# Organic Syntheses

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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.

Synthesis of Quinolines by Electrophilic Cyclization of *N*-(2-Alkynyl)Anilines: 3-Iodo-4-Phenylquinoline
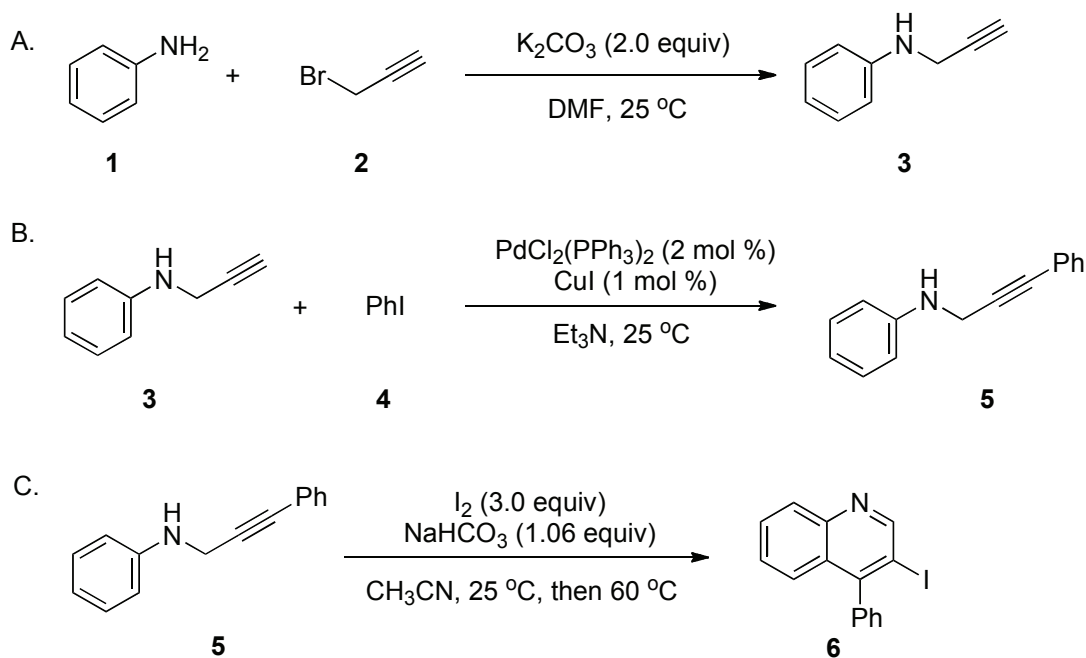
Submitted by Yu Chen, Anton Dubrovskiy, and Richard C. Larock.[1,2]
Checked by Nicolas Armanino and Erick M. Carreira.

1. Procedure

A. *N-(2-Propynyl)aniline* (**3**). An oven-dried 500-mL, three-necked, round-bottomed flask equipped with a 25-mm egg-shaped magnetic stirring bar, a thermometer, a pressure-equalizing dropping funnel, and a rubber septum is charged with aniline (**1**, 22.35 g, 240.0 mmol, 4.0 equiv) (Notes 1 and 2), potassium carbonate (16.58 g, 120.0 mmol, 2.0 equiv) (Note 3), and *N,N*-dimethylformamide (DMF, 300 mL) (Note 4). The mixture is stirred for 5 min at room temperature. A solution of propargyl bromide (**2**, 7.14 g, 80% solution in toluene, 6.68 mL, 60.0 mmol, 1.0 equiv) (Note 5) in *N,N*-dimethylformamide (DMF, 25 mL) is added to the flask dropwise (Note 6). The reaction mixture is stirred at room temperature for 6 h (Note 7). The reaction mixture is filtered under reduced pressure (Note 8). The original three-necked round-bottomed flask and the Büchner funnel are rinsed with 150 mL of diethyl ether. The combined filtrate is transferred to a 1-L separatory funnel and washed with brine (300 mL). The aqueous phase is

extracted twice with diethyl ether (2 × 150 mL). The combined organic phases are washed with water (100 mL) and dried over anhydrous magnesium sulfate (MgSO₄) (Note 9), filtered through a fritted glass funnel, rinsed with diethyl ether (50 mL), and concentrated by rotary evaporation (25 °C, 40 mmHg) to give a dark brown oil. The residue is purified by flash column chromatography on silica gel (Note 10) to afford 6.52–6.85 g (83–87%) of *N*-(2-propynyl)aniline (**3**) as a light yellow oil (Note 11).

