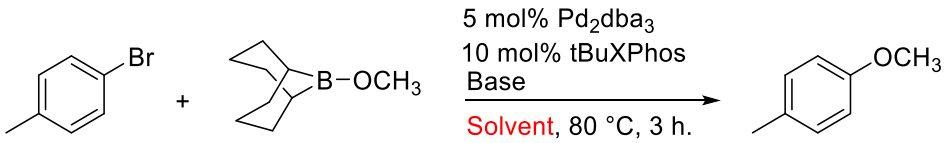
A. Influence of the Base



Entry	Equivalents	Base	pKa	Yield (%)
1	1.5	NaOAc	4.8	0
2	1.5	Cs_2CO_3	10.3	54
3	1.5	KOMe	16.0	80
4	1.0	KO*i*Pr	16.5	62
5	1.5	KO*t*Bu	17.0	54
6	1.5	TBAF	-	0
7	1.5	TBAT	-	0
8	2.0	CsF	-	66

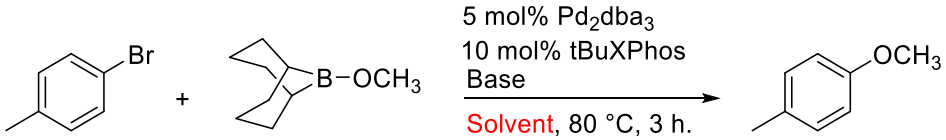
Table S1: Influence of the base on the yield of cross coupled product.

B. Influence of the Solvent



Entry	Base	Solvent	Dielectric constant ε_r	Yield (%)
1	1.5 eq. Cs_2CO_3	***d*$_8$-THF**	7.58	54
2	1.5 eq. Cs_2CO_3	C_6D_6	2.27	12
3	1.5 eq. Cs_2CO_3	DMF	36.7	~ 10 - 15

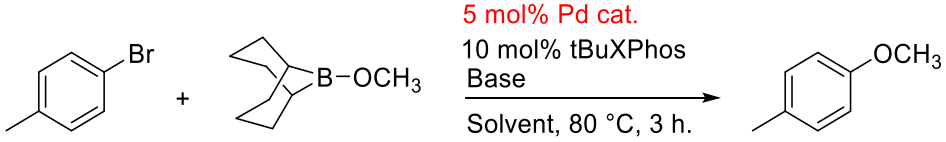
Table S2: Influence of the solvent on the yield of cross coupled product.



Entry	Base	Solvent	Dielectric constant ε_r	Yield (%)
4	1.0 eq. KO*t*Bu	***d*$_8$-THF**	7.58	54
5	1.0 eq. KO*t*Bu	dioxane	2.25	n.d. (poor)
6	2.0 eq. CsF	***d*$_8$-THF**	7.58	66
7	2.0 eq. CsF	CD_3CN	37.5	60 - 68

Table S2: Influence of the solvent on the yield of cross coupled product.

C. Influence of the Palladium Catalyst

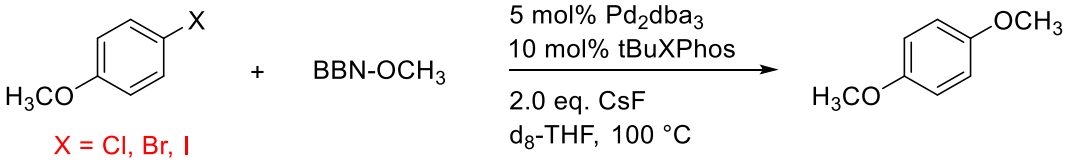


Entry	Pd Catalyst	Base	Solvent	Yield (%)
1	**Pd_2dba_3**	1.5 eq. Cs_2CO_3	*d*$_8$-THF	54
2	$Pd(OAc)_2$	1.5 eq. Cs_2CO_3	*d*$_8$-THF	33
3	**Pd_2dba_3**	2.0 eq. CsF	*d*$_8$-THF	66
4	$Pd(OAc)_2$	2.0 eq. CsF	*d*$_8$-THF	~ 50
5	$Pd(OAc)_2$	2.0 eq. CsF	C_6D_6	traces

Table S3: Influence of the palladium catalyst on the yield of cross-coupled product.

D. Influence of the Aryl Halide

A J. Young NMR tube was charged with the corresponding aryl halide **3** (1.0×10^{-4} mol, 1 eq.), 2 eq. of CsF (30.4 mg, 2×10^{-4} mol, 2 eq.), 10 mol% *t*BuXPhos (4.2 mg, 1.0×10^{-5} mol, 0.10 eq.), 5 mol% Pd_2dba_3 (4.6 mg, 5.0×10^{-6} mol, 0.050 eq.) and 0.3 mL of d_8-THF. Finally, BBN-OMe **2** (1.0 M in hexanes) (100 µL, 1.0×10^{-4} mol, 1 eq.) was added to the reaction mixture. Mesitylene was used as internal standard. The reactions were kept overnight at 100 °C and followed by ^{1}H NMR spectroscopy.



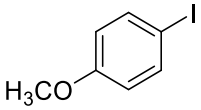
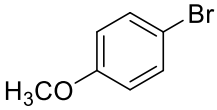
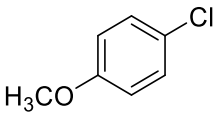
Entry	Substrate	Reaction time (h.)	Yield (%)
1		18	15 - 17
2		23	45
3		23	54

Table S4: Influence of the halide on the yield of cross-coupled product.

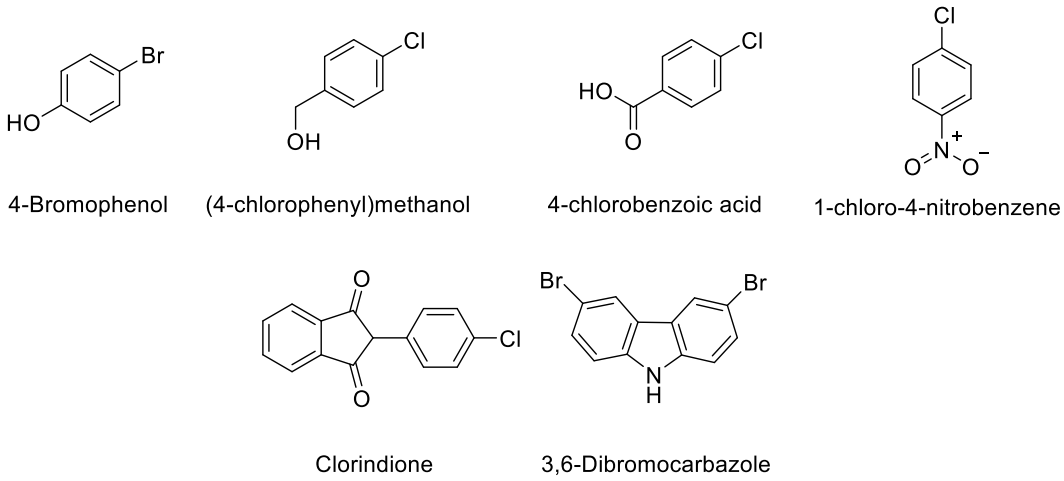
E. Influence of the Temperature

The reactions were finally run at 100 °C to reach maximal conversion for less activated substrates.

We noted that most substrates were converted into the corresponding product during the first 3 hours. Afterwards the reaction rate drastically slowed down.

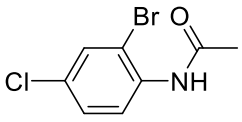
F. Limitations

The reaction does not tolerate alcohols (4-bromophenol), carboxylic acid and primary or secondary amines (3,6-dibromocarbazole).



Scheme S1: Alcohols and amine, which do not undergo Suzuki cross coupling with BBN-OCH_3.

Highly substituted and electron rich substrates, such as 5-bromo-2,4-dimethoxypyrimidine, didn't undergo Suzuki cross coupling with BBN-OCH_3 **2**, but instead led to extensive β-hydride elimination to generate the corresponding reduced arene.



N-(2-bromo-4-chlorophenyl)acetamide

When both Csp^2-Cl and Csp^2-Br substituents are included in the substrate, competitive methoxylations led to a mixture of methoxylated products, difficult to separate implying a limitation in term of selectivity towards the methoxylation at the chloro-position.

IV. General Reaction Conditions

A. Set-Up

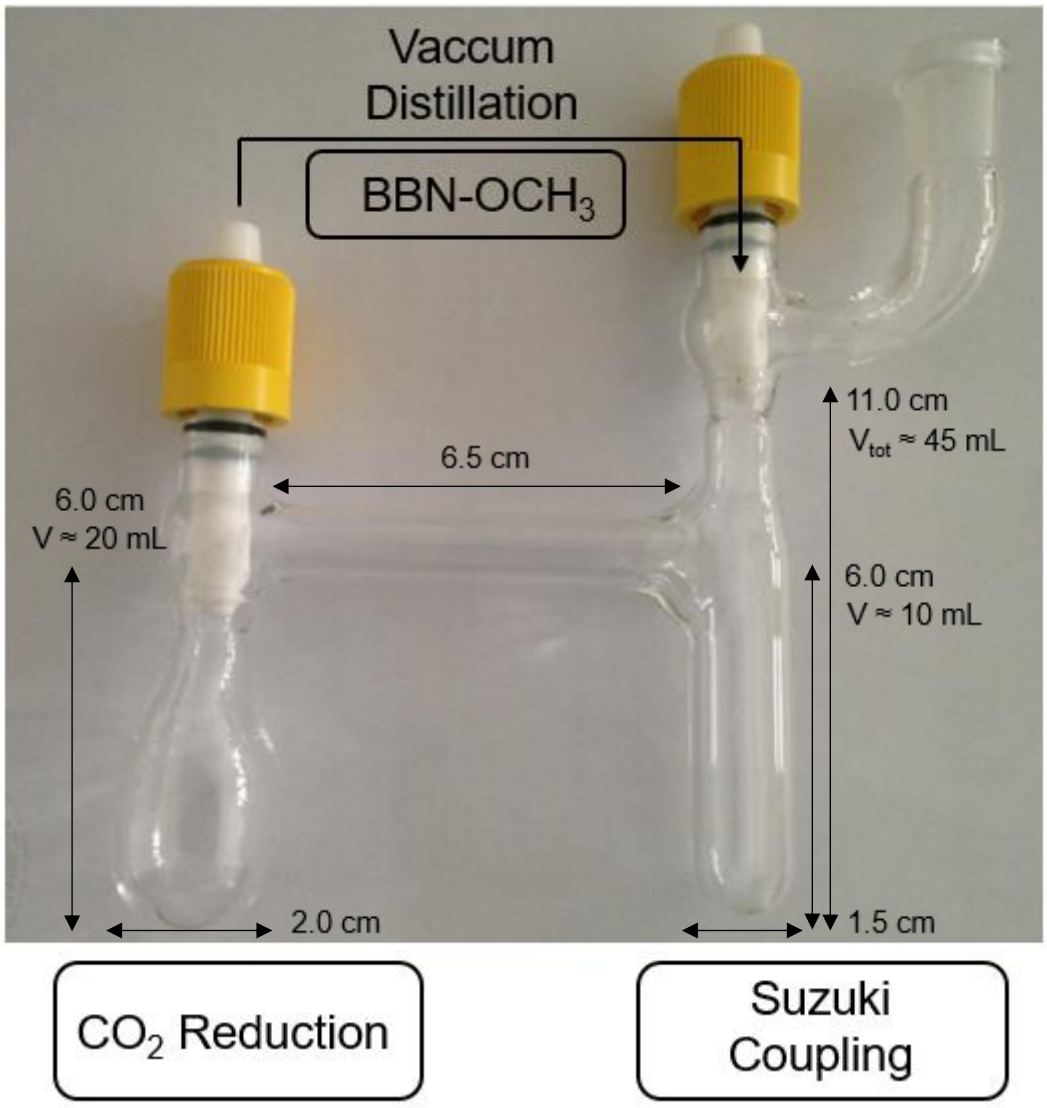


Figure S4: Double chamber set-up for $^{13}CO_2$ reduction in BBN-O$^{13}CH_3$ **[^{13}C]2** with subsequent palladium catalyzed Suzuki cross coupling between BBN-O$^{13}CH_3$ **[^{13}C]2** and aryl chlorides **3**.

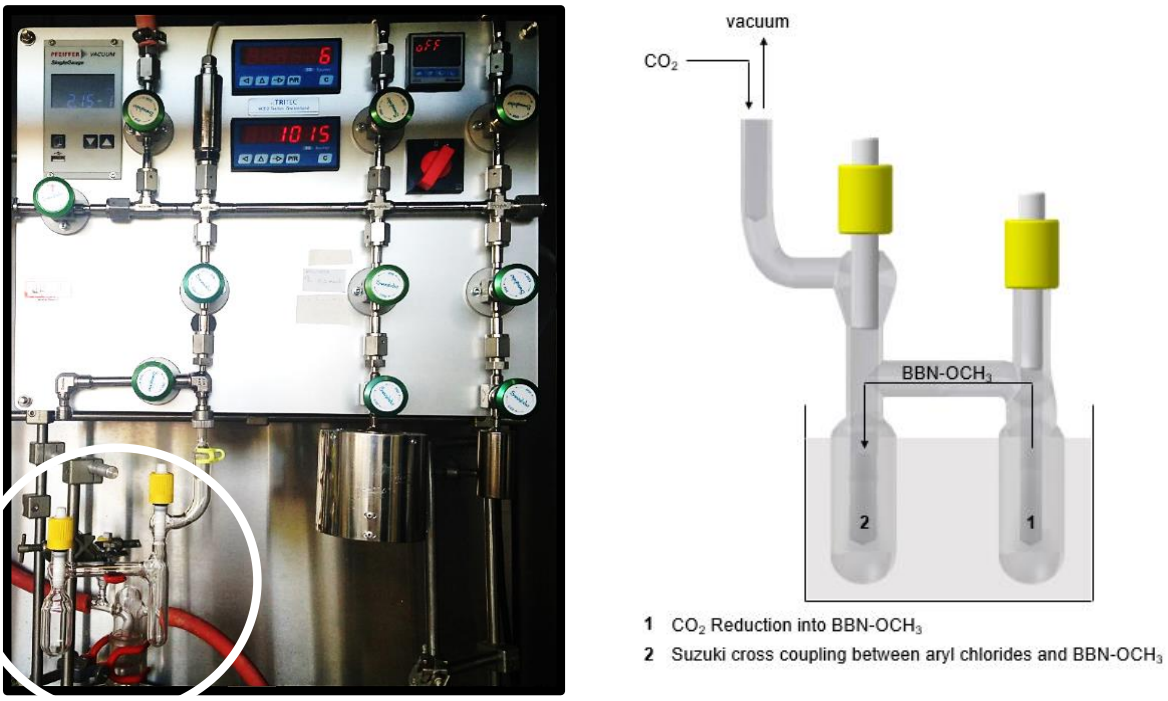


Figure S5: Double chamber connected to the RC Tritec.

B. General Reaction Procedure for both Carbon-13 and Carbon-14 Labeling

General Protocol

Both vessels of the double chamber set-up were equipped with small magnetic stirring bars. 1.5 eq. of $(9\text{-BBN})_2$ dimer **1** (366.0 mg, 1.5×10^{-3} mol, 1.5 eq.) together with 5 mol% of Verkade's base VB^{Me} (16.2 mg, 7.5×10^{-5} mol, 0.075 eq., 5 mol% *vs.* $(9\text{-BBN})_2$) were added to the reduction chamber. 2 eq. of CsF (303.8 mg, 2.0×10^{-3} mol, 2.0 eq.), 1eq. of substrate **3** if it is a solid (1.0×10^{-3} mol, 1.0 eq.), 10 mol% of *t*BuXPhos (42.5 mg, 1.0×10^{-4} mol) and 5 mol% of Pd_2dba_3 (45.8 mg, 5.0×10^{-5} mol) were then weighted into the Suzuki chamber. Afterwards, 4 mL of THF were added to the reduction chamber, which was tightly closed. The reagents in the Suzuki chamber were dissolved in 2 mL of THF. If the substrate **3** is a liquid, it was introduced at this point to the Suzuki chamber (1.0×10^{-3} mol, 1.0 eq.).

The whole set-up was then connected to the RC Tritec and the solutions were frozen in liquid nitrogen. Both chambers were opened to a vacuum pump in order to degas them, before adding 1.0 eq. of $^{13}CO_2$ (1.0×10^{-3} mol, 1.0 eq.). The reaction was stirred for 3 h. at RT and quantitatively generated BBN-$O^{13}CH_3$ **[^{13}C]2**, which needed to be distilled from the reduction chamber to the Suzuki chamber.

Thereafter, both solutions were frozen in liquid nitrogen and the set-up was put under static vaccum through a Schlenk line. The trap-to-trap distillation started by keeping the reduction chamber at RT, while the Suzuki chamber was plunged into liquid nitrogen. When nearly all liquid had been transferred to the second vessel, the reduction chamber was heated to 100 °C in order to properly distill all BBN-O$^{13}CH_3$ (230 °C < Bpt < 260 °C). The vacuum distillation can be finished by using the heat gun. The set-up was then brought back to RT and an atmospheric pressure of argon.

The reduction chamber was closed and the Suzuki coupling was stirred overnight (18 h.) at 100 °C. The double chamber was tilted to avoid collecting solvents around the stopper of the reduction chamber. The red solution turned orange and palladium black fell out of the solution.

Titration

The reaction was cooled down to RT. The yield was determined by ^{1}H NMR using CH_2Cl_2 as internal standard and a D1 = 40. Two titrations were carried out for each run (0.5 mL solution + 10 µL CH_2Cl_2 in a J. Young tube).

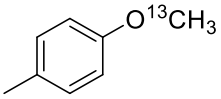
Work-up

The reaction mixture was diluted with 10 mL of CH_2Cl_2. The organic phase was washed with 15 mL of H_2O. The aqueous phase was then washed with 15 mL of CH_2Cl_2. The combined organic fractions were finally washed with 35 mL of brine and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude mixture was purified by column chromatography (SiO_2).

V. Characterization

A. Carbon-13 Labeled Compounds

[^{13}C] 4-Methylanisole [2, 3] **([^{13}C]4b)**



$C_7{}^{13}CH_{10}O$
MW: 123.08 g.mol^{-1}
Yield: 44%
Pale Yellow liquid

After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/Et_2O 100:1 and when the product comes out move to pentane/Et_2O 50:1) [^{13}C] 4-methylanisole **[^{13}C]4b** was obtained with 44 % yield (54.2 mg, 4.40 × 10^{-4} mol) as a very pale yellow liquid.

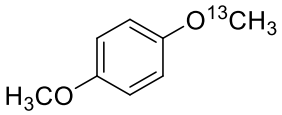
^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 2.30 (s, 3H, C*H*$_3$), 3.79 (d, $^1J_{C\text{-}H}$ = 143.6 Hz, 3H, O^{13}C*H*$_3$), 6.82 (d, ^3J = 8.4 Hz, 2H, C*H*-C(O^{13}CH$_3$)), 7.10 (d, ^3J = 8.4 Hz, 2H, C*H*-C(CH$_3$)).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 20.6 (*C*H$_3$), 55.4 (O^{13}*C*H$_3$), 113.8 (d, $^3J_{C\text{-}C}$ = 4.1 Hz, *C*H-C(O^{13}CH$_3$)), 129.9 (*C*(CH$_3$)), 130.0 (*C*H-C(CH$_3$)), 157.6 (d, $^2J_{C\text{-}C}$ = 2.1 Hz, *C*(O^{13}CH$_3$)).

FTIR (cm^{-1}) 2944, 2905, 2831, 1612, 1585, 1508, 1464, 1435, 1294, 1230, 1175, 1109, 1034, 1018, 912, 825, 733, 717, 708.

MS (EI**)** ***m/z*** 123 (100), 122 (50), 107 (35), 92 (15), 91 (25), 79 (30), 77 (50).

[^{13}C] 4-Methoxyanisole [3, 4] **([^{13}C]4c)**



$C_7{}^{13}CH_{10}O_2$
MW: 139.07 g.mol^{-1}
Yield: 53%
White Solid

After purification by column chromatography (SiO_2, pentane/Et_2O 40:1) [^{13}C] 4-methoxyanisole **[^{13}C]4c** is obtained as a white solid with 53 % yield (73.8 mg, 5.30 × 10^{-4} mol).

