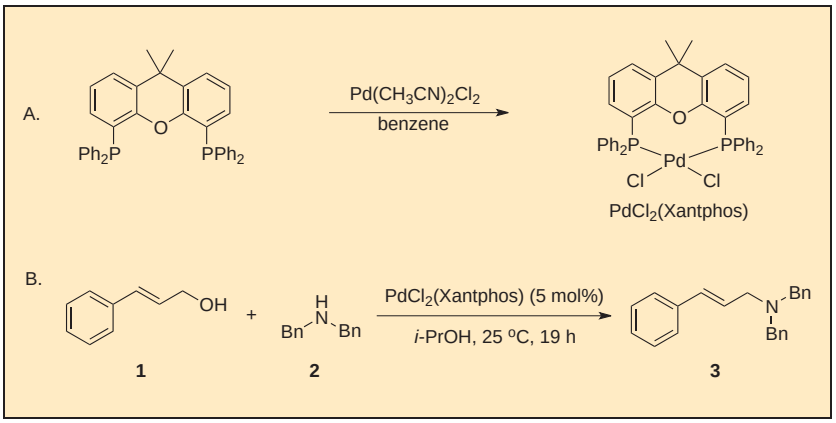
Organic Syntheses

Palladium-Catalyzed Direct Amination of Allylic Alcohols at Room Temperature

Bao Gao, Lixin Li, Guoying Zhang, and Hanmin Huang*[1]

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, China

Checked by Steven A. Loskot and Brian M. Stoltz



Procedure

A. *Pd(Xantphos)Cl*$_2$. An oven-dried, 100-mL Schlenk flask containing a magnetic stir bar (2.5 x 0.8 cm Teflon-coated) (Note 1) is fitted with a reflux conderser and connected to a vacuum line via a one-stopcock adapter in the side arm. The flask is flushed with nitrogen (Note 2) and charged with $Pd(CH_3CN)_2Cl_2$ (1.0 g, 3.86 mmol, 1 equiv) (Note 3), Xantphos (2.46 g, 4.24 mmol, 1.1 equiv) (Note 4) and benzene (80 mL) (Note 5). The reaction mixture is stirred for 48 h at 110 °C (oil bath). After cooling to room temperature, the yellow solid is collected by filtration. The solid is successively washed with benzene (3 x 30 mL) and Et_2O (3 x 30 mL), then

dried under vacuum (1.0 mmHg) for 5 h to give Pd(Xantphos)Cl_2 (2.88 g, 98%) (Note 6) as a yellow solid in 99.2% purity, as determined by quantitative ^{1}H NMR spectroscopy (Note 7).

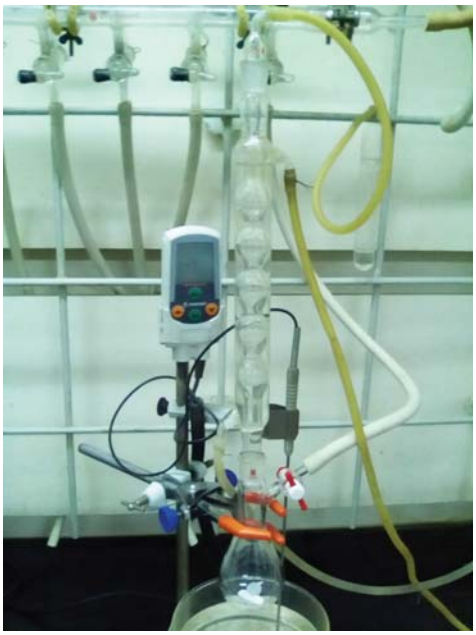


Figure 1. Reaction assembly for synthesis of Pd(Xantphos)Cl_2

B. *(E)-N,N-Dibenzyl-3-phenylprop-2-en-1-amine*. An oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar (2.5 x 0.8 cm Teflon-coated, ovoid-shaped) is connected to a vacuum line via a one-stopcock adapter in the side arm. The flask is flushed with nitrogen and charged with Pd(Xantphos)Cl_2 (945 mg, 1.25 mmol, 0.05 equiv) and *i*-PrOH (30 mL) (Note 8). The reaction mixture is stirred for one min at room temperature, subsequently (*E*)-3-phenylprop-2-en-1-ol (3.35 g, 25.0 mmol, 1.0 equiv) (Note 9) is added via syringe in one portion (Note 10). Then dibenzylamine (4.8 mL, 25 mmol, 1 equiv) (Note 11) is added via syringe in one portion, and the reaction mixture is stirred for 19 h at room temperature (Notes 12 and 13). The solvent is concentrated in water-aspirator vacuum at (30 mmHg, 40 °C) to obtain the crude product as the viscous brown oil. The resulting residue is purified by column chromatography on silica gel (Note 14) to furnish 7.1 g (91% yield) of ethyl (*E*)-3-(2-acetamido-4-methylphenyl)acrylate as a colorless oil (Notes 15 and 16) with a purity of

98.3%, as determined by quantitative ^{1}H NMR spectroscopy and GC analysis (Notes 17 and 18).

Figure 2. Reaction assembly for synthesis of product 3

Notes

1. All glassware was thoroughly washed and dried in an oven at 100 °C. Teflon-coated magnetic stirring bars were washed with alcohol and dried.
2. This operation is performed by opening the nitrogen inlet from the side arm and flushing the flask for 3 min.
3. $Pd(CH_3CN)_2Cl_2$ was purchased from Sigma-Aldrich, (99% purity, yellow solid) and used as received.
4. Xantphos was purchased from Sigma-Aldrich, (97% purity, white solid) and used as received.
5. Benzene was purchased from Sigma-Aldrich, (99.8% purity, colorless liquid) and used as received.
6. A second reaction on the same scale provided 2.82 g (96%) of Pd(Xantphos)Cl_2.
7. Pd(Xantphos)Cl_2 exhibits the following characteristics: ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.87 (s, 6H), 7.06 (td, J = 7.8, 2.5 Hz, 8H), 7.16 – 7.25 (m, 4H), 7.29 – 7.38 (m, 10H), 7.44 (ddd, J = 9.0, 7.7, 1.4 Hz, 2H), 7.73 (dt, J = 7.8, 1.1 Hz, 2H); ^{13}C NMR (101 Hz, CD_2Cl_2) δ: 26.8, 37.4, 37.4, 37.4,

119.9, 119.9, 120.4, 120.4, 125.4, 125.4, 125.5, 125.5, 125.5, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.7, 129.6, 130.1, 130.4, 130.6, 134.9, 135.0, 136.0, 136.0, 136.0, 154.8, 154.8, 154.9, 154.9; ^{31}P NMR (162 MHz, CD_2Cl_2) δ: 21.8. The purity of product Pd(Xantphos)Cl_2 was determined using ^{1}H QNMR analysis. ^{1}H QNMR was performed using a mixture of Pd(Xantphos)Cl_2 (36.2 mg) and 1,3,5-trimethoxybenzene (15.3 mg) (Alfa Aesar, ≥99% purity, white solid, as an internal standard) in CD_2Cl_2. The purity was calculated according to standard method as 99.7 wt%.

