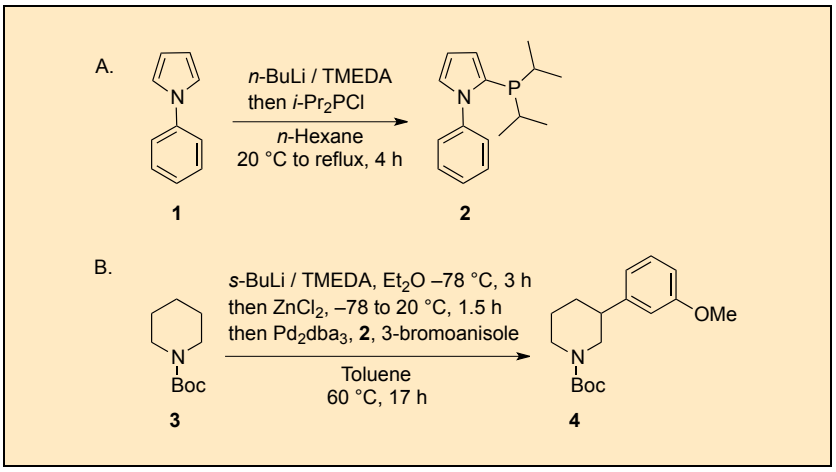
Organic Syntheses

Palladium-catalyzed β-Selective C(sp^3)–H Arylation of *N*-Boc-Piperidines

Anthony Millet and Olivier Baudoin*[1]

Université Claude Bernard Lyon 1, CNRS UMR 5246 – Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CPE Lyon, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France

Checked by Louis C. Morrill and Richmond Sarpong



Procedure

Caution! sec-Butylithium is very pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity or by cannula.

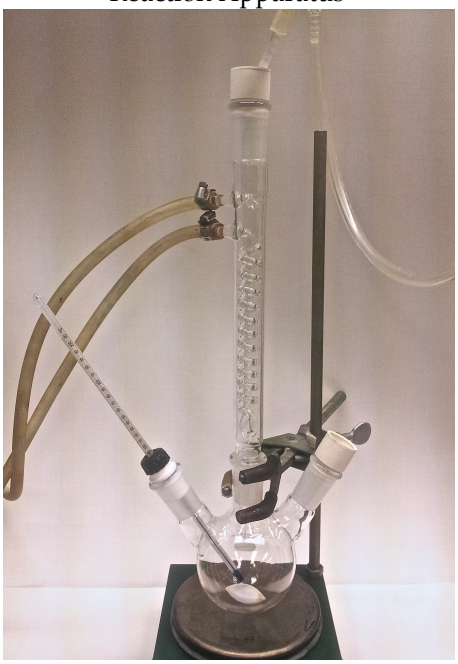
A. *2-(Diisoproylphosphanyl)-1-phenylpyrrole* (**2**). A 250-mL, three-necked, round-bottomed flask equipped with a 3.7-cm Teflon-coated magnetic

Published on the Web 3/17/2015
© 2015 Organic Syntheses, Inc.

stirbar, a condenser capped by a rubber septum and a thermometer is placed in a 19 °C water bath and charged with 1-phenylpyrrole (**1**) (4.30 g, 30 mmol, 1.0 equiv) (Note 1). The third neck of the flask is closed by a rubber septum and connected to a combined nitrogen/vacuum line and evacuated/back-filled with nitrogen twice. *n*-Hexane (45 mL) (Note 2) is added by syringe, followed by TMEDA, also by syringe, (6.75 mL, 5.23 g, 45 mmol, 1.5 equiv) (Note 3), and the mixture is stirred (200 rpm) at 19 °C until complete dissolution. *n*-Butyllithium (13.3 mL, 30 mmol, 1.0 equiv) (2.26 M in hexanes) (Note 4) is added dropwise over 10 min using a syringe pump (Note 5). The rubber septum on the 250-mL, three-necked flask is replaced by a glass stopper and the water bath is replaced by an oil bath. The reaction mixture is heated to reflux for 3 h, giving a brown solution. Chlorodiisopropylphosphine (4.77 mL, 4.58 g, 30 mmol, 1.0 equiv) (Note 6) in 10 mL of hexanes (Note 2) was added dropwise at reflux through the condenser over 5 min using a syringe pump to give a beige precipitate, and the mixture is refluxed for an additional hour. The reaction is cooled to between 0-5 °C using an ice/water bath before slow addition of 50 mL of degassed water (Note 7). The quenched reaction is stirred (200 rpm) for 10 min at 0–5 °C to give a clear solution. The solution is transferred to a 250-mL separatory funnel, the layers are separated, and the aqueous layer is extracted with hexanes (2 x 75 mL) (Note 2). The organic layer are combined and washed with brine (75 mL) (Note 8), dried over 5 g of magnesium sulfate (Note 9), filtered through a 150-mL medium porosity sintered glass funnel into a 500-mL round-bottomed flask. The residue is washed with hexanes (25 mL) (Note 2), and the resulting solution is concentrated by rotary evaporation (40 °C, 20 mmHg). The oil is transferred to a 100-mL round-bottomed flask, washing with 5 mL of hexanes, and concentrated by rotary evaporation (40 °C, 20 mmHg), to afford 7.87 g of a brown oil. The crude mixture is dried under high-vacuum (20 °C, 0.5 mmHg) and under stirring using a 1-cm Teflon-coated magnetic stirbar until crystallization of a brown solid. The flask is sealed with a rubber septum, connected to a combined nitrogen/vacuum line and evacuated/back-filled with nitrogen twice. The solid is dissolved in 10 mL of degassed methanol (Note 10) upon heating to 50 °C. The solution is allowed to cool to room temperature, and then cooled at –18 °C using a low temperature freezer for 15 h. The resulting crystals are collected by filtration through a 25-mL medium porosity sintered glass funnel, washed with 5 mL of ice-cold methanol twice, and then transferred to a 50-mL round-bottomed flask and dried for 4 h at

0.05 mmHg to provide 3.61–3.73 g (46–48% yield) of compound **2** as a white powder (Note 11).

Reaction Apparatus



B. *tert-Butyl 3-(3-methoxyphenyl)piperidine-1-carboxylate (**4**)*. A 500-mL, three-necked, round-bottomed flask equipped with a 4.7-cm Teflon-coated magnetic stirbar, a thermometer and a 250-mL pressure equalizing dropping funnel capped by a rubber septum is charged with *tert*-butyl piperidine-1-carboxylate (**3**) (7.98 mL, 7.69 g, 41.5 mmol, 1.0 equiv) (Note 12). The third neck of the flask is connected to a combined nitrogen/vacuum line using a glass adapter and evacuated/back-filled with nitrogen twice. Diethyl ether (65 mL) (Note 13) is added to the stirred (200 rpm) reaction mixture followed by the addition of TMEDA (7.47 mL, 5.79 g, 49.8 mmol, 1.2 equiv) by syringe (Note 3). The solution is subsequently cooled to –78 °C using a dry-ice/acetone bath. *s*-Butyllithium (48.8 mL, 49.8 mmol, 1.2 equiv) (1.02 M in cyclohexane) (Note 14) is added dropwise over 30 min *via* the pressure equalizing dropping funnel (Note 15), to give a yellow cloudy solution which is stirred for 3 h at –78 °C. Zinc chloride (99.6 mL, 49.8 mmol, 1.2 equiv) (0.5 M in THF) (Note 16) is added

dropwise over 45 min *via* the pressure equalizing dropping funnel (Note 17). The resulting mixture is stirred for 30 min at –78 °C, allowed to warm to 20 °C by removing the dry-ice/acetone bath, and stirred for 30 min. The reaction mixture is rapidly transferred to a 500-mL round-bottomed flask, which has been previously evacuated/back-filled with nitrogen twice. The clear orange solution is concentrated by rotary evaporation (44 °C, 80 mmHg). A 4.7-cm Teflon-coated magnetic stirbar is added to the flask before it is closed with a rubber septum and connected to a combined nitrogen/vacuum line. The resulting white cloudy solution is concentrated for 15 min under vacuum (0.05 mmHg) and then back-filled with nitrogen. Meanwhile, a 100-mL round-bottomed flask containing a 2.5-cm Teflon-coated magnetic stirbar is charged with tris(dibenzylideneacetone)dipalladium(0) (950 mg, 1.04 mmol, 0.025 equiv) (Note 18) and 2-(diisopropylphosphanyl)-1-phenylpyrrole (**2**) (538 mg, 2.07 mmol, 0.05 equiv), closed with a rubber septum, connected to a combined nitrogen/vacuum line and evacuated/back-filled with nitrogen twice. Toluene (60 mL) (Note 19) is added by syringe , and the solution is stirred (200 rpm) for 20 min at 20 °C. The resulting catalyst solution is added to the above piperidinylzinc reagent *via* syringe, and the 100 mL flask is washed with toluene (35 mL) (Note 19), before addition of 3-bromoanisole (3.65 mL, 29.1 mmol, 0.7 equiv) (Note 20). The resulting red-brown solution is heated by oil bath (60 °C) and stirred (200 rpm) for 17 h. After cooling to room temperature, a saturated aqueous solution of ammonium chloride (150 mL) (Note 21) is added, followed by ethyl acetate (75 mL) (Note 22). The bi-phasic solution is transferred to a 500-mL separatory funnel and layers are separated. The aqueous layer is extracted with ethyl acetate (2 x 75 mL) (Note 22). The combined organic layers are washed with brine (150 mL) (Note 8), dried over magnesium sulfate (10 g) (Note 9), filtered through a 150-mL medium porosity sintered glass funnel, which is washed with ethyl acetate (25 mL) (Note 22). The resulting solution is concentrated by rotary evaporation (45 °C, 40 mmHg) to afford 22.4 g of an orange oil containing a precipitate (Note 23). This crude mixture is dissolved in dichloromethane (100 mL) (Note 24), charged with silica gel (30 g) (Note 25) then concentrated by rotary evaporation (20 °C, 35 mmHg), followed by 10 min under 0.05 mmHg at 20 °C. The silica-adsorbed reaction mixture is charged on a column (9 cm width, 10 cm height) containing 275 g of silica gel and eluted with 4 L of 5% ethyl acetate-*n*-hexanes collecting 50 mL fractions. A first fraction containing a mixture of α- and β-arylated products is obtained in fractions 43-50, which are concentrated by rotary

evaporation (45 °C, 50 35 mmHg) to afford 1.36 g of a mixture of compounds. The second fraction containing the desired product (4.13–4.21 g) is obtained in fractions 51-80, which are concentrated by rotary evaporation (45 °C, 5 mmHg). The first fraction is dissolved in dichloromethane (50 mL) and silica gel (6 g) is added before being concentrated by rotary evaporation (20 °C, 35 mmHg), followed by 10 min under 0.05 mmHg at 20 °C. The silica-adsorbed reaction mixture is charged on a column (4 cm width, 12 cm height) containing 70 g of silica gel and eluted with 1.5 L of 5% ethyl acetate/*n*-hexanes, collecting 20 mL fractions. The desired product (0.82–0.90 g) is obtained in fractions 30-70, which are concentrated by rotary evaporation (45 °C, 5 mmHg). The combined product containing fractions are dried for 2 h under 0.05 mmHg at 20 °C to afford 4.95–5.11 g (58–60% yield) of compound **4** as a yellow oil (Notes 26 and 27).