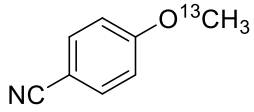
^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 3.77 (d, $^1J_{C\text{-}H}$ = 143.2 Hz, 3H, O^{13}C*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 6.85 (s, 4H, C*H*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 55.8 (O*C*H$_3$ + O^{13}*C*H$_3$), 114.8 (s, *C*H-C(OCH$_3$)), 114.8 (d, $^3J_{C\text{-}C}$ = 4.0 Hz, *C*H-C(O^{13}CH$_3$)), 153.9 (*C*(OCH$_3$) + *C*(O^{13}CH$_3$)).

FTIR (cm^{-1}) 2951, 2908, 2833, 1508, 1466, 1435, 1294, 1261, 1230, 1177, 1111, 1034, 1014, 944, 825, 706.

MS (EI) ***m/z*** 139 (100), 124 (70), 123 (70), 96 (30), 95 (30).

[^{13}C] 4-Methoxybenzonitrile [5, 6] **([^{13}C]4d)**



$C_7{}^{13}CH_7NO$
MW: 134.06 $g.mol^{-1}$
Yield: 76 %
White solid

After purification by column chromatography (SiO_2, start with pentane/CH_2Cl_2 7:1, when the product is coming out switch to pentane/CH_2Cl_2 1:1) [^{13}C] 4-methoxybenzonitrile **[^{13}C]4d** is obtained as a white solid with 76 % yield (102 mg, 7.60×10^{-4} mol).

^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 3.85 (d, $^1J_{C\text{-}H}$ = 144.8 Hz, 3H, O^{13}C*H*$_3$), 6.93 – 6.96 (m, 2H, C*H*-C(O^{13}CH$_3$)), 7.56 – 7.60 (m, 2H, C*H*-C(CN)).

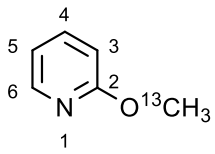
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 55.7 (O^{13}*C*H$_3$), 104.1 (*C*(CN)), 114.9 (d, $^3J_{C\text{-}C}$ = 4.2 Hz, *C*H-C(O^{13}CH$_3$)), 119.3 (*C*N), 134.1 (*C*H-C(CN)), 163.0 (d, $^2J_{C\text{-}C}$ = 2.3 Hz, *C*(O^{13}CH$_3$)).

FTIR (cm^{-1}) 3015, 2970, 2941, 2916, 2898, 2839, 2216, 1604, 1577, 1508, 1458, 1442, 1433, 1420, 1304, 1254, 1175, 1114, 1008, 986, 828, 808, 681, 544.

MS (EI) ***m/z*** 134 (100), 103 (50), 90 (55), 64 (20), 63 (20).

HRMS (ESI-TOF) ***m/z*** calcd for $C_7{}^{13}CH_7NO$ $[M+H]^+$: 135.0634, found: 135.0632.

[^{13}C] 2-Methoxypyridine [7] **([^{13}C]4e)**



$C_5{}^{13}CH_7NO$
MW: 110.06 $g.mol^{-1}$

After purification by column chromatography (SiO_2, pentane/Et_2O 40:1), 17 mg of [^{13}C] 2-methoxypyridine **[^{13}C]4e** were obtained as colorless liquid. Most product was lost after evaporation of the solvent, as it forms an azeotrope with Et_2O. No isolated yield will therefore be reported for this product.

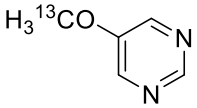
^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 3.93 (d, $^{1}J_{C\text{-}H}$ = 145.6 Hz, 3H, $O^{13}CH_3$), 6.72 – 6.76 (m, 1H, *H*$_3$), 6.83 – 6.88 (m, 1H, *H*$_5$), 7.52 – 7.59 (m, 1H, *H*$_4$), 8.14 – 8.19 (m, 1H, *H*$_6$).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 53.4 ($O^{13}CH_3$), 111.1 (d, $^{3}J_{C\text{-}C}$ = 2.1 Hz, *C*$_3$), 116.8 (*C*$_5$), 138.6 (*C*$_4$), 147.0 (*C*$_6$), 164.3 (d, $^{2}J_{C\text{-}C}$ = 2.7 Hz, *C*$_2$).

FTIR (cm^{-1}) 2960, 2924, 2855, 1703, 1603, 1572, 1480, 1443, 1416, 1310, 1288, 1203, 1142, 1096, 1041, 1008, 986, 808, 781.

MS (EI) ***m/z*** 110 (25), 109 (30), 79 (30), 52 (20), 40 (100).

[^{13}C] 5-Methoxypyrimidine [8, 9] **([^{13}C]4f)**



$C_4{}^{13}CH_6N_2O$
MW: 111.05 g.mol^{-1}
Yield: 42 %
Yellow solid

After purification by column chromatography (SiO_2, CH_2Cl_2/MeOH 100:1) [^{13}C] 5-methoxypyrimidine **[^{13}C]4f** is obtained as a yellow solid with 42 % yield (46.7 mg, 4.20×10^{-4} mol).

^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 3.90 (d, $^{1}J_{C\text{-}H}$ = 145.2 Hz, 3H, $O^{13}CH_3$), 8.40 (s, 2H, C-C*H*-N), 8.83 (s, 1H, N-C*H*-N).

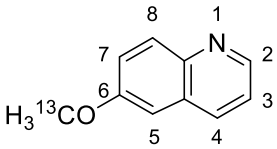
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 55.9 ($O^{13}CH_3$), 143.3 (d, $^{3}J_{C\text{-}C}$ = 4.2 Hz, (C-*C*H-N), 151.6 (N-*C*H-N), 160.7 (*C*($O^{13}CH_3$)).

FTIR (cm^{-1}) 3049, 2935, 2871, 1703, 1653, 1574, 1559, 1465, 1448, 1413, 1344, 1273, 1206, 1179, 1156, 1114, 1035, 1001, 917, 887, 813, 721, 615.

MS (EI) ***m/z*** 111 (100), 84 (10), 68 (30), 57 (50), 40 (30).

HRMS (ESI-TOF) ***m/z*** calcd for $C_4{}^{13}CH_6N_2O$ $[M+H]^+$: 112.0586, found: 112.0587.

[^{13}C] 6-Methoxyquinoline [10, 11, 12] **([^{13}C]4g)**



$C_9{}^{13}CH_9NO$
MW: 160.07 g.mol^{-1}
Yield: 46 %
Yellow liquid

After purification by column chromatography (SiO_2, wet the column with pentane/EtOAc 9:1, then switch to pentane/EtOAc 8:2) [^{13}C] 6-methoxyquinoline **[^{13}C]4g** is obtained as a yellow liquid with 46 % yield (73.7 mg, 4.60 × 10^{-4} mol).

^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 3.89 (d, $^1J_{C\text{-}H}$ = 144 Hz, 3H, O^{13}C*H*$_3$), 7.03 (d, ^4J = 2.8 Hz, 1H, *H*$_5$ or *H*$_7$), 7.31 – 7.38 (m, 2H, *H*$_3$ + *H*$_5$ or *H*$_7$), 7.99 (d, ^3J = 9.6 Hz, 1H, *H*$_4$ or *H*$_8$), 8.03 (dd, ^3J = 8.6 Hz, ^5J = 1.2 Hz, 1H, *H*$_4$ or *H*$_8$), 8.74 (dd, ^3J = 4.4 Hz, ^4J = 1.6 Hz, 1H, *H*$_2$).

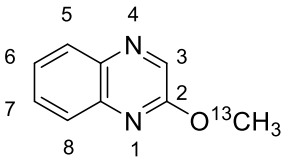
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 55.6 (O^{13}*C*H$_3$), 105.2 (d, $^3J_{C\text{-}C}$ = 4.7 Hz, *C*$_5$ or *C*$_7$), 121.4 (*C*$_3$), 122.3 (d, $^3J_{C\text{-}C}$ = 3.4 Hz, *C*$_5$ or *C*$_7$), 129.4 (CH-*C*^{IV}-CH), 130.9 (*C*$_4$ or *C*$_8$), 134.9 (*C*$_4$ or *C*$_8$), 144.5 (N-*C*^{IV}-CH), 148.0 (*C*$_2$), 157.8 (d, $^2J_{C\text{-}C}$ = 2.2 Hz, *C*$_6$-OCH$_3$).

FTIR (cm^{-1}): 2993, 2950, 2929, 2832, 1654, 1624, 1597, 1574, 1499, 1473, 1456, 1429, 1379, 1323, 1261, 1246, 1226, 1186, 1160, 1114, 1035, 1013, 951, 909, 845, 832, 790, 771, 710, 618.

MS (EI) ***m/z*** 160 (90), 144 (10), 129 (25), 116 (100), 89 (40), 63 (20).

HRMS (ESI-TOF) ***m/z*** calcd for $C_9{}^{13}CH_9NO$ [M+H]$^+$: 161.0790, found: 161.0792.

[^{13}C] 2-Methoxyquinoxaline [13, 14] **([^{13}C]4h)**



$C_8{}^{13}CH_8N_2O$
MW: 161.07 g.mol^{-1}
Yield: 28%
White Solid

After purification by column chromatography (SiO_2, start with pentane/toluene 20:1, when the product starts to come out gradually increase the polarity. The following pentane/toluene ratios 10:1, 5:5 and 2:8 have been used) [^{13}C] 2-methoxyquinoxaline **[^{13}C]4h** is obtained as a white solid with 28 % yield (45.0 mg, 2.79 × 10^{-4} mol).

^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 4.09 (d, $^1J_{C\text{-}H}$ = 146.8 Hz, 3H, O^{13}C*H*$_3$), 7.52 – 7.58 (m, 1H, *H*$_6$ or *H*$_7$), 7.63 – 7.69 (m, 1H, *H*$_6$ or *H*$_7$), 7.84 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, *H*$_5$ or *H*$_8$), 8.02 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, *H*$_5$ or *H*$_8$), 8.46 (s, 1H, *H*$_3$).

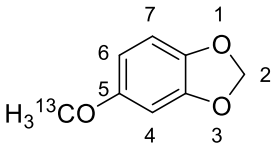
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) ***δ*** 53.8 ($O^{13}CH_3$), 126.6 (*C*$_6$ or *C*$_7$), 127.3 (*C*$_5$ or *C*$_8$), 129.1 (*C*$_5$ or *C*$_8$), 130.2 (*C*$_6$ or *C*$_7$), 139.0 (*C*$_{4a}$), 139.7 (d, $^3J_{C\text{-}C}$ = 2.1 Hz, *C*$_3$), 140.5 (*C*$_{8a}$), 157.8 (d, $^2J_{C\text{-}C}$ = 2.7 Hz, *C*$_2$).

FTIR (cm^{-1}) 3004, 2977, 2939, 1612, 1574, 1507, 1496, 1477, 1454, 1440, 1395, 1392, 1344, 1336, 1313, 1283, 1270, 1233, 1209, 1203, 1139, 1136, 1121, 1118, 1025, 1011, 999, 972, 957, 921, 909, 873, 793, 756, 709, 679, 612.

MS (EI) ***m/z*** 161 (100), 131 (75), 103 (50), 90 (80), 76 (20), 63 (25), 50 (15), 39 (20).

HRMS (ESI-TOF) ***m/z*** calcd for $C_8{}^{13}CH_8N_2O$ $[M+H]^+$: 162.0743, found: 162.0742.

[^{13}C] 5-Methoxybenzo[1,3]dioxole [15, 16] **([^{13}C]4i)**



$C_7{}^{13}CH_8O_3$
MW: 153.05 $g.mol^{-1}$
Yield: 48 %
Yellow liquid

After purification by column chromatography (SiO_2, start with pentane/CH_2Cl_2 20:1, when the starting material starts to come out switch to pentane/CH_2Cl_2 10:1 and when the product starts to come out switch to pentane/CH_2Cl_2 5:1) [^{13}C] 5-methoxybenzo[1,3]dioxole **[^{13}C]4i** is obtained as a yellow liquid with 48 % yield (73.5 mg, 4.80×10^{-4} mol).

^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 3.74 (d, $^1J_{C\text{-}H}$ = 143.2 Hz, 3H, $O^{13}CH_3$), 5.91 (s, 2H, CH_2), 6.32 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, *H*$_6$), 6.50 (d, ^4J = 2.4 Hz, 1H, *H*$_4$), 6.71 (d, ^3J = 8.4 Hz, 1H, *H*$_7$).

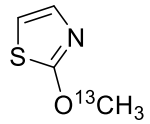
$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) ***δ*** 56.1 ($O^{13}CH_3$), 97.6 (d, $^4J_{C\text{-}C}$ = 3.8 Hz, *C*$_4$), 101.2 (CH_2), 104.8 (d, $^3J_{C\text{-}C}$ = 4.3 Hz, *C*$_6$), 108.0 (*C*$_7$), 141.7 (O-C^{IV}-C$_7$), 148.4 (O-C^{IV}-C$_4$), 155.3 (d, $^2J_{C\text{-}C}$ = 2.2 Hz, *C*$_5$).

FTIR (cm^{-1}) 2997, 2946, 2896, 2831, 1632, 1609, 1503, 1486, 1465, 1451, 1430, 1363, 1340, 1285, 1268, 1242, 1191, 1174, 1129, 1102, 1090, 1037, 1016, 937, 919, 836, 814, 788, 757, 746, 715, 633, 615.

MS (EI) ***m/z*** 153 (100), 137 (100), 107 (40), 79 (55), 53 (30), 51 (35).

HRMS (ESI-TOF) ***m/z*** calcd for $C_7{}^{13}CH_8O_3$ $[M+H]^+$: 154.0579, found: 154.0573.

[^{13}C] 2-Methoxythiazole [17, 18] **([^{13}C]4j)**



$C_3{}^{13}CH_5NSO$
MW: 116.01 g.mol^{-1}
NMR Yield: 23%

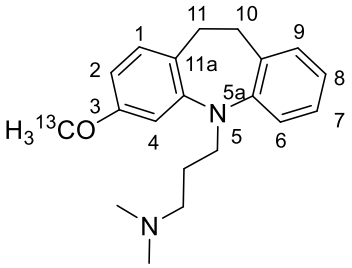
Regarding the poor ^{1}H NMR yield (23% *vs*. CH_2Cl_2 as internal standard) and the important product losses upon purification, [^{13}C] 2-methoxythiazole **[^{13}C]4j** has not been purified by column chromatography. Nevertheless ^{1}H and ^{13}C peaks could be assigned from the crude reaction mixture and mass analysis was carried out.

^{1}H NMR (400 MHz, THF) ***δ*** 4.02 (d, $^{1}J_{C\text{-}H}$ = 147.2 Hz, 3H, O^{13}C*H*$_3$), 6.77 (d, ^{3}J = 4.0 Hz, 1H, S-C*H*), 7.06 (d, ^{3}J = 4.0 Hz, 1H, N-C*H*).

^{13}C{^{1}H} NMR (100 MHz, THF) ***δ*** 58.3 (O^{13}*C*H$_3$), 111.8 (S-*C*H), 137.7 (N-*C*H), 175.8 (d, *C*(O^{13}CH$_3$)).

MS (EI) ***m/z*** 116 (45), 115 (30), 100 (30), 58 (30), 56 (45), 40 (100).

[^{13}C] 3-Methoxyimipramine ([^{13}C]4r)



$C_{19}{}^{13}CH_{26}N_2O$
MW: 311.21 g.mol^{-1}
Yield: 85%
Yellow oil

After purification by column chromatography (SiO_2, pentane/EtOAc 9:1 + 1% Et_3N) [^{13}C] 3-methoxyimipramine **[^{13}C]4r** is obtained as a yellow sticky oil with 85 % yield (265.0 mg, 8.51×10^{-4} mol).

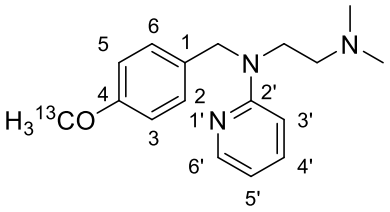
^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 1.77 (quint, ^3J = 7.2 Hz, 2H, N-CH_2-C*H_2*-CH_2-N(CH_3)$_2$), 2.18 (s, 6H, N(C*H_3*)$_2$), 2.34 (t, ^3J = 7.2 Hz, 2H, C*H_2*-N(CH_3)$_2$), 3.09 – 3.20 (m, 4H, *H_{10}* + *H_{11}*), 3.78 (t, ^3J = 7.2 Hz, 2H, N-C*H_2*), 3.79 (d, $^1J_{C\text{-}H}$ = 143.4 Hz, 3H, O^{13}C*H_3*), 6.50 (dd, ^3J = 8.4 Hz, ^4J = 2.5 Hz, 1H, *H_2*), 6.70 (d, ^4J = 2.5 Hz, 1H, *H_4*), 6.95 (td, ^3J = 7.2 Hz, ^4J = 1.2 Hz, 1H, *H_7* or *H_8*), 7.01 (d, ^3J = 8.4 Hz, 1H, *H_1*), 7.09 – 7.18 (m, 3H, *H_6*, *H_9*, *H_7* or *H_8*).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 26.2 (N-CH_2-*C*H_2-CH_2-N(CH_3)$_2$), 31.8 (*C_{10}* or *C_{11}*), 32.2 (*C_{10}* or *C_{11}*), 45.6 (N(*C*H_3)$_2$), 48.9 (N-*C*H_2), 55.3 (O^{13}*C*H_3), 57.7 (*C*H_2-N(CH_3)$_2$), 106.3 (d, $^3J_{C\text{-}C}$ = 3.8 Hz, *C_4*), 107.1 (d, $^3J_{C\text{-}C}$ = 4.1 Hz, *C_2*), 120.4 (*C_6*, *C_7* or *C_8*), 122.8 (*C_6*, *C_7* or *C_8*), 125.9 (*C_{11a}*), 126.4 (*C_6*, *C_7* or *C_8*), 129.6 (*C_9*), 130.6 (*C_1*), 135.1 (*C_{9a}*), 148.3 (*C_{5a}*), 149.1 (*C_{4a}*), 158.3 (d, $^2J_{C\text{-}C}$ = 2.3 Hz, *C_3*).

FTIR (cm^{-1}) 2930, 2893, 2816, 2763, 1607, 1597, 1585, 1573, 1507, 1489, 1473, 1458, 1448, 1437, 1286, 1253, 1217, 1196, 1160, 1132, 1112, 1097, 1061, 1038, 845, 800, 755, 746.

HRMS (ESI-TOF) ***m/z*** calcd for $C_{19}{}^{13}CH_{26}N_2O$ $[M+H]^+$: 312.2151, found: 312.2153.

[^{13}C] Mepyramine ([^{13}C]4s)



$C_{16}{}^{13}CH_{23}N_3O$
MW: 286.19 g.mol^{-1}
Yield: 70%
Yellow oil

After purification by column chromatography (SiO_2, start with pentane/EtOAc 9:1 + 1% Et_3N, move to pentane/EtOAc 8:2 + 1% Et_3N, when the product is coming out switch to pentane/EtOAc 3:7 + 1% Et_3N) [^{13}C] mepyramine **[^{13}C]4s** was obtained as a yellow sticky oil with 70 % yield (200.5 mg, 7.00×10^{-4} mol).

^{1}H NMR (400 MHz, $CDCl_3$) ***δ*** 2.25 (s, 6H, N(CH_3)$_2$), 2.49 (t, ^3J = 7.4 Hz, 2H, CH_2-N(CH_3)$_2$), 3.64 (t, ^3J = 7.4 Hz, 2H, N-CH_2-CH_2-N(CH_3)$_2$), 3.75 (d, $^1J_{C\text{-}H}$ = 143.6 Hz, 3H, O$^{13}CH_3$), 4.70 (s, 2H, Anisole-CH_2-N), 6.45 (d, ^3J = 8.4 Hz, 1H, $CH_{pyridine}$), 6.49 – 6.54 (m, 1H, $CH_{pyridine}$), 6.83 (d, ^3J = 8.4 Hz, 2H, $CH_{anisole}$), 7.16 (d, ^3J = 8.4 Hz, 2H, $CH_{anisole}$), 7.32 – 7.40 (m, 1H, $CH_{pyridine}$), 8.16 (dd, ^3J = 4.8 Hz, ^4J = 1.2 Hz, 1H, $CH_{pyridine}$).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) ***δ*** 45.8 (N(CH_3)$_2$), 46.5 (N-CH_2-CH_2-N(CH_3)$_2$), 51.2 (Anisole-CH_2-N), 55.2 (O$^{13}CH_3$), 56.7 (CH_2-N(CH_3)$_2$), 105.7 ($C_{pyridine}$), 111.7 ($C_{pyridine}$), 113.9 (d, $^3J_{C\text{-}C}$ = 3.9 Hz , C_3 + C_5), 128.2 (C_2 + C_6), 130.8 (C_1), 137.2 ($C_{pyridine}$), 148.1 ($C_{pyridine}$), 158.2 ($C_{2'}$), 158.6 (d, $^2J_{C\text{-}C}$ = 2.2 Hz, C_4).

