Aqueous Suzuki Coupling Reactions of Basic Nitrogen-Containing Substrates in the Absence of Added Base and Ligand: Observation of High Yields under Acidic Conditions

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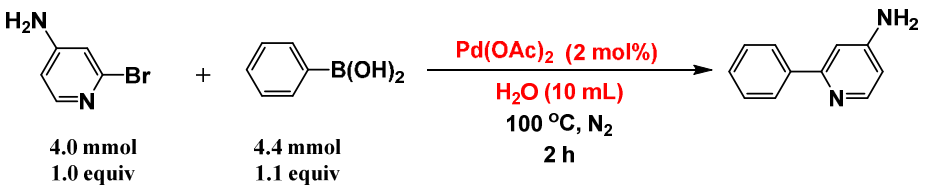
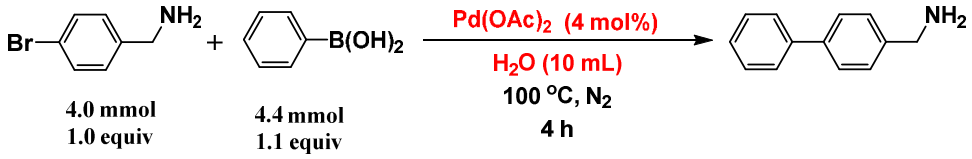
Contents

1. Results of Mercury Test



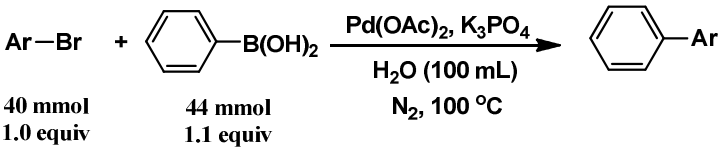
Hg (equiv) relative to Pd	**GC Yield (%)**	**Initial pH**	**Final pH**
0	100	6.5	2.3
20	98.1	6.3	3.6
50	72.6	6.6	5.1
150	38.5	6.5	5.0
300	40.6	6.3	5.0



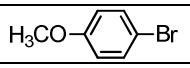
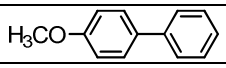
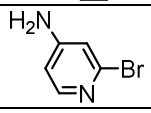
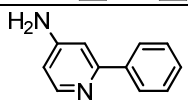
Hg (equiv) relative to Pd	**GC Yield (%)**	**Initial pH**	**Final pH**
0	88.8	8.6	2.1
10	63.1	8.9	5.7
25	44.7	-	-
150	25.1	8.7	6.7

2. Analytic Methods

2.1. Comparison of Reaction Yields Determined by Various Analytic Methods



The isolated yields for two model reactions are consistent with the yields determined by GC and ^{1}H NMR. As a consequence, GC and/or ^{1}H NMR were employed for in-situ determination of the yields for the coupling reactions for a wide variety of aryl substrates in this work.

Aryl Bromide	Product	$Pd(OAc)_2$ (equiv)	K_3PO_4 (equiv)	Time (h)	Yield (%)		
					Isolated*	GC-FID	^{1}H NMR
		5	2.1	4	75	74.1	76
		2	1.0	1	100	100	100
*by column chromatographic separation.							

2.2. GC-FID Chromatograms and Calibration Curves

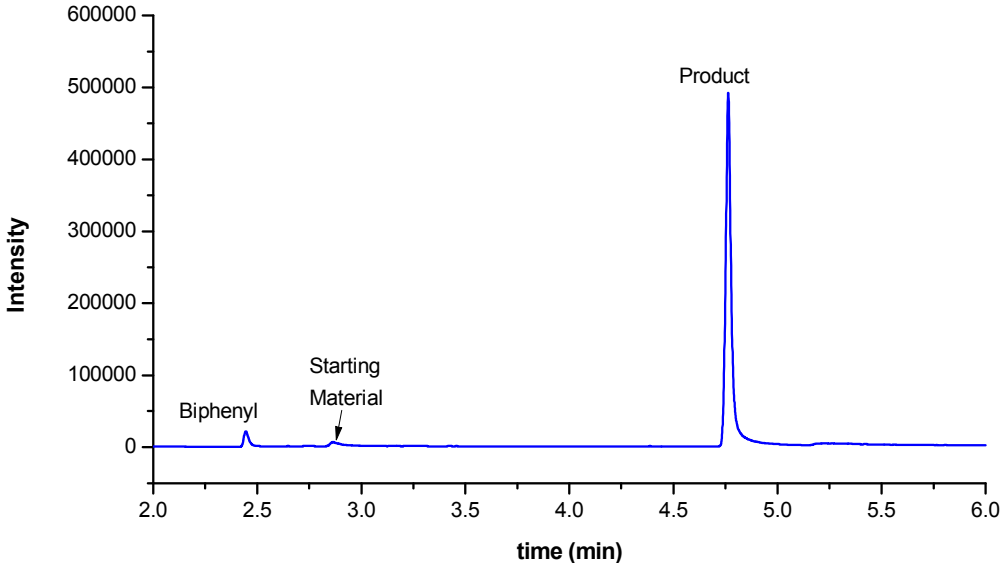


Figure S1. GC-FID chromatogram of the $Pd(OAc)_2$ (0.2 mmol) catalyzed reaction between 4-amino-2-bromopyridine (10 mmol) and $PhB(OH)_2$ (11 mmol) in water (25 mL) without added base in N_2 at 100 ^{o}C for 2 h, after workup.