8. *i*-PrOH was purchased from Sigma-Aldrich, (≥99.7% purity, colorless liquid) and used as received.
9. (*E*)-3-Phenylprop-2-en-1-ol (cinnamyl alcohol) was purchased from Sigma-Aldrich, (98% purity, white solid) and used as received.
10. Cinnamyl alcohol was immersed in a water bath at 45 °C for 30 min before use to facilitate its addition via syringe, because of the low melting point of cinnamyl alcohol (30–33 °C). A preheated (45–50 °C) 5-mL glass syringe fitted with a short needle (50 mm) was used in order to avoid solidification of the reagent during the addition. Alternatively, cinnamyl alcohol (3.35 g) could be also dissolved in *i*-PrOH (2 mL) and then added into Schlenk flask as a solution under nitrogen atmosphere.
11. Dibenzylamine was purchased from Sigma-Aldrich, (97% purity, colorless liquid) and used as received.
12. The initially yellow color of the reaction mixture is changed to orange after 10 min stirring, and subsequently becomes orange-yellow after additional 2 h of stirring. The reaction was performed at room temperature in a water bath.
13. The consumption of (*E*)-3-phenylprop-2-en-1-ol is monitored by TLC analysis on silica gel with *n*-hexane:EtOAc (15:1) as eluent. (*E*)-3-Phenylprop-2-en-1-ol (**1**), R_f = 0.20; Dibenzylamine (**2**) R_f= 0.01; product (**3**) R_f = 0.85.
14. The product was purified by flash chromatography on a column (5 x 40 cm) of 100 g of silica gel and eluted with 0.8 L of PE: EtOAc (100:1) followed by 1.0 L of petroleum ether: EtOAc (30:1). The elution was used as received, the boiling point of petroleum ether is 60 °C – 90 °C.
15. The desired product is obtained in fractions 5 through 12, each tube contains 90–100 mL eluent, which are concentrated by rotary evaporation (40 °C, 30 mmHg) and dried under vacuum (1.0 mmHg) for 2 h to give 7.1 g (91%) of **3** as a colorless oil. The product exhibits the following characteristics: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.27 (dd, *J* = 6.5, 1.3 Hz, 2H), 3.67 (s, 4H), 6.34 (dt, *J* = 15.9, 6.5 Hz, 1H), 6.58 (dd, *J* = 15.9,

1.5 Hz, 1H), 7.25 – 7.45 (m, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 55.9, 58.0, 126.3, 126.9, 127.4, 127.8, 128.3, 128.6, 128.9, 132.5, 137.3, 139.7; HRMS (ESI) calcd. for $C_{23}H_{24}N$ [M+H]: 314.1903, found: 314.1911.

16. A second reaction on the same scale provided 7.0 g (90%) of product **3**. When the ratio of **1** and **2** is 1:1.25, **3** was obtained in 83% yield. However, when the load of the catalyst Pd(Xantphos)Cl_2 was reduced to 1.0 mol%, only trace amount of **3** was obtained.
17. The analysis is performed applying gas chromatography (GC). GC conditions: gas chromatography instrument 7890A GC-System from Agilent Technologies equipped with HP-5 column (30 m × 0.32 mm, film 0.25 μm); flow: 1.5 mL/min; injection temperature: 280 °C; temperature profile: initial temperature = 80 °C for 5 min, temperature gradient = 25 °C/min, final temperature = 280 °C for 30 min; Retention time of **3**: 13.028 min.
18. The purity of product **3** was determined using ^{1}H QNMR analysis. ^{1}H QNMR was performed using a mixture of product **3** (31.9 mg) and 1,3,5-trimethoxybenzene (24.0 mg) (Alfa Aesar, ≥99% purity, white solid, as an internal standard) in $CDCl_3$. The purity was calculated according to standard method as 97 wt%.

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

Allylic amines are important compounds that have intrigued chemists due to their unique usage and wide existence in natural products, pharmaceuticals, functional materials, and agrochemicals. In addition, allylamines also serve as attractive precursors in a variety of organic transformations (Figure 3).[2] As such, the development of efficient and sustainable methods for the production of allylic amines is important to the chemical industry and medicinal chemistry, and has attracted a great deal of attention over the past decades.[3]