FTIR (cm^{-1}) 2968, 2941, 2901, 2860, 2820, 2768, 1595, 1559, 1510, 1490, 1460, 1436, 1420, 1350, 1327, 1301, 1288, 1243, 1171, 1161, 1150, 1107, 1096, 1052, 1041, 1019, 977, 952, 924, 889, 817, 767, 732.

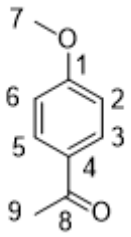
HRMS (ESI-TOF) ***m/z*** calcd for $C_{16}{}^{13}CH_{23}N_3O$ $[M+H]^+$: 287.1947, found: 287.1949.

Compounds **4k** to **4q** were prepared directly using a commercial solution of BBN-OMe (1.0 M in hexanes) on a 1 mmol scale (see page S8, Optimization of the Palladium Catalyzed Suzuki Cross Coupling), according to the following procedure:

A 9 mL heavy-wall borosilicate glass tubes (ACE pressure tube, L × O.D. 10.2 cm × 19 mm, from Sigma Aldrich, ref. Z564567-1EA) was charged with the corresponding substituted chlorobenzene (1 mmol, 1 eq.), 2 eq. of CsF (303.8 mg, 2.0×10^{-3} mol, 2.0 eq.), 10 mol% of *t*BuXPhos (42.5 mg, 1.0×10^{-4} mol) and 5 mol% of Pd_2dba_3 (45.8 mg, 5.0×10^{-5} mol). Afterwards, 2 mL of THF were added. After 18 h at 100 °C, the reaction was quenched according to the general procedure.

1-(4-methoxyphenyl) ethan-1-one [20] **([^{12}C]4k)**

$C_{12}H_{10}O_2$
MW: 150.18 g.mol-1
Yield: 52%
Orange solid



After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/CH_2Cl_2 9:1) methyl 3-methoxybenzoate was obtained with 52 % yield (79 mg, 5.3×10^{-4} mol) as an orange solid.

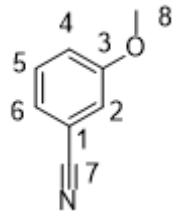
^{1}H NMR (400 MHz, CDCl3) δ 2.53 (s, 3H, *H*$_9$), 3.85 (s, 3H, *H*$_7$), 6.95 – 6.86 (m, 2H, *H*$_{2+}$*H*$_6$), 7.97 – 7.88 (m, 2H, *H*$_{3+}$*H*$_5$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 26.28 (*C*$_9$), 55.59 (*C*$_7$), 113.67 (*C*$_{2+}$*C*$_6$), 130.49 (*C*$_{3+}$*C*$_5$), 163.49 (*C*$_1$), 196.72 (*C*$_8$).

HRMS (ESI-TOF) ***m***/z calcd for $C_9H_{10}O_2$ $[M+H]^+$: 151.0759, found: 151.0759.

FTIR (cm^{-1}) 2921, 2839, 1673, 1598, 1575, 1508, 1417, 1357, 1305, 1265, 1171, 1148, 1113, 1074, 1026, 956, 835, 805, 741, 703, 632.

3-methoxybenzonitrile [21] **([^{12}C]4l)**



C_8H_7NO
MW: 133.05 g.mol-1
Yield: 60%
Pale yellow solid

After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/EtOAc 98:2) methyl 3-methoxybenzoate was obtained with 60 % yield (80 mg, 6.0×10^{-4} mol) as a pale yellow solid.

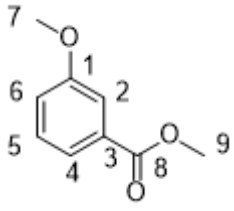
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H, H_8), 7.08 – 7.04 (m, 2H, H_4+H_5), 7.17 (dt, ^3J =7.6 Hz, ^4J =1.2 Hz, 1H, H_6), 7.33 – 7.26 (m, 1H, H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.58 (C_8), 113.17 (C_1), 116.86 (C_4), 118.72 (C_7), 119.32 (C_2), 124.50 (C_6), 130.32 (C_5), 159.60 (C_3).

HRMS (ESI-TOF) ***m***/z calcd for C_8H_7NO $[M+H]^+$: 134.0606, found: 134.0609.

FTIR (cm^{-1}) 2935, 2938, 2229, 1651, 1596, 1577, 15074, 1842, 1421, 1446, 1317, 1281, 1255, 1170, 1147, 1031, 973, 922, 845, 790, 741, 701, 685, 607.

Methyl 3-methoxybenzoate [22] **([^{12}C]4m)**



$C_9H_{10}O_3$
MW: 166.06 g.mol-1
Yield: 62%
Pale yellow oil

After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/CH_2Cl_2 9:1) methyl 3-methoxybenzoate was obtained with 62 % yield (104 mg, 6.2×10^{-4} mol) as a pale yellow oil.

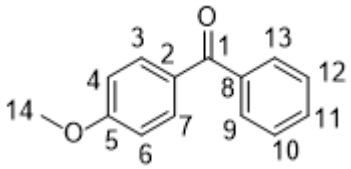
^{1}H NMR (400 MHz, CDCl3) δ 3.76 (s, 1H, H_7), 3.83 (s, 1H, H_9), 7.01 (ddd, ^{3}J = 8.3 Hz, ^{4}J = 2.7 Hz, ^{4}J = 1.0 Hz, 1H, H_6), 7.29 – 7.22 (m, 1H, H_2), 7.48 (dd, ^{3}J = 2.6 Hz, ^{3}J = 1.5 Hz, 1H, H_5), 7.57 – 7.52 (m, 1H, H_4),

^{13}C NMR (100 MHz, CDCl3) δ 52.12 (C_9), 55.40 (C_7), 113.99 (C_2), 119.56 (C_6), 121.97 (C), 129.36 (C_5), 131.47(C_3), 159.57 (C_1), 167.02 (C_8).

HRMS (ESI-TOF) ***m***/z calcd for $C_9H_{10}O_3$ $[M+H]^+$: 167.0708, found: 167.0708.

FTIR (cm^{-1}) 2951, 2837, 1718, 1600, 1586, 1488, 1454, 1433, 1320, 1276, 1222, 1183, 1098, 1075, 1042, 988, 806, 783, 753, 682.

(4-methoxyphenyl)(phenyl)methanone [23] **([^{12}C]4o)**



$C_{14}H_{12}O_2$
MW: 212.08 g.mol-1
Yield: 63%
Pale yellow oil

After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/CH_2Cl_2 95:5) methyl 3-methoxybenzoate was obtained with 63 % yield (134 mg, 6.3× 10^{-4} mol) as a pale yellow oil.

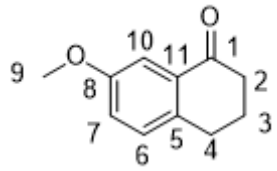
1H NMR (400 MHz, CDCl3) δ 3.81 (s, 3H, H_{14}), 6.92 – 6.84 (m, 1H, H_4+H_6), 7.39 (dd, ^{3}J =10.4 Hz, ^{3}J = 4.6 Hz, 2H, H_{10}+H_{12}), 7.48 (m, 1H, H_{11}), 7.71 – 7.62 (m, 2H, H_3+H_7), 7.80 – 7.72 (m, 2H, H_9+H_{13}).

^{13}C NMR (101 MHz, CDCl3) δ 55.49 (C_{14}), 113.57 (C_4+C_6), 128.18 (C_{10}+C_{12}), 129.72 (C_9+C_{13}), 130.20 (C_2), 131.87 (C_{11}), 132.55 (C_3+C_7), 138.26 (C_8), 163.24 (C_5), 195.54 (C_1).

HRMS (ESI-TOF) ***m***/z calcd for $C_{14}H_{12}O_2$ $[M+H]^+$: 213.0916, found: 213.0917.

FTIR (cm^{-1}) 2931, 2839, 1650, 1596, 1576, 1507, 1445, 1418, 1315, 1304, 1280, 1171, 1148, 1116, 1027, 937, 922, 843, 792, 740, 700, 607, 635.

7-methoxy-3, 4-dihydronaphthalen-1(2H)-one [24] **([^{12}C]4p)**



$C_{11}H_{12}O_2$
MW: 176.08 g.mol-1
Yield: 53%
Pale yellow oil

After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/CH_2Cl_2 9:1) methyl 3-methoxybenzoate was obtained with 53 % yield (94 mg, 5.3×10^{-4} mol) as a very pale yellow oil.

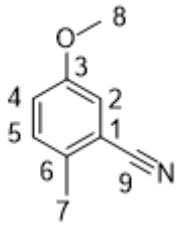
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 – 2.05 (q, ^3J = 6.4, 2H, *H3*), 2.67 – 2.58 (t, ^3J = 6.4 Hz, 2H, *H4*), 2.89 (t, ^3J = 6.1 Hz, 2H, *H2*), 3.82 (s, 3H, *H9*), 7.04 (dd, ^3J =8.4 Hz, ^4J = 2.8 Hz, 1H, *H7*), 7.15 (d, ^3J = 8.4 Hz, 1H, *H6*), 7.51 (d, ^4J = 2.8 Hz, 1H, *H10*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 23.50 (*C3*), 28.89 (*C4*), 39.00 (*C2*), 55.49 (*C9*), 109.10 (*C10*), 121.74 (*C7*), 129.97 (*C6*), 133.39 (*C11*), 137.13 (*C5*), 158.34 (*C8*), 198.31 (*C1*).

HRMS (ESI-TOF) ***m***/z calcd for $C_{11}H_{12}O_2$ $[M+H]^+$: 177.0916, found: 177.0915.

FTIR (cm^{-1}) 2938, 2835, 1678, 1604, 1574, 1494, 1462, 1422, 1348, 1325, 1276, 1257, 1232, 1184, 1171, 1060, 1033, 956, 878, 819, 747, 693.

3-methoxybenzonitrile [25] **([^{12}C]4q)**



C_9H_9NO
MW: 147.18 g.mol-1
Yield: 67%
Pale yellow solid

After purification by column chromatography (SiO_2, start with pentane, when the impurities come out switch to pentane/EtOAc 98:2) methyl 3-methoxybenzoate was obtained with 67 % yield (99 mg, 6.7×10^{-4} mol) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H, H_7), 3.79 (s, 3H, H_8), 7.02 (dd, ^{3}J = 8.5 Hz, ^{4}J = 2.8 Hz, 1H, H_4), 7.07 (d, ^{4}J = 2.7 Hz, 1H, H_2), 7.19 (d, ^{3}J = 8.5 Hz, 1H, H_5).

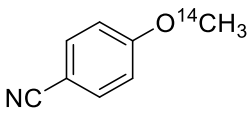
^{13}C NMR (101 MHz, $CDCl_3$) δ 19.27(C_7), 55.56(C_8), 113.17(C_1), 116.45(C_2), 118.08(C_9), 119.54(C_4), 131.28(C_5), 133.77(C_6), 157.52(C_3).

HRMS (ESI-TOF) ***m***/z calcd for C_9H_9NO $[M+H]^+$: 148 .0762, found: 148 .0766

FTIR (cm^{-1}) 2924, 2228, 1651, 1597, 1577, 1507, 1446, 1304, 1280, 1256, 1170, 1147, 1031, 937, 922, 845, 790, 741, 701, 685, 681, 607.

B. Carbon-14 Labeled Compounds

[^{14}C] 4-Methoxybenzonitrile [5, 6] ([^{14}C]4d)



$C_7{}^{14}CH_7NO$
MW: 135.14 g.mol^{-1}
Yield: 37%
White Solid

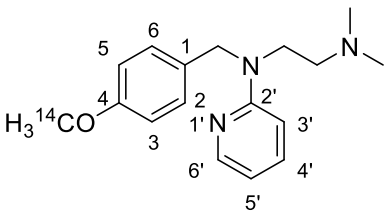
[^{14}C] 4-Methoxybenzonitrile **[^{14}C]4d** was prepared according to the general procedure, using 1.5 eq. of (9-BBN)$_2$ dimer **1** (91.5 mg, 3.75×10^{-4} mol, 1.5 eq.) together with 5 mol% of Verkade's base VB^{Me} (4.1 mg, 1.88×10^{-5} mol, 0.075 eq., 5 mol% *vs*. (9-BBN)$_2$) in the reduction chamber and 2 eq. of CsF (76.0 mg, 5.0×10^{-4} mol, 2.0 eq.), 1eq. of substrate **3d** (2.5×10^{-4} mol, 1.0 eq.), 10 mol% of *t*BuXPhos (10.6 mg, 2.5×10^{-5} mol) and 5 mol% of Pd_2dba_3 (11.5 mg, 1.25×10^{-5} mol) in the Suzuki chamber.
1.2 eq. of $^{14}CO_2$ (3×10^{-4} mol, 693 MBq) was used. The crude product was purified by Flash Chromatography on SiO_2 gel (eluent DCM/Heptane 50:50) affording the [^{14}C] 4-methoxybenzonitrile **[^{14}C]4d** as white solid (186.517 MBq, 0.093 mmol, 37%).

$^{14}CO_2$ Specific activity: 2.172 GBq mmol^{-1}

Specific activity (MS (ESI)): 1.990 GBq mmol^{-1}

TLC (silicagel 60F254, EtOAc/Hept (30/70)) Rf = 0.21. Radiochemical purity: ≥99 %.

[^{14}C] Mepyramine ([^{14}C]4s)



$C_{16}{}^{14}CH_{23}N_3O$
MW: 287.38 g.mol^{-1}
Yield: 35%
Yellowish oil

[^{14}C] Mepyramine **[^{14}C]4s** was prepared according to the general procedure, using 1.5 eq. of (9-BBN)$_2$ dimer **1** (91.5 mg, 3.75×10^{-4} mol, 1.5 eq.) together with 5 mol% of Verkade's base VB^{Me} (4.1 mg, 1.88×10^{-5} mol, 0.075 eq., 5 mol% *vs*. (9-BBN)$_2$) in the reduction chamber and

2 eq. of CsF (76.0 mg, 5.0×10^{-4} mol, 2.0 eq.), 1eq. of substrate **3s** (72.5 mg, 2.5×10^{-4} mol, 1.0 eq.), 10 mol% of *t*BuXPhos (10.6 mg, 2.5×10^{-5} mol) and 5 mol% of Pd_2dba_3 (11.5 mg, 1.25×10^{-5} mol) in the Suzuki chamber.

1.2 eq. of $^{14}CO_2$ (3×10^{-4} mol, 693 MBq) was used. The crude product was purified by Flash Chromatography on SiO_2 gel (Eluent gradient pentane/EtOAc 9/1 + 1% Et_3N, then pentane/EtOAc 8/2 + 1% Et_3N, and pentane/EtOAc 3/7 + 1% Et_3N) affording the [^{14}C] Mepyramine **[^{14}C]4l** as a yellow sticky oil solid (179.764 MBq, 0.088 mmol, 35%).

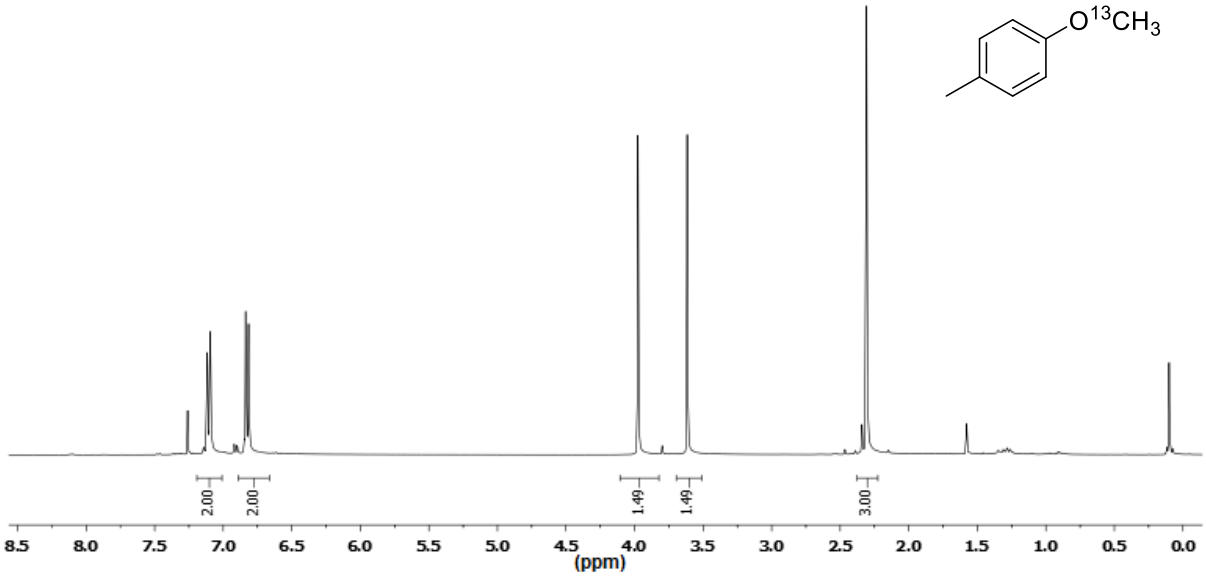
$^{14}CO_2$ Specific activity: 2.172 GBq $mmol^{-1}$

Specific activity (MS (ESI)): 2.025 GBq $mmol^{-1}$

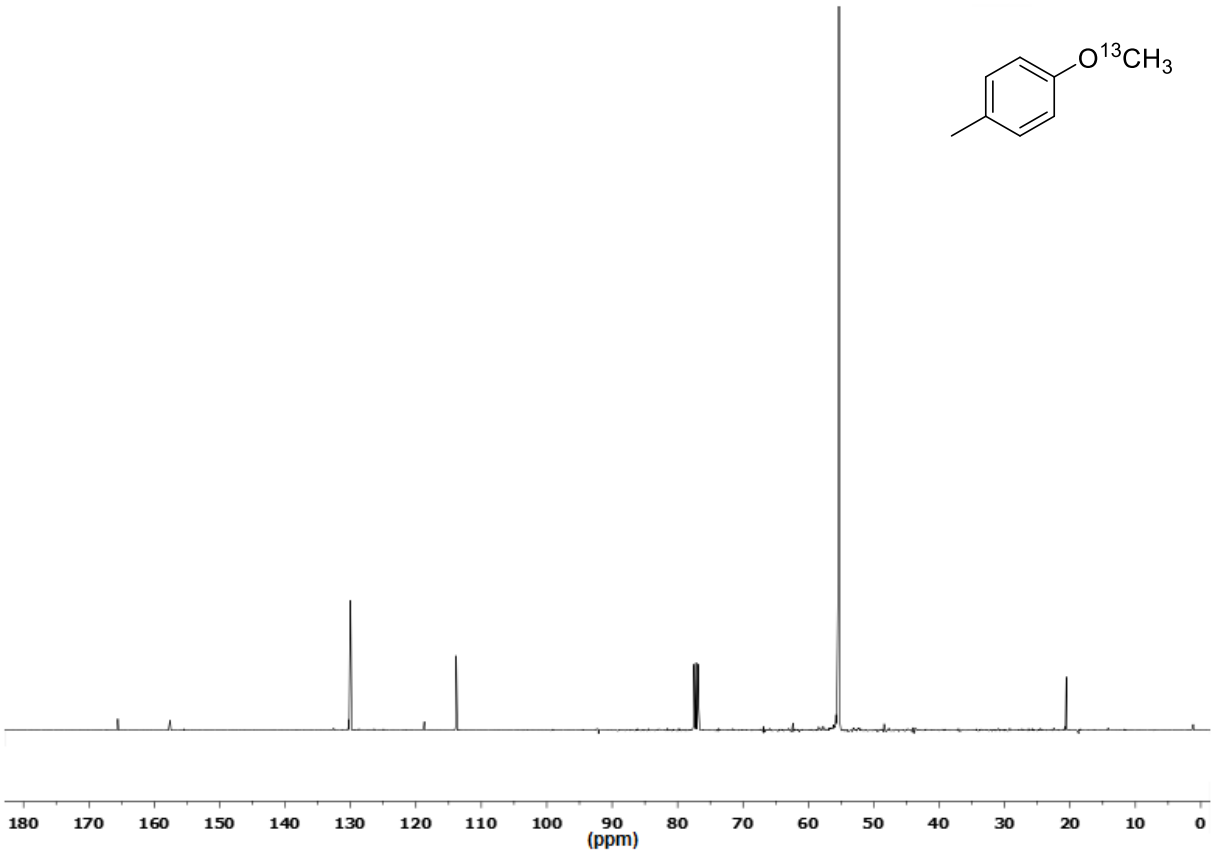
TLC (silicagel 60F254, EtOAc/Hept (30/70)) Rf = 0.14. Radiochemical purity: ≥99 %.