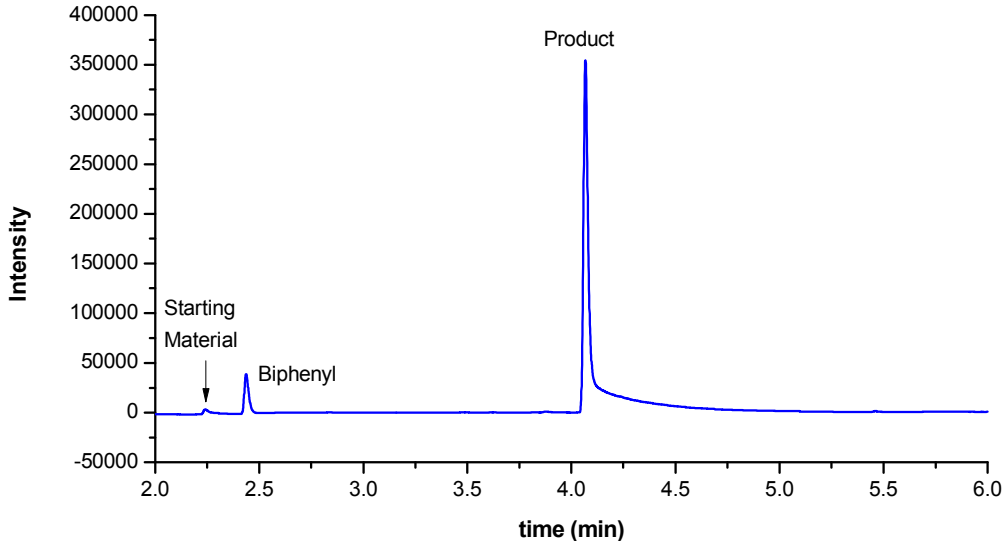


Figure S2. GC-FID chromatogram of the $Pd(OAc)_2$ (0.4 mmol) catalyzed reaction between 4-bromobenzylamine (10 mmol) and $PhB(OH)_2$ (11 mmol) in water (25 mL) without added base in N_2 at 100 ^oC for 4 h, after workup.

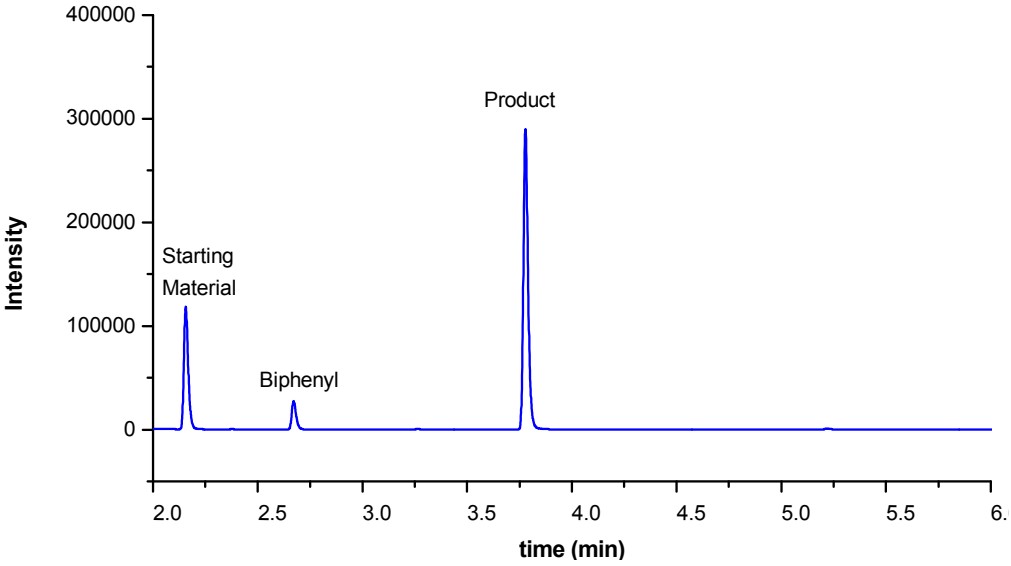
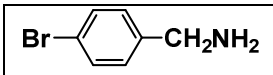


Figure S3. GC-FID chromatogram of the $Pd(OAc)_2$ (2 mmol) catalyzed reaction between 4-bromoanisole (40 mmol), $PhB(OH)_2$ (44 mmol), K_3PO_4 (40 mmol) in water (100 mL) in N_2 at 100 ^oC for 4 h, after workup.

Calibration curves were created from pure substrate and product standards (commercial or synthesized). Stock solutions (0.1 M, 5 or 10 mL) were made using methanol as solvent. Multiple samples of concentrations between 0.005 M and 0.05 M were then made

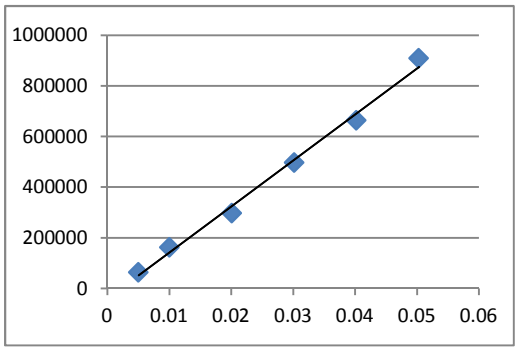
from dilution of the stock solution with methanol and analyzed by GC-FID fitted with a capillary column (30 m × 0.32 mm × 1.00 µm, length × inside diameter × film thickness). Plots of concentration versus area were created for each compound using Microsoft Excel and a trendline analysis used to provide the calibration curve and confirm that the plot followed a straight line. This procedure was exemplified by the calibration curve for 4-bromobenzylamine shown in the table below.