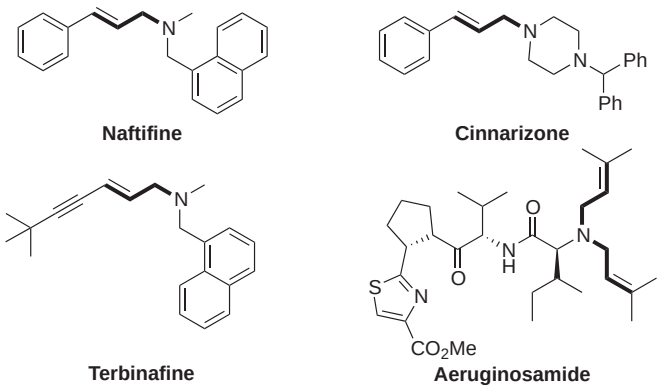
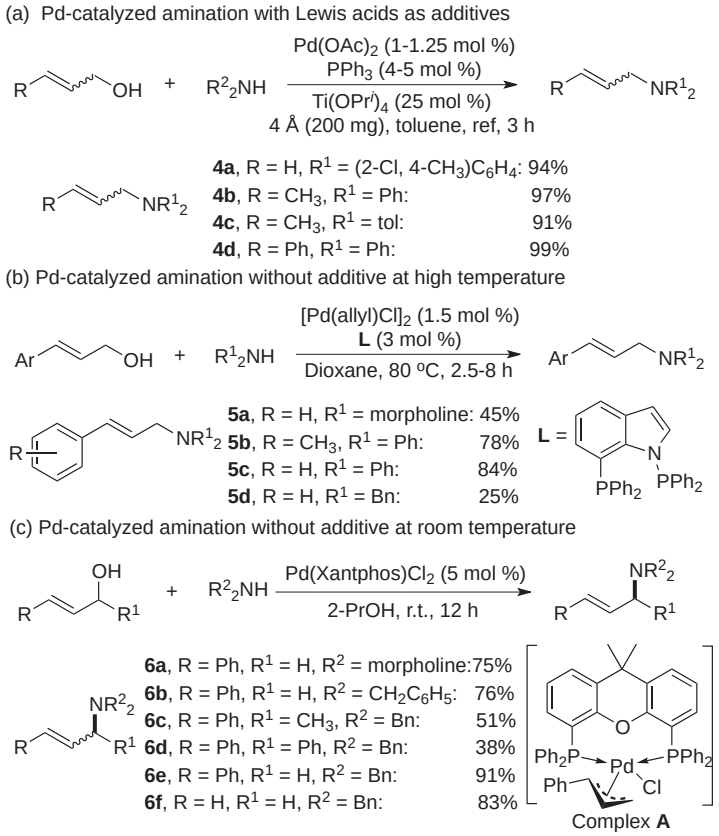


Figure 3. Examples of Allylamine-containing Pharmaceuticals

Among many types of synthetic methods available for constructing the allylamine scaffold,[3] the transition-metal-catalyzed amination of allylic alcohols has proven to be one of the most efficient approaches for the synthesis of allylic amines[4] due to the high atom economy (water is produced as the only by-product) and step economy. In 1999, Yang and Moritani reported the direct coupling of allylic alcohols with amines through Pd-catalyzed amination, wherein the Lewis acid ($Ti(OiPr)_4$) as promoter was added to enhance the leaving ability of the hydroxy group in the presence of molecular sieves at the high temperature (Scheme 1a).[5]



Scheme 1. Palladium(II)-catalyzed Amination of Allyl Alcohols

Notable progress was made by using $[Pd(allyl)Cl]_2$ complexes with 1,7-bis(diphenylphosphino)-1H-indole. The reactions proceeded smoothly in

1,4-dioxane at 80 °C without any additives; however, use of this bisphosphine ligand, which is not easily prepared, is still quite rare (Scheme 1b).[6] Our research group found that the use of the less expensive and readily available Pd(Xantphos)Cl_2 catalyst enabled the direct amination of allylic alcohols with amines at room temperature in the absence of additives (Scheme 1c).[7] This method is compatible with a variety of functional groups and can be used to prepare a wide range of linear allylic amines in good to excellent yields with high stereoselectivity. Moreover, this method was utilized to synthesize the antihistamine pharmaceutical cinnarizine.[8]

In summary, a simple palladium(II) complex has been identified to be an efficient catalyst for the direct amination of allylic alcohols with amines via C-O bond cleavage. This simple reaction can be performed at room temperature and can be used for synthesis of a broad range of linear allylamines, which are important for natural product synthesis and drug discovery. Considering the practical importance of this atom- and step-economical amination reaction, significant further applications are expected.

References

1. State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, China. E-mail: hmhuang@licp.cas.cn. This work was supported by the National Natural Science Foundation of China (21222203 and 21172226).
2. (a) Towse, G. *J. Laryngol. Otol*. **1980**, *94*, 1009; (b) Shupak, A.; Doweck, I.; Gordon, C. R.; Spitzer, O. *Clin Pharmacol Ther*. **1994**, *55*, 670; (c) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; (d) Chen, Z.; Ye, T. *New J. Chem*. **2006**, *30*, 518.
3. (a) Cheik, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685; (b) Overman, L. E.; Carpenter, N. E. *Org. React*. **2005**, *66*, 1; (c) Miyabe, H.; Takemoto, Y. *Synlett.* **2005**, 1641; (d) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349; (e) Hartwig, H. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461; (f) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926; (g) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931.
4. (a) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234; (b) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M.

Angew. Chem. Int . Ed. **2007**, *46*, 409; (c) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3139; (d) Mora, G.; Deschamps, B.; van Zutphen, S.; Goff, X. F. L.; Ricard, L.; Floch, P. L. *Organometallics* **2007**, *26*, 1846; (e) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett.* **2007**, *9*, 3371; (f) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 14317; (g) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2009**, *11*, 2377; (h) Tao, Y.; Wang, B.; Wang, B.; Qu, L.; Qu, J. *Org. Lett.* **2010**, *12*, 2726; (i) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2011**, *132*, 11917; (j) Hikawa, H.; Yokoyama, Y. *J. Org. Chem.* **2011**, *76*, 8433; (k) Das, K.; Shibuya, R.; Nakahara, Y.; Germain, N.; Ohshima, T.; Mashima, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 150; (l) Wagh, Y. S.; Sawant, D. N.; Dhake, K. P.; Bhanage, B. M. *Catal. Sci. Technol.*, **2012**, *2*, 835.

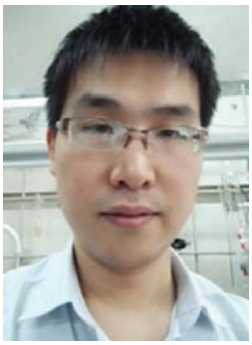
5. Yang, S. -C.; Hung, C.-W. *J. Org. Chem*. **1999**, *64*, 5000.
6. Ghosh, R.; Sarkar, A. *J. Org. Chem*. **2011**, *76*, 8508.
7. Wang, M.; Xie, Y.; Li, J.; Huang, H. *Synlett* **2014**, *25*, 2781.
8. (a) Towse, G. *J. Laryngol. Otol*. 1**980**, *94*, 1009; (b) Singh, B. N. *Br. J. Clin. Pharmacol.* **1986**, *21*, 109S; (c) Shupak, A.; Doweck, I.; Gordon, C. R.; Spitzer, O. *Clin. Pharmaclo. Ther*. **1994**, *55*, 670.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