VI. ^{1}H and ^{13}C NMR Spectra of ^{13}C-labeled compounds

[^{13}C] 4-Methylanisole ([^{13}C]4b)

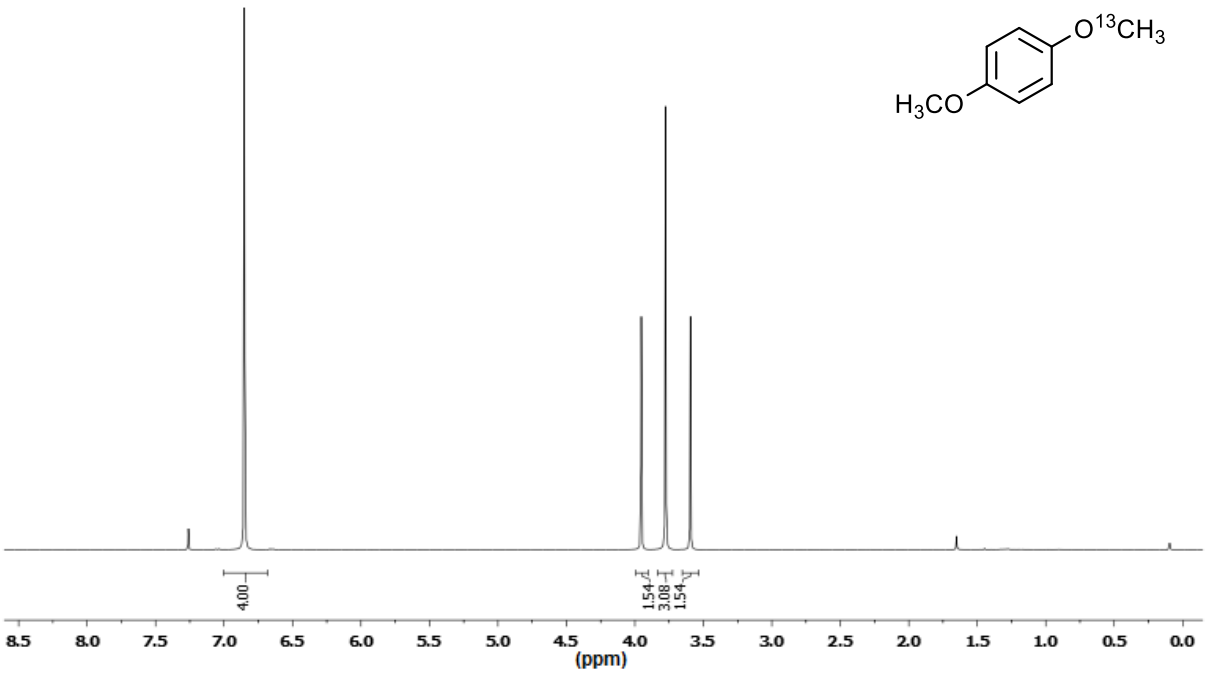


^{1}H NMR Spectrum of [^{13}C]4-Methylanisole **[^{13}C]4b** in $CDCl_3$.

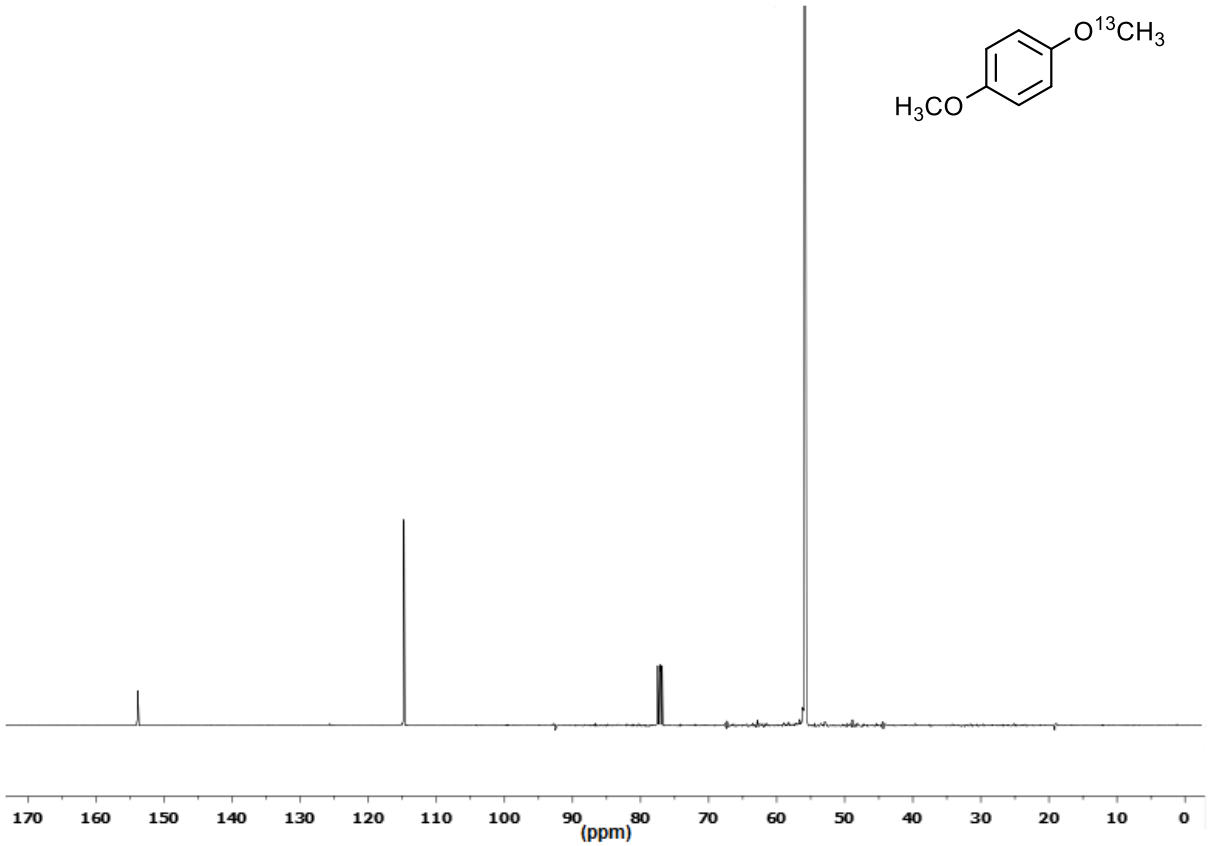


^{13}C NMR Spectrum of [^{13}C]4-Methylanisole **[^{13}C]4b** in $CDCl_3$.

[^{13}C] 4-Methoxyanisole ([^{13}C]4c)

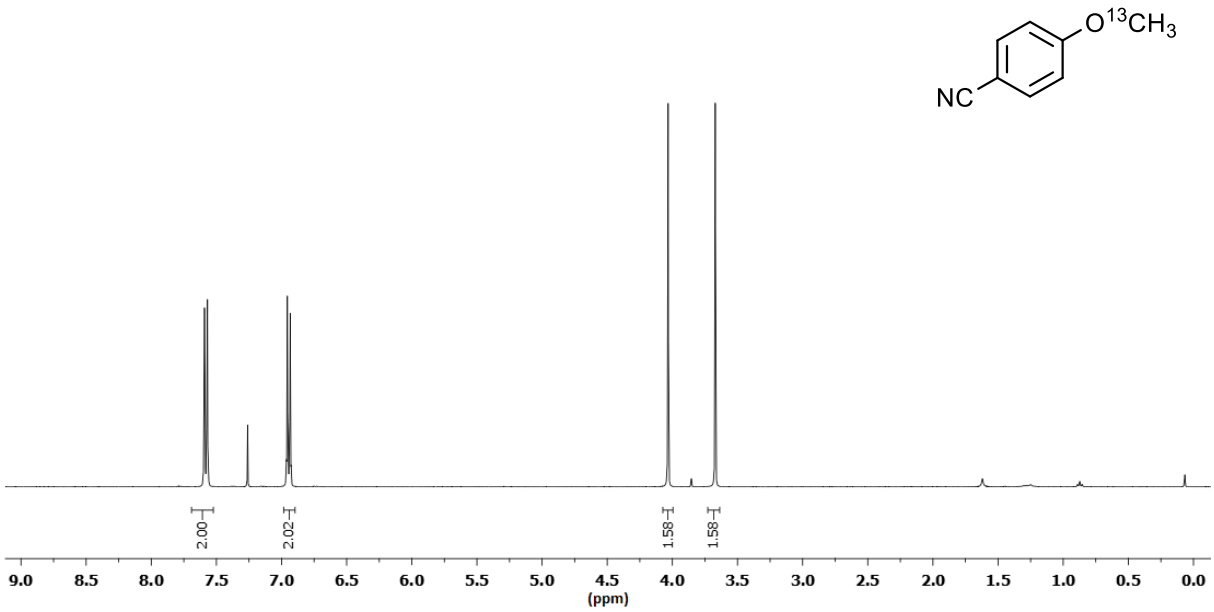


^{1}H NMR Spectrum of [^{13}C]4-Methoxyanisole **[^{13}C]4c** in $CDCl_3$.

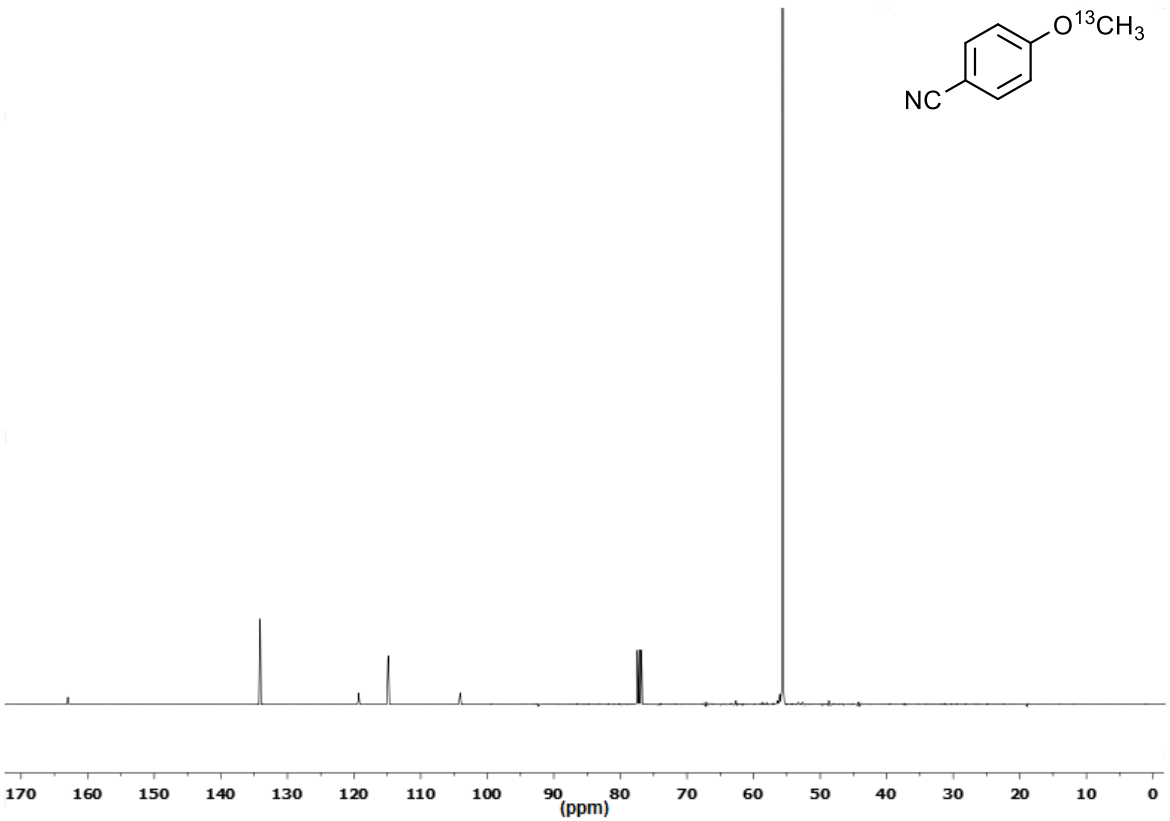


^{13}C NMR Spectrum of [^{13}C]4-Methoxyanisole **[^{13}C]4c** in $CDCl_3$.

[^{13}C] 4-Methoxybenzonitrile ([^{13}C]4d)

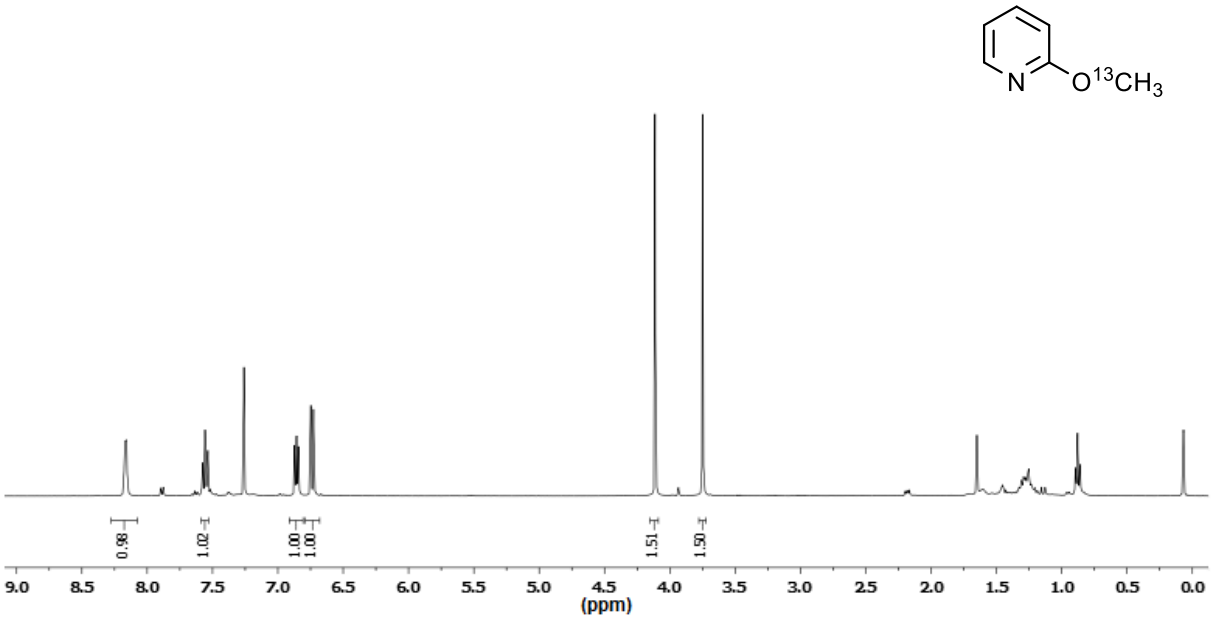


^{1}H NMR Spectrum of [^{13}C]4-Methoxybenzonitrile **[^{13}C]4d** in $CDCl_3$.

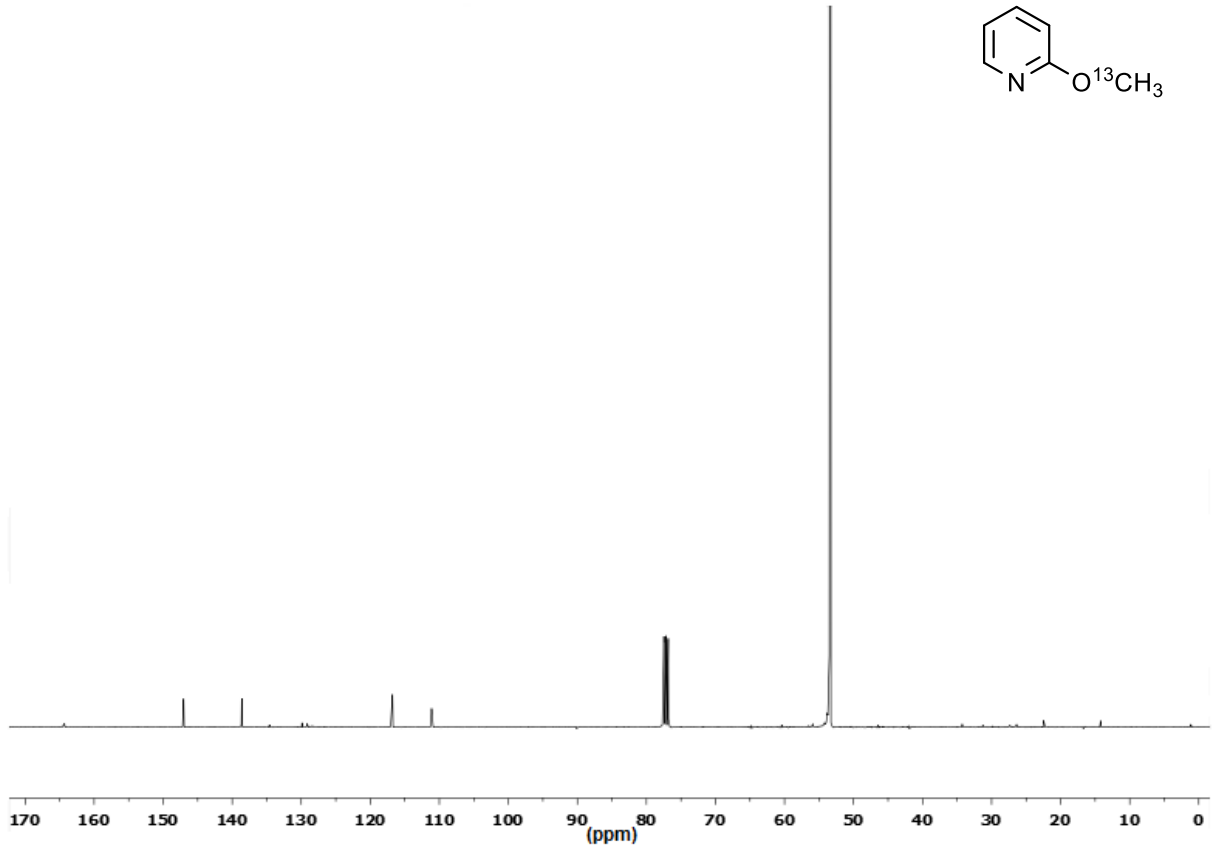


^{13}C NMR Spectrum of [^{13}C]4-Methoxybenzonitrile **[^{13}C]4d** in $CDCl_3$.

[^{13}C] 2-Methoxypyridine ([^{13}C]4e)

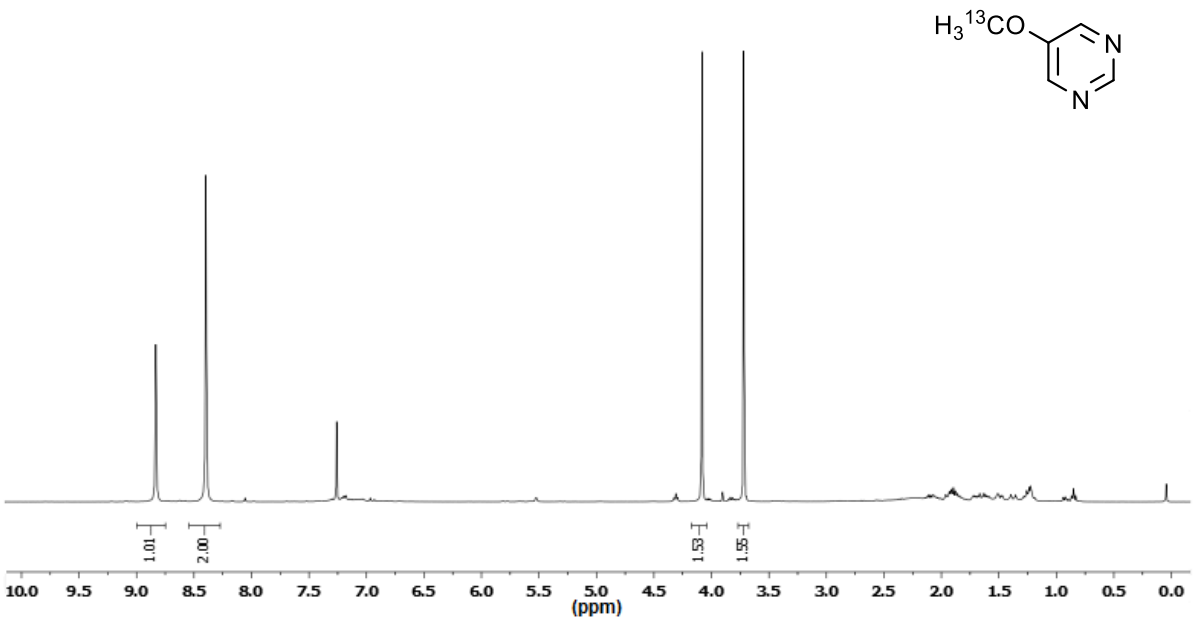


^{1}H NMR Spectrum of [^{13}C]2-Methoxypyridine **[^{13}C]4e** in $CDCl_3$.