Mr: 186.05 g/mol

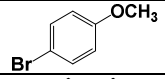
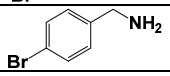
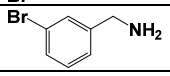
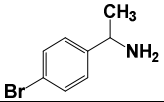
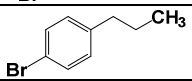
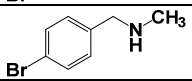
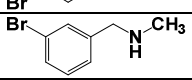
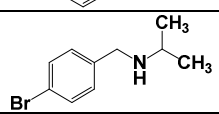
Stock Solution in MeOH	Mass	Volume	Concentration
	0.0936 g	5 mL	0.1006 M

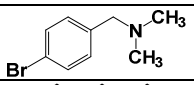
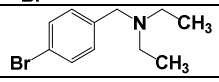
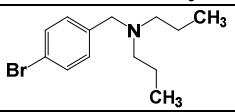
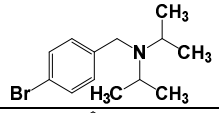
GC Sample NO	Concentration (M)	Area	Retention Time (min)
1	0.005031	63888.8	2.242
2	0.01006	162146.7	2.239
3	0.02012	297391.4	2.237
4	0.03019	496825.0	2.237
5	0.04025	663488.7	2.237
6	0.05031	909017.0	2.236



y = 18169978.679 x - 40166.219
(R^2 = 0.993)

List of Calibration Curves

Substrates Ar-Br	Source *C = Commercial S = Synthesized*	Calibration Curve		
		Slope	Intercept	R^2
	C	12547136.432	0	0.999
	C	18169978.679	-40166.219	0.993
	C	17658197.645	-34410.309	0.998
	C	17929564.744	-23990.503	1.000
	C	20446060.427	41460.156	1.000
	C	22027895.288	-45605.831	0.999
	C	21443335.872	-52325.718	0.998
	S	26280220.038	33259.320	0.999

Substrates Ar-Br	Source *C = Commercial* *S = Synthesized*	Calibration Curve		
		Slope	Intercept	R^2
	S	23496483.640	-33206.284	0.999
	S	32292410.277	-54988.486	0.999
	S	37846827.485	-50367.608	1.000
	S	33972419.737	-65782.087	0.997
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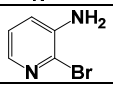
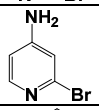
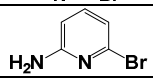
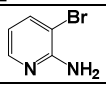
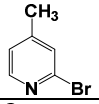
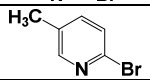
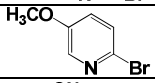
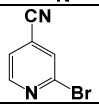
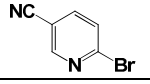
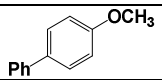
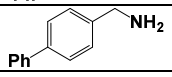
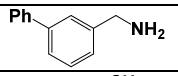
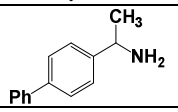
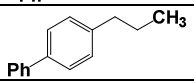
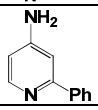
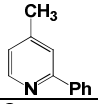
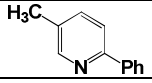
	C	12398707.527	-23492.968	0.999
	C	9902853.230	0	1.000
	C	12025779.559	-24524.976	0.999
	C	12690919.599	-10902.424	0.999
	C	10994830.651	-8710.411	1.000
	C	13939331.948	0	0.999
	C	12368244.282	-17543.399	1.000
	C	13738077.730	-29482.410	0.997
	C	13939331.948	0	0.999

Products	Source *C = Commercial* *S = Synthesized*	Calibration Curve		
		Slope	Intercept	R^2
	C	34556455.924	0	0.999
	C	29322919.378	-93825.871	1.000

	C	29588530.766	-51355.658	0.998
	C	32629381.558	-56985.831	0.999
	C	31029708.878	-38807.821	0.999
	C	25195036.522	-25881.097	0.999
	C	25563000.449	-11151.367	1.000
	C	20923221.180	0	1.000
	C	33647221.690	-35723.356	1.000
	C	25195036.522	-25881.098	1.000

2.3. Examples of ^{1}H NMR Spectra for Crude Products

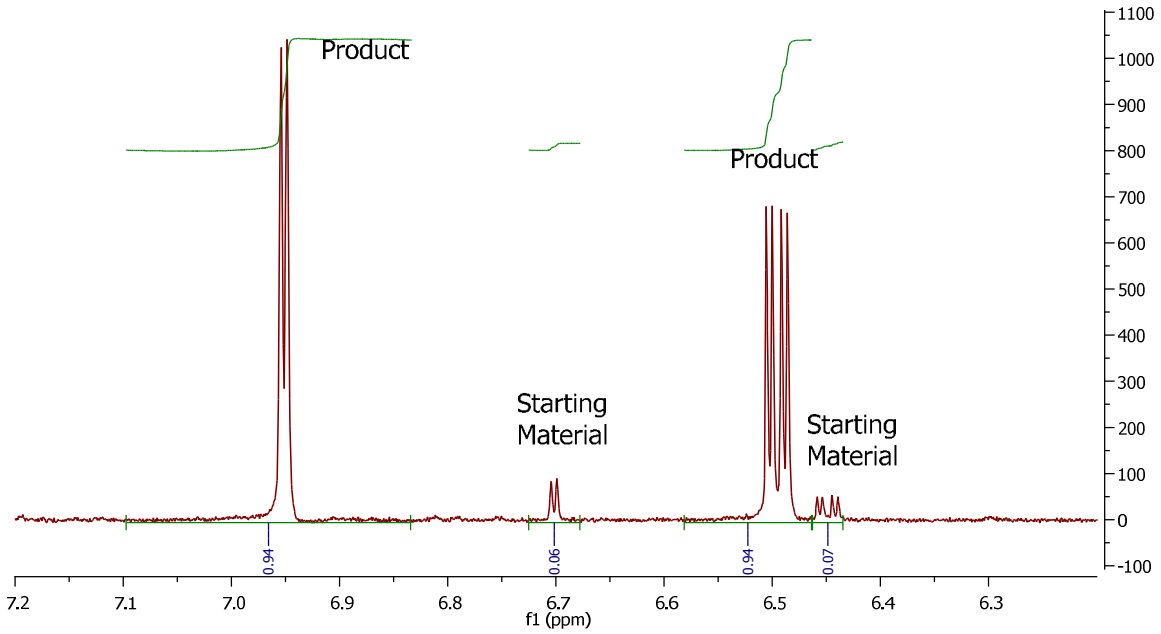


Figure S4. ^{1}H NMR (400 MHz in $CDCl_3$) of the $Pd(OAc)_2$ (0.2 mmol) catalyzed reaction between 4-amino-2-bromopyridine (10 mmol) and phenylboronic acid (11 mmol) in water (25 mL) without added base in N_2 at 100 ^oC for 2 h, after workup.