Dibenzylamine; (103-49-1)
1,3,5-Trimethoxybenzene; (621-23-8)
i-PrOH: Isopropyl alcohol; (67-63-0)
(*E*)-3-Phenylprop-2-en-1-ol; (104-54-1)
$PdCl_2(CH_3CN)_2$: Bis(acetonitrile)palladium(II) chloride; (14592-56-4)
Xantphos: 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene; (161265-03-8)

Hanmin Huang was born in Hubei, China, and completed his M.S. degree at the Huazhong University of Science & Technology. He obtained his Ph.D. degree in 2003 at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences (CAS), under the supervision of Professor Huilin Chen and Professor Zhuo Zheng. He then moved to Nagoya University and worked as a JSPS postdoctoral research fellow with Professor Masato Kitamura. In 2008, he initiated his independent research in the Lanzhou Institute of Chemical Physics, CAS. In March 2016, he moved to the University of Science and Technology of China as a full professor. His current research interests are focused on organometallic chemistry and the development of new and efficient synthetic methodologies for green organic synthesis.

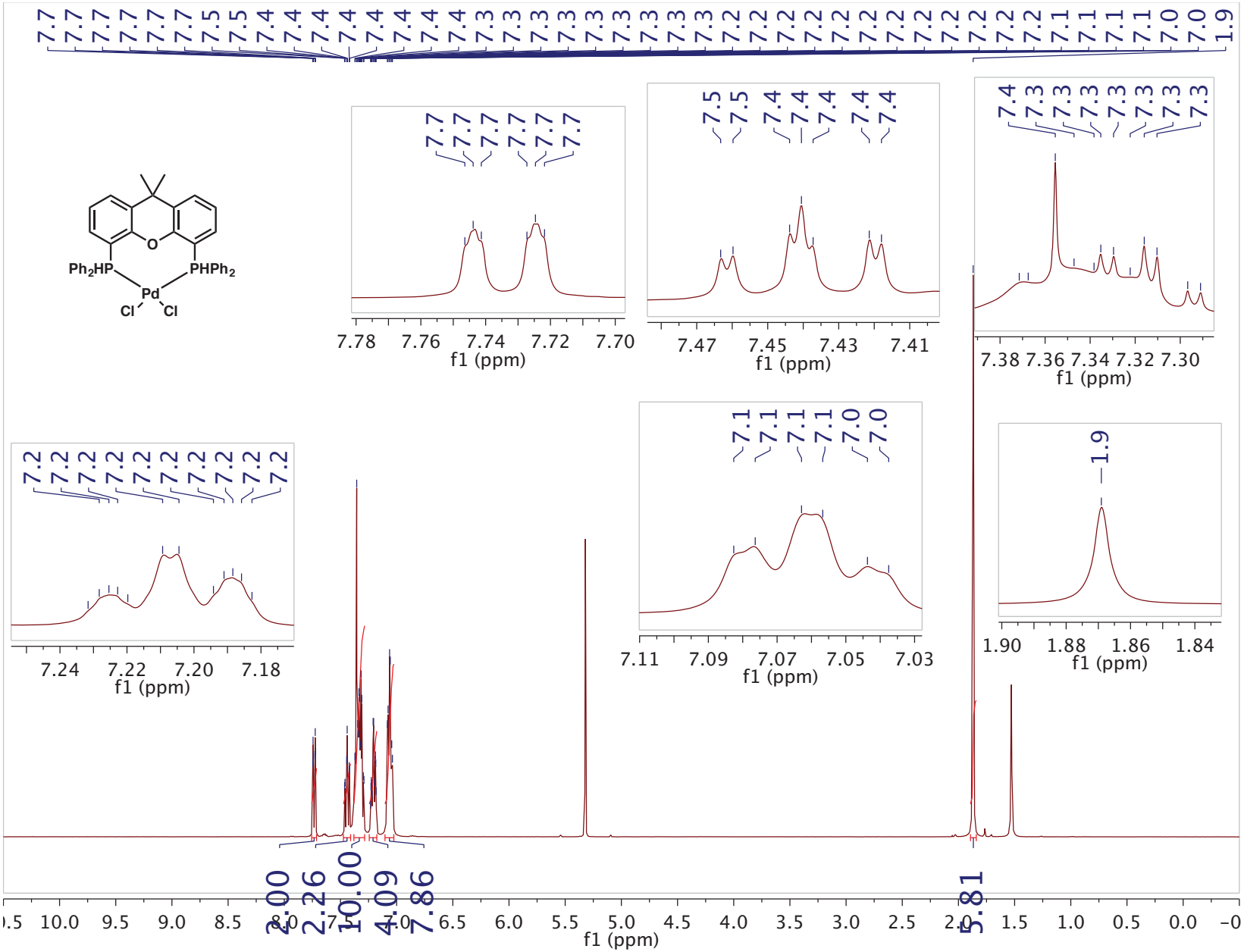
Bao Gao was born in 1987 in Shanxi, China. He received his B.S. in chemistry at Yanbian University in 2010 and completed his M.S in chemistry on organic functional materials at Lanzhou University in 2013. He is now pursuing his Ph.D. in the group of Prof. Hanmin Huang at University of Chinese Academy of Sciences (2013-present). His current research interests include organometallic chemistry and carbonylative reaction.

