



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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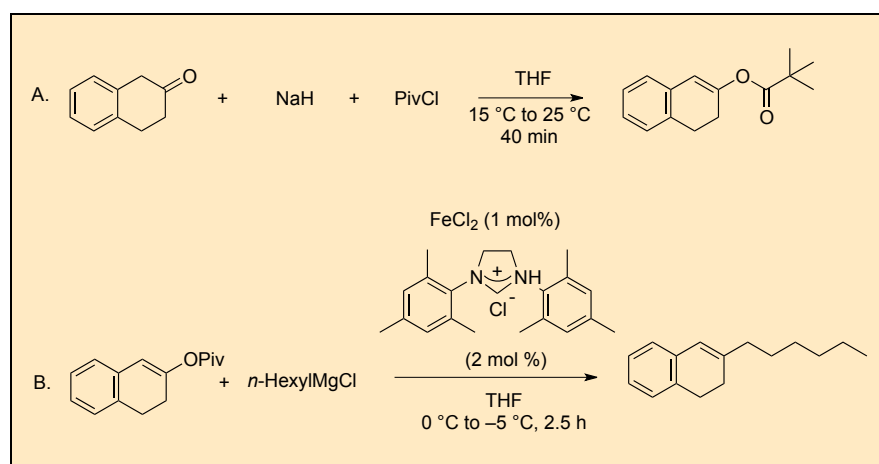
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Cross-Coupling of Alkenyl/Aryl Carboxylates with Grignard Reagents via Fe-Catalyzed C-O Bond Activation

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Procedure

A. *3,4-Dihydronaphthalen-2-yl pivalate*. A 1-L three-necked round-bottomed flask is equipped with a 4-cm x 8mm octagonal Teflon coated stir-bar (Note 1). The left neck is fitted with a glass stopper. The center neck is fitted with a Claisen adapter to which is attached a 50 mL pressure-equalizing addition funnel capped with a rubber septum on one joint and reflux condenser with a N₂ inlet on the other. The right neck is capped with

a rubber septum (Note 2). The glass stopper is removed and the flask is charged with sodium hydride (6.00 g, 150 mmol, 1.5 equiv, 60% dispersion in mineral oil) (Note 3). The glass stopper is replaced and the flask is purged for 10 min with N₂ with a vent needle on the right rubber septum. After the addition of THF (200 mL) (Note 4) by syringe through the right rubber septum, the mixture is stirred at room temperature for 10 min to give a grey suspension. The right rubber septum is then replaced with a glass stopper. 2-Tetralone (13.4 mL, 14.8 g, 100 mmol, 1.0 equiv) (Note 5) is then transferred to the addition funnel via syringe and subsequently added dropwise from the addition funnel to the NaH suspension over a period of 8 min. During the addition of 2-tetralone, H₂ gas evolves while the reaction mixture becomes warm to the touch and turns into an opaque yellow suspension (Note 6). The addition funnel is then rinsed with an additional portion of THF (10 mL) (Note 7). After stirring the reaction mixture for 30 min, pivaloyl chloride (18.6 mL, 18.3 g, 150 mmol, 1.5 equiv) (Note 8) is added dropwise to the yellow suspension from the same addition funnel over a period of 10 min. The addition funnel is then rinsed with THF (20 mL) (Note 7). After stirring the reaction for an additional 30 min, TLC analysis indicated the consumption of starting material (Product R_f=0.35, 5% EtOAc in hexanes, visualized under 254 nm UV light (Note 10)). One of the glass stoppers is then removed and water (2.0 mL) is added dropwise using a pipette (Note 9). After H₂ release subsides, water (98 mL) is added followed by ethyl acetate (50 mL). The mixture is stirred vigorously for 30 min and then transferred to a 500 mL separatory funnel giving a yellow organic layer and a clear, colorless aqueous layer. The layers are separated. The aqueous phase is extracted with ethyl acetate (2 x 50 mL) and the organic phases combined. The combined organic phases are washed with 5% aqueous NaOH solution (2 x 100 mL of a solution prepared with 10.5 g NaOH in 200 mL water) and with saturated aqueous NaCl solution (2 x 100 mL). The yellow organic phase is dried over anhydrous Na₂SO₄ and gravity filtered through a cotton plug and the filtrate collected in a 1-L round-bottomed flask. The Na₂SO₄ is rinsed with EtOAc (2 x 25 mL). The combined organics are concentrated under reduced pressure (190 mmHg, 20 °C) to provide a dark brown-yellow oil. The crude oil is loaded onto a fritted chromatography column (8.0 cm outer diameter) that had been dry-packed with silica gel (300 g) (Note 10) and wetted with hexanes under air pressure. The crude product is eluted with 900 mL of hexanes followed by 2000 mL of CH₂Cl₂:hexanes (30:70) and the eluent is collected in 700 mL fractions in 1L Erlenmeyer flasks (Note 11). Fractions 2, 3, and 4 are