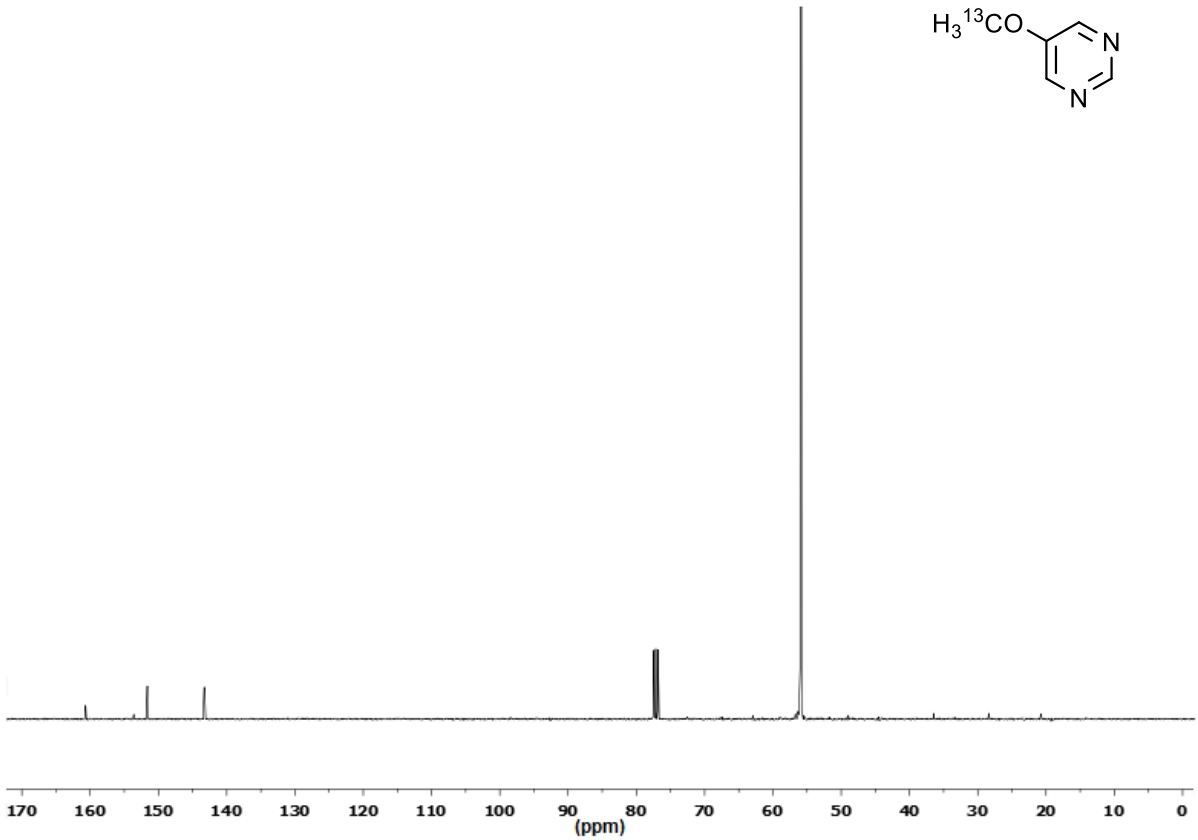


^{13}C NMR Spectrum of [^{13}C]2-Methoxypyridine **[^{13}C]4e** in $CDCl_3$.

[^{13}C] 5-Methoxypyrimidine ([^{13}C]4f)

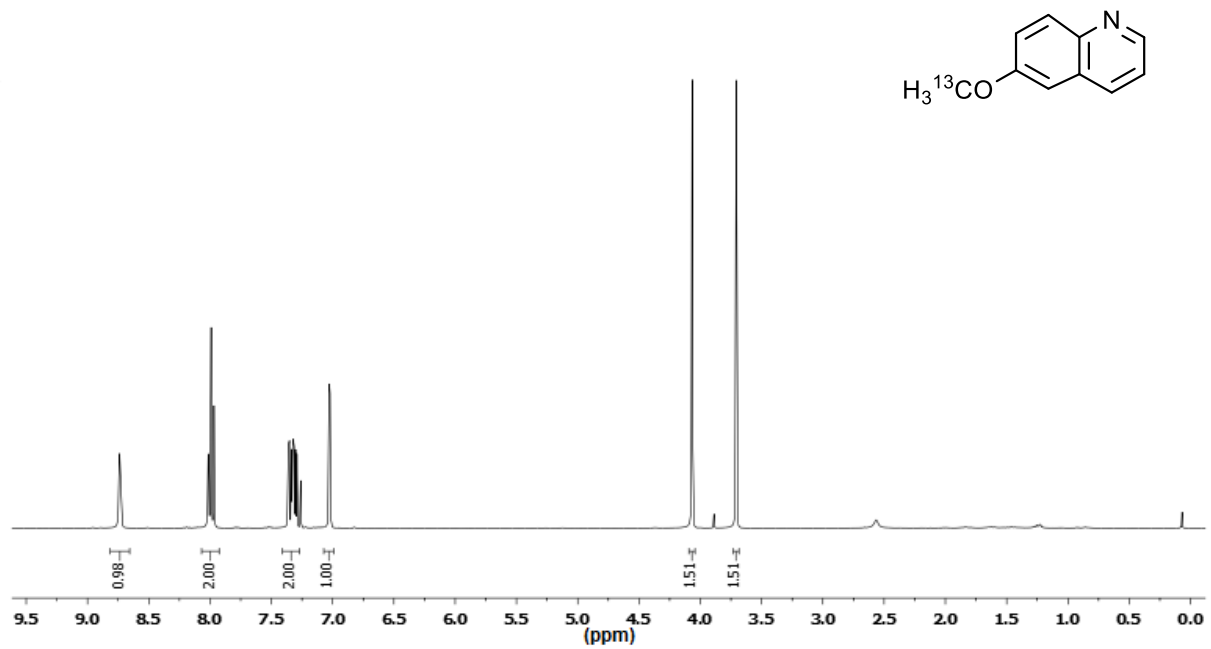


^{1}H NMR Spectrum of [^{13}C]5-Methoxypyrimidine **[^{13}C]4f** in $CDCl_3$.

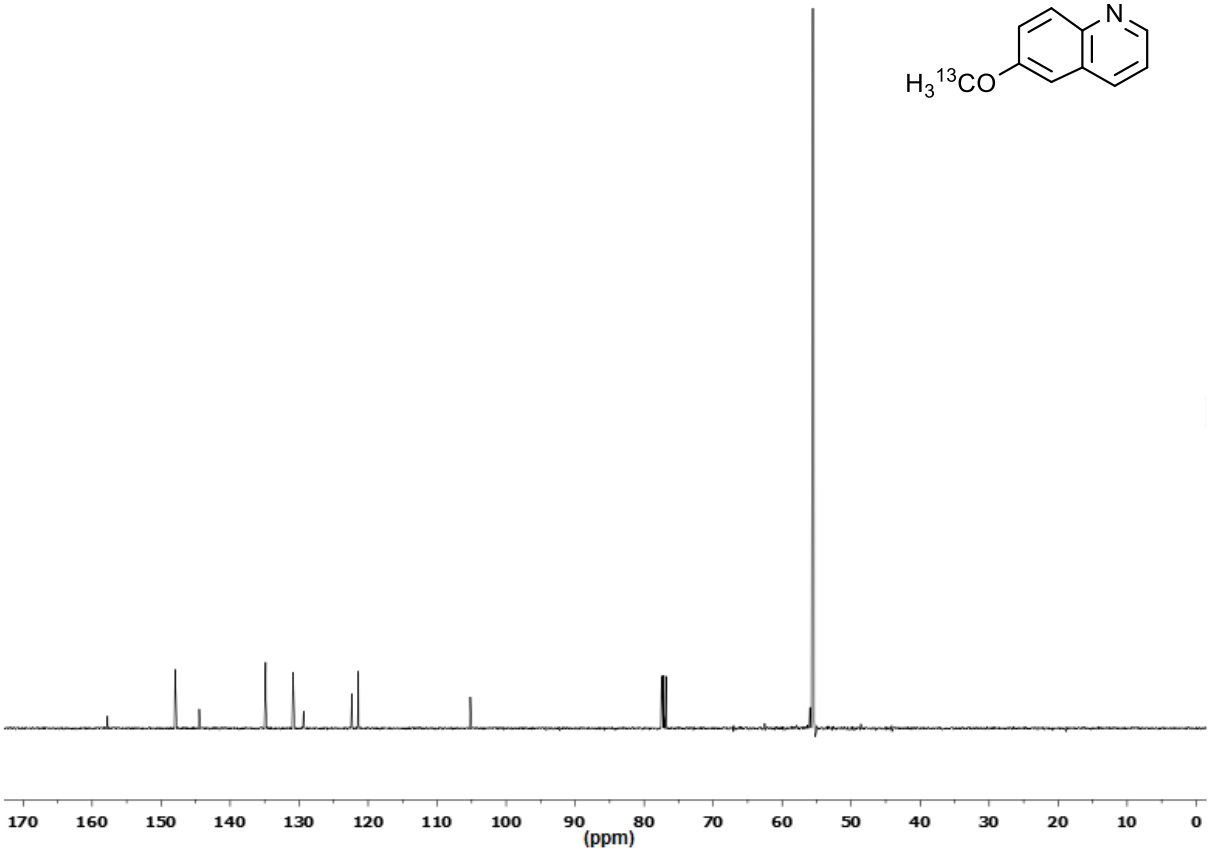


^{13}C NMR Spectrum of [^{13}C]5-Methoxypyrimidine **[^{13}C]4f** in $CDCl_3$.

[^{13}C] 6-Methoxyquinoline ([^{13}C]4g)

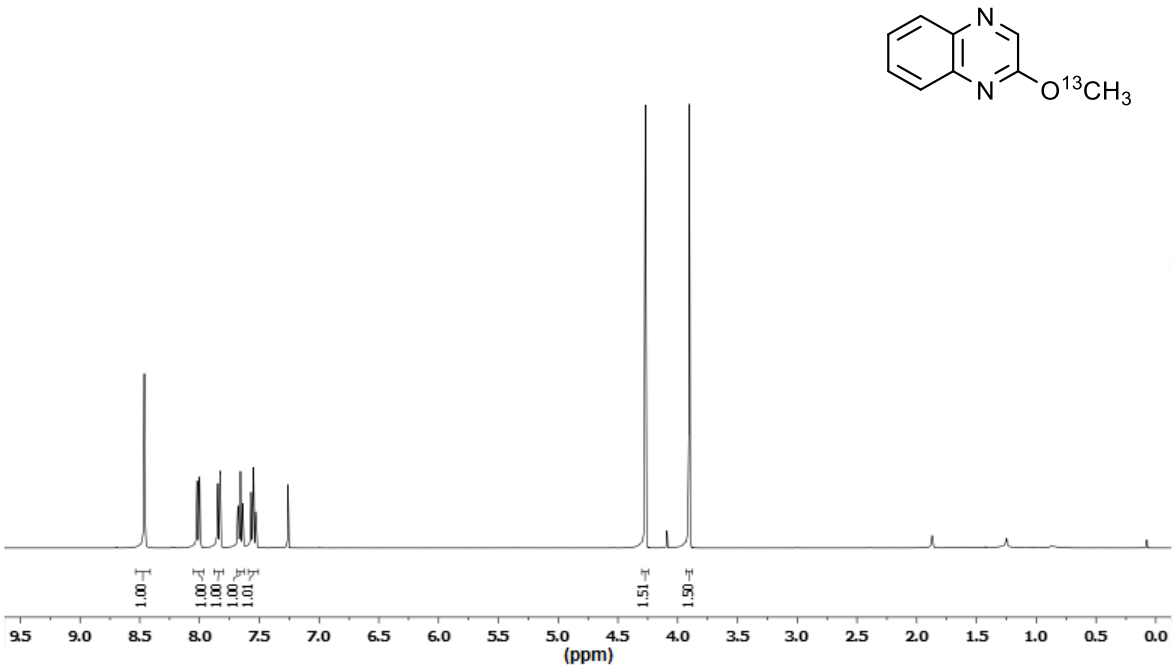


^{1}H NMR Spectrum of [^{13}C]6-Methoxyquinoline **[^{13}C]4g** in $CDCl_3$.

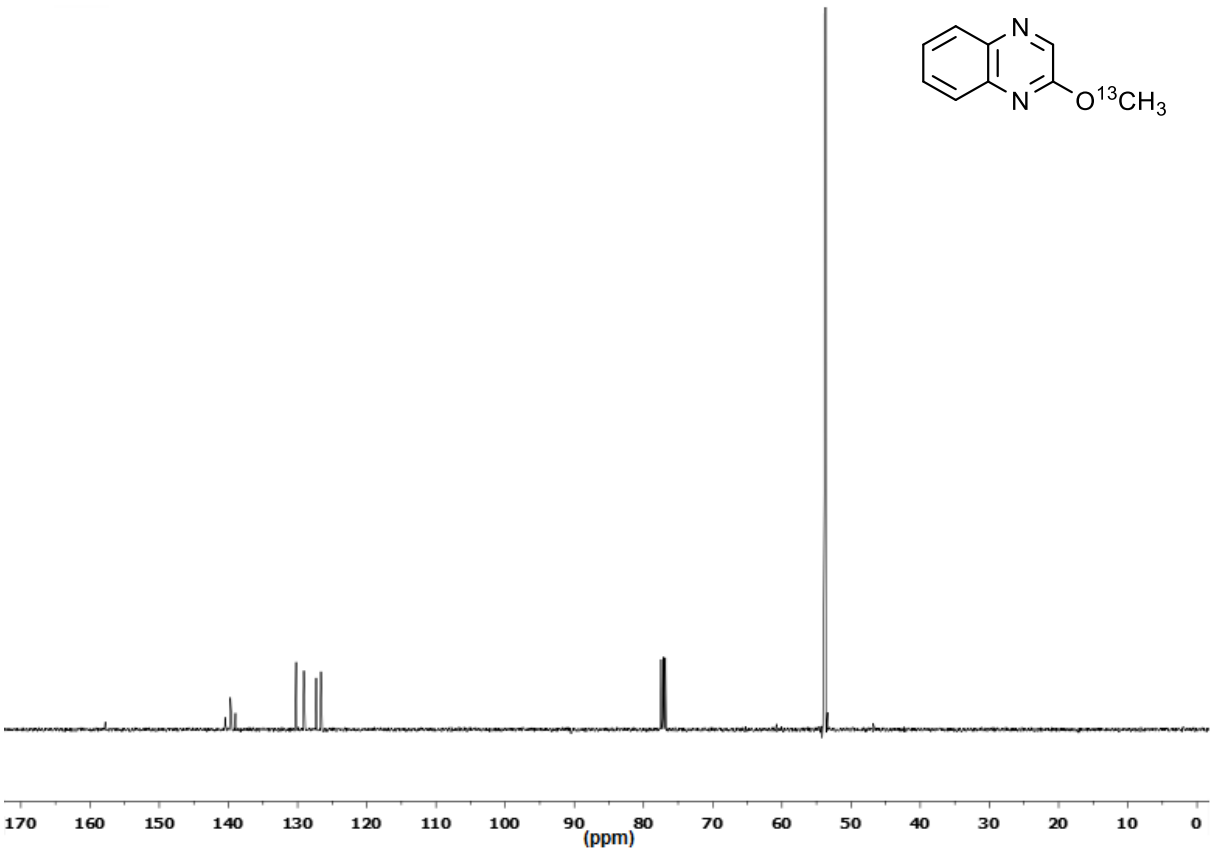


^{13}C NMR Spectrum of [^{13}C]6-Methoxyquinoline **[^{13}C]4g** in $CDCl_3$.

[^{13}C] 2-Methoxyquinoxaline ([^{13}C]4h)

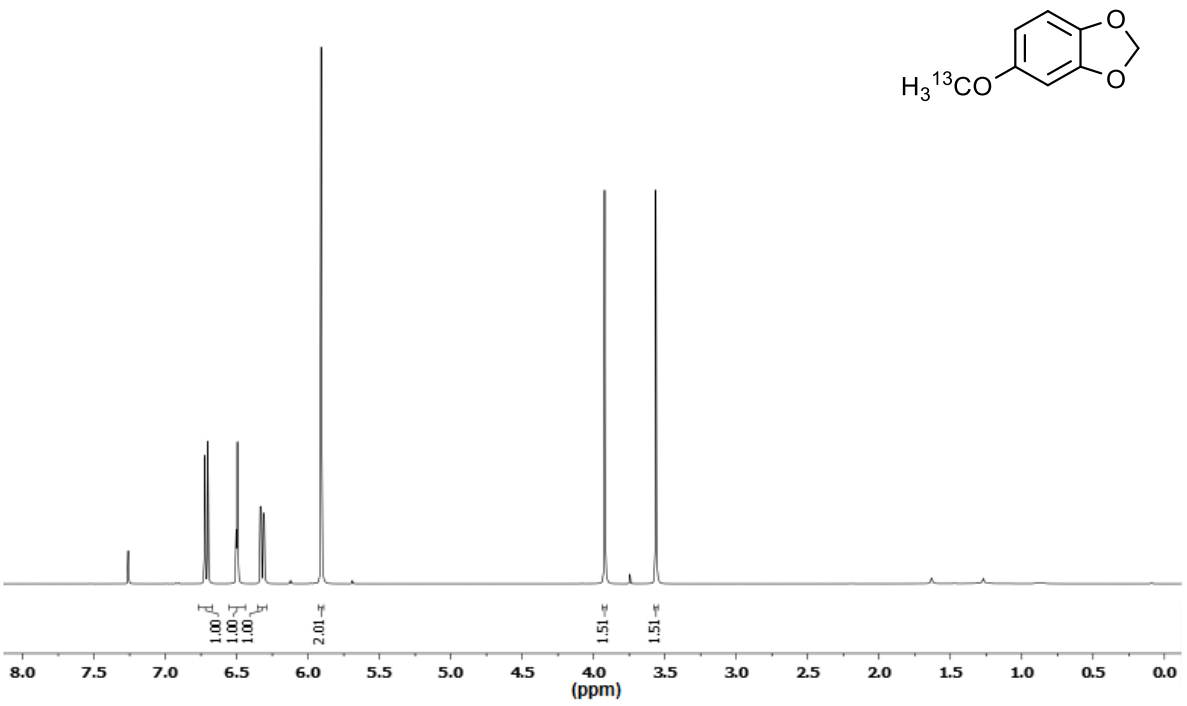


^{1}H NMR Spectrum of [^{13}C]2-Methoxyquinoxaline **[^{13}C]4h** in $CDCl_3$.