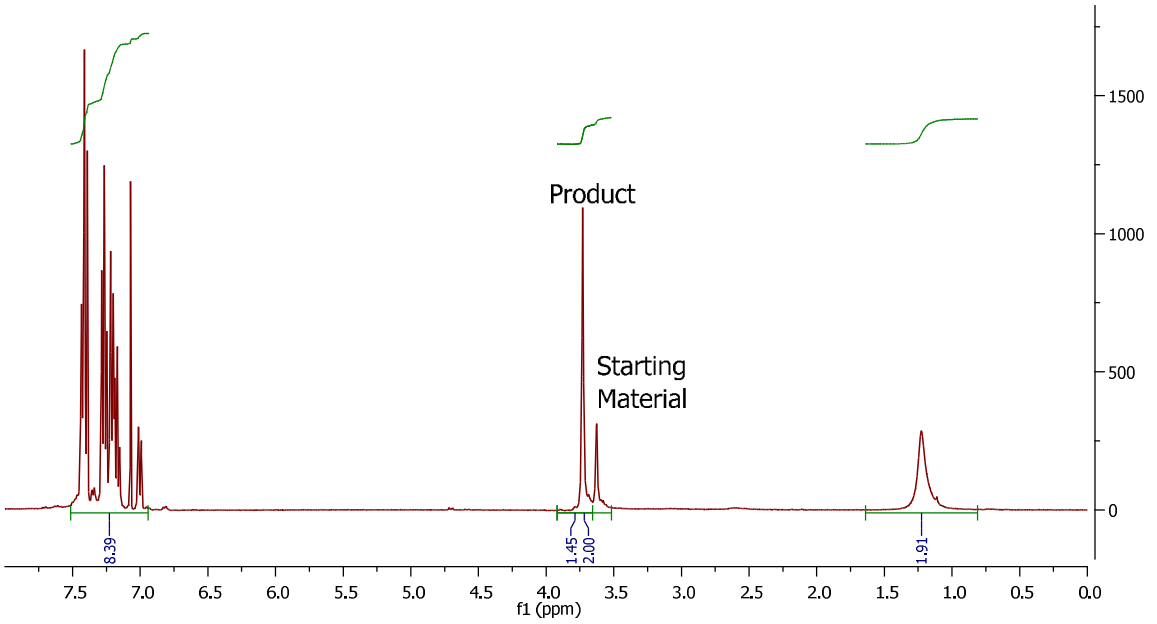


Figure S5. ^{1}H NMR (400 MHz in $CDCl_3$) of the $Pd(OAc)_2$ (0.2 mmol) catalyzed reaction between 4-bromobenzyl amine (10 mmol) and phenylboronic acid (11 mmol) in water (25 mL) without added base in N_2 at 100 ^{o}C for 4 h, after workup.

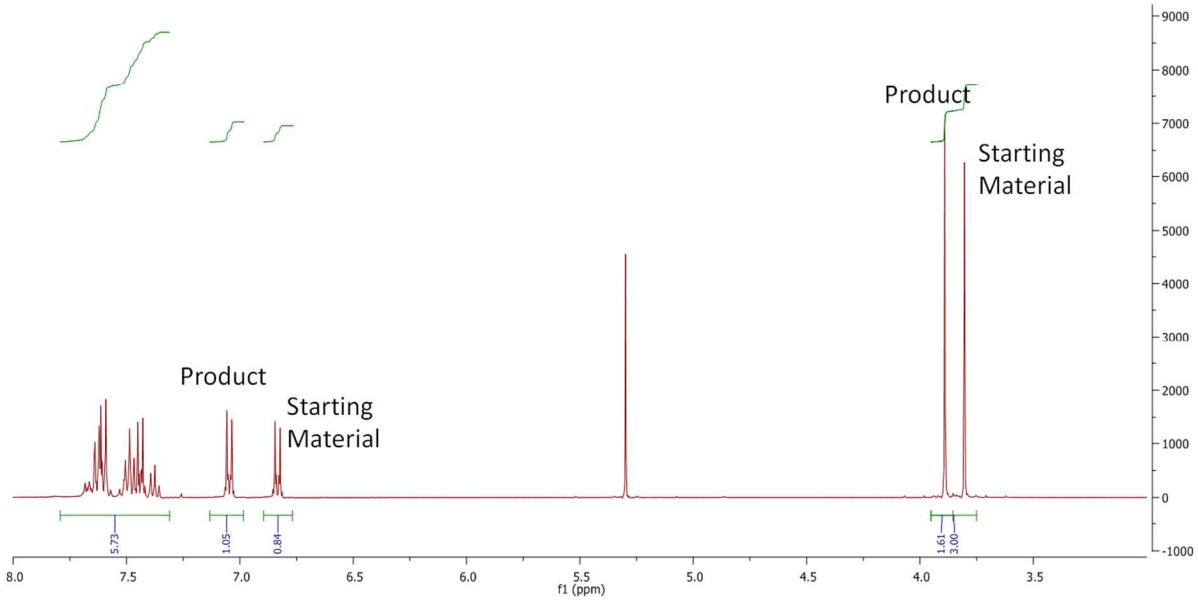


Figure S6. ^{1}H NMR (400 MHz in $CDCl_3$) of the $Pd(OAc)_2$ (2 mmol) catalyzed reaction between 4-bromoanisole (40 mmol), $PhB(OH)_2$ (44 mmol), K_3PO_4 (40 mmol) in water (100 mL) in N_2 at 100 ^{o}C for 4 h, after workup.

NMR spectra were used to determine amount of starting material and product in reaction mixtures after workup by comparison to standards of each compound. NMR Yields were calculated according to the following:

$$Yield_{NMR} = \frac{I_{prod}}{I_{SM} + I_{prod}}$$

Where I_{prod}. and I_{SM} denote the area integrals of the product and substrate respectively. The chemical shifts for each product and starting material were confirmed *via* prepared standards and are consistent to reports in the literature.