combined in a 3.0 L round-bottomed flask and concentrated under reduced pressure (190 mmHg, 20 °C, 150 rpm) to give 22.5 g (98%) of 3,4-dihydronaphthalen-2-yl pivalate as light yellow-green oil (Note 12).

B. *3-Hexyl-1,2-dihydronaphthalene*. To a 500-mL three-necked round-bottomed flask is added a 3 cm x 8 mm Teflon-coated octagonal stir bar (Note 1). The left neck is equipped with a N₂ gas inlet adapter, the center neck with a rubber septum, and right neck with an alcohol thermometer attached to a rubber thermometer adapter. To the flask is added iron(II) chloride (63.5 mg, 0.5 mmol, 0.01 equiv) (Note 13) and NHC ligand (344.8 mg, 1.0 mmol, 0.02 equiv) (Note 14), after which the flask is purged with N₂ for 10 min with a vent needle in the center rubber septum. The flask is charged with 3,4-dihydronaphthalen-2-yl pivalate (11.3 mL, 11.5 g, 50 mmol, 1.0 equiv), which is added by 12 mL syringe, and THF (70.0 mL) (Note 4), which is also added by syringe. The mixture is stirred at room temperature (20.1 °C) for 20 min after which the dark brown suspension is moved to an ice-salt bath and cooled to -4.1 °C (Note 15). *n*-HexylMgCl (50.0 mL of a 2.0 M solution in THF, 100 mmol, 2 equiv) (Note 16) is added dropwise by 60 mL plastic syringe over a period of 43 min using a syringe-pump set to a rate of 1.16 mL/min so as to maintain an internal temperature between -5 °C and 0 °C. Upon addition of the Grignard reagent, the reaction mixture turned brown-yellow in color and over the course of the addition became a darker brown-yellow solution.

After the addition of Grignard reagent, the solution is allowed to stir for 1.5 h in the ice-water bath before quenching the reaction with 1.0 M aqueous HCl (3.0 mL) (Product R_f=0.46, hexanes, visualized under 254 nm UV light) (Note 10). After 1 min, an additional 70 mL of aqueous 1.0 M HCl solution is added during which time a slight exotherm is observed. The mixture is warmed to 25 °C and 20 mL EtOAc is then added (Note 17). The mixture is vigorously stirred for 15 min and then transferred to a 500 mL separatory funnel. The layers are allowed to separate over a period of 30 min into a red/brown organic layer and a faintly red aqueous layer. The layers are separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic phases are washed with saturated aqueous NaCl (2 x 50 mL) and subsequently dried over MgSO₄. The solution is gravity filtered through a plug of cotton into a 1 L round-bottomed flask. The MgSO₄ is then washed with EtOAc (2 x 25 mL), and the combined filtrate concentrated under reduced pressure by rotary evaporation (190 mmHg, 25 °C, 150 rpm).

The crude product is purified by column chromatography. A fritted chromatography column (8.0 cm outer diameter) is dry-packed with 180.0 g of silica gel (Note 10) and wetted with hexanes under air pressure. The crude oil is loaded directly onto the column and the solvent front lowered to the top of the silica gel. The flask is then washed twice with 5 mL portions of hexanes and then loaded onto the column with the solvent front lowered to the top of the silica gel. A 1.0 cm layer of sand is placed on top of the column. Hexanes (950 mL) is used as an eluent, which is collected as 2 x 100 mL fractions, then a 50 mL fraction, and then 7 x 100 mL fractions. Fractions 4-10 are combined and concentrated under reduced pressure by rotary evaporation (190 mmHg, 20 °C, 150 rpm) to afford 3-hexyl-1,2-dihydronaphthalene as a clear colorless oil (10.3 g, 96%) (Note 18).