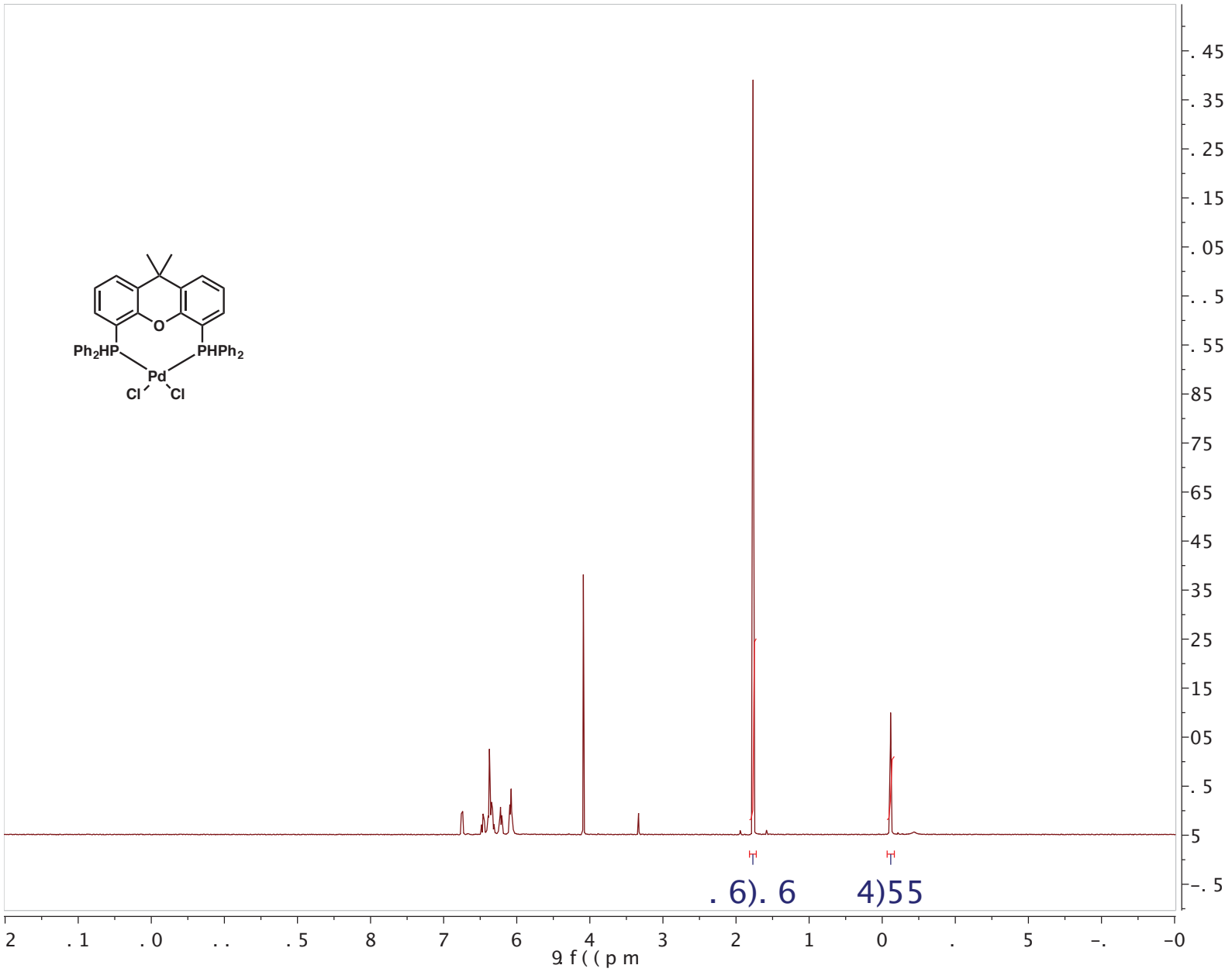


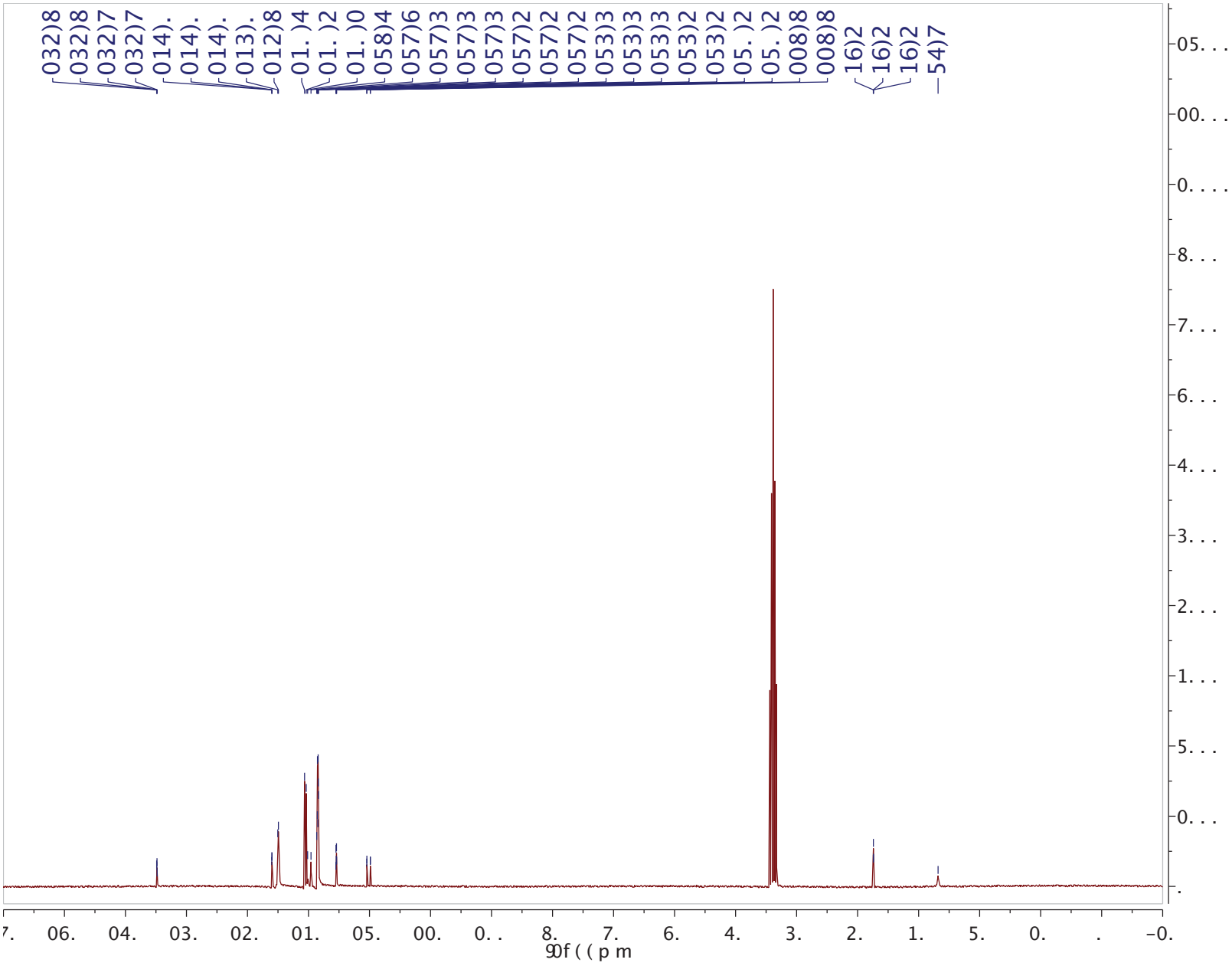
Lixin Li was born in 1987 in Henan, China. He received his B.S. degree and M.S. degree from Henan University in 2010 and 2013 respectively, Now he is pursuing his Ph.D. at the University of Chinese Academy of Sciences (2014-present) under the supervision of Professor Hanmin Huang. His current research interests are focused on palladium-catalyzed the cleavage of C-N bonds.