Reaction Apparatus

Notes

1. 1-Phenylpyrrole (99%) was purchased from Sigma-Aldrich and used as received.
2. *n*-Hexane (puriss., pa, ACS Reagent, ≥99% (GC)) were purchased from Sigma-Aldrich, and distilled under nitrogen from sodium benzophenone ketyl. The solvent is withdrawn from the receiver flask with a syringe. Hexanes (mixture of isomers, Sigma-Aldrich) were used for extractions and chromatography.
3. *N,N,N′,N′*-Tetramethylethylenediamine (99%) was purchased from Sigma-Aldrich and distilled under nitrogen from calcium hydride before use.
4. A 2.5 M solution of *n*-butyllithium in hexanes under Sure/Seal was purchased from Sigma-Aldrich, and the concentration was determined by titration with biphenyl-4-methanol to be 2.26 M prior to use according to the reported method: Juaristi, E.; Martinez-Richa, A.; Garcia-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem*. **1983**, *48*, 2603-2606.
5. The temperature increases to 31 °C during the addition, and a yellow solution is obtained.
6. Chlorodiisopropylphosphine (96%) was purchased from Acros-Organics, and used as received.
7. Water was degassed by argon-bubbling for 1 h.
8. Sodium chloride (ACS reagent, ≥99%) was purchased from Sigma-Aldrich and added to water until saturation.
9. Magnesium sulfate (Sec Pur) was purchased from Fisher scientific and used as received.
10. Methanol (puriss, pa, ACS reagent, ≥99.9% (GC)) was purchased from Avantor Performance Materials and degassed by argon-bubbling for 1 h before being passed through an activated alumina column using a GlassContour solvent system. The solvent is withdrawn from the receiver flask with a syringe.
11. Analytical data for 2-(diisopropylphosphanyl)-1-phenylpyrrole (**2**): R_f = 0.22 (100% hexanes, TLC: silica gel 60 Å porosity SiliaplateTM glass backed TLC plates/250 μm thickness, F-254 indicator obtained from Silicycle, visualized with 254 nm UV lamp) (1-phenylpyrrole (**3**) R_f = 0.35, 100% hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, J = 7.0 Hz, 3 H), 0.93–0.99 (m, 6 H), 1.01 (d, J = 7.0 Hz, 3 H), 1.98 (hept, J = 7.0 Hz, 2 H), 6.37 (dd, J = 3.6, 2.9 Hz, 1 H), 6.54 (dd, J = 3.6, 1.6 Hz, 1 H),

7.00 (td, J = 2.9, 1.6 Hz, 1 H), 7.30–7.46 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 19.1 (d, J = 8.3 Hz), 20.1 (d, J = 18.2 Hz), 24.6 (d, J = 8.3 Hz), 109.1, 117.2 (d, J = 4.3 Hz), 126.2, 127.4, 127.9 (d, J = 4.4 Hz), 128.1, 128.6, 141.1; ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ: –18.7; ATR-FTIR (cm^{-1}): ν 959, 1023, 1128, 1187, 1315, 1420, 1453, 1493, 1510, 1595, 2861, 2898, 2922, 2944, 2962, 3040, 3061, 3089; HRMS (EI) calculated for $C_{16}H_{22}NP$ ([$M^{+\bullet}$]): 259.1490, found: 259.1488; mp = 55–56 °C (MeOH); Anal calcd for $C_{16}H_{22}NP$: C, 74.10; H, 8.55; N, 5.40, Found: C, 74.02; H, 8.49; N, 5.60; compound **4** was stored under nitrogen before use.

12. *N*-Boc piperidine (98%) was purchased from Sigma-Aldrich and used as received.
13. Diethyl ether (puriss., pa, ACS certified, BHT stabilized, ≥99% (GC)) was purchased from Fisher Scientific and degassed by argon-bubbling for 1 h before being passed through an activated alumina column using a GlassContour solvent system. The solvent is withdrawn from the receiver flask with a syringe.
14. A 1.4 M solution of *s*-butylithium in cyclohexane under Sure/Seal was purchased from Sigma-Aldrich, and the concentration was determined by titration with biphenyl-4-methanol to be 1.02 M prior to use according to the reported method: Juaristi, E.; Martinez-Richa, A.; Garcia-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem*. **1983**, *48*, 2603-2606.
15. The temperature increases to –73 °C during the addition.
16. Zinc Chloride (0.5 M solution in THF) was purchased from Acros Organics under AcroSeal, and used as received.
17. The internal temperature increases to –70 °C, and a white cloudy solution is obtained.
18. Tris(dibenzylideneacetone)dipalladium(0) (97%) was purchased from Sigma-Aldrich, and used as received.
19. Toluene (puriss., pa, ACS certified, HPLC grade, ≥99.8% (GC)) was purchased from Fisher Scientific and degassed by argon-bubbling for 1 h before being passed through an activated alumina column using a GlassContour solvent system. The solvent is withdrawn from the receiver flask with a syringe.
20. 3-Bromoanisole (98%+) was purchased from Alfa Aesar and used as received.
21. Ammonium chloride (99.5%) was purchased from Acros Organics, and added to water until saturation.
22. Ethyl acetate (puriss., pa, ACS certified, ≥99.9% (GC)) was purchased from Fisher Scientific and used as received.

23. TLC of crude mixture (10% EtOAc/hexanes, visualized with $KMnO_4$ stain): *tert*-butyl piperidine-1-carboxylate (**2**) (R_f = 0.53), *tert*-butyl 2-(3-methoxyphenyl)piperidine-1-carboxylate (R_f = 0.46), *tert*-butyl 3-(3-methoxyphenyl)piperidine-1-carboxylate (R_f = 0.41).
24. Dichloromethane (puriss., pa, ACS certified, ≥99.9% (GC)) was purchased from Fisher Scientific and used as received.
25. Silica 60 Å (0.04-0.063 mm) was purchased from Fisher Scientific.
26. Analytical data for *tert*-butyl 3-(3-methoxyphenyl)piperidine-1-carboxylate (**4**): R_f = 0.41 (10% EtOAc/hexanes, TLC: silica gel 60 Å porosity SiliaplateTM glass backed TLC plates/250 μm thickness, F-254 indicator obtained from Silicycle, visualized with 254 nm UV lamp and subsequently using $KMnO_4$ stain (see Note 28)); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 9 H), 1.52–1.68 (m, 2 H), 1.71–1.79 (m, 1 H), 1.96–2.06 (m, 1 H), 2.52–2.91 (br m, 3 H), 3.80 (s, 3 H), 4.00–4.35 (br m, 2 H), 6.74–6.80 (m, 2 H), 6.83 (d, J = 7.7 Hz, 1 H), 7.20–7.27 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 25.5, 28.5, 31.8, 42.6, 44.2 (br), 50.8 (br), 55.2, 79.4, 111.7, 113.2, 119.5, 129.5, 145.3, 154.9, 159.7; ATR-FTIR (cm^{-1}): ν 699, 786, 853, 1040, 1132, 1147, 1155, 1231, 1263, 1364, 1390, 1582, 1601, 1688, 2837, 2856, 2933, 2974, 3003; HRMS (EI) calculated for $C_{17}H_{25}NO_3$ ([$M^{+\bullet}$]): 291.1834, found: 291.1840; Anal calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81, Found: C, 69.96; H, 8.71; N, 4.83;
27. Analytical gas chromatography with mass spectroscopy (GC/MS) analysis was carried out on a Shimadzu QP2010 GCMS apparatus under electronic impact (EI) and equipped with a SLB-5ms column (15.0 m x 0.10 mm) containing a 0.10 μm film thickness with a flow rate of 0.58 mL per min with 474 kPa He. The temperature profile is the following one: 1 min at 90 °C, temperature increase to 220 °C at a rate of 8 °C per min, then temperature increase to 300 °C at a rate of 40 °C per min, then 300 °C for 4.5 min. Retention times: *tert*-butyl piperidine-1-carboxylate (**3**): 6.53 min; 1-phenylpyrrole (**1**): 6.98 min; 2-(diisopropylphosphanyl)-1-phenylpyrrole (**2**): 14.46 min; *tert*-butyl 2-(3-methoxyphenyl)piperidine-1-carboxylate (α-arylated product): 17.47 min; *tert*-butyl 3-(3-methoxyphenyl)piperidine-1-carboxylate (**4**): 18.32 min.
28. The $KMnO_4$ stain was prepared using 1.5 g of $KMnO_4$ and 10 g of K_2CO_3 dissolved in 200 mL of water and 1.25 mL of 10% weight NaOH solution.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

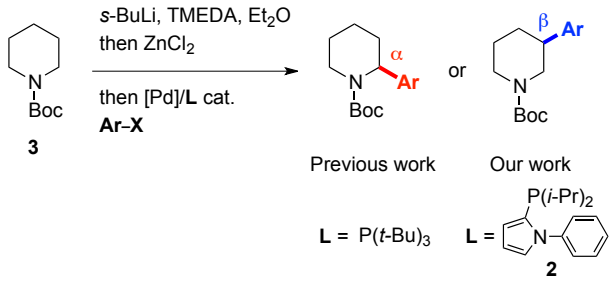
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

3-Arylpiperidines are important building blocks in pharmaceutical research.[2] They are usually synthesized through the construction of the piperidine ring or the reduction of a 3-arylpyridine precursor, because the inert character of the C–H bonds in β-position to the nitrogen atom is commonly thought to preclude direct β-functionalization.[3] From the end of the 1990's, the direct arylation in position 2 of *N*-Boc-piperidine **3** (Boc =

tert-butoxycarbonyl) has been developed, via a sequence of Boc-directed-lithiation α to the nitrogen atom, followed by transmetalation to zinc and Negishi cross-coupling (Scheme 1).[4] In 2011, Knochel and co-workers reported an unexpected case of diastereoselective arylation of *N*-Boc-2-methylpiperidine occurring in β-position, in contrast to other *N*-Boc-substituted-piperidines undergoing α-arylation.[4e] Inspired by this observation and in extension to our previous work on the migrative β-arylation of ester enolates,[5] we turned to the development of a general palladium-catalyzed migrative β-arylation of *N*-Boc-piperidines involving ligand-controlled selectivity (Schemes 1-2).[6] This methodology allows a rapid access to a large variety of 3-arylpiperidines from commercially available *N*-Boc-piperidine and aryl bromides, with good β/α arylation selectivities (up to 97:3),[7] and moderate-to-good yields (up to 71%).