Notes

1. The flask and stir bar were flame-dried under vacuum, cooled to room temperature under vacuum, and then placed under N₂ atmosphere.
2. The submitters used a 500 mL three-necked round-bottomed flask equipped with a balloon and a stopper and proceeded to suspend 3.72 g of 96% NaH in 130 mL of THF. After stirring the suspension for 5 min, a solution of 2-tetralone (14.6 g, 13.2 mL, 100 mmol, 1.0 equiv) in 70 mL THF was added dropwise via syringe over a period of 25 min. After the completion of the addition of 2-tetralone, the system was warmed to 25 °C (oil bath temperature) and stirred for 5 h under N₂ atmosphere. A solution of PivCl (30.1 g, 31 mL, 250 mmol, 2.5 equiv) in 30 mL THF was then added by syringe over a period of 3 min. After stirring the reaction for an additional 8 h, TLC analysis showed the completion of the reaction. The checkers found that increasing the rates of addition and reducing the overall reaction time resulted in better yields of the product.
3. NaH (60% oil dispersion in mineral oil, grey in color) was purchased from Sigma Aldrich Co. and used as received.
4. The submitters distilled THF over sodium using benzophenone as indicator. The checkers used non-stabilized THF purchased from Fischer Scientific and passed through a column of activated alumina.

5. The submitters used 2-tetralone (96% purity) from a domestic chemical company Beijing Ouhe Technology Co. The checkers used 2-tetralone (99%) purchased from Sigma Aldrich Co. and used as received.
6. When the reaction was exposed to the air, the reaction turns purple/black in color.
7. THF was added to the addition funnel with a closed stopcock. The entire volume of the washing solvent was added all at once to the reaction by fully opening the stopcock.
8. Pivaloyl chloride (99%) was purchased from Sigma Aldrich Co. and used as received.
9. Caution: Strong effervescence was observed upon addition of the quenching solution.
10. Silica gel SilicaFlash® F60 (40-63 μm /230-500 mesh) was purchased from Silicycle. Glass-backed extra hard layer TLC plates, 60 \AA (250 μm thickness) were also purchased from Silicycle containing F-254 indicator.
11. EtOAc, hexanes, and CH_2Cl_2 (all ACS Grade) used in chromatography columns and TLC solvents were all purchased from Fisher Scientific and used as received.
12. The procedure was performed at half-scale in 98% by the checkers. The characterization data of the product was as follows: 3,4-dihydronaphthalen-2-yl pivalate:² ^1H NMR (CDCl_3 , 400 MHz) δ : 1.31 (s, 9 H), 2.49 (t, $J = 8.4$ Hz, 2 H), 3.00 (t, $J = 8.4$ Hz, 2 H), 6.20 (t, $J = 1.2$ Hz, 1 H), 6.99–7.03 (m, 1 H), 7.07–7.19 (m, 3 H). ^{13}C NMR (CDCl_3 , 101 MHz) δ : 26.5, 27.4, 28.9, 39.3, 114.7, 126.4, 126.9, 127.0, 127.5, 133.5, 133.6, 151.6, 177.0. IR (cm^{-1}): ν 2974, 1745, 1129. HRMS (ESI): ($\text{M}+\text{H}^+$) 231.1385, Found: 231.1383. Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{O}_2$, C, 78.23; H, 7.88; Found, C, 77.97; H, 7.86. $R_f = 0.35$ (5% EtOAc in hexanes as solvent for TLC and visualized under 254 nm UV light (Note 10)).
13. FeCl_2 (98% purity) was purchased from Strem Chemicals Inc. and used as received.
14. The checkers purchased 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride from Sigma Aldrich Co. and used it as received. The submitters synthesized the NHC ligand using an *Organic Syntheses* procedure.³
15. This temperature refers to the internal temperature of the reaction.
16. A 2.0 M solution of *n*-hexylMgCl in THF was obtained from Acros Organics and used as received. The submitters observed that a 1.8 M

solution of *n*-hexylMgCl in THF from J&K Co. can also be used without difference in efficiency.