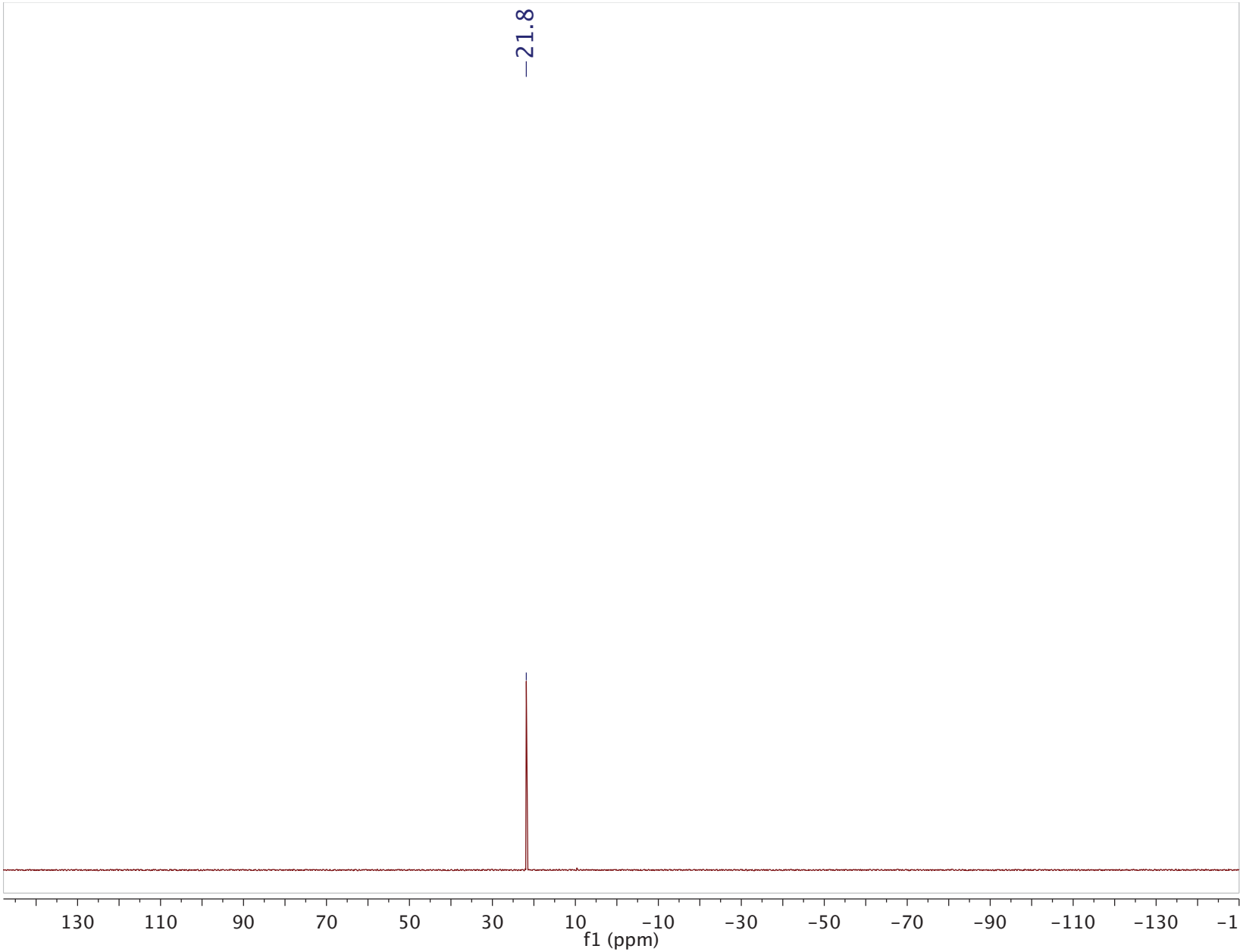
Guoying Zhang was born in 1986 in Shandong, China. He received his B.S. from University of Jinan in 2009 and received M.S. from Wenzhou University in 2012.He is now pursuing his Ph.D. in the group of Prof. Hanmin Huang at University of Chinese Academy of Sciences (2012-present). His current research interests include organometallic chemistry and catalysis.