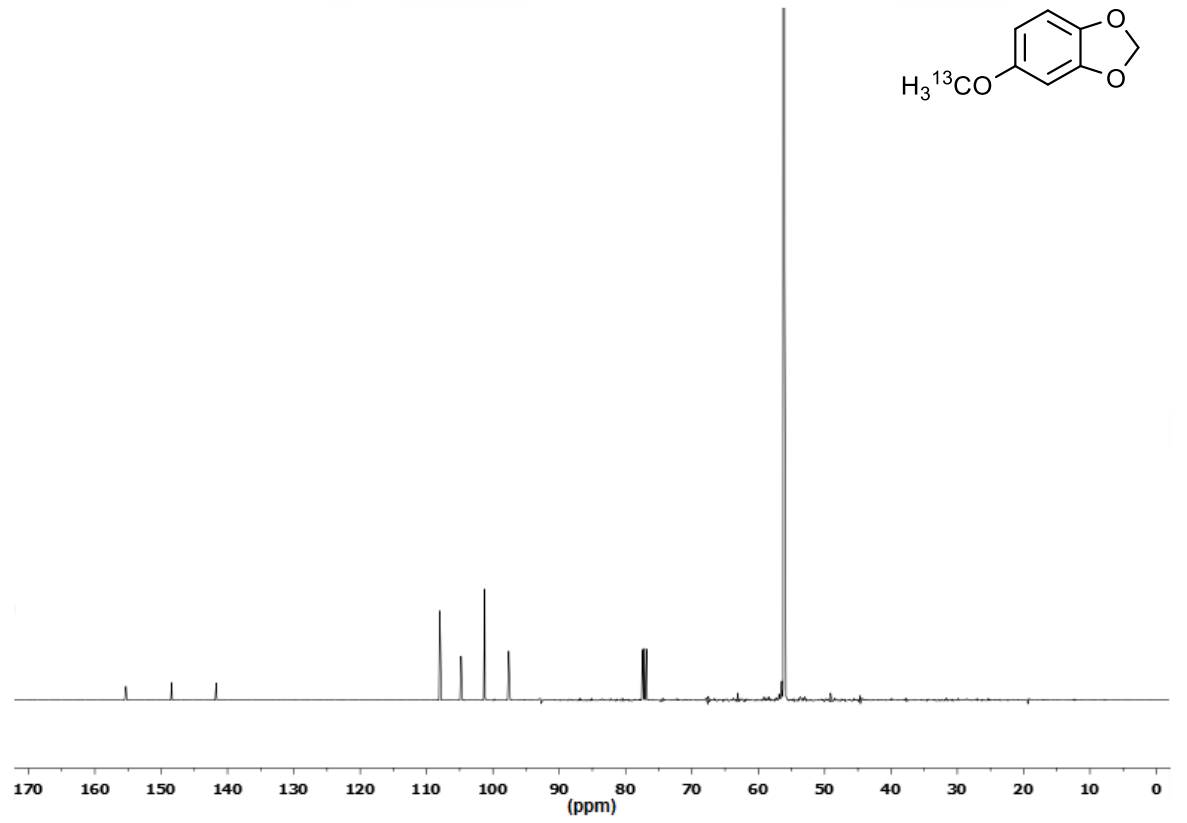


^{13}C NMR Spectrum of [^{13}C]2-Methoxyquinoxaline **[^{13}C]4h** in $CDCl_3$.

[^{13}C] 5-Methoxybenzo[1,3]dioxole ([^{13}C]4i)

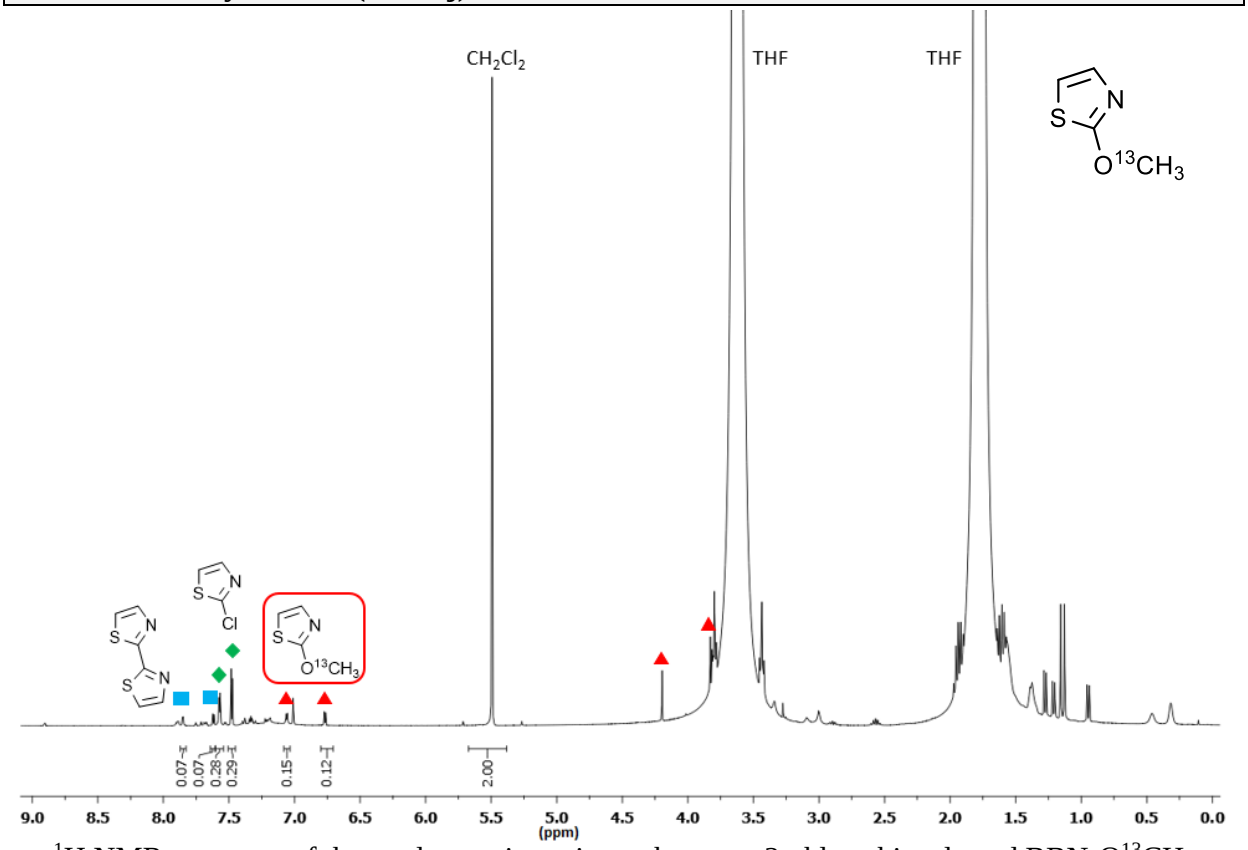


^{1}H NMR Spectrum of [^{13}C]5-Methoxybenzo[1,3]dioxole **[^{13}C]4i** in $CDCl_3$.

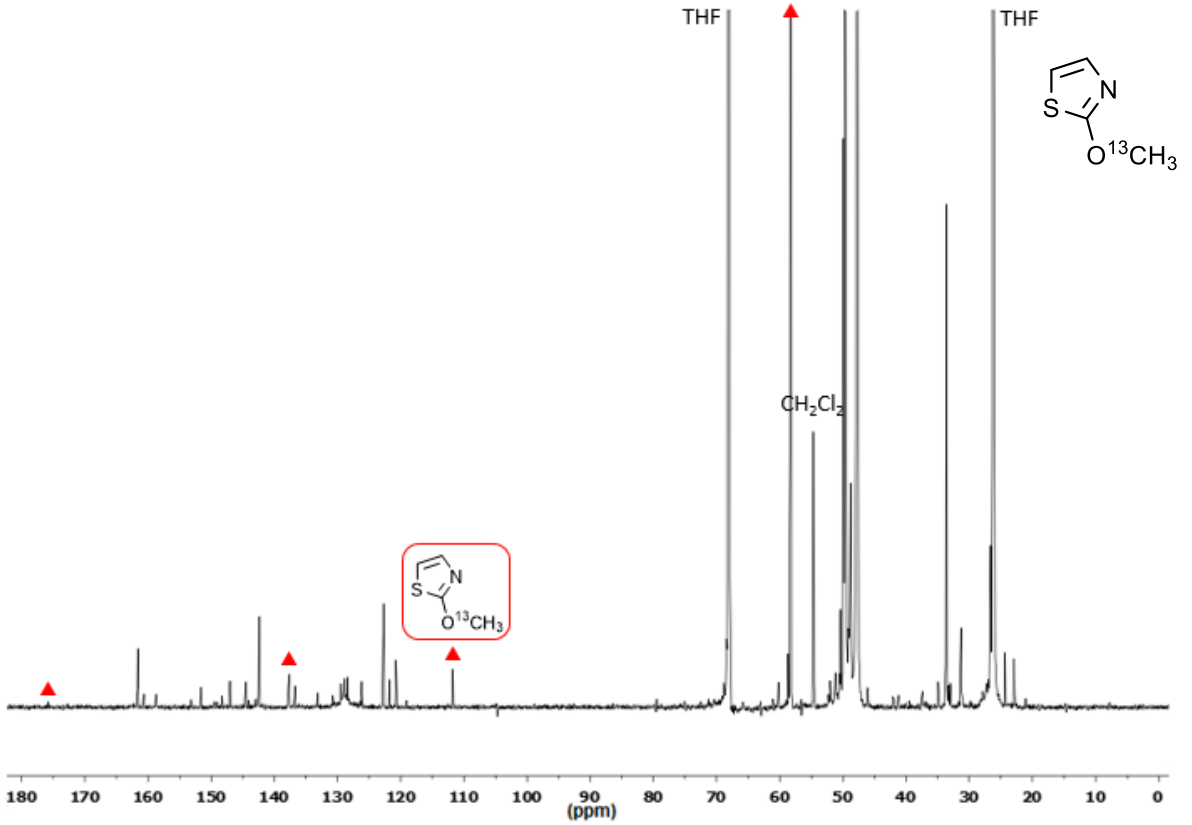


^{13}C NMR Spectrum of [^{13}C]5-Methoxybenzo[1,3]dioxole **[^{13}C]4i** in $CDCl_3$.

[^{13}C] 2-Methoxythiazole ([^{13}C]4j)

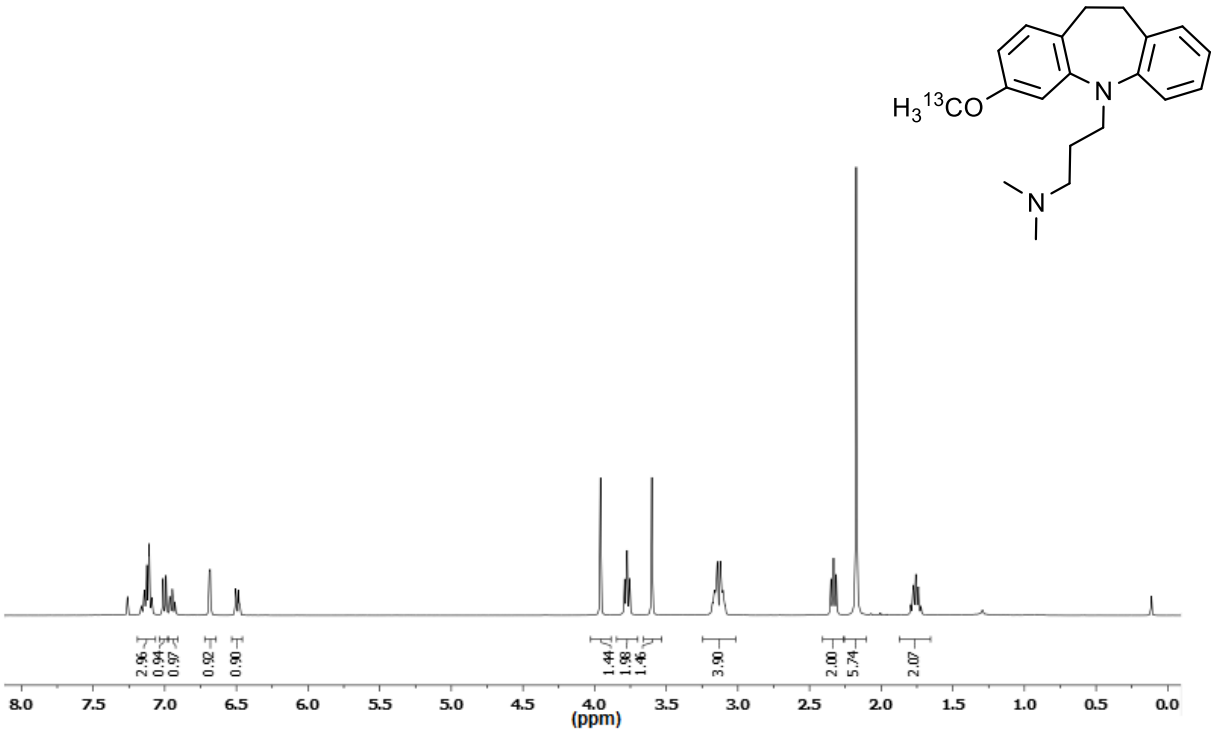


^{1}H NMR spectrum of the crude reaction mixture between 2-chlorothiazole and BBN-O^{13}CH$_3$ using CH_2Cl_2 as internal standard.

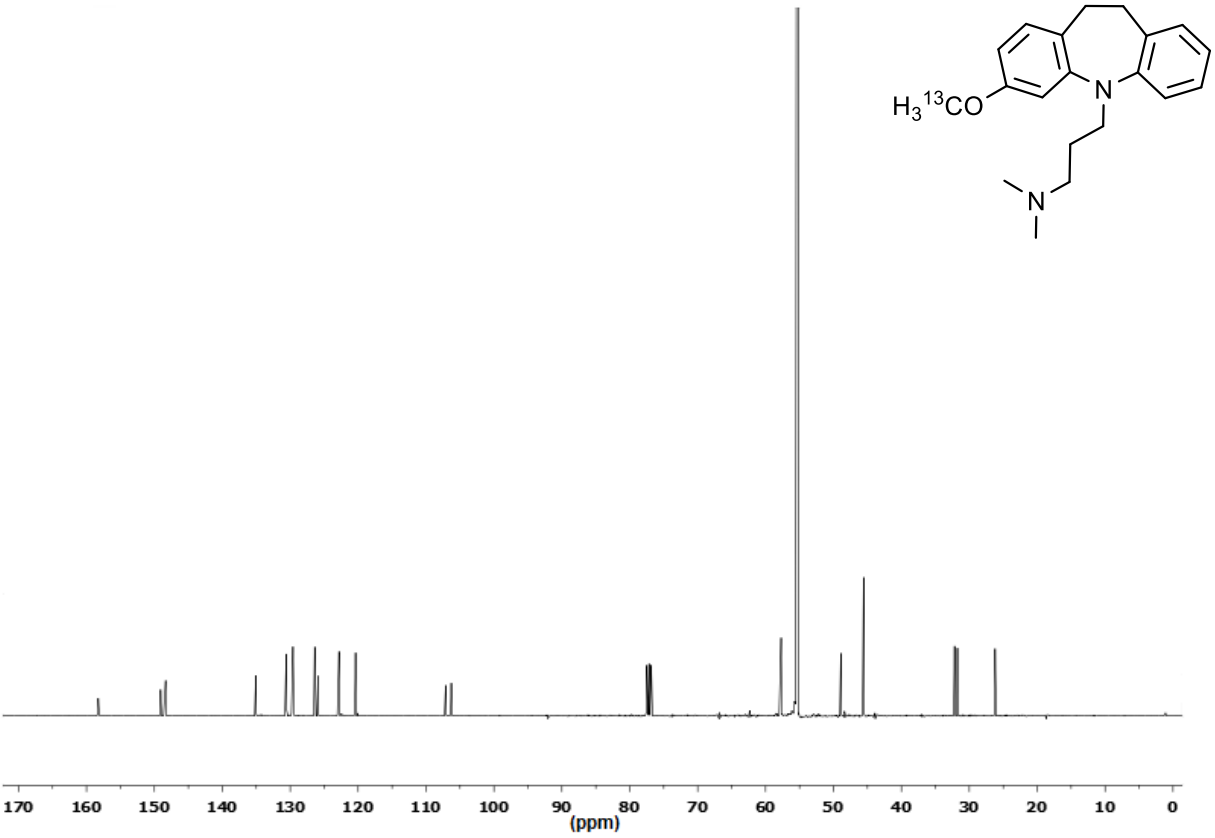


^{13}C NMR spectrum of the crude reaction mixture between 2-chlorothiazole and BBN-O^{13}CH$_3$.

[^{13}C] 3-Methoxyimipramine ([^{13}C]4k)

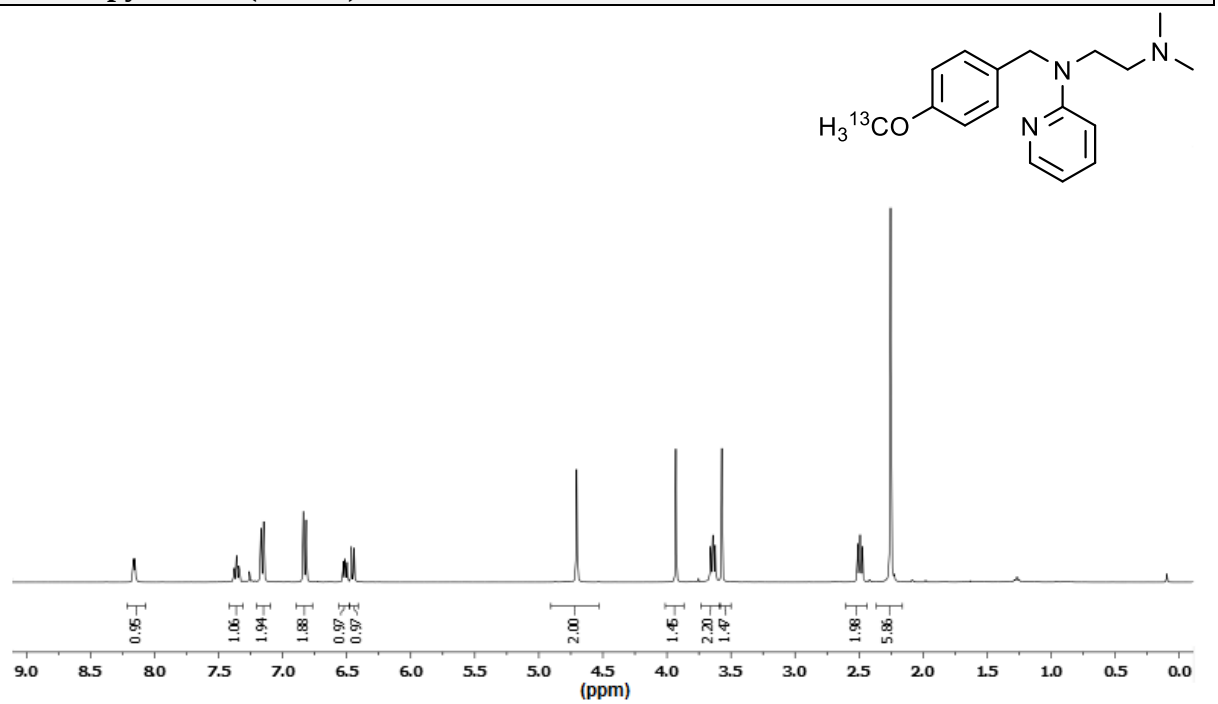


^{1}H NMR Spectrum of [^{13}C]3-Methoxyimipramine **[^{13}C]4k** in $CDCl_3$.

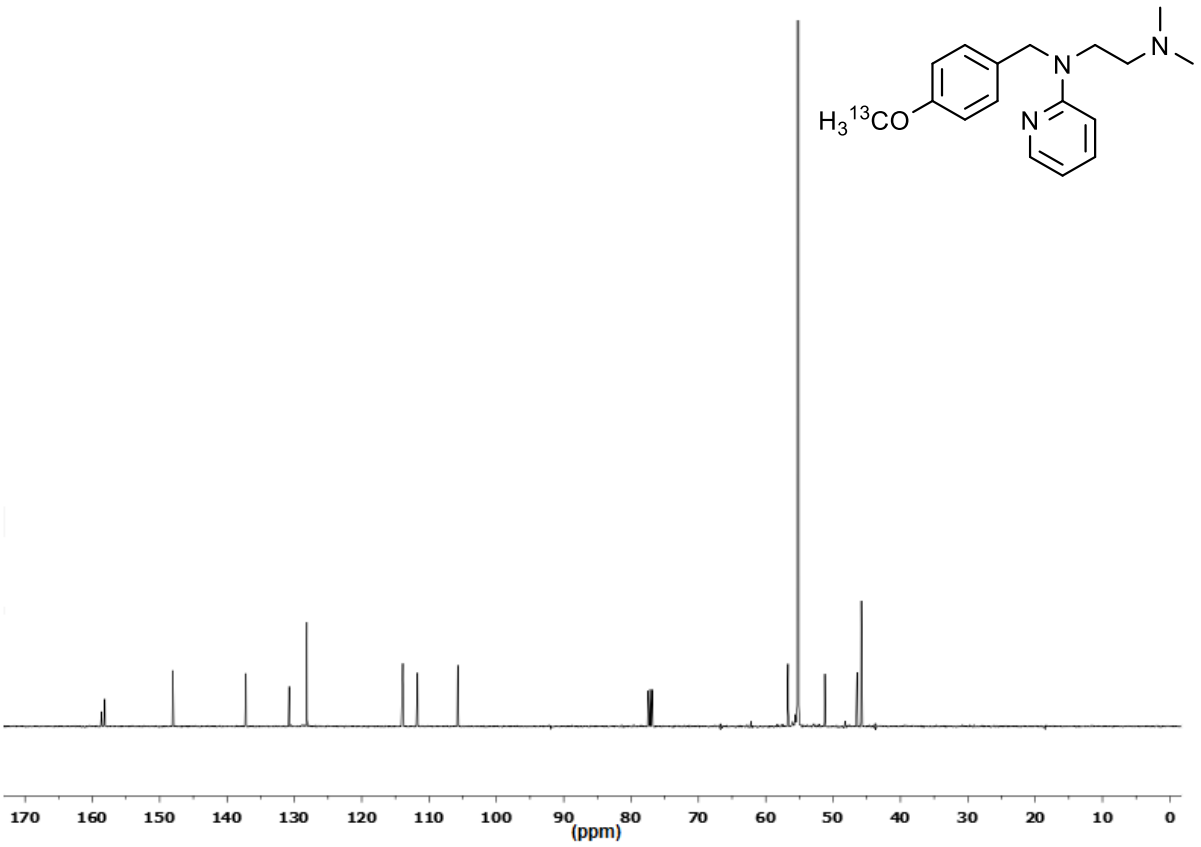


^{13}C NMR Spectrum of [^{13}C]3-Methoxyimipramine **[^{13}C]4k** in $CDCl_3$.