17. The submitters used NH₄Cl (40 mL) to quench the reaction and observed the formation of a white emulsion. The checkers found that quenching procedure with 1 M HCl avoids the formation of an emulsion thus allowing for a more efficient work-up.
18. The procedure was performed at half-scale in 95% by the checkers. The characterization data of the product 3-hexyl-1,2-dihydronaphthalene. ¹H NMR (CDCl₃, 400 MHz) δ: 0.87-0.98 (m, 3 H), 1.26-1.42 (m, 6 H), 1.48-1.59 (m, 2 H), 2.21 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 8.3 Hz, 2 H), 2.79 (t, *J* = 8.3 Hz, 2 H), 6.23 (s, 1 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 7.05-7.18 (m, 3 H). ¹³C NMR (CDCl₃, 101 MHz) δ: 14.5, 23.0, 27.7, 27.9, 28.6, 29.4, 32.1, 37.8, 122.4, 125.6, 126.3, 126.7, 127.5, 134.8, 135.4, 142.9. MS (C₁₆H₂₂): 214 (M⁺). HRMS (ESI) (M+H⁺) 215.1800, Found: 215.1796. IR (cm⁻¹): ν 2926, 2855, 1485, 1453. Anal. Calcd. for C₁₆H₂₂, C, 89.65; H, 10.35; Found, C, 89.40; H, 10.32; The submitters analyzed their reaction by GC analysis: retention time of the product was 6.25 min, > 98% purity. GC 6820, oven: initial temp = 80 °C, initial time = 2 min, rate = 25 °C/min, final temp = 250 °C, final time = 4 min; Inlet: initial temp=250 °C; Column: capillary column, length = 30 m, diameter=320 μm; Detector (FID): temperature = 30 °C. R_f=0.46 (100% hexanes as solvent for TLC and visualized under 254 nm UV light (Note 10)).

Handling and Disposal of Hazardous Chemicals

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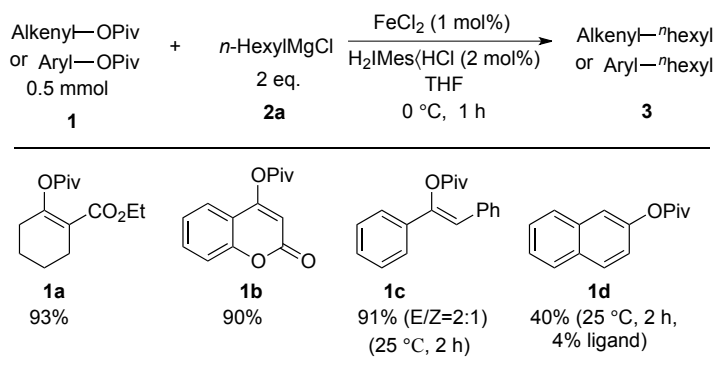
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disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Transition metal-catalyzed cross-coupling reactions are useful methods to construct C-C bonds and have been widely used in organic synthesis. However, the generally used halide-coupling partners have some disadvantages: high costs and pollution to the environment. The use of carboxylates as coupling partners can overcome these disadvantages. The coupling of carboxylates with Grignard reagents proceeds smoothly with high yield and efficiency under mild conditions.⁴ The use of cheap, stable, and non-toxic iron salts as catalysts make it possible for application in industry.

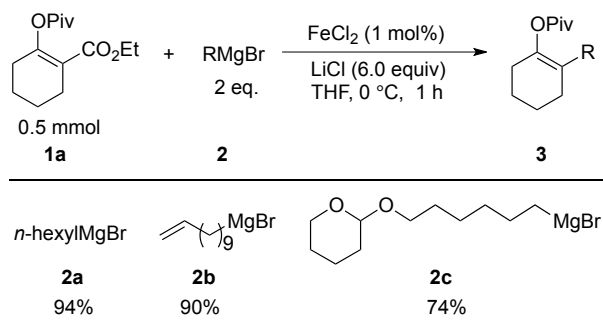
Both cyclic and acyclic alkenyl pivalates give good yields (Scheme 1, **1a** and **1c**). In the presence of both an alkenyl or aryl ester, the alkenyl pivalate reacted selectively (Scheme 1, **1b**). Aryl pivalates are also capable of reacting, although in a lower yield (Scheme 1, **1d**); however, the reactions of inactivated alkenyl carboxylates such as 1-cyclohexenyl pivalate have been unsuccessful under these conditions.



Scheme 1. Examples of different alkenyl pivalates

For the Grignard reagent, although magnesium bromides have almost no reactivity under the same conditions, the addition of LiCl can overcome this problem with no ligand necessary (Scheme 2).⁴ Under these modified conditions, various Grignard reagents could be coupled and several

functional groups tolerated. However, methyl Grignard reagents were unreactive. Secondary and tertiary Grignard reagents did not react either.