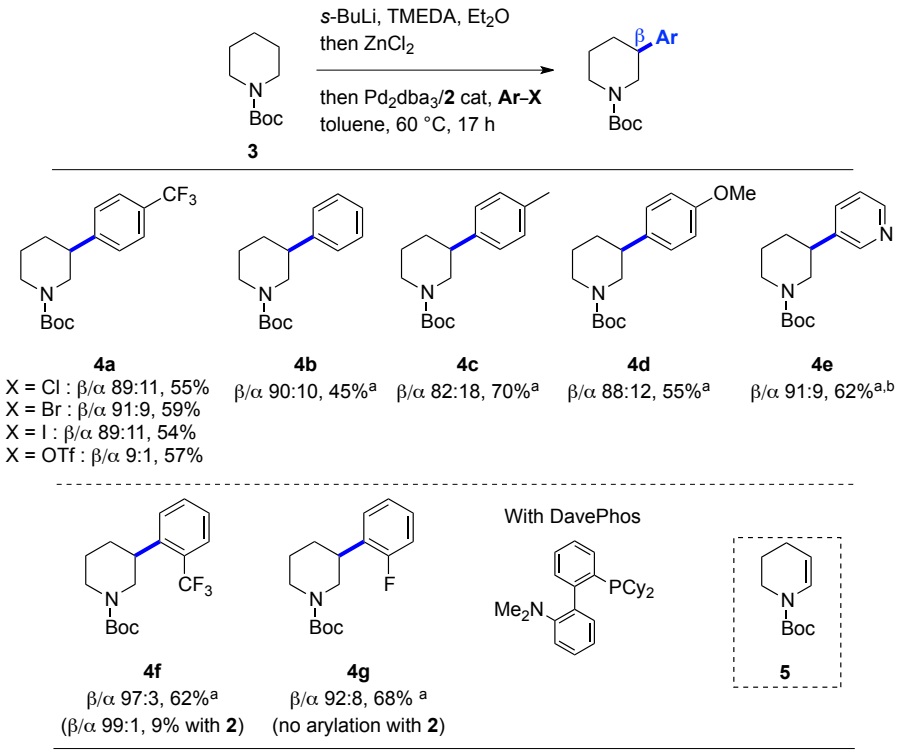


Scheme 1. α vs. β-Arylation

DFT calculations showed that the Pd migration occurs from a Pd–CH agostic complex in which the piperidine ring adopts the twist-boat conformation, and proceeds through a sequence of β-H-elimination/rotation/insertion. Calculations also indicated that α and β-reductive eliminations are the two selectivity-determining steps. In addition, it was shown that the ligand flexibility is a key element in the control of the arylation selectivity, with flexible biarylphosphines such as **2** favoring the β-arylation product, whereas more rigid phosphines such as P(*t*-Bu)$_3$ favor the α-arylated product.

In our initial work, typical reactions were performed from 0.5 mmol (92.6 mg) of *N*-Boc-piperidine **3** ([**3**] = 0.33 M) and 0.35 mmol (44 μL) of 3-bromoanisole using 2.5 mol% of Pd_2dba_3 and 5 mol% of ligand **2**. Under optimized conditions on a larger scale (7.69 g of *N*-Boc-piperidine), the

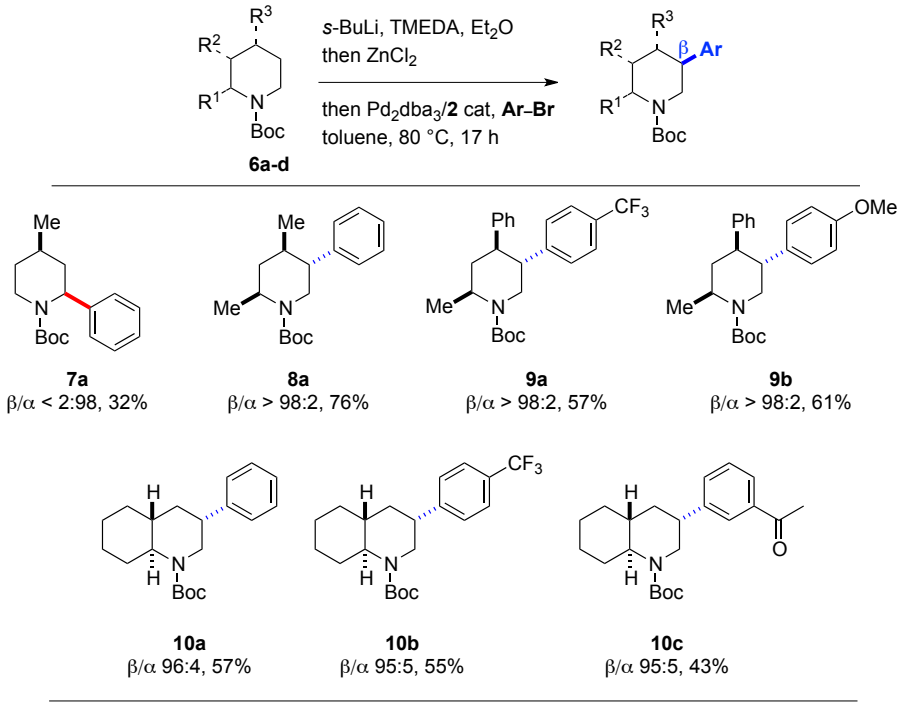
reaction concentration could be increased to 0.43 M, whereas a decrease of the catalyst loading led to incomplete conversion of 3-bromoanisole. The β-arylation of *N*-Boc-piperidine was shown to be effective with a large variety of aryl and heteroaryl electrophiles, including those bearing sensitive substituents, and containing halide or triflate leaving groups (Scheme 2, **4a-e**). The reaction of aryl bromides containing an *ortho* electron-withdrawing group failed in presence of the standard phenylpyrrole-based ligand **2** due to the almost exclusive formation of ene-carbamate **5**, but a good reactivity was recovered using DavePhos as the ligand (Scheme 2, **4f-g**). The reactions in Scheme 2 and 3 have been performed using the original conditions.[6]



β/α arylation selectivity was determined on crude mixture by GCMS or ^{1}H NMR analysis.
[a] X = Br; [b] 80 °C.

Scheme 2. β-Arylation of *N*-Boc-Piperidine

The study of substituted piperidines led to interesting observations. The reaction of *N*-Boc-4-methylpiperidine was found to be diastereoselective (r.d. > 95:5), but occurred in α position (Scheme 3, **7a**). In contrast, 2,4-disubstituted *N*-Boc-piperidines and *N*-Boc-decahydroquinoline furnished trisubstituted piperidines in a highly β-selective and *trans*-diastereoselective manner (Scheme 3, **8a-10c**), due to favorable conformational effects.



β/α selectivity was determined on the crude mixture by GCMS or ^{1}H NMR analysis.

Scheme 3. β-Arylation of Substituted *N*-Boc-Piperidines

In summary, a general and practical palladium-catalyzed migrative Negishi coupling was developed to directly access 3-aryl-*N*-Boc-piperidines in good to excellent selectivity, and with yields between 43 and 76%. The design of a new flexible phenylpyrrole-based phosphine ligand proved to be a key element to induce both efficiency and β-selectivity.

References

1. Université Claude Bernard Lyon 1, CNRS UMR 5246 – Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, CPE Lyon, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France. E-mail: olivier.baudoin@univ-lyon1.fr. This work was financially supported by Agence Nationale de la Recherche (Programme Blanc 2011 "EnolFun") and Institut Universitaire de France.
2. (a) Wilkström, H.; Sanchez, D.; Lindberg, P.; Hacksell, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson J. L. G.; Svensson, U.; Hjorth, S.; Clarck, D.; Carlsson, A. *J. Med. Chem*. **1984**, *27*, 1030–1036. (b) Amat, B.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 5343–5351. (c) Wallace, D. J.; Brands, K. J. M.; Bremeyer, N.; Brewer, S. E.; Desmond, R.; Emerson, K. M.; Foley, J.; Fernandez, P.; Hu, W.; Keen, S. P.; Mullens, P.; Muzzio, D.; Sajonz, P.; Tan, L.; Wilson, R. D.; Zhou, G.; Zhou, G. *Org. Process Res. Dev.* **2011**, *15*, 831–840.
3. Buffat, M. G. T. *Tetrahedron*, **2004**, *60*, 1701–1729.
4. (a) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726–7735. (b) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc*. **2006**, *128*, 3538–3539. (c) Coldham. I.; Leonori, D. *Org. Lett*. **2008**, *10*, 3923–3925. (d) Beng T. K.; Gawley, R. E. *Org. Lett.* **2011**, *13*, 394–397. (e) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774–4777.
5. (a) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis C. E.; Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261–7265. (b) Larini, P.; Kefalidis, C. E.; Jazzar, R.; Renaudat, A.; Clot, E.; Baudoin, O. *Chem.–Eur. J.* **2012**, *18*, 1932–1944. (c) Aspin, S. ; Goutierre, A.-S.; Larini, P.; Jazzar, R.; Baudoin, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 10808–10811. (d) Aspin, S.; López-Suárez, L.; Larini, P.; Goutierre, A.-S.; Jazzar, R.; Baudoin, O. *Org. Lett.* **2013**, *15*, 5056–5059.
6. Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci*. **2013**, *4*, 2241–2247.
7. The α- and β-arylated products can be separated by silica gel chromatography.