3. NMR Spectra

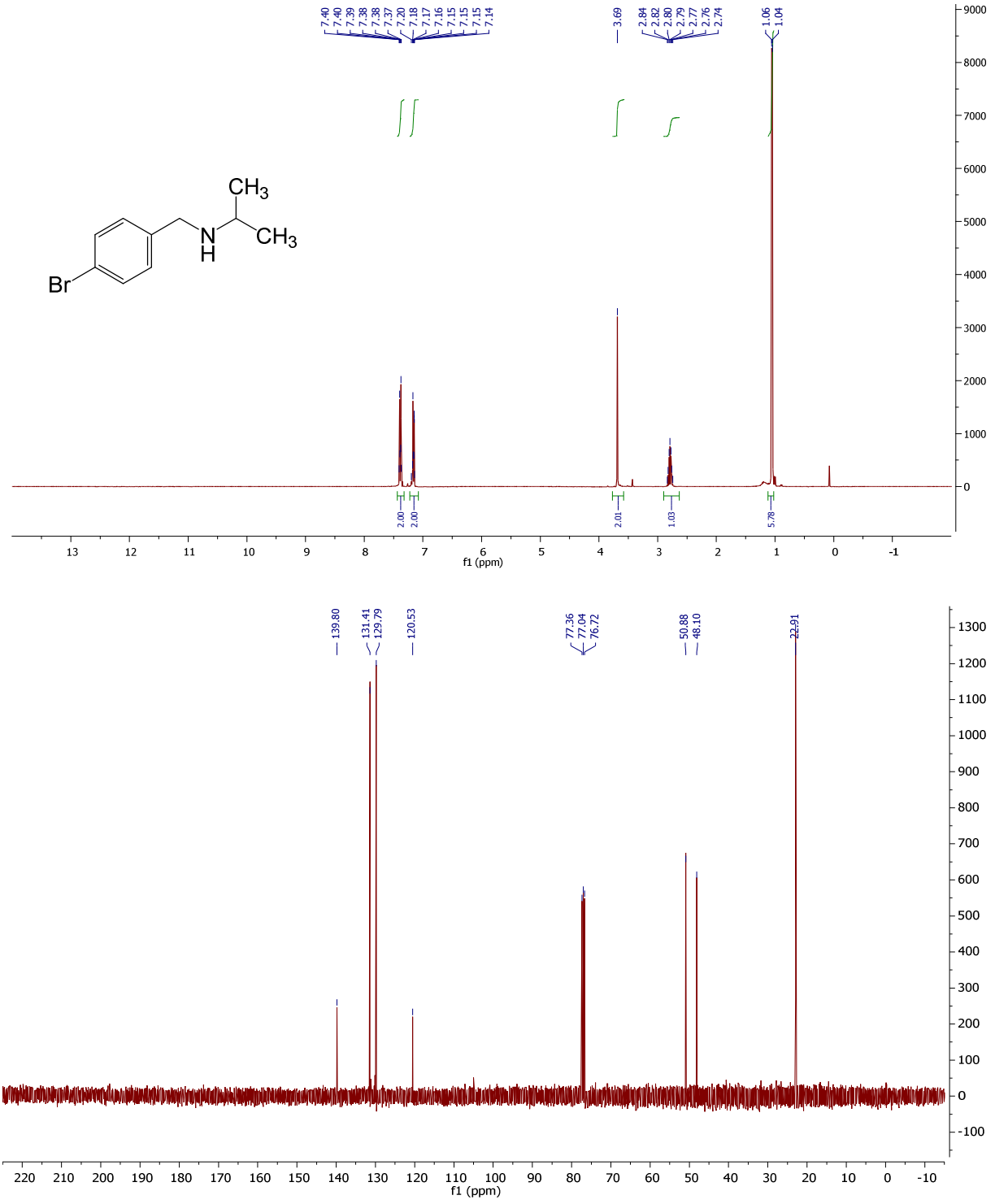


Figure S7. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 4-bromo-*N*-isopropylbenzylamine in $CDCl_3$