Scheme 2. Examples of different Grignard reagents

References

1. Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Green Chemistry Center, Peking University, Beijing 100871 and State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China. Support of this work by Peking University and the grant from National Sciences of Foundation of China (Nos. 20672006, 20821062) and the "973" Project from National Basic Research Program of China (2009CB825300) is gratefully acknowledged. E-mail: zshi@pku.edu.cn
2. Ruberu, S. R.; Fox, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 6310–6317.
3. Hans, M.; Delaude, L. *Org. Synth.* **2010**, *87*, 77–87.
4. Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656–14657.

Appendix

Chemical Abstracts Nomenclature (Registry Number)

Sodium hydride (60% in oil dispersion): Sodium Hydride; (7646-69-7)

2-Tetralone: 2(1H)-Naphthalenone, 3,4-dihydro-; (530-93-8)

Pivaloyl chloride: Pivalyl chloride; (3282-30-2)

Iron (II) chloride: iron dichloride; (7758-94-3)

1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride; (173035-10-4)

n-HexylMgCl: *n*-Hexylmagnesium chloride; (44767-62-6)



Bi-Jie Li was born in 1985 in Hubei, China. He received his BS degree from Peking University in 2007, after which he continued his graduate studies in Professor Zhang-Jie Shi's group. He earned his PhD from Peking University in 2012 from Professor Zhang-Jie Shi's group after his research in C-H and C-O activation. He is now taking up a postdoctoral fellowship at U.C. Berkeley with Prof. J. F. Hartwig.



Xi-Sha Zhang was born in 1988 in Henan, China. He received his BS degree from Zhengzhou University in 2010. He is currently a fourth-year graduate student with Professor Shi at Peking University.



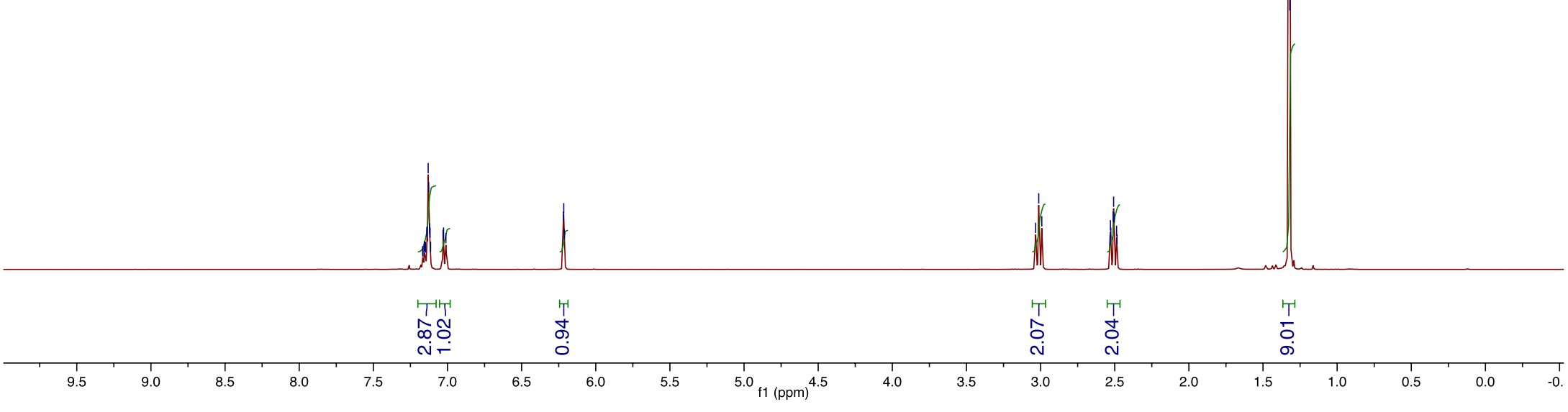
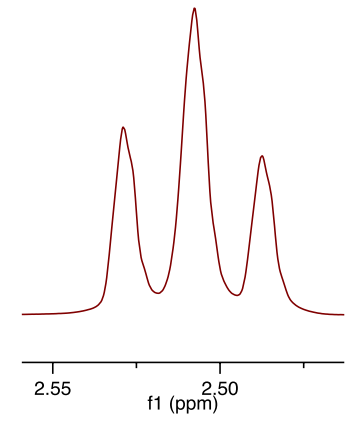
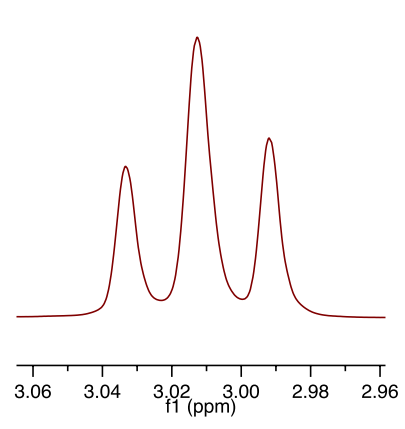
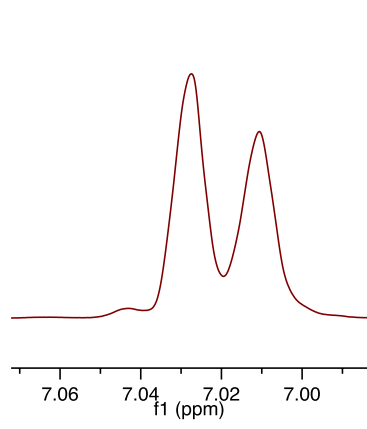
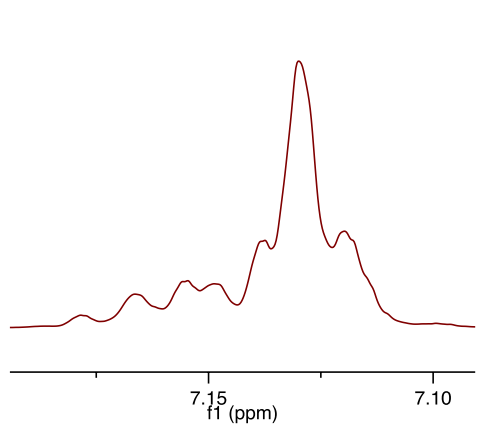
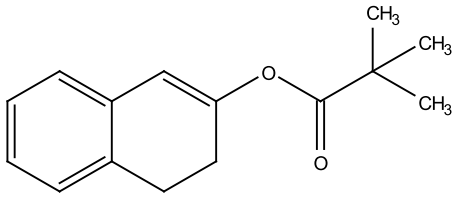
Zhang-Jie Shi obtained his BS at East China Normal University in 1996, and PhD with Professor Sheng-Ming Ma in the Shanghai Institute of Organic Chemistry (SIOC) in 2001. After his postdoctoral work with Professor Gregory L. Verdine at Harvard University and Professor Chuan He at the University of Chicago, he joined the chemistry faculty of Peking University in 2004, where he was promoted to a full Professor in 2008. His current research interests focus on transition metal catalyzed functionalization of inert chemical bonds and small molecules.