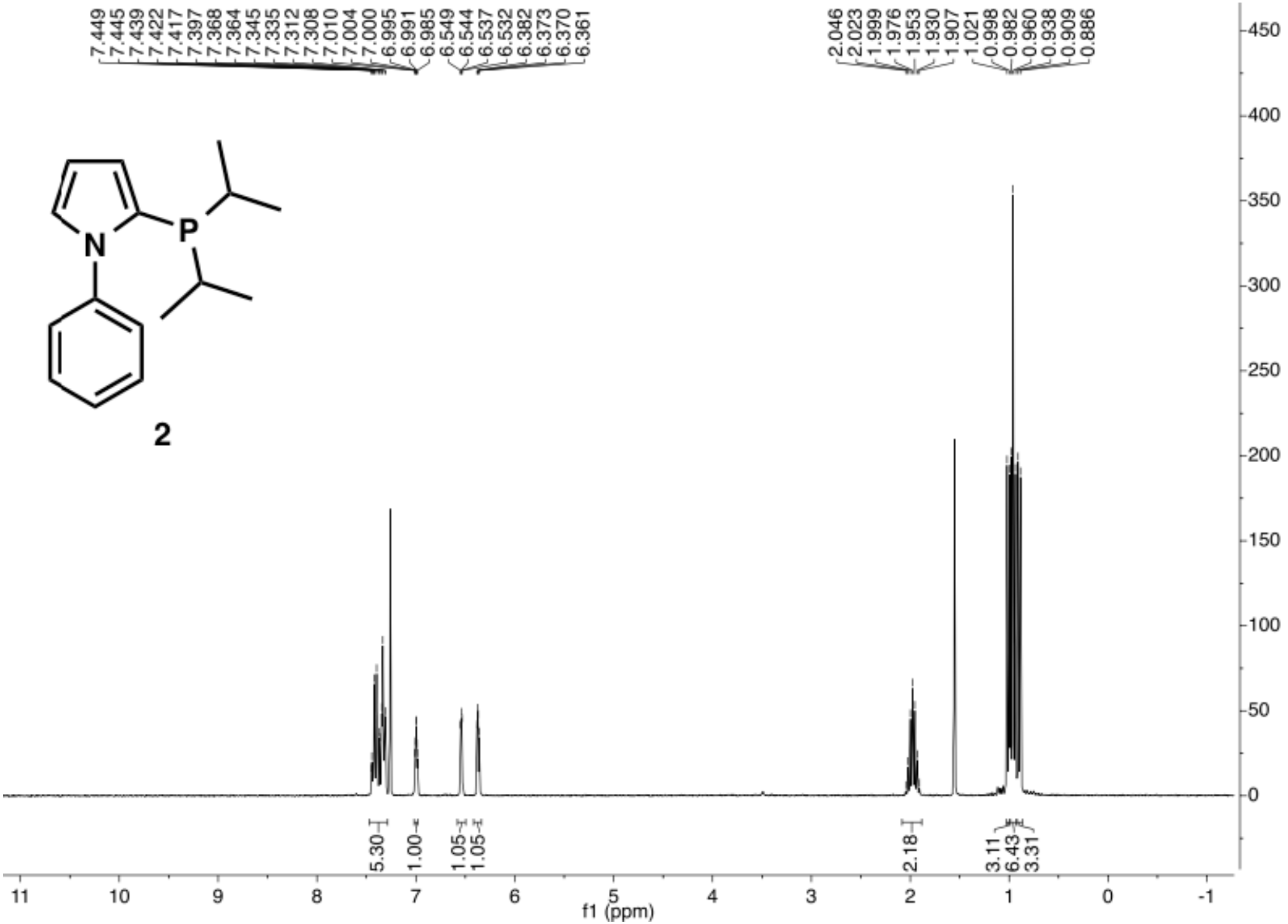
Appendix
Chemical Abstracts Nomenclature (Registry Number)

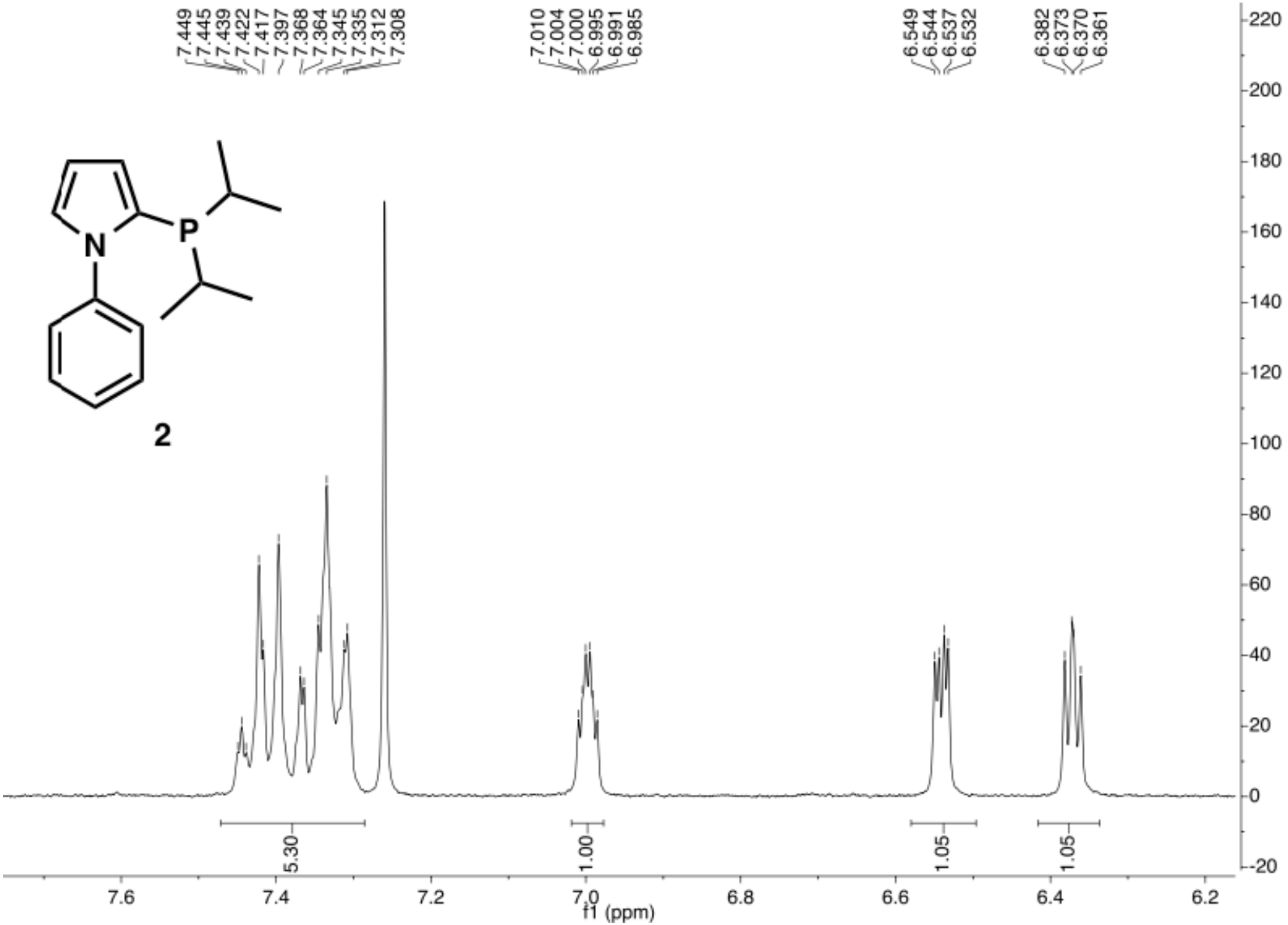
1-Phenylpyrrole (635-90-5)
N,*N*,*N*′,*N*′-Tetramethylethylenediamine (110-18-9)
n-Butyllithium (109-72-8)
Chlorodiisopropylphosphine (40244-90-4)
s-Butyllithium (598-30-1)
Zinc chloride (7646-85-7)
Tris(dibenzylideneacetone)dipalladium (0) (51364-51-3)
3-Bromoanisole (2398-37-0)

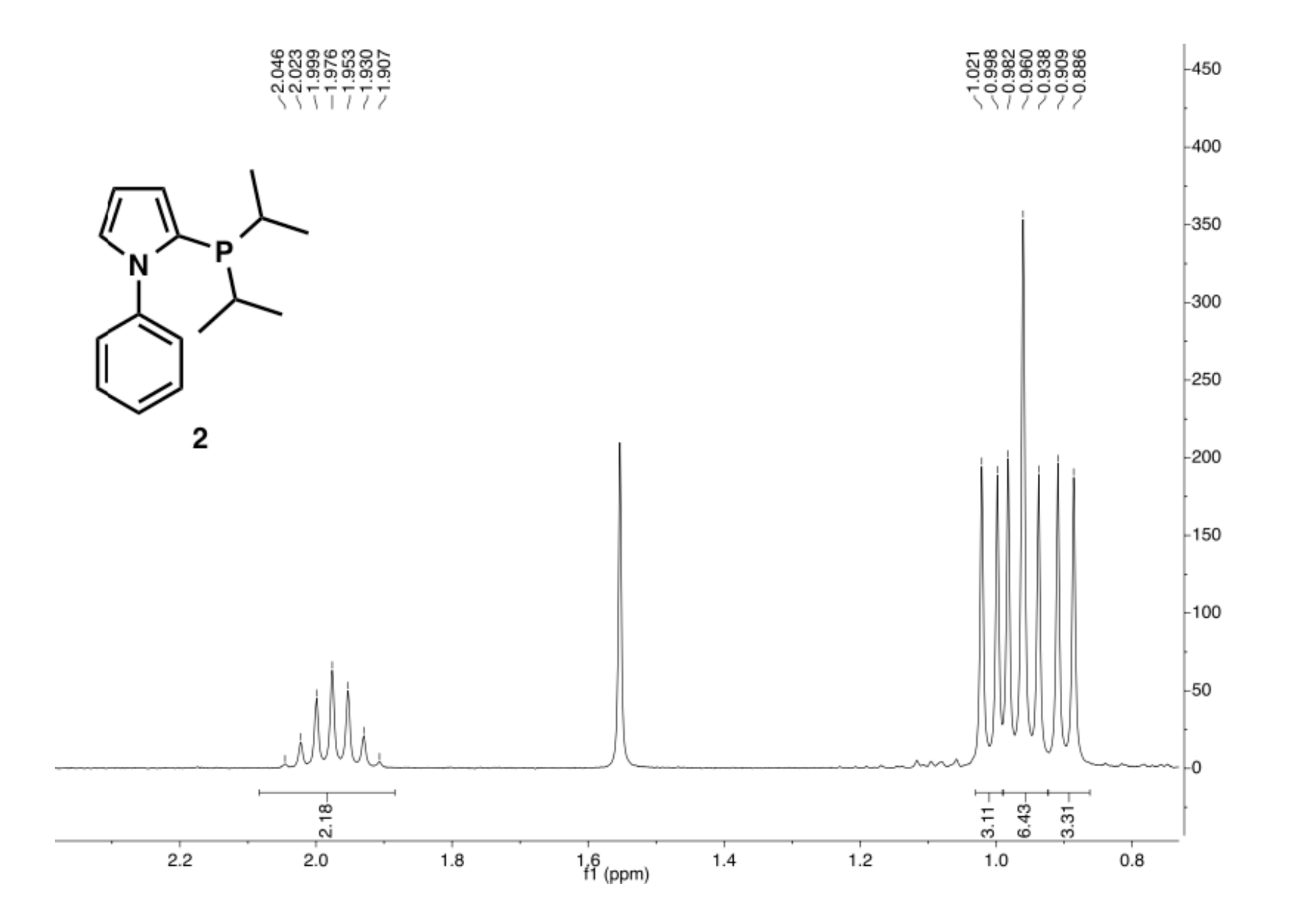
Anthony Millet was born in France in 1986. After an internship at Chimie Paristech in the group of Dr. Véronique Michelet, he received his M.Sc. in organic chemistry from University Pierre et Marie Curie (Paris VI). He is currently a Ph.D. student in the group of Prof. Olivier Baudoin at the University of Lyon (France). His research interests include the intermolecular functionalization of unactivated C(sp^3)–H bonds.