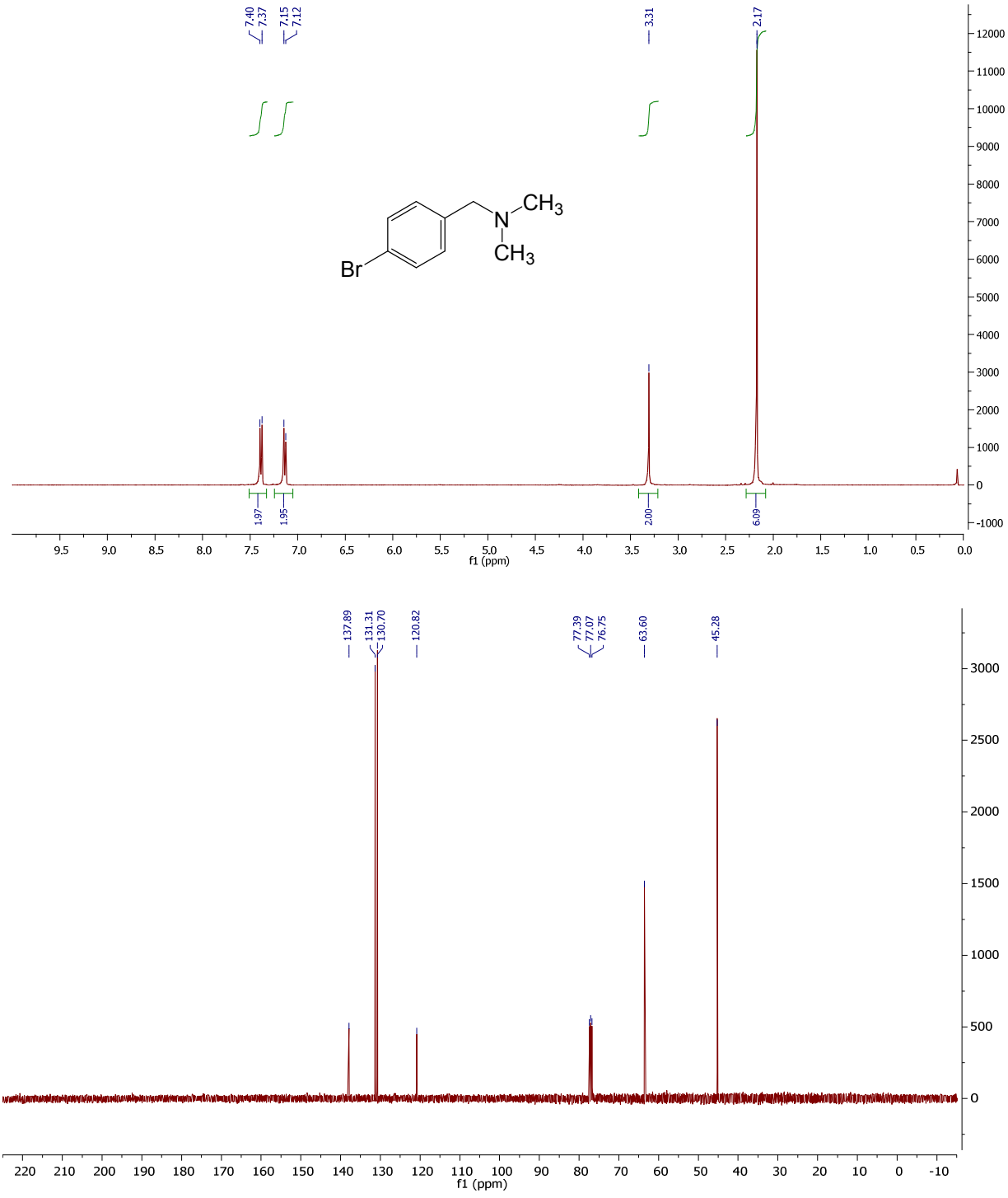


Figure S8. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 4-bromo-*N*,*N*-dimethylbenzylamine in $CDCl_3$

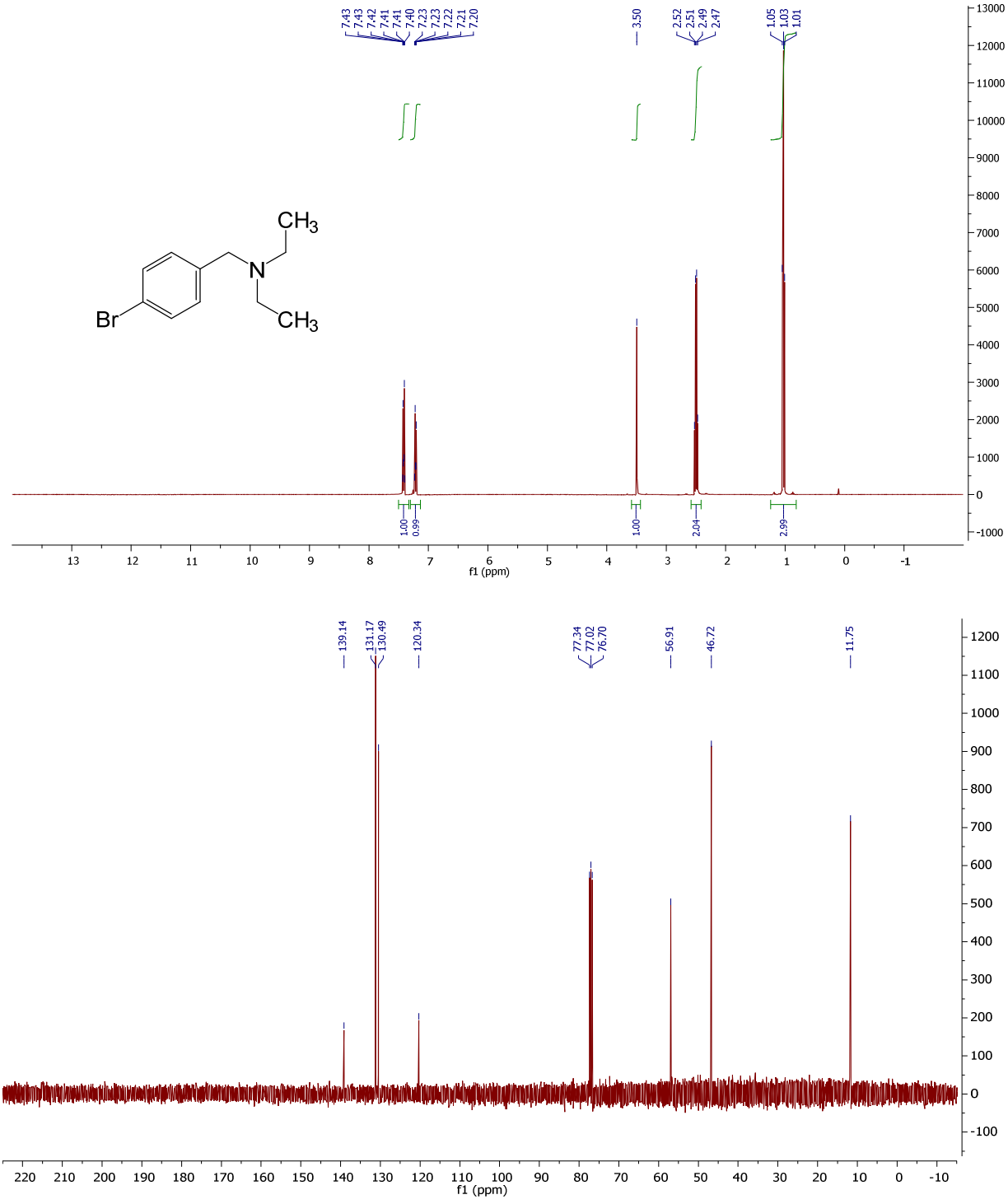


Figure S9. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 4-bromo-*N*,*N*-diethylbenzylamine in $CDCl_3$