[^{13}C] Mepyramine ([^{13}C]4l)

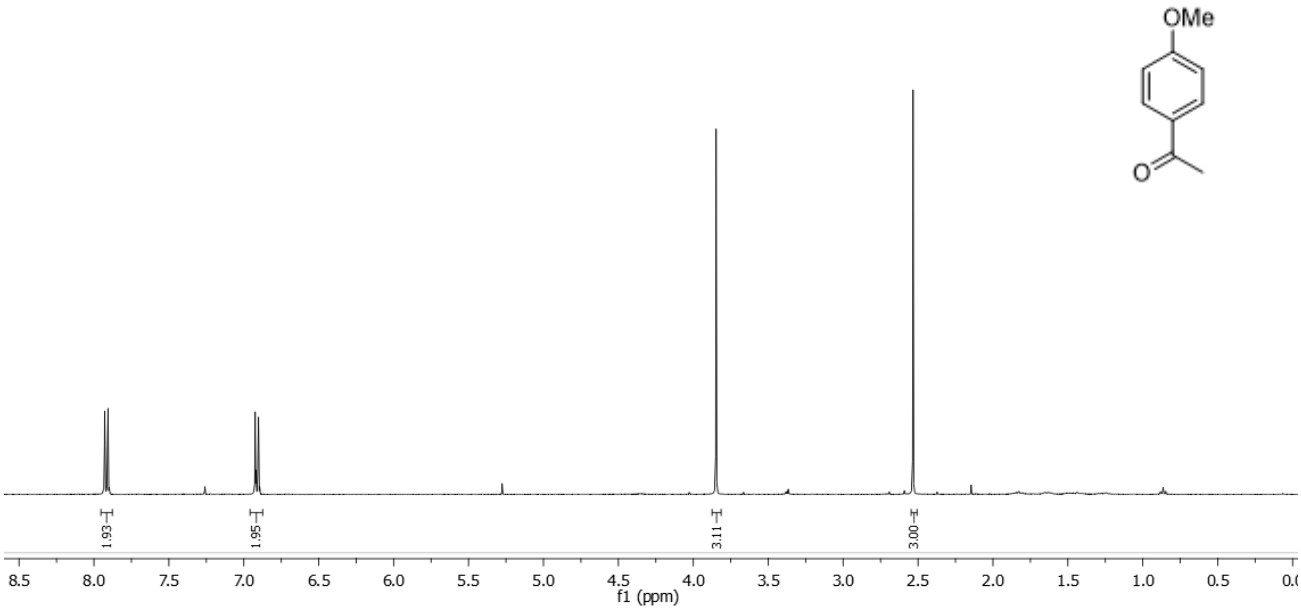


^{1}H NMR Spectrum of [^{13}C]Mepyramine **[^{13}C]4l** in $CDCl_3$.

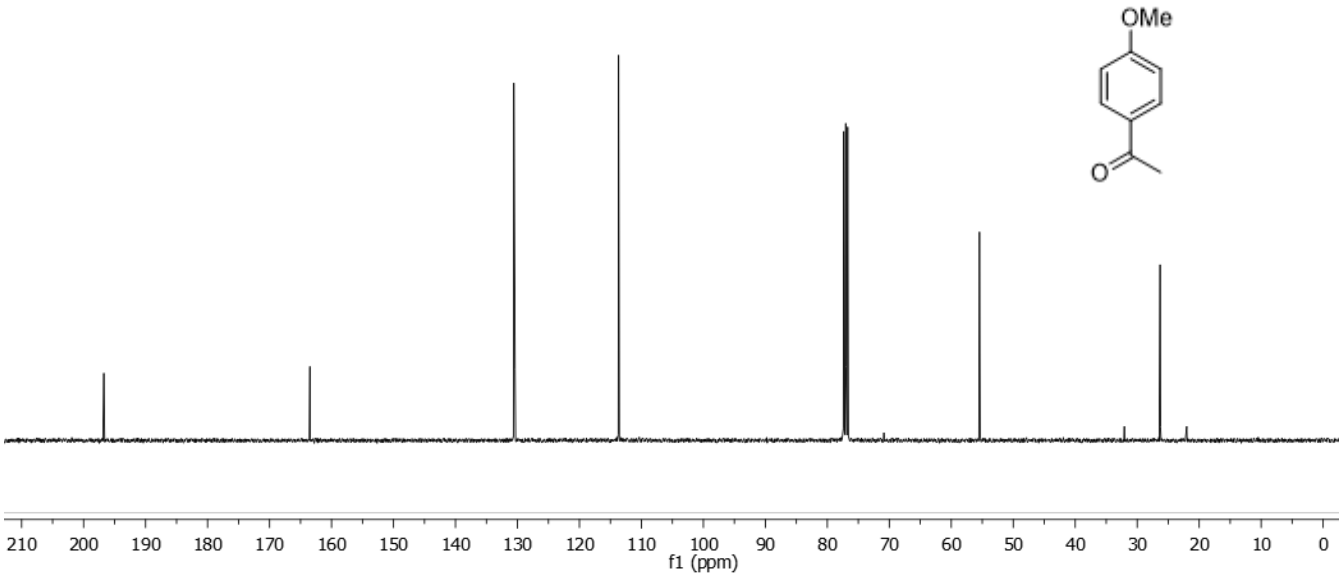


^{13}C NMR Spectrum of [^{13}C]Mepyramine **[^{13}C]4l** in $CDCl_3$.

1-(4-methoxyphenyl) ethan-1-one ([^{12}C]4k)

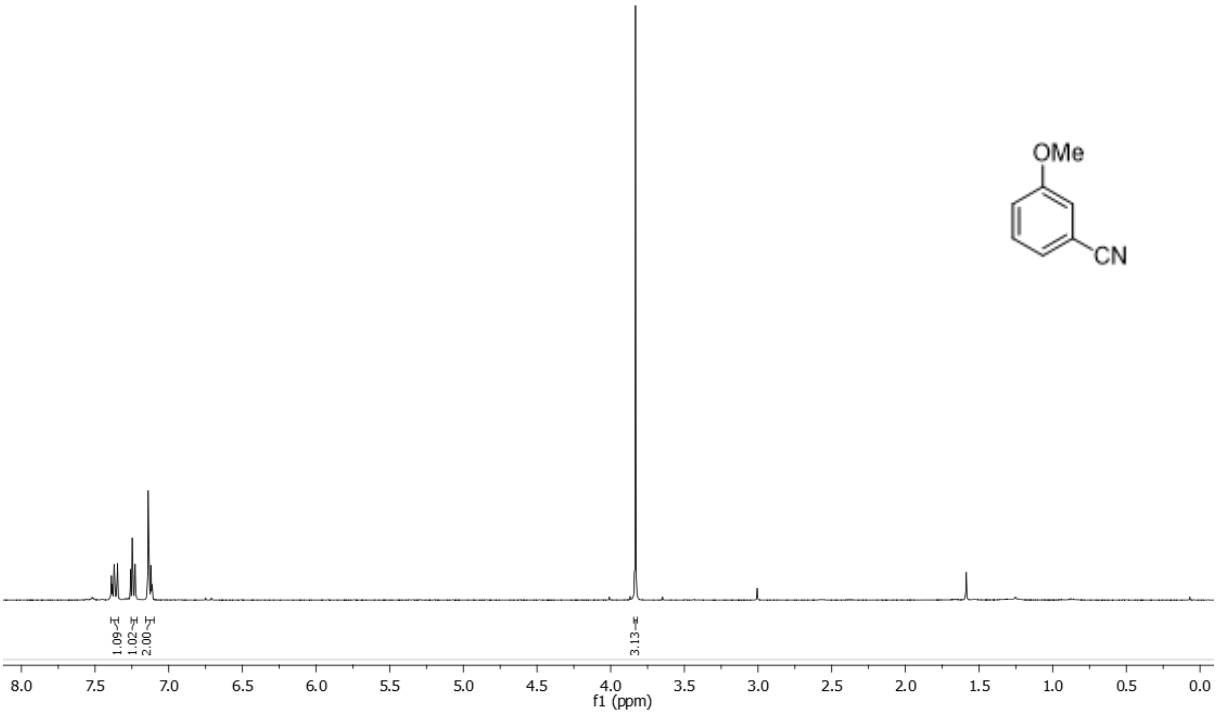


^{1}H NMR Spectrum of 1-(4-methoxyphenyl) ethan-1-one **[^{12}C]4k** in $CDCl_3$.

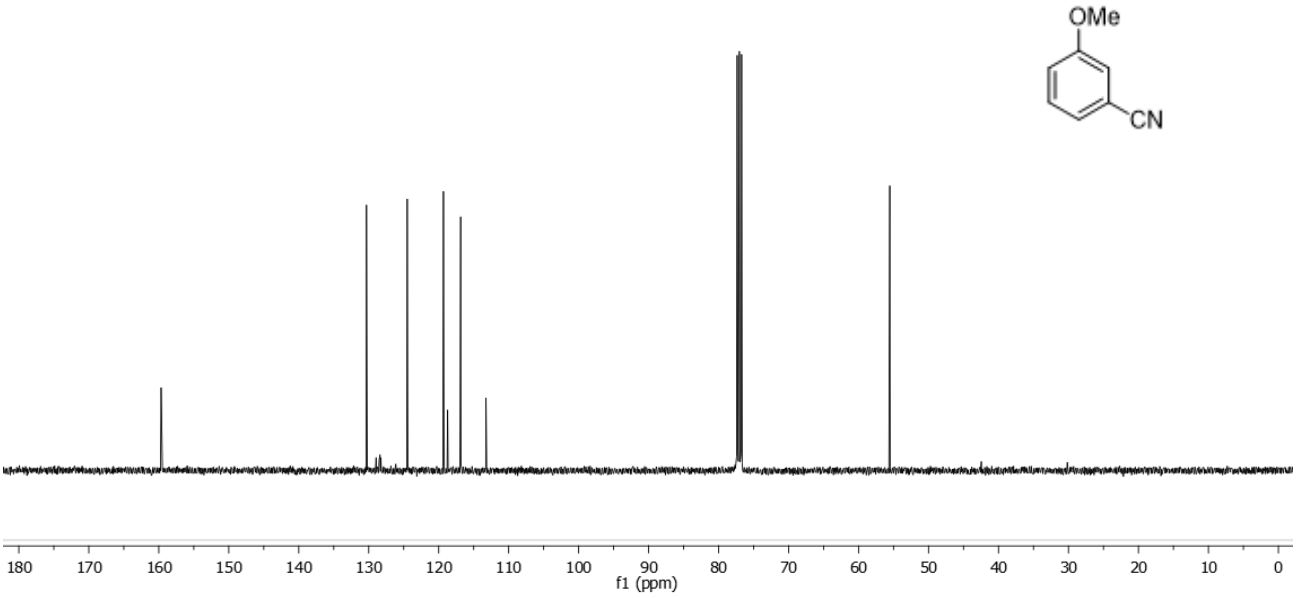


^{13}C NMR Spectrum of 1-(4-methoxyphenyl) ethan-1-one **[^{12}C]4k** in $CDCl_3$.

3-methoxybenzonitrile ([^{12}C]4l)

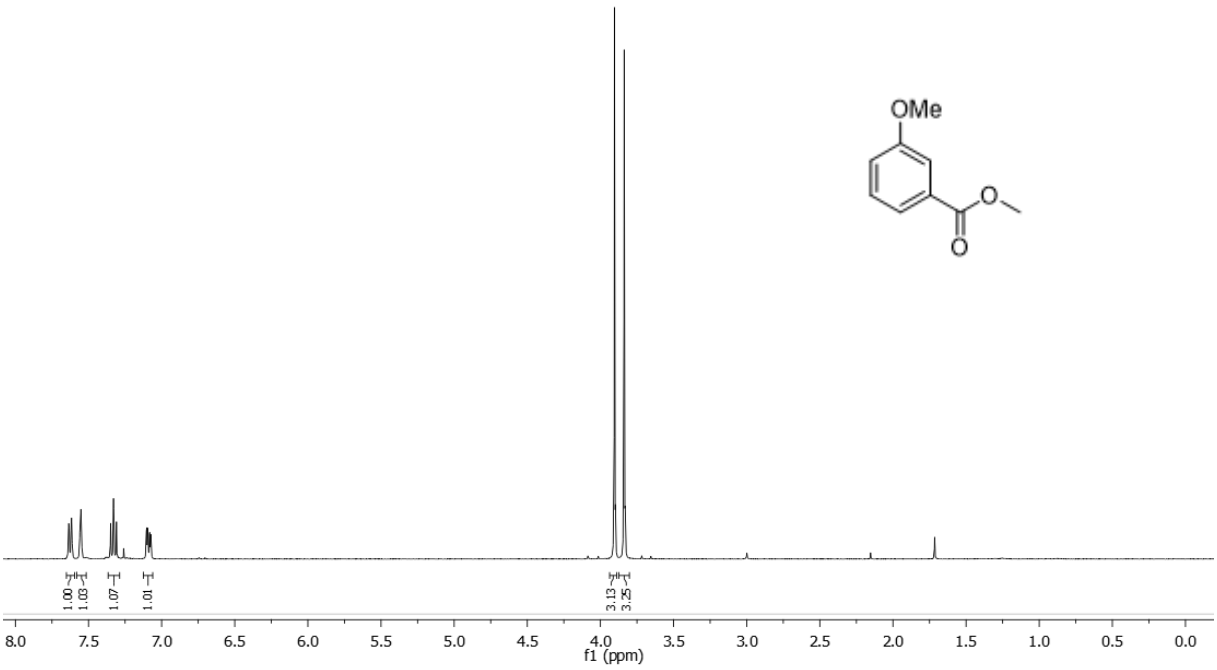


^{1}H NMR Spectrum of 3-methoxybenzonitrile **[^{12}C]4l** in $CDCl_3$.

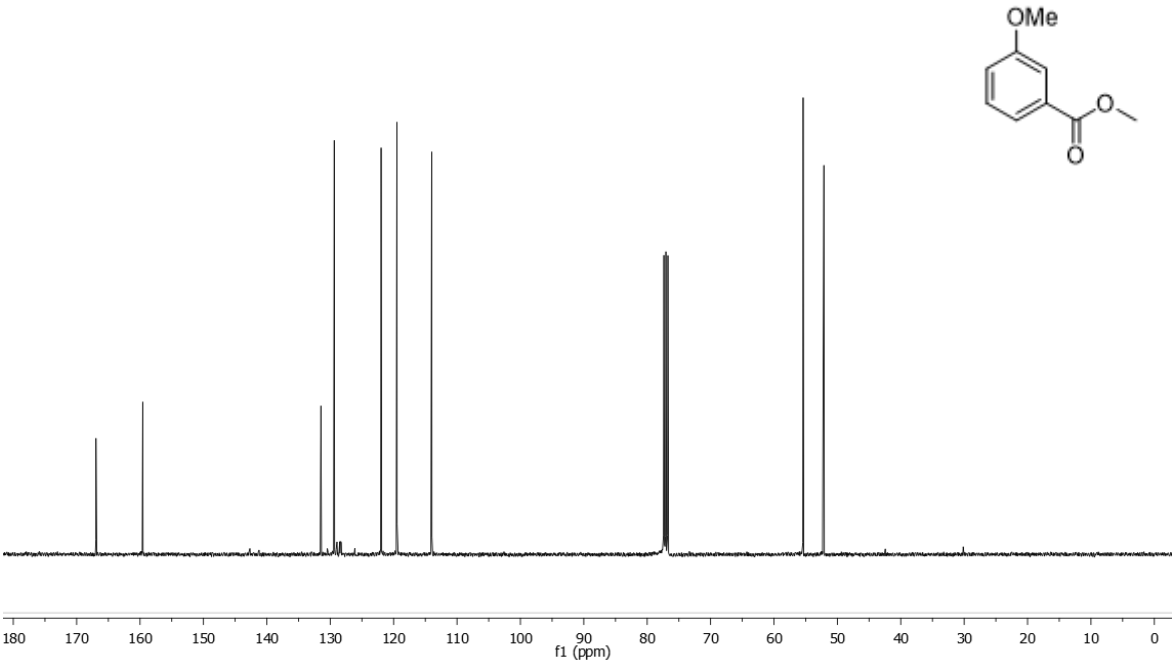


^{13}C NMR Spectrum of 3-methoxybenzonitrile **[^{12}C]4l** in $CDCl_3$.

Methyl 3-methoxybenzoate ([^{12}C]4m)

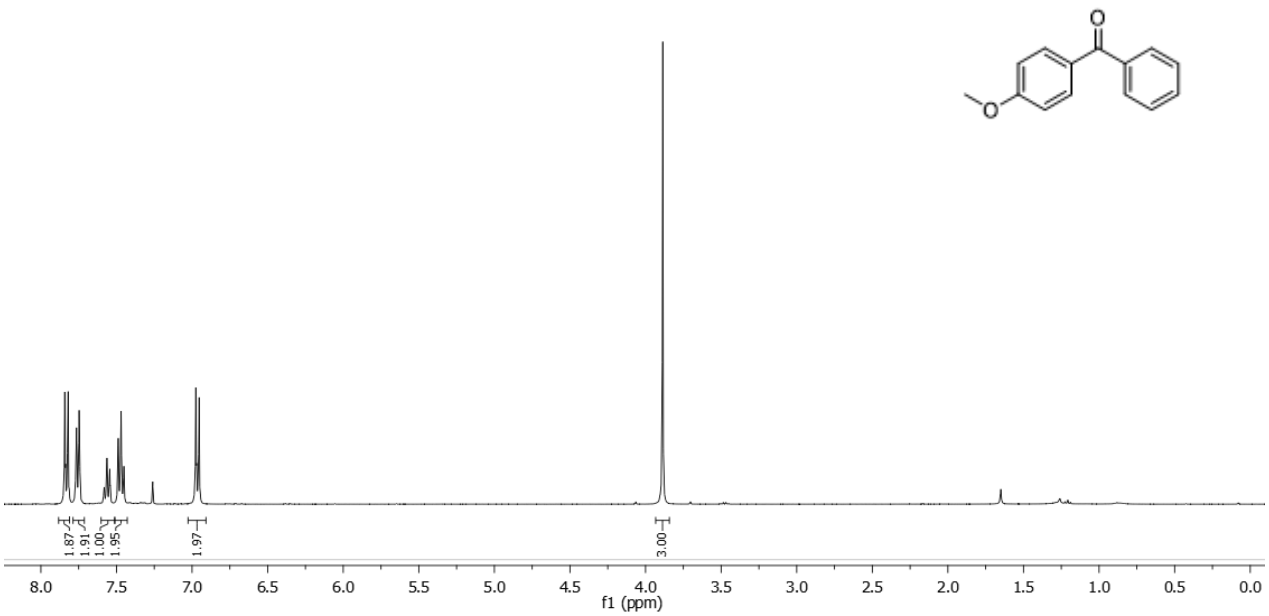


^{1}H NMR Spectrum of Methyl 3-methoxybenzoate **[^{12}C]4m** in $CDCl_3$.