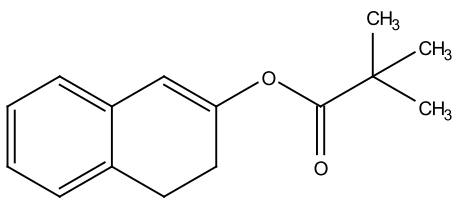


Heemal Dhanjee obtained his BA in Mathematics and Molecular and Cell Biology at the University of California, Berkeley in 2007. He subsequently moved to California State University, Northridge and performed research in organic synthesis under the supervision of Professor Thomas Minehan. He is currently pursuing graduate research at Baylor University under the guidance of Professor John L. Wood.

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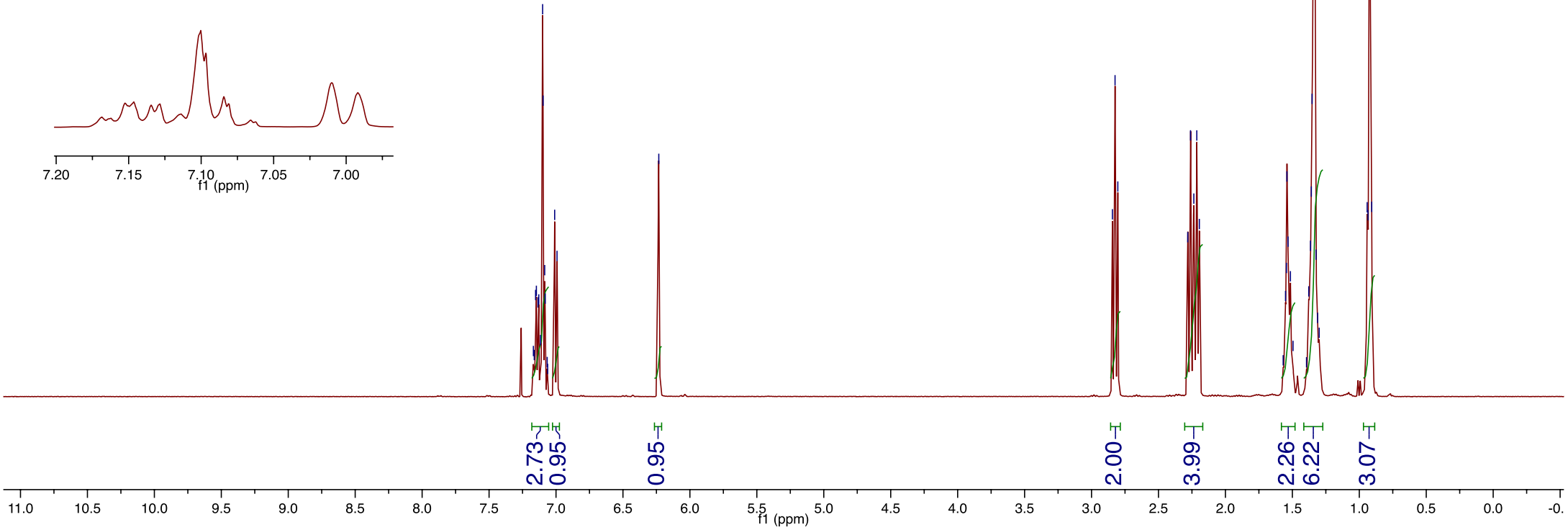
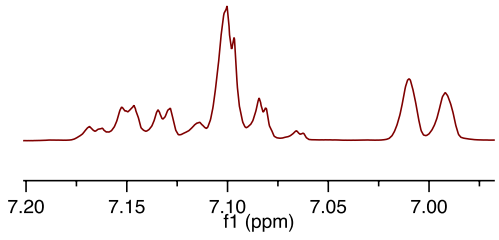
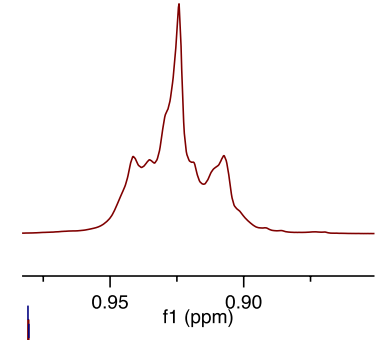
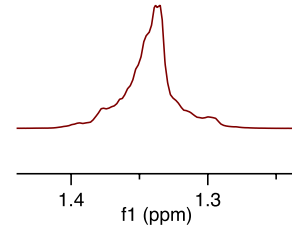
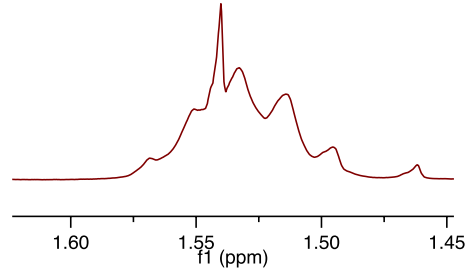
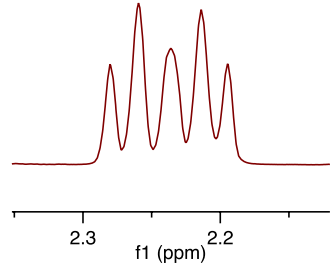
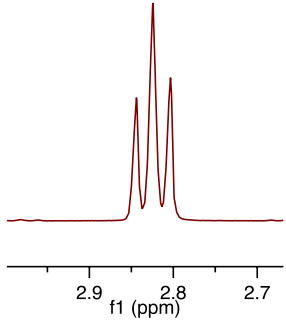
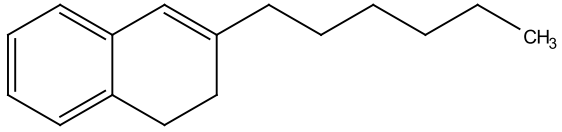
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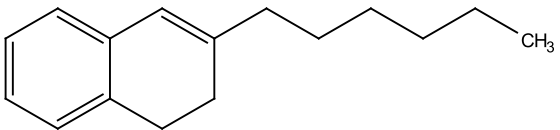
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