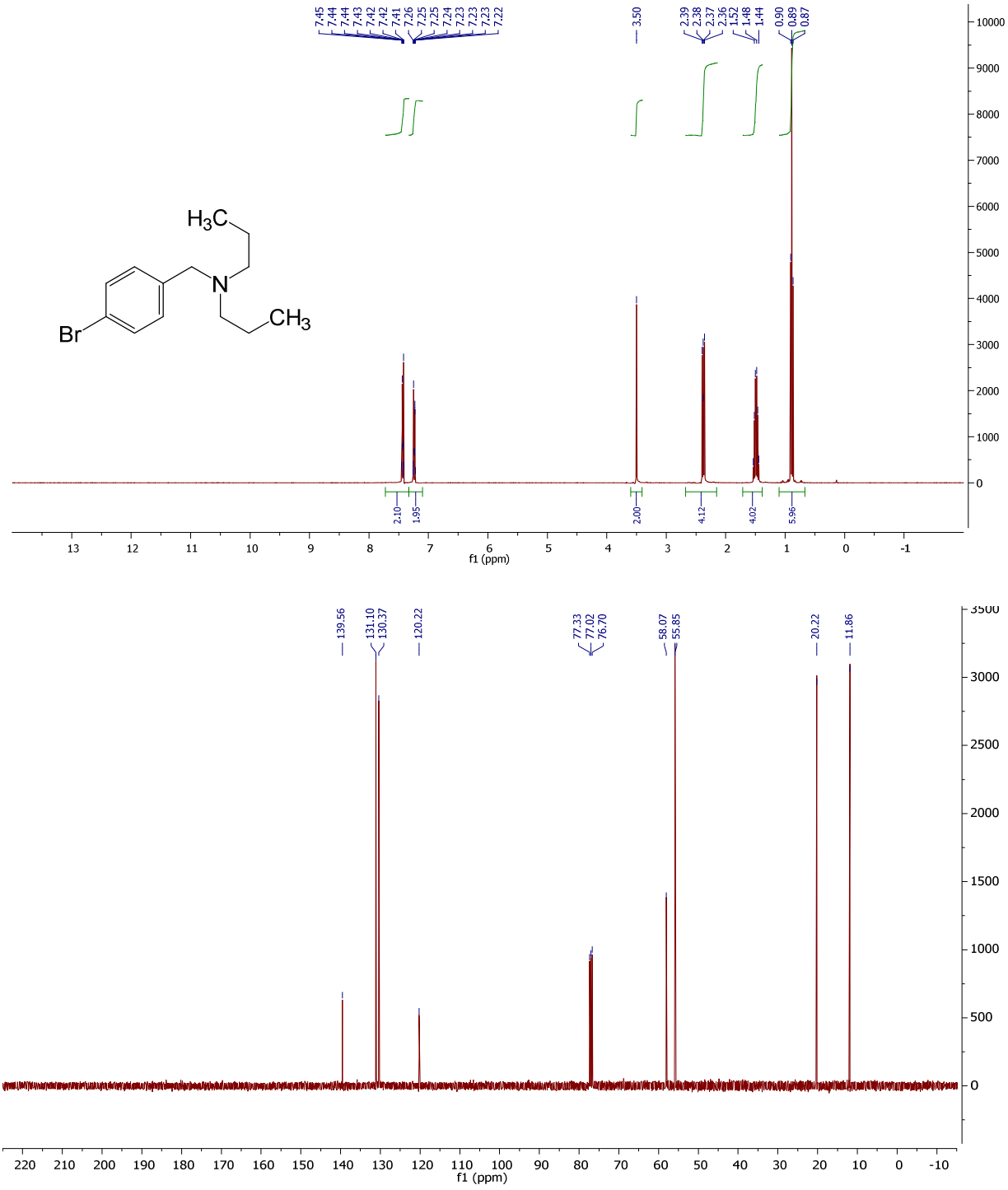


Figure S10. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 4-bromo-*N*,*N*-dipropylbenzylamine in $CDCl_3$