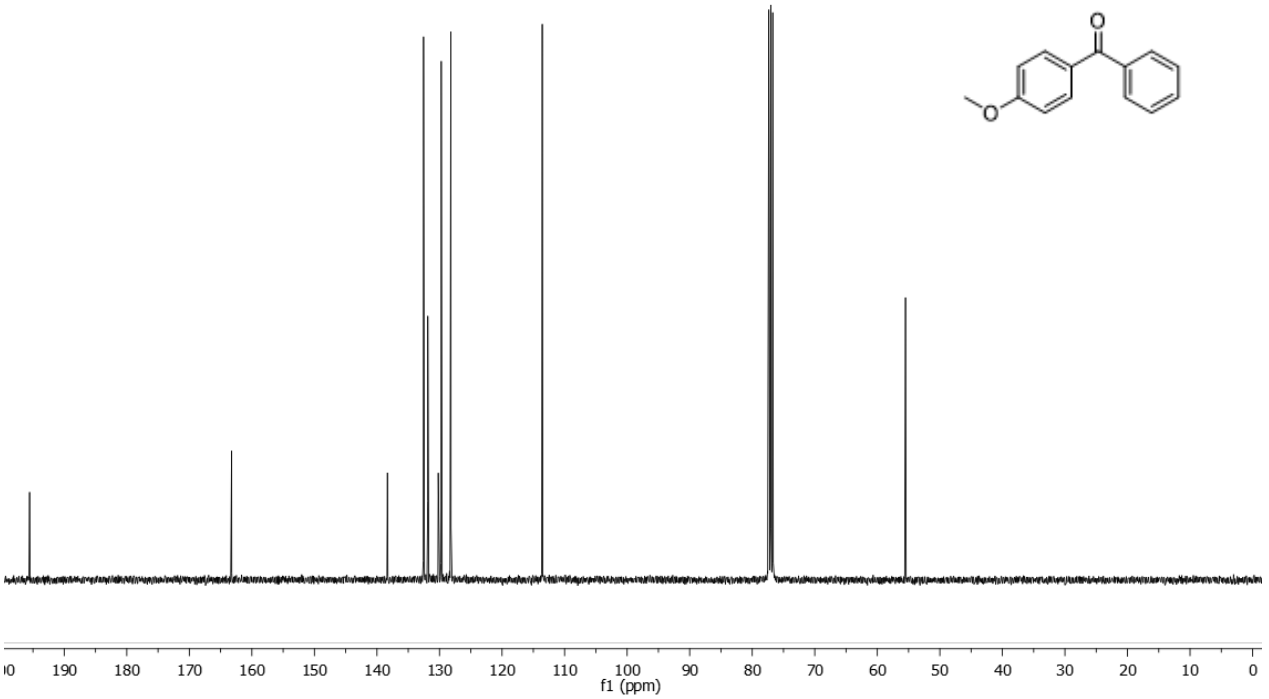


^{13}C NMR Spectrum of Methyl 3-methoxybenzoate **[^{12}C]4m** in $CDCl_3$.

(4-methoxyphenyl)(phenyl)methanone ([^{12}C]4o)

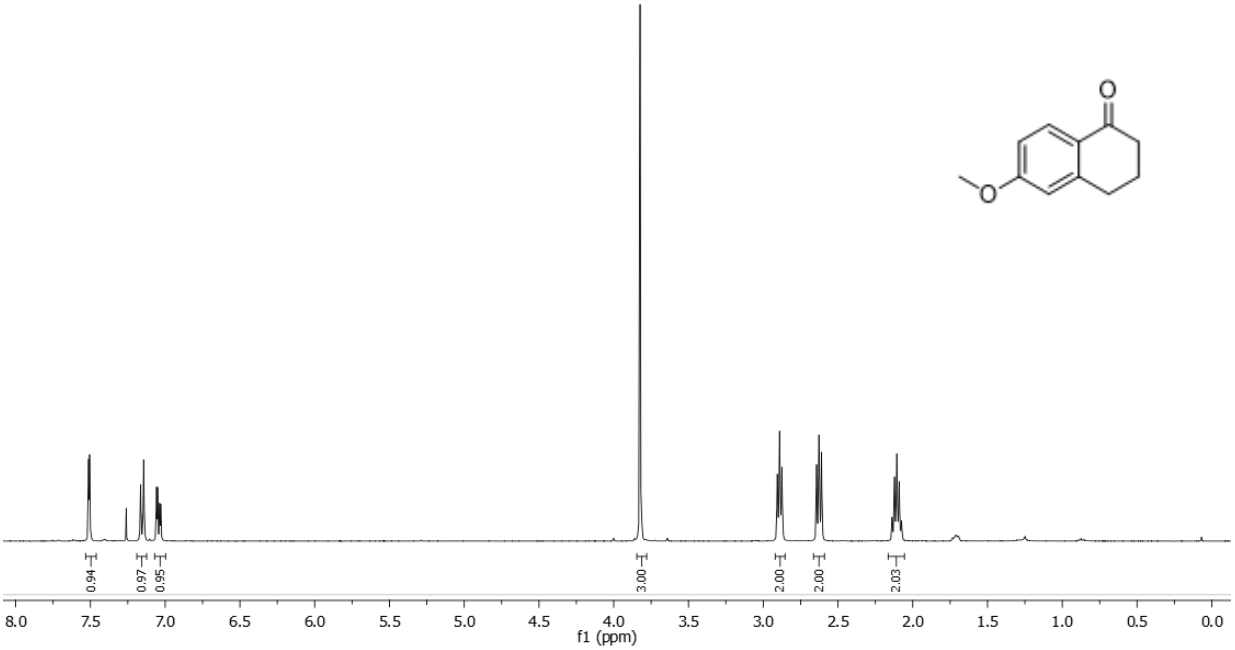


^{1}H NMR Spectrum of (4-methoxyphenyl)(phenyl)methanone **[^{12}C]4o** in $CDCl_3$.

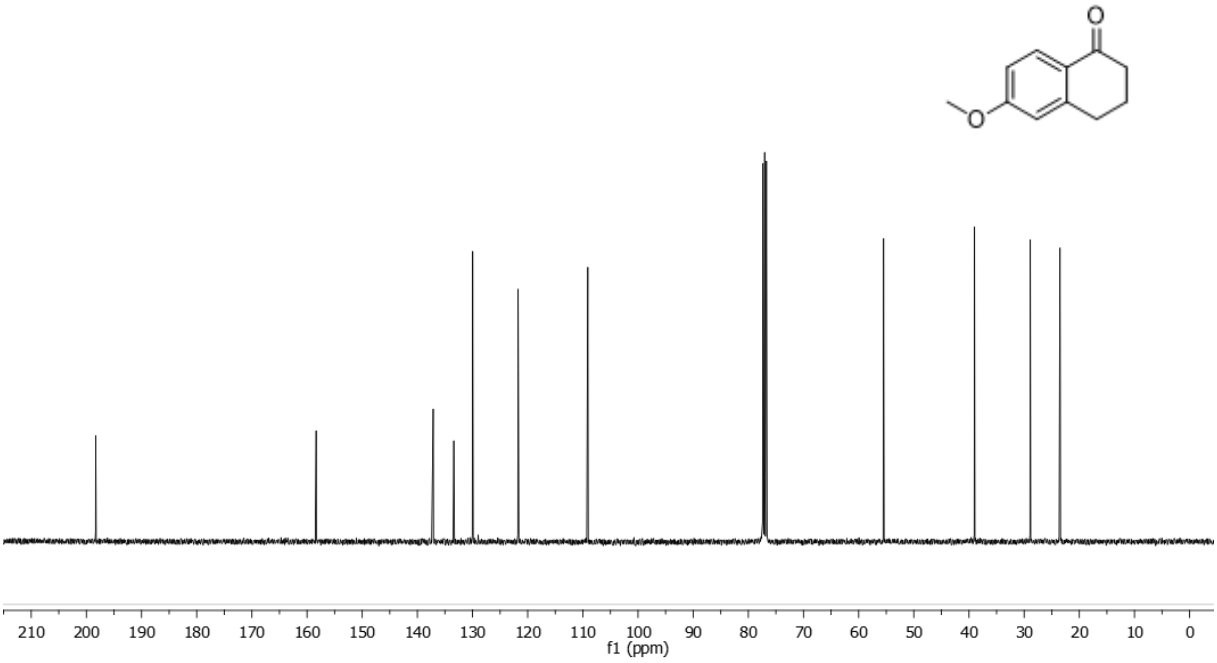


^{13}C NMR Spectrum of (4-methoxyphenyl)(phenyl)methanone **[^{12}C]4o** in $CDCl_3$

7-methoxy-3, 4-dihydronaphthalen-1(2H)-one ([^{12}C]4p)

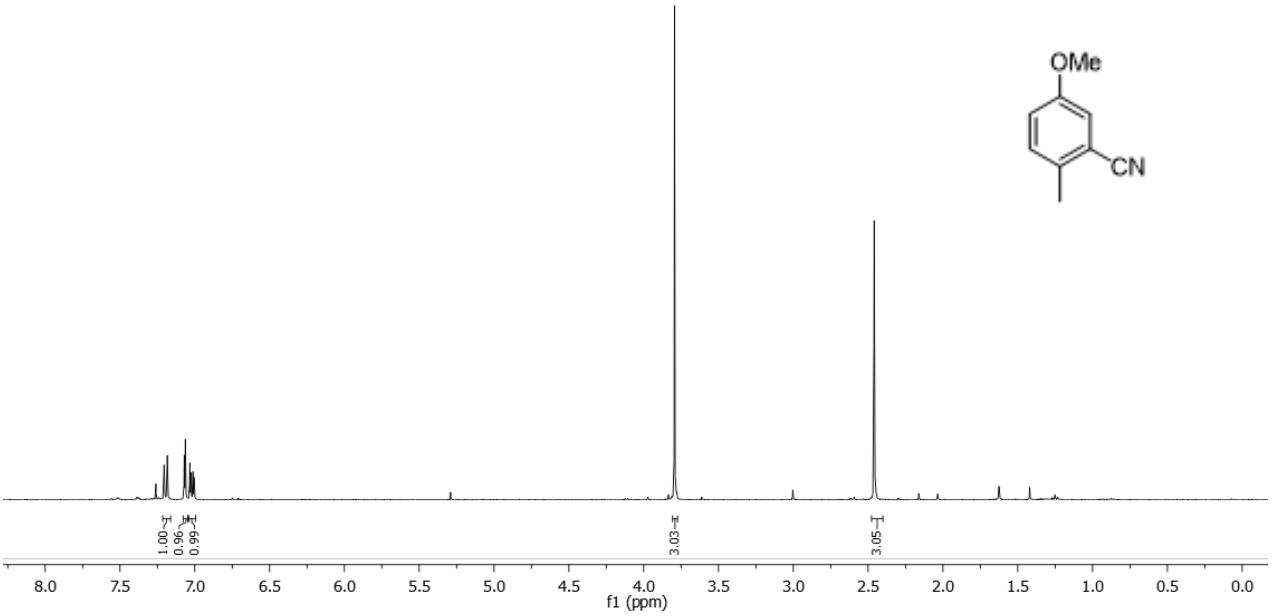


^{1}H NMR Spectrum of 7-methoxy-3, 4-dihydronaphthalen-1(2H)-one **[^{12}C]4p** in $CDCl_3$.

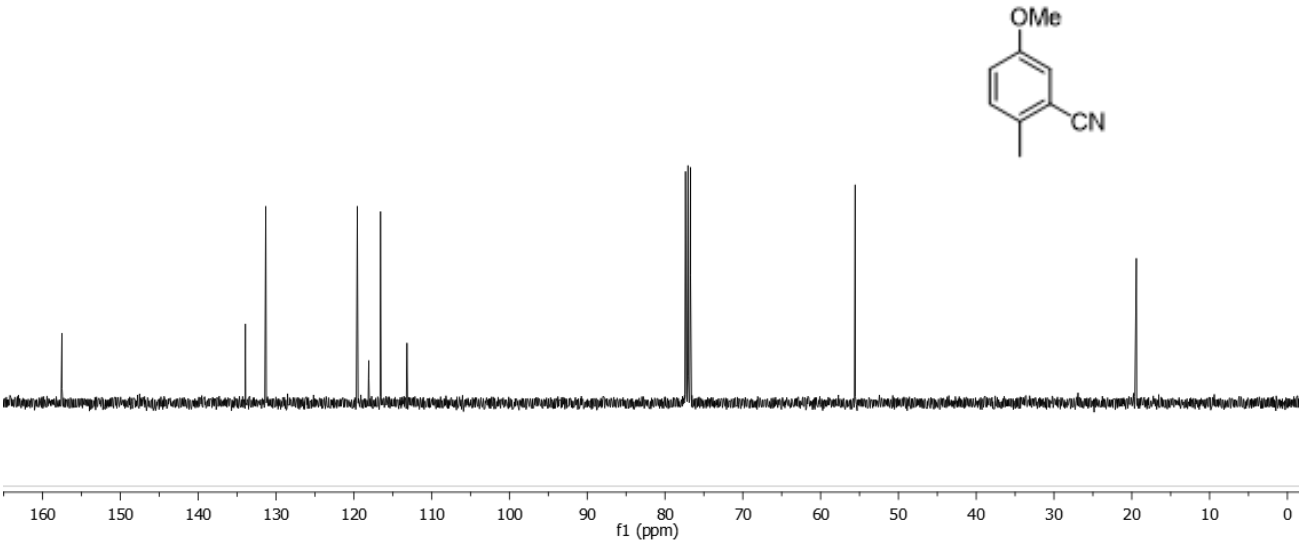


^{13}C NMR Spectrum of 7-methoxy-3, 4-dihydronaphthalen-1(2H)-one **[^{12}C]4p** in $CDCl_3$

3-methoxy-6-methyl benzonitrile ([^{12}C]4q)



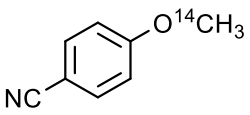
^{1}H NMR Spectrum of 3-methoxy-6-methylbenzonitrile **[^{12}C]4q** in $CDCl_3$.



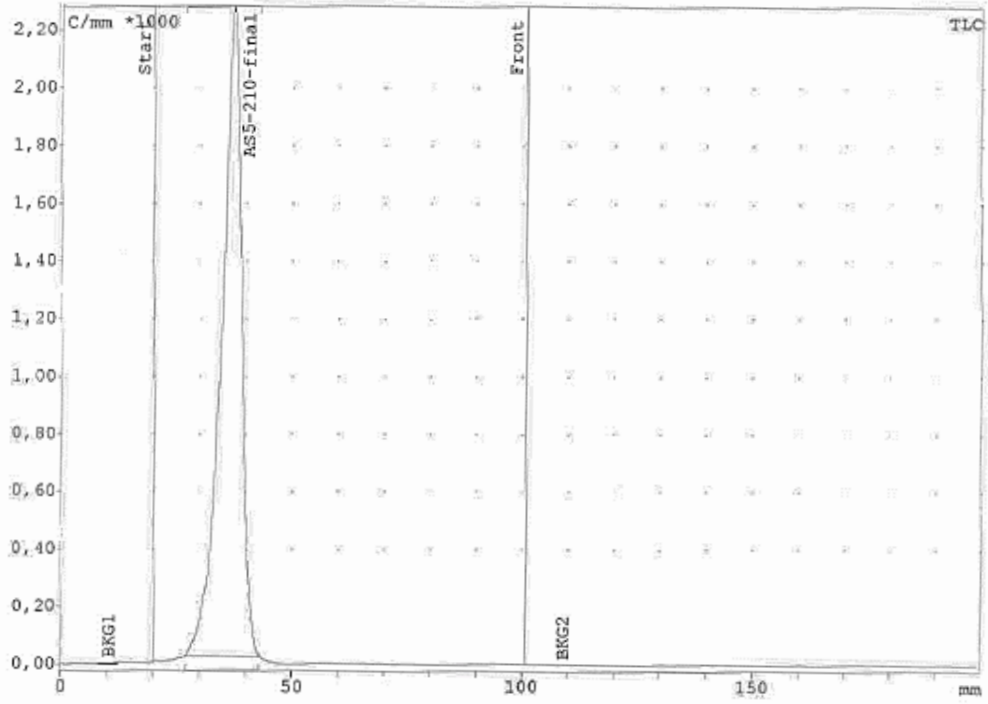
^{13}C NMR Spectrum of 3-methoxy-6-methylbenzonitrile **[^{12}C]4q** in $CDCl_3$.

VII. TLC of ^{14}C-Labelled Compounds

[^{14}C] 4-Methoxybenzonitrile [19] ([^{14}C]4d)



$C_7{}^{14}CH_7NO$
MW: 135.14 g.mol^{-1}
Yield: 37%
White Solid



Description de l'échantillon

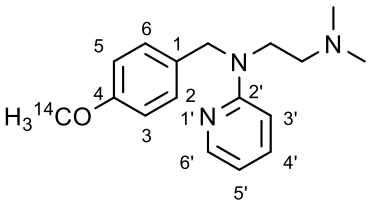
Etude:	ANTOINE		
Mesure:	AS5-210-14C_03.rta, commencé:		06/12/2019 10:34
Méthode:	C14		
Origine:	20 mm	Front 101 mm	
Meas. time:	0,1 min	Résolution: 0,4 mm	
Tray number:	2,0	Position de scan:	230,0 mm
Haute tension:	1620,0 V		

Détecteur de radioactivité: raytest RITA
Autre Square flow cell #0
Cell volume 0 ul

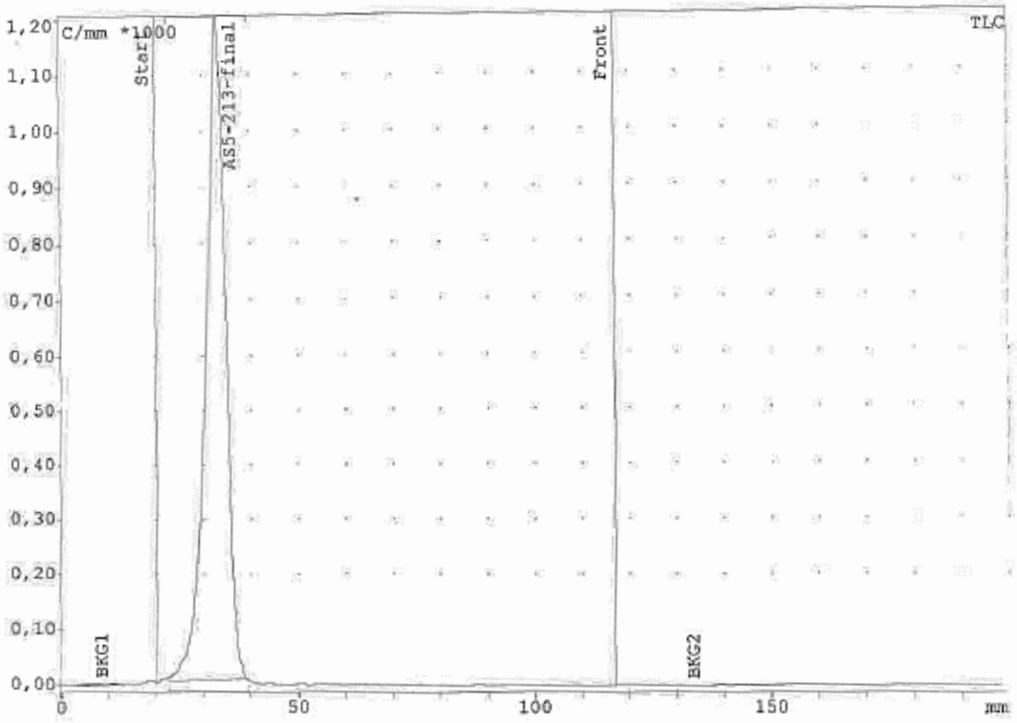
Intégration TLC

Substance	R/F	Type	Aire	%Aire
			Counts	%
AS5-210-final	0,214	BB	11292,11	100,00
Sum in ROI			11292,11	
Aire totale			11940,75	
Aire RF			11897,00	
BKG1			2,045	
2 ROIs BKG			1,116	
Remainder RF			604,89	5,08
Remainder (Tot)			648,64	5,43

[^{14}C] Mepyramine ([^{14}C]4l)



$C_{16}{}^{14}CH_{23}N_3O$
MW: 287.38 g.mol^{-1}
Yield: 35%
Yellowish oil



Description de l'échantillon

Etude:	ANTOINE		
Mesure:	AS5-213-14C-final_01.rta, commencé:	20/12/2019	15:26
Méthode:	C14		
Origine:	20 mm	Front 117 mm	
Meas. time:	0,1 min	Résolution: 0,4 mm	
Haute tension:	1620,0 V		
Détecteur de radioactivité: raytest RITA			
Autre Square flow cell #0			
Cell volume 0 ul			

Intégration TLC

Substance	R/F	Type	Aire	%Aire
			Counts	%
AS5-213-final	0,136	BB	5824,416	100,00
Sum in ROI			5824,416	
Aire totale			6110,037	
Aire RF			6070,000	
BKG1			1,1111	
2 ROIs BKG			0,5882	
Remainder RF			245,58	4,05
Remainder (Tot)			285,62	4,67

VIII. References

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