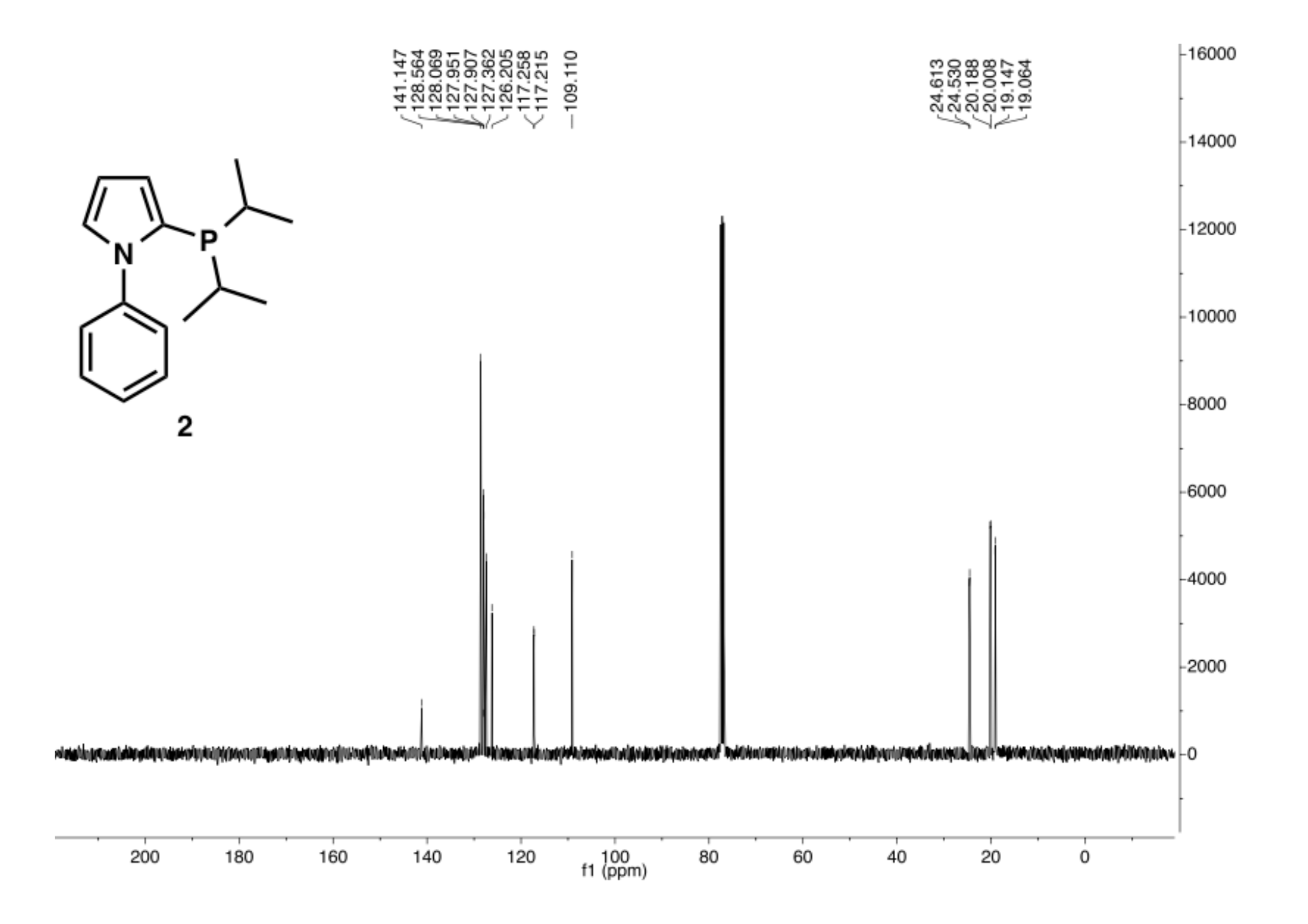
Olivier Baudoin studied chemistry at Ecole Nationale Supérieure de Chimie de Paris (1995). He completed his Ph.D. in 1998 in the group of Prof. Jean-Marie Lehn in Paris. He then worked as a post-doctoral fellow with Prof. K. C. Nicolaou in the Scripps Research Institute (La Jolla). He joined Institut de Chimie des Substances Naturelles (Gif-sur-Yvette) in 1999 as a CNRS researcher and obtained his Habilitation diploma in 2004. In 2006, he was appointed as a Professor at the University Claude Bernard Lyon 1, and was promoted to First Class Professor in 2011. He was the recipient of the CNRS Bronze Medal in 2005, the Scholar Award of the French Chemical Society, Organic Division in 2010, and was appointed as a junior member of Institut Universitaire de France in 2009-14.

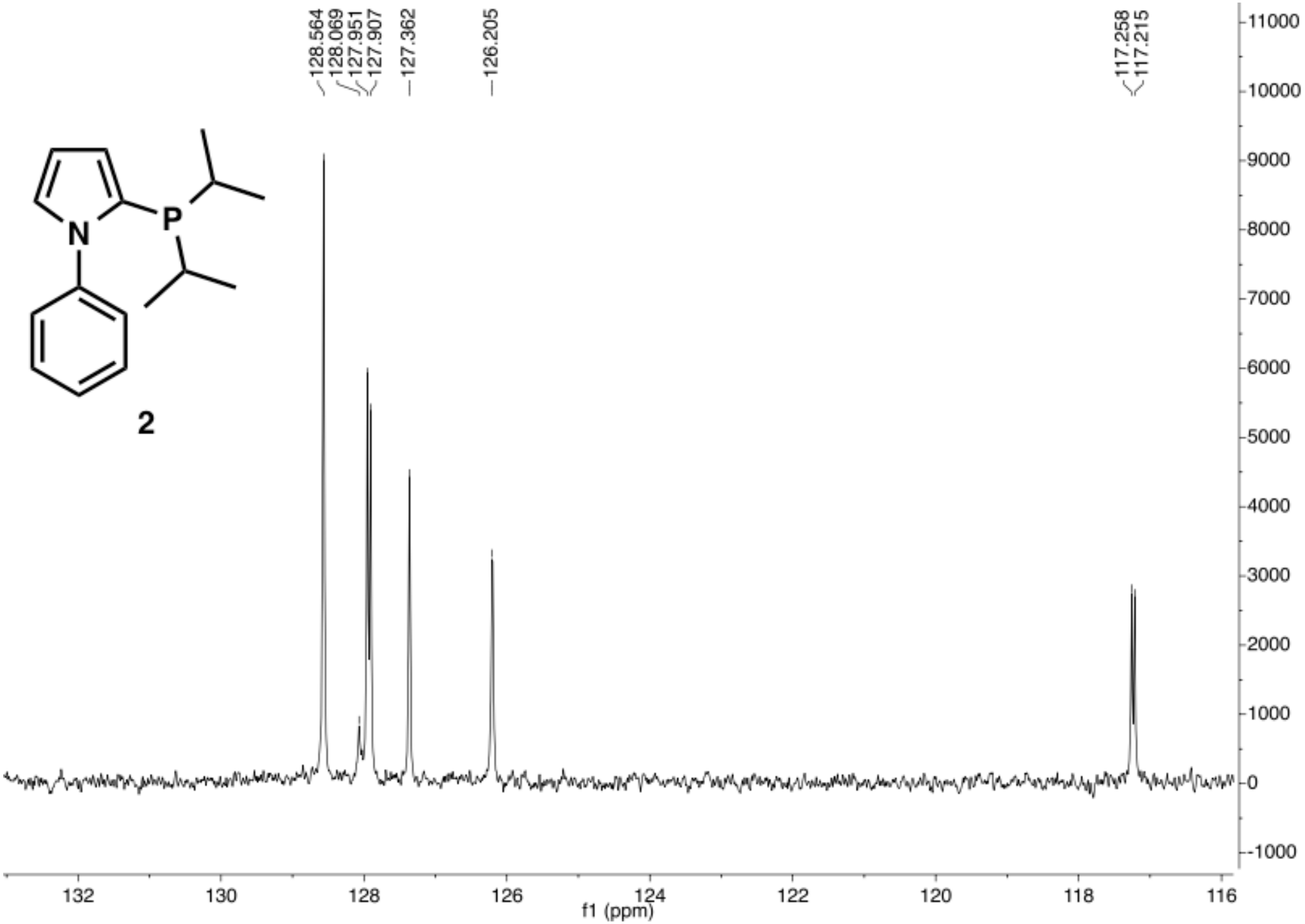
Louis C. Morrill studied chemistry at the University of St Andrews, obtaining his MChem (2010) and Ph.D. (2014) degrees under the direction of Prof. Andrew Smith, investigating Lewis base organocatalysis. He is currently a Postdoctoral Research Fellow with Prof. Richmond Sarpong at UC Berkeley, exploring the total synthesis of complex diterpenoid alkaloid natural products. Commencing June 2015, he will take up an independent position at Cardiff University as a University Research Fellow (URF) in synthetic organic chemistry.