B. *N-(3-Phenyl-2-propynyl)aniline* (**5**)*.* An oven-dried 500-mL, three-necked round-bottomed flask equipped with a 25-mm egg-shaped magnetic stirring bar, a thermometer, and two rubber septa (Note 12) is flushed with argon (Note 13) and charged with *N*-(2-propynyl)aniline (**3**, 4.76 g, 36.28 mmol, 1.0 equiv), triethylamine (225 mL) (Note 14), iodobenzene (**4**, 4.47 mL, 8.15 g, 40.0 mmol, 1.1 equiv) (Note 15) and bis(triphenylphosphine)palladium dichloride (510 mg, 0.73 mmol, 0.02 equiv) (Note 16). Copper iodide (69 mg, 0.36 mmol, 0.01 equiv) (Note 17) is then added in a single portion to the flask. The reaction mixture is stirred at room temperature for 6 h (Notes 18 and, 19). The reaction mixture is filtered under reduced pressure (Note 20). The original three-necked, round-bottomed flask and the Büchner funnel are rinsed with 150 mL of diethyl ether. The combined organic phases are transferred to a 1-L separatory funnel and washed with brine (300 mL). The aqueous phase is extracted twice with diethyl ether (2 × 100 mL). The combined organic phases are dried over anhydrous magnesium sulfate (MgSO₄) (Note 21), filtered through a fritted glass funnel, rinsed with diethyl ether (50 mL), and concentrated by rotary evaporation (25 °C, 40 mmHg) to give a dark brown oil. The residue is purified by flash column chromatography on silica gel (Note 22) to afford 6.48–6.61 g (86–88%) of *N*-(3-phenyl-2-propynyl)aniline (**5**) as a light yellow oil (Note 23).

C. *3-Iodo-4-phenylquinoline* (**6**). An oven-dried, 500-mL, three-necked, round-bottomed flask equipped with a 25-mm egg-shaped magnetic stirring bar, a thermometer, and two rubber septa is charged with *N*-(3-phenyl-2-propynyl)aniline (**5**, 5.23 g, 25.23 mmol, 1.0 equiv), sodium bicarbonate (2.24 g, 26.67 mmol, 1.06 equiv) (Note 24) and acetonitrile (126 mL) (Note 25). The reaction mixture is stirred at room temperature for 20 min. One rubber septum is replaced with a pressure-equalizing dropping funnel. A warm solution of iodine (19.2 g, 75.65 mmol, 3.0 equiv) (Note 26) in acetonitrile (126 mL) is added to the reaction mixture through the pressure-equalizing dropping funnel over 4 h with vigorous stirring (Notes

27, 28 and 29). An additional 35 mL of acetonitrile is added at the end of the addition to rinse the crystallized iodine from the pressure-equalizing dropping funnel into the reaction flask. The reaction mixture is stirred at room temperature for 18 h. The pressure-equalizing dropping funnel is replaced with a reflux condenser. The reaction flask is immersed in a preheated oil bath (at 70 °C) and the reaction mixture is stirred at 60 ºC (temperature inside the reaction flask) for an additional 26 h (Note 30). The reaction mixture is cooled down to room temperature. The reflux condenser is replaced with a pressure-equalizing dropping funnel. An aqueous solution of $Na_2S_2O_3·5H_2O$ (37.55 g, 151.29 mmol, 2 equiv with respect to iodine, in 150 mL water) is added to the reaction mixture through the pressure-equalizing dropping funnel over 6 min with stirring (Notes 31 and 32). After the addition, the reaction mixture is stirred at room temperature for 20 min. The resulting mixture is transferred into a 1-L separatory funnel and extracted with 100 mL of diethyl ether. The aqueous phase is further extracted three times with diethyl ether (100 mL, 50 mL, and 25 mL). The combined organic phases are dried over anhydrous magnesium sulfate ($MgSO_4$) (Note 33), filtered through a fritted glass funnel, rinsed with diethyl ether (4 × 50 mL), and concentrated by rotary evaporation (25 °C, 40 mm Hg) to give a dark orange powder. The residue is purified by recrystallization from hot 2-propanol (Notes 34, 35 and 36) or by flash column chromatography on silica gel (Note 37) to afford 5.46 g (65%) of 3-iodo-4-phenylquinoline (**6**) as a light orange powder (Notes 38 and 39).

2. Notes

1. Aniline (**1**, 99.9%) was purchased from Fisher Scientific and used as received. The checkers used aniline (reagent plus 99%) purchased from Aldrich Chemical Co., Inc.

2. A variety of ratios of aniline/propargyl bromide have been investigated. An excess of aniline (4 equiv to propargyl bromide) was found the most beneficial for the monoalkylation of aniline.

3. Potassium carbonate (K_2CO_3, 99.5%, anhydrous) was purchased from Fisher Scientific and used as received. The checkers used potassium carbonate (ACS) from Merck.

4. *N,N*-Dimethylformamide (DMF, 99.8%) was purchased from Fisher Scientific and used as received. The checkers used DMF (ACS reagent) from Aldrich Chemical Co., Inc.

5.   A solution of propargyl bromide (80% in toluene) was purchased from Aldrich Chemical Co., Inc. and used as received.