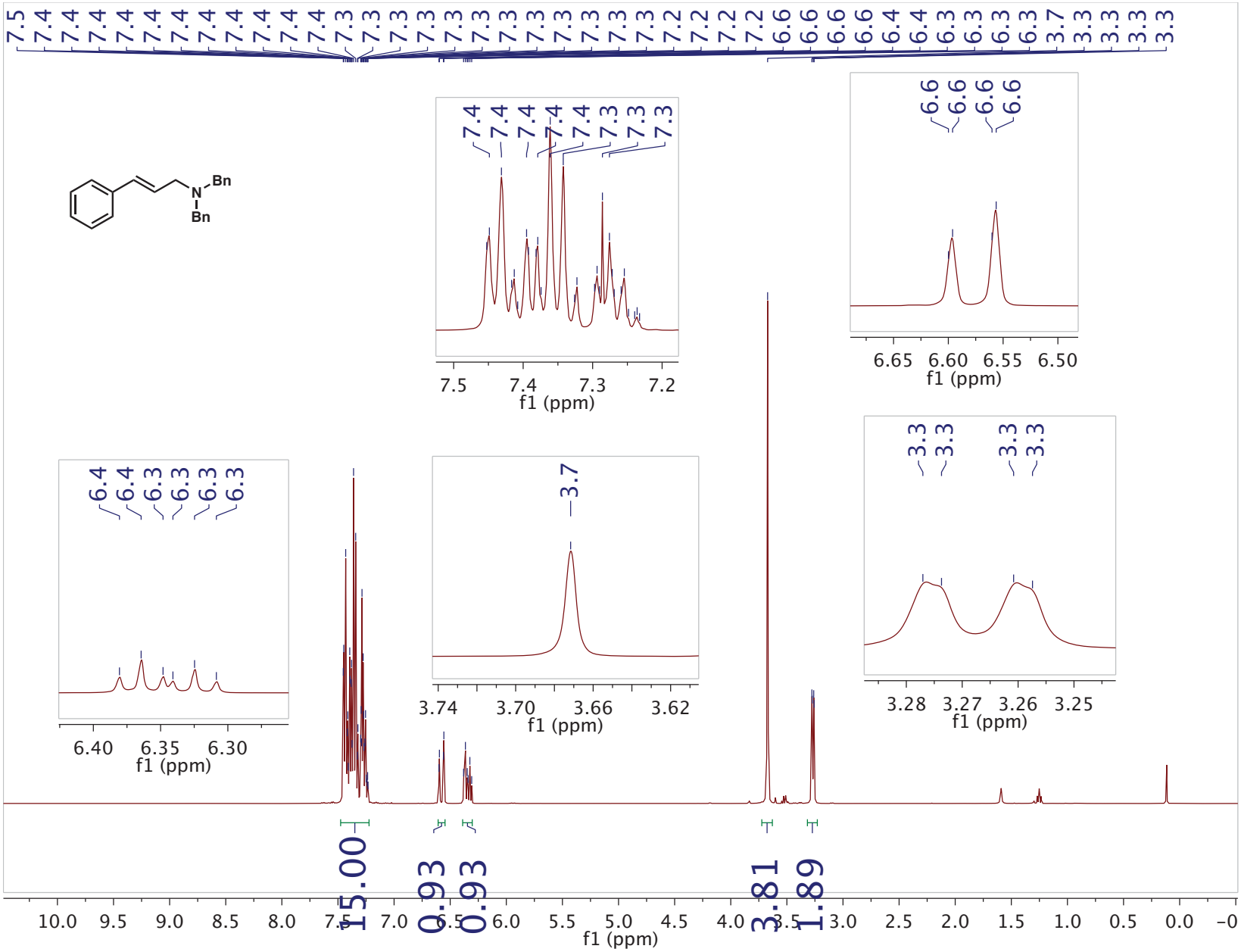
Steven A. Loskot was born in San Jose, CA in 1991. He received hi B.S. degree in Biochemistry from Seattle University in 2014 where he conducted research for Professor Joseph M. Langenhan. He is now pursuing his graduate studies at the California Institute of Technology under the guidance of Professor Brian M. Stoltz. His graduate research focuses on the total synthesis of novel natural products.