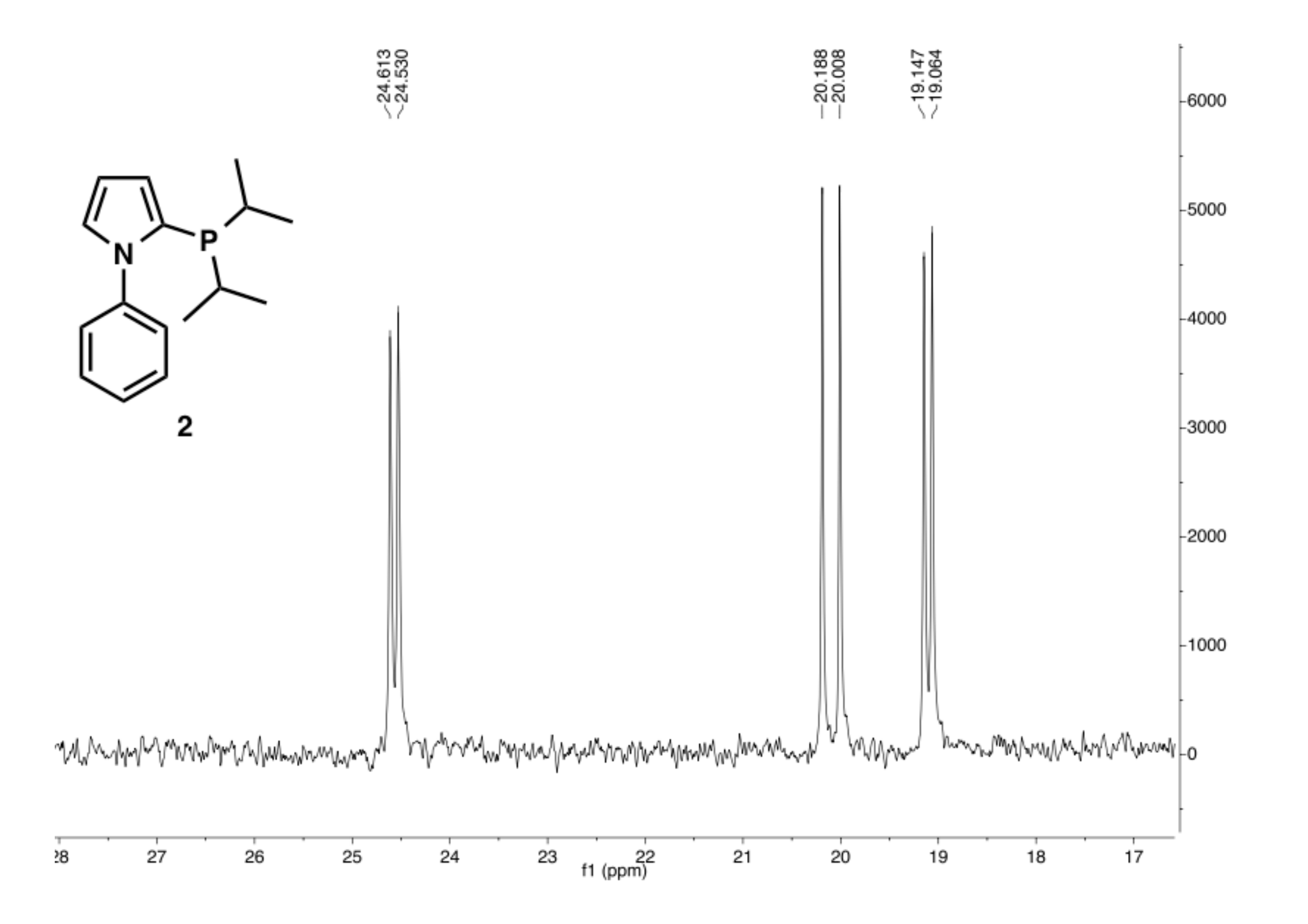

7.449
7.445
7.439
7.422
7.417
7.397
7.368
7.364
7.345
7.335
7.312
7.308
7.010
7.004
7.000
6.995
6.991
6.985
6.549
6.544
6.537
6.532
6.382
6.373
6.370
6.361
2.046
2.023
1.999
1.976
1.953
1.930
1.907
1.021
0.998
0.982
0.960
0.938
0.909
0.886
N
P
2
5.30
1.00
1.05
1.05
2.18
3.11
6.43
3.31
f1 (ppm)

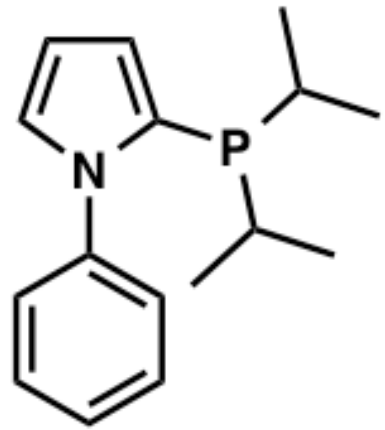

7.449
7.445
7.439
7.422
7.417
7.397
7.368
7.364
7.345
7.335
7.312
7.308
7.010
7.004
7.000
6.995
6.991
6.985
6.549
6.544
6.537
6.532
6.382
6.373
6.370
6.361
N
P
2
5.30
1.00
1.05
1.05
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
f1 (ppm)
220
200
180
160
140
120
100
80
60
40
20
0
-20


2.046
2.023
1.999
1.976
1.953
1.930
1.907
1.021
0.998
0.982
0.960
0.938
0.909
0.886
N
P
2
2.18
3.11
6.43
3.31
f1 (ppm)

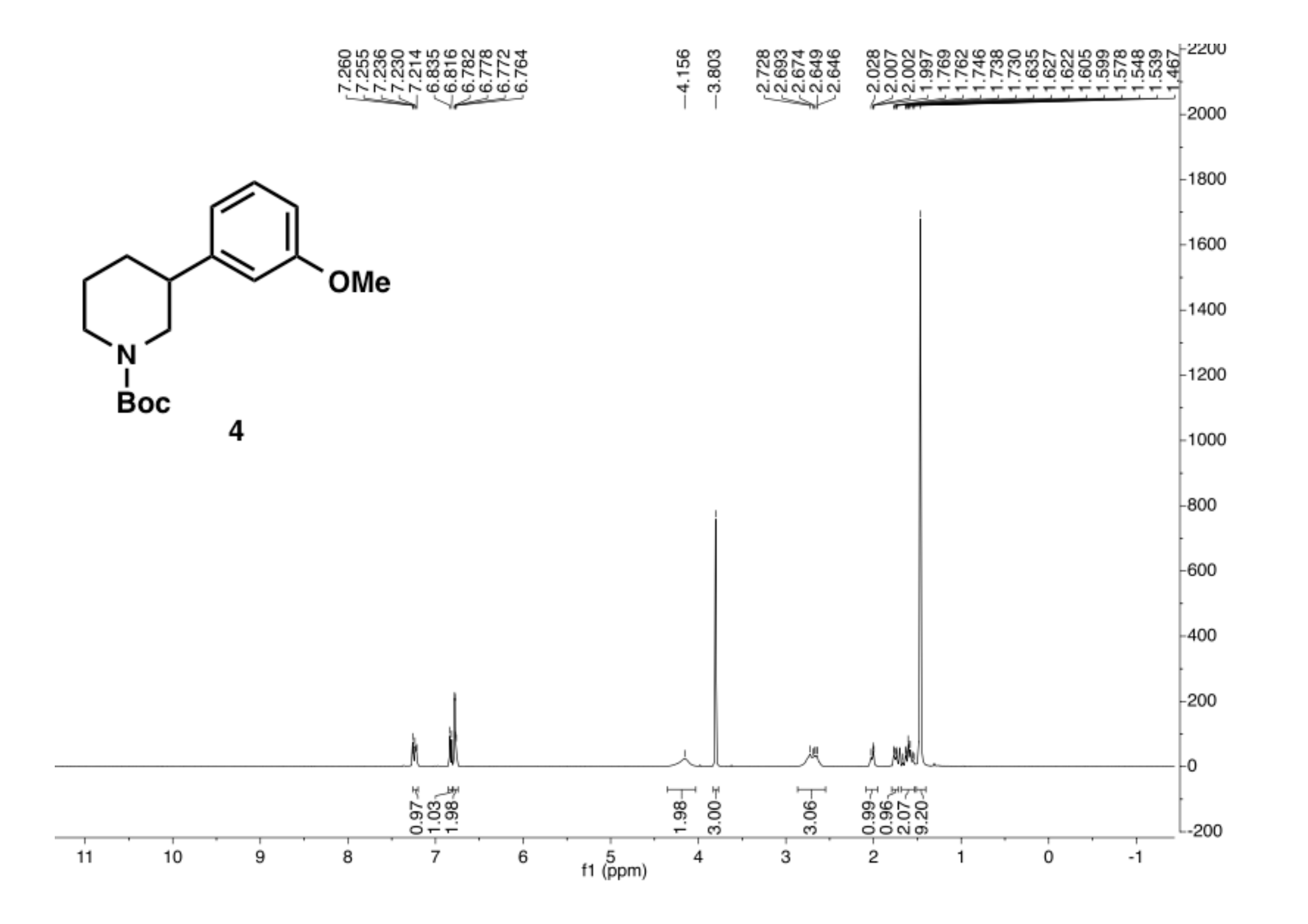

141.147
128.564
128.069
127.951
127.907
127.362
126.205
117.258
117.215
109.110
24.613
24.530
20.188
20.008
19.147
19.064
N
P
2
16000
14000
12000
10000
8000
6000
4000
2000
0
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