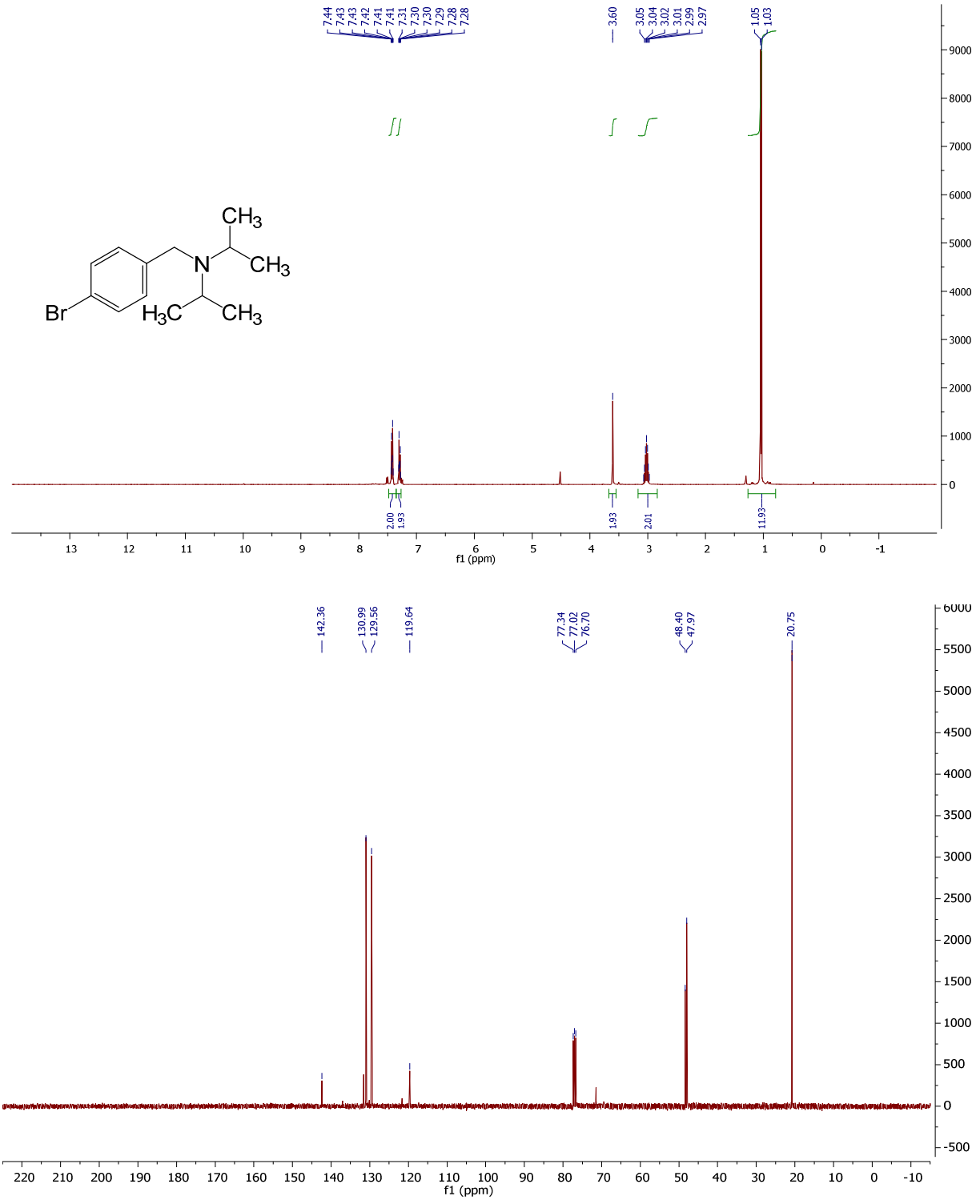


Figure S11. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 4-bromo-*N*,*N*-diisopropylbenzylamine in $CDCl_3$

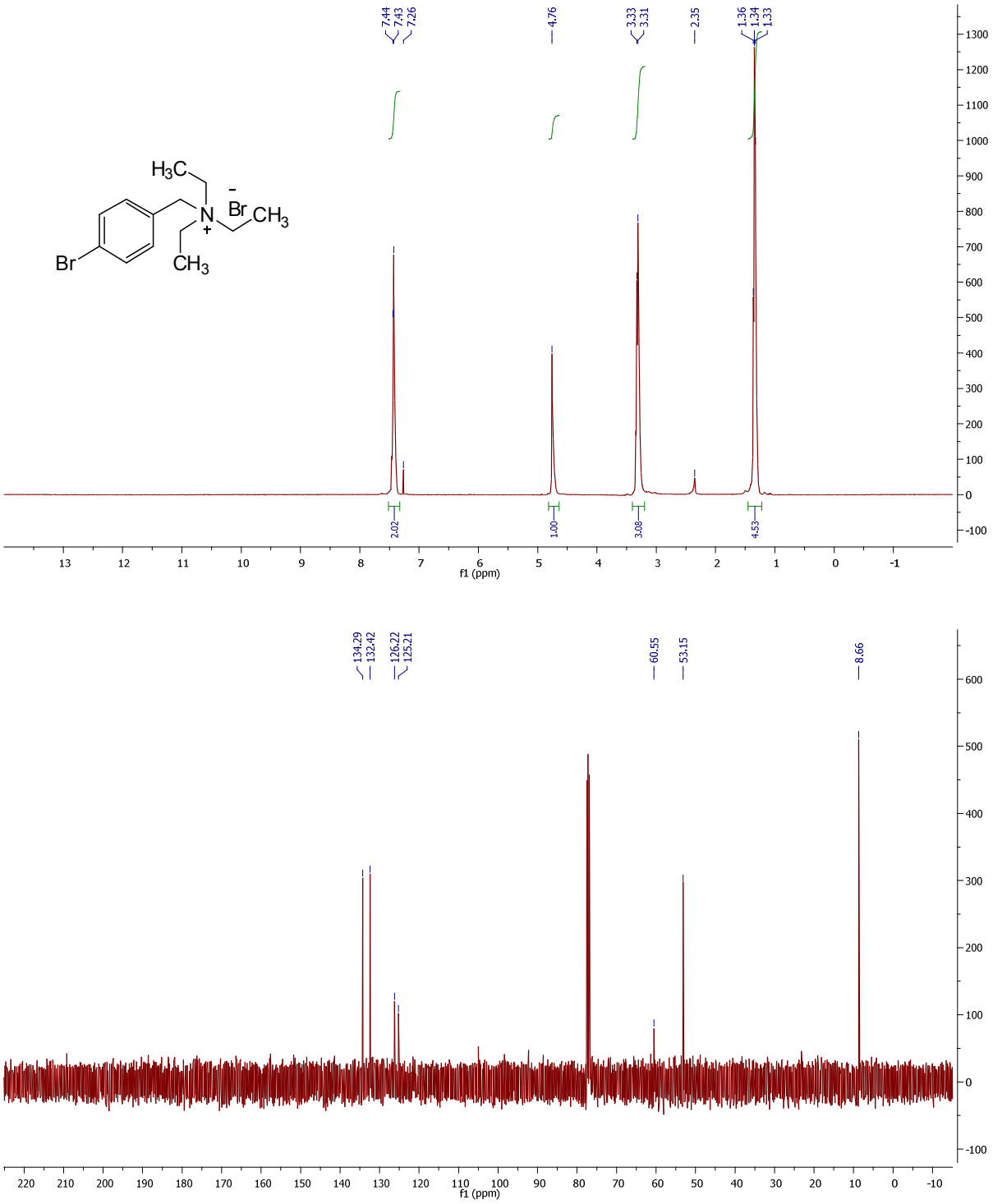


Figure S12. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of *N*-(4-Bromobenzyl)-*N*,*N*,*N*-triethylammonium bromide in $CDCl_3$