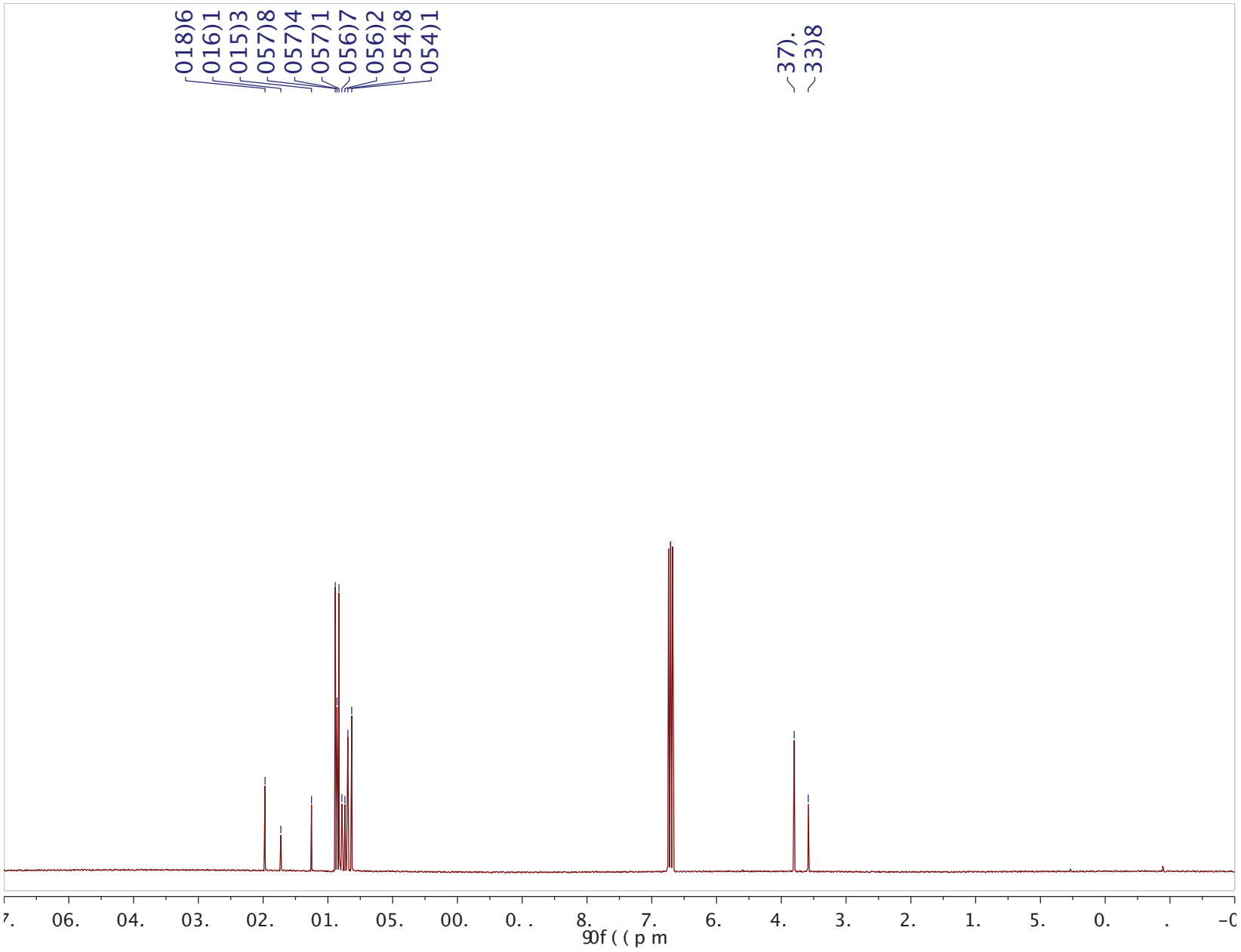

Ph2HP
PHPh2
Pd
Cl
Cl
f1 (ppm)
2.00
2.26
10.00
4.09
7.86
5.81

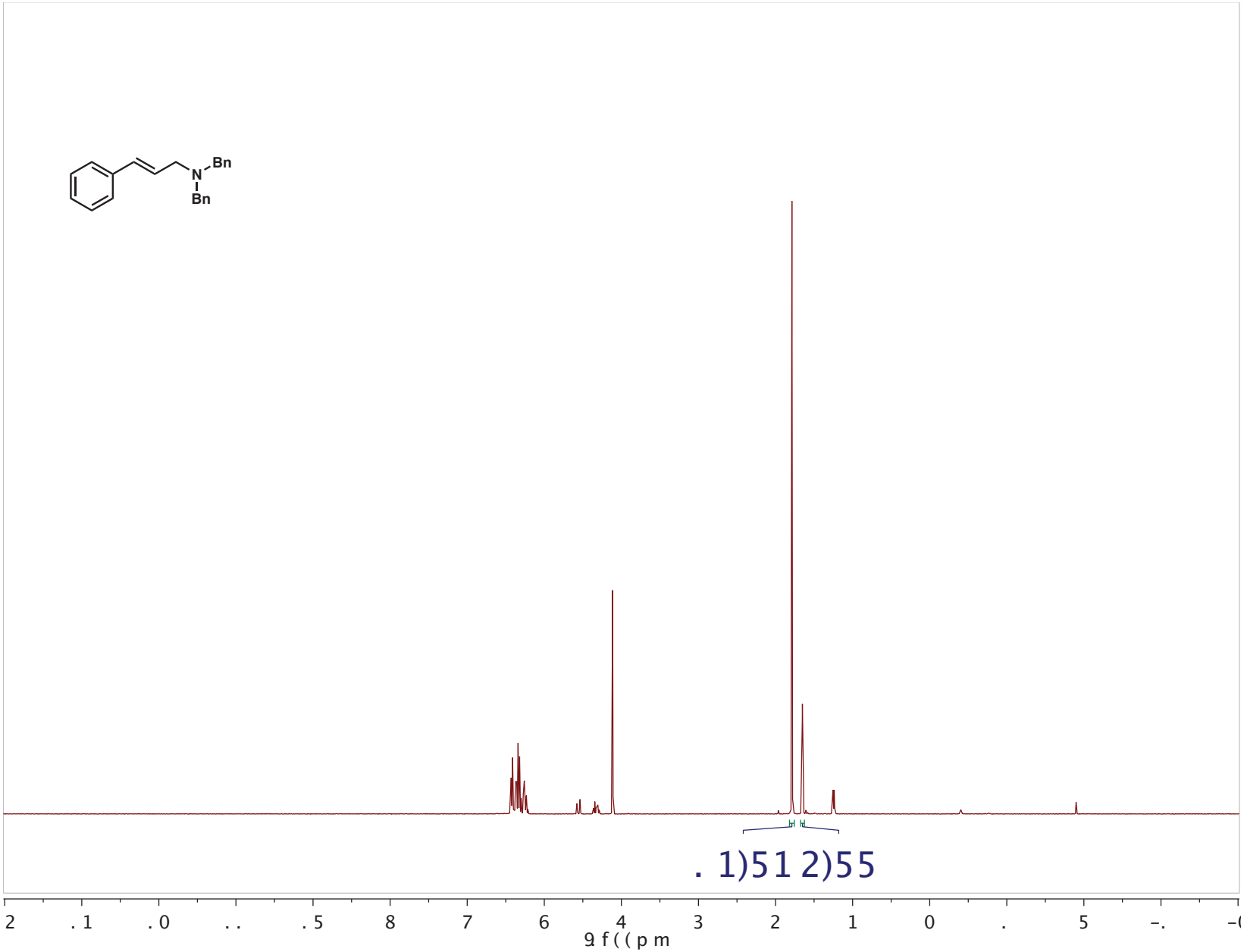

Ph2HP
PHPh2
O
Pd
Cl
Cl
. 6). 6
4)55
9 f ((p m


032)8
032)8
032)7
032)7
014).
014).
014).
013).
012)8
01.)4
01.)2
01.)0
058)4
057)6
057)3
057)3
057)3
057)2
057)2
057)2
053)3
053)3
053)3
053)2
053)2
05.)2
05.)2
008)8
008)8
16)2
16)2
16)2
—54)7
05...
00....
0....
8...
7...
6...
4...
3...
2...
1...
5...
0...
.
7.
06.
04.
03.
02.
01.
05.
00.
0..
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
−0.
9Of((pm


21.8
130
110
90
70
50
30
10
−10
−30
−50
−70
−90
−110
−130
−1
f1 (ppm)


7.5 7.4 7.4 7.4 7.4 7.4 7.4 7.4 7.4 7.4 7.4 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.2 7.2 7.2 7.2 6.6 6.6 6.6 6.6 6.4 6.4 6.3 6.3 6.3 6.3 3.7 3.3 3.3 3.3 3.3
N
Bn
Bn
7.5 7.4 7.3 7.2
f1 (ppm)
6.6 6.6 6.6 6.6
6.65 6.60 6.55 6.50
f1 (ppm)
6.4 6.4 6.3 6.3 6.3 6.3
6.40 6.35 6.30
f1 (ppm)
3.7
3.74 3.70 3.66 3.62
f1 (ppm)
3.3 3.3 3.3 3.3
3.28 3.27 3.26 3.25
f1 (ppm)
15.00
0.93
0.93
3.81
1.89
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0
f1 (ppm)


018)6
016)1
015)3
057)8
057)4
057)1
056)7
056)2
054)8
054)1
37).
33)8
7.
06.
04.
03.
02.
01.
05.
00.
0. .
8.
7.
6.
4.
3.
2.
1.
5.
0.
.
−0
9 0f ((p m


Bn
N
Bn
. 1)51 2)55
2 . 1 . 0 . . . 5 8 7 6 4 3 2 1 0 . 5 −.
9 f ((p m