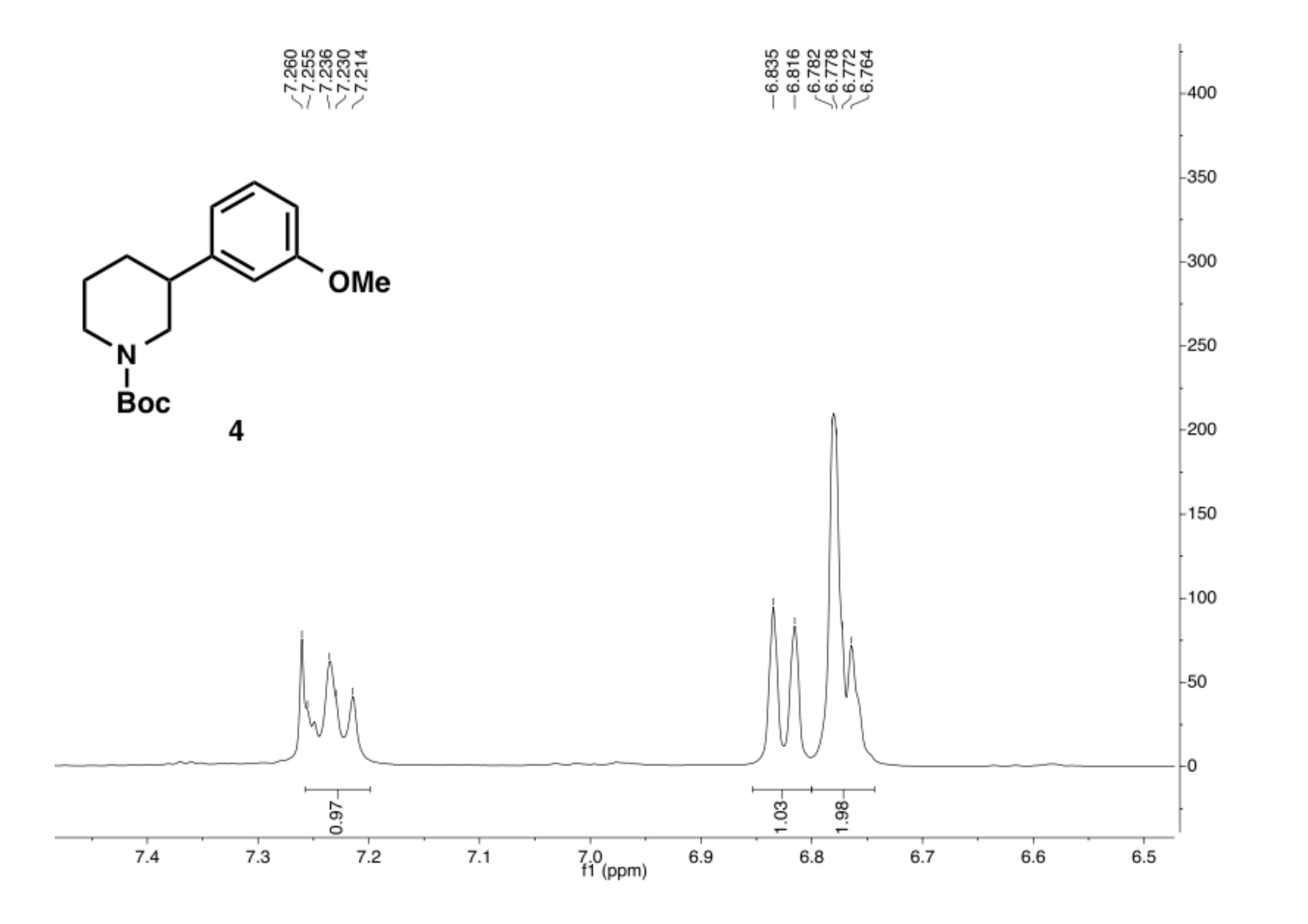

128.564
128.069
127.951
127.907
127.362
126.205
117.258
117.215
N
P
2
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
132
130
128
126
124
122
120
118
116
f1 (ppm)

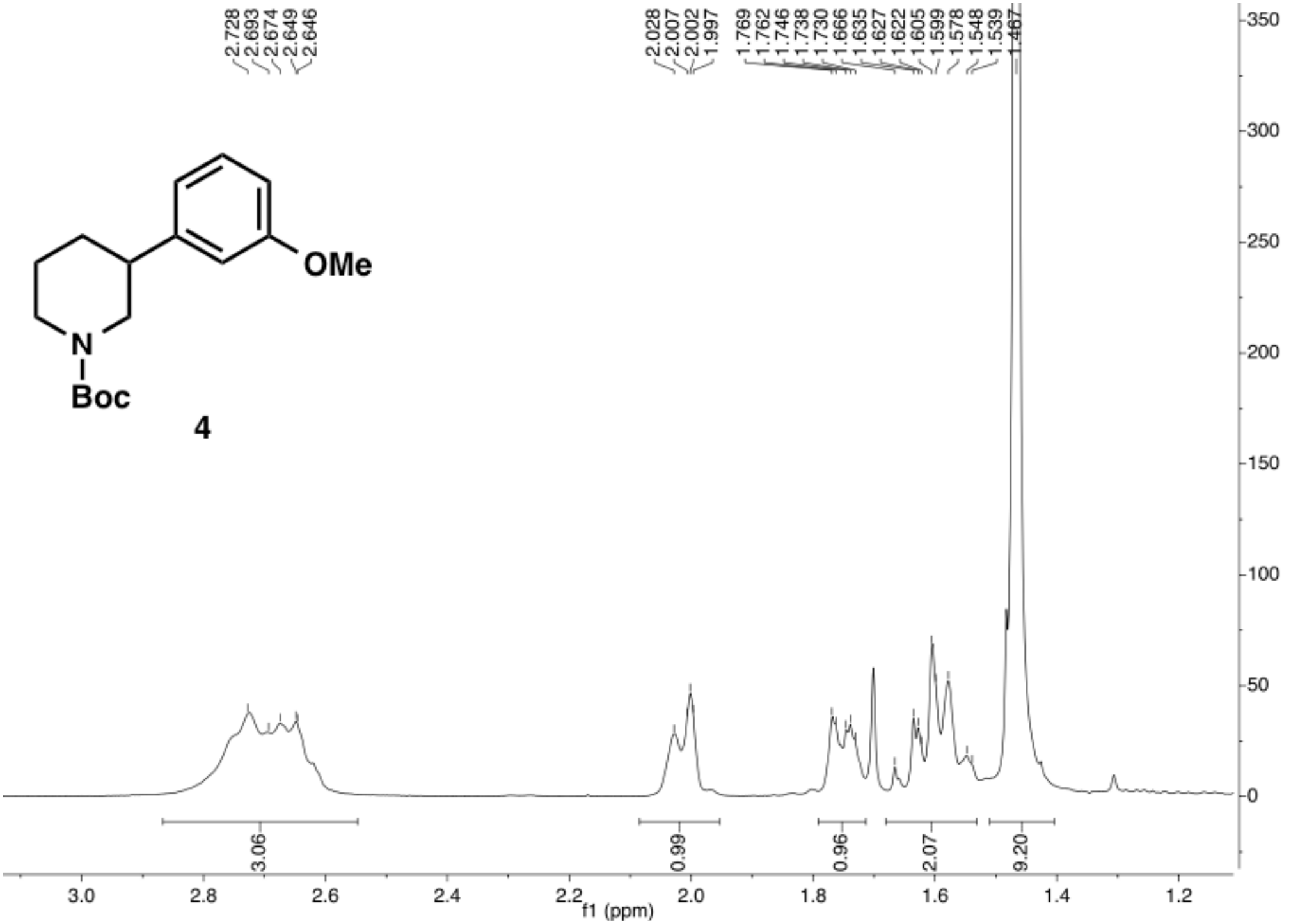

24.613
24.530
20.188
20.008
19.147
19.064
6000
5000
4000
3000
2000
1000
0
N
P
2
28
27
26
25
24
23
22
21
20
19
18
17
f1 (ppm)

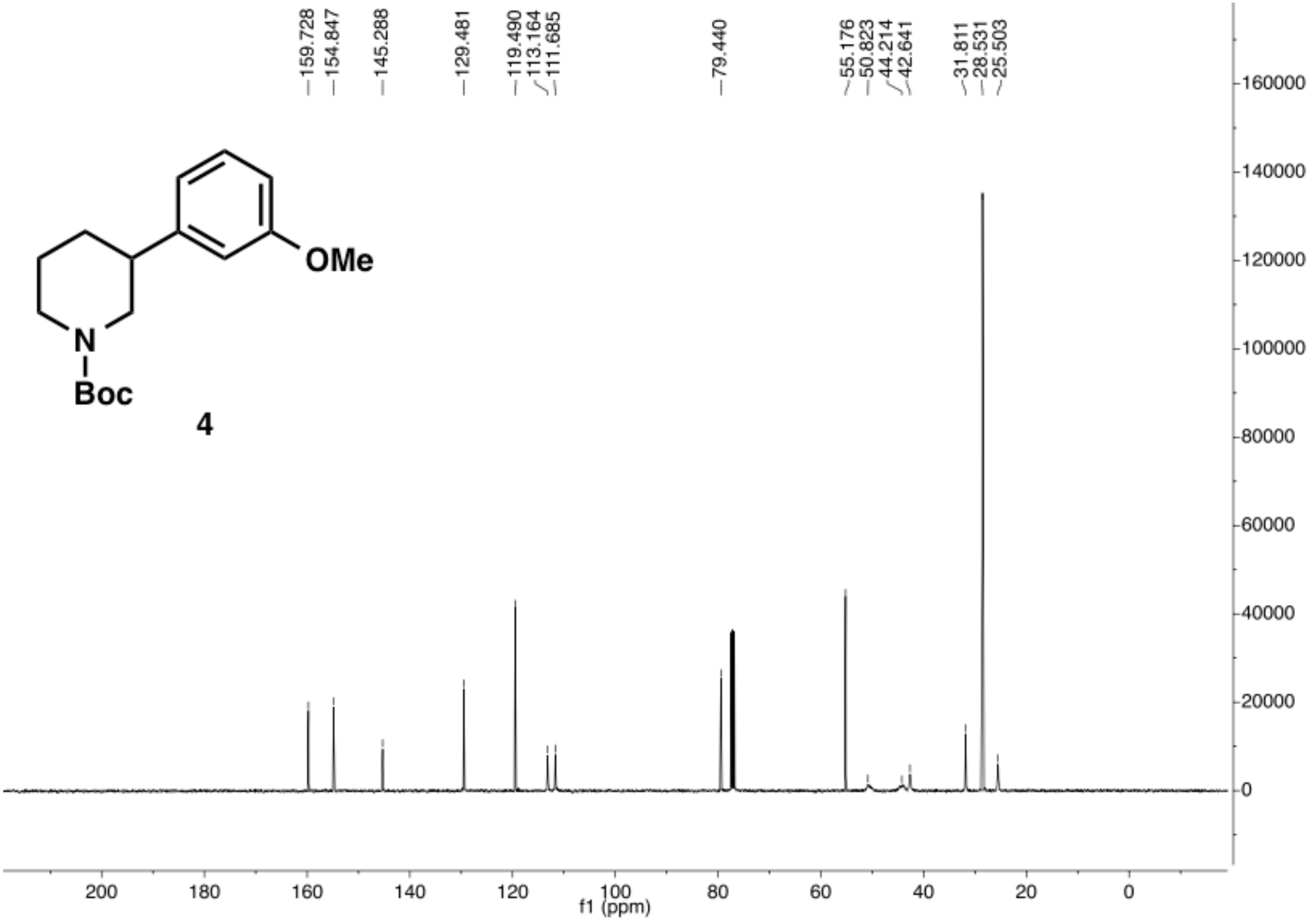


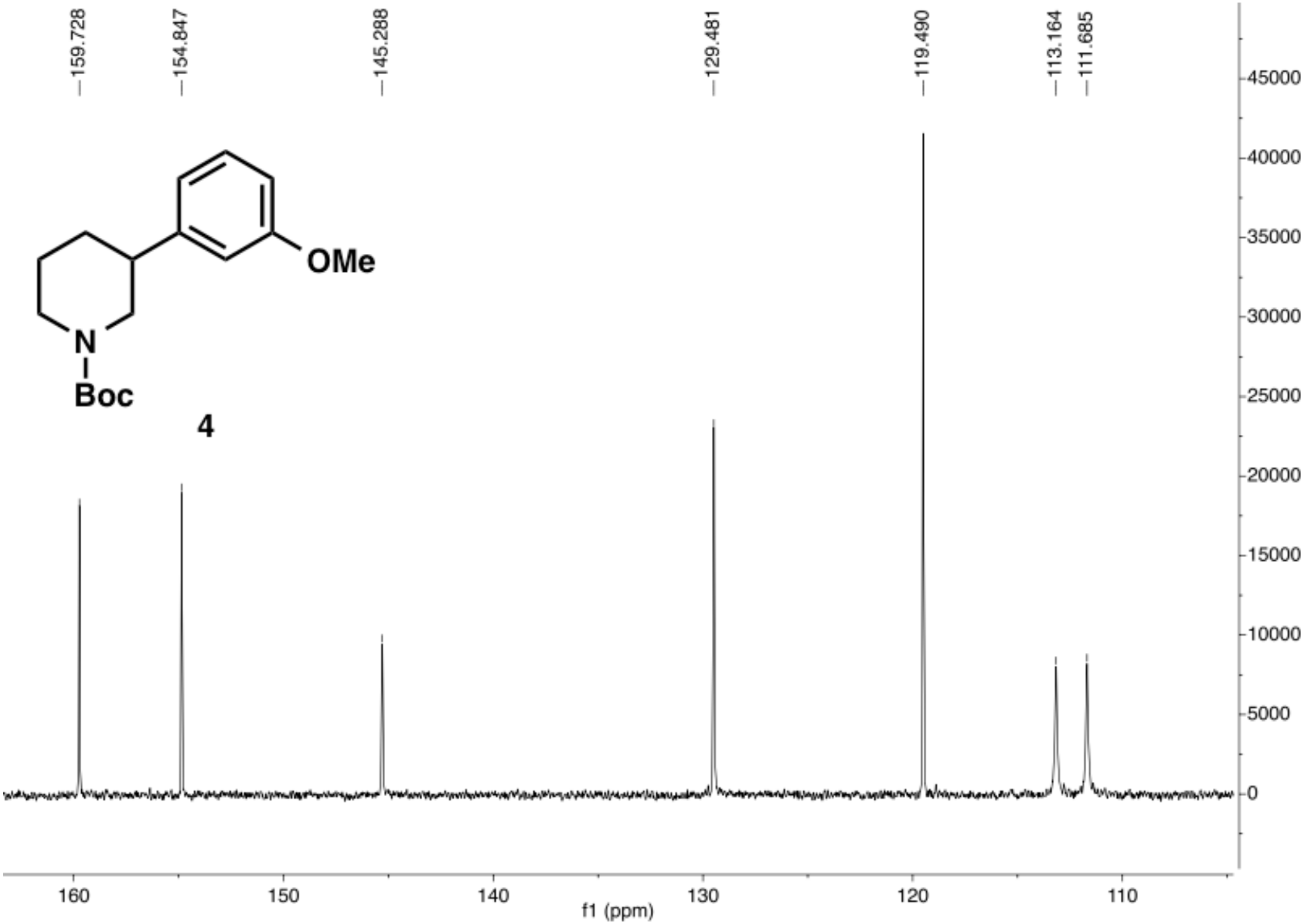
2

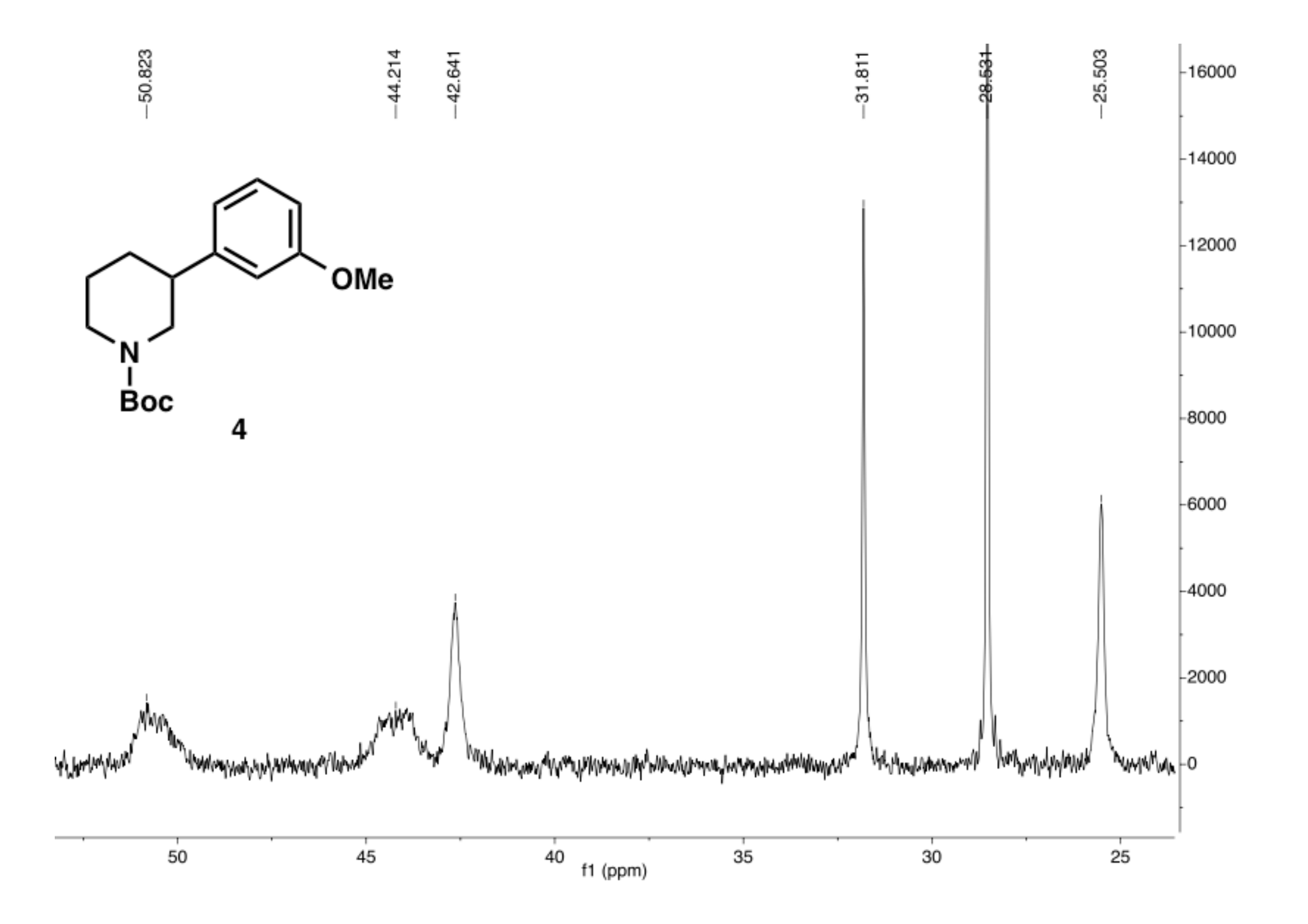

7.260
7.255
7.236
7.230
7.214
6.835
6.816
6.782
6.778
6.772
6.764
4.156
3.803
2.728
2.693
2.674
2.649
2.646
2.028
2.007
2.002
1.997
1.769
1.762
1.746
1.738
1.730
1.635
1.627
1.622
1.605
1.599
1.578
1.548
1.539
1.467
OMe
N
Boc
4
0.97
1.03
1.98
1.98
3.00
3.06
0.99
0.96
2.07
9.20
f1 (ppm)


7.260
7.255
7.236
7.230
7.214
6.835
6.816
6.782
6.778
6.772
6.764
OMe
N
Boc
4
0.97
1.03
1.98
f1 (ppm)


2.728
2.693
2.674
2.649
2.646
2.028
2.007
2.002
1.997
1.769
1.762
1.746
1.738
1.730
1.666
1.635
1.627
1.622
1.605
1.599
1.578
1.548
1.539
1.467
OMe
N
Boc
4
350
300
250
200
150
100
50
0
3.06
0.99
0.96
2.07
9.20
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
f1 (ppm)


159.728
154.847
145.288
129.481
119.490
113.164
111.685
79.440
55.176
50.823
44.214
42.641
31.811
28.531
25.503
OMe
N
Boc
4
160000
140000
120000
100000
80000
60000
40000
20000
0
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


159.728
154.847
145.288
129.481
119.490
113.164
111.685
OMe
N
Boc
4
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
160
150
140
130
120
110
f1 (ppm)


50.823
44.214
42.641
31.811
28.531
25.503
OMe
N
Boc
4
16000
14000
12000
10000
8000
6000
4000
2000
0
50
45
40
35
30
25
f1 (ppm)