6.   During the addition of propargyl bromide (**2**), the internal temperature of the reaction mixture increased from 25 to 29 °C and then gradually decreased to 25 °C. The addition took 10 min.

7.   The authors recommend that the reaction be stopped after 6 hours in order to obtain a high yield of the desired monoalkylated aniline. Longer reaction times cause the generation of undesired dialkylated aniline.

8.   The reaction mixture was filtered through the sintered glass Buchner funnel under 32 mmHg pressure.

9.   Anhydrous magnesium sulfate was purchased from Fisher Scientific and used as received. To ensure proper dryness, 25 g of $MgSO_4$ were added to the organic phase and the resulting mixture was kept at room temperature for 20 min with occasional stirring.

10. Column chromatography was performed on a 5-cm diameter column, wet-packed with 300 g of silica gel (230-400 mesh) in hexanes. The length of silica gel was 35 cm. Dichloromethane (5 mL) was used to ensure the complete transfer of the crude compound onto the column. The following solvent systems were used: hexane (300 mL), hexane/ethyl acetate (30/1, 1000 mL), hexane/ethyl acetate (25/1, 1000 mL), hexane/ethyl acetate (20/1, 1500 mL). After elution of 1.2 L of solvent, 90 fractions of 25 mL were collected. Fractions 26 through 90 contained the desired product and were concentrated by rotary evaporation (40 °C bath, 20 mmHg), and dried under a vacuum (0.6 mmHg) at 25 °C with stirring for 20 h until a constant weight (6.52–6.85 g) was obtained. Fractions 20-25 contained a mixture of the desired product and dialkylated aniline, and fractions after 90 contained a mixture of the desired product and the unreacted aniline. These fractions were not collected.

11. The physical properties of *N*-(2-propynyl)aniline (**3**) follow: R_f = 0.41 (TLC analysis performed on glass-backed silica gel TLC plates with a UV254 indicator, obtained from Sorbent Technologies; 10:1 hexane/ethyl acetate is used as the eluent; the product is visualized with a 254 nm UV lamp); IR (thin film): 3401, 3287, 1602, 1504, 1315, 1259, 751, 693 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.25 (t, *J* = 2.4 Hz, 1 H), 3.92 (s, br, 1 H), 3.97 (d, *J* = 2.4 Hz, 2 H), 6.70 – 6.76 (m, 2 H), 6.82 (tt, *J* = 7.3, 1.1 Hz, 1 H),7.21 – 7.31 (m, 2 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 33.7, 71.3, 81.0, 113.6, 118.7, 129.3, 146.8; HRMS *m/z* calcd. for C$_9$H$_{10}$N [M+H]$^+$, 132.0808,

found 132.0806; Anal. Calcd. for C_9H_9N: C, 82.41; H, 6.92; N, 10.68; found: C, 82.33; H, 6.97; N, 10.62.

12. One rubber septum is fitted with an argon inlet.

13. Dry argon (99.996%) was flushed through the flask for 2 min.

14. Triethylamine (Et_3N, 99.5%) was purchased from Aldrich Chemical Co., Inc. and used as received.

15. Iodobenzene (PhI, 98%) was purchased from Aldrich Chemical Co., Inc. and used as received.

16. Bis(triphenylphosphine)palladium dichloride [$PdCl_2(PPh_3)_2$] was donated by Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. and used as received. The checkers used bis(triphenylphosphine)palladium dichloride [$PdCl_2(PPh_3)_2$] (99%) from Aldrich Chemical Co., Inc..

17. Copper iodide (CuI, 99.5%) was purchased from Aldrich Chemical Co., Inc. and used as received.

18. One hour after the reaction had started, the internal temperature of the reaction mixture had increased from 25 to 30 °C with a suspension of yellow flakes present in the solution. After an additional hour, the internal temperature decreased to 25 °C.

19. Completion of the reaction was judged by the disappearance of the starting material (**3**) on TLC (SiO_2, eluent: 10:1 hexane/ethyl acetate, R_f = 0.41).

20. The reaction mixture was filtered through the sintered glass Büchner funnel under 32 mmHg pressure.

21. Anhydrous magnesium sulfate was purchased from Fisher Scientific and used as received. To ensure proper dryness, 20 g of $MgSO_4$ were added to the organic phase and the resulting mixture was kept at room temperature for 20 min with occasional stirring.

22. Column chromatography was performed on a 5 cm diameter column, wet-packed with 385 g of silica gel (230-400 mesh) in hexanes. The length of silica gel was 41 cm. Dichloromethane (10 mL) was used to ensure the complete transfer of the material onto the column. The following solvent systems were used: hexane (125 mL), hexane/ethyl acetate (80/1, 400 mL), hexane/ethyl acetate (60/1, 300 mL), hexane/ethyl acetate (50/1, 300 mL), hexane/ethyl acetate (40/1, 300 mL), hexane/ethyl acetate (30/1, 600 mL), hexane/ethyl acetate (25/1, 500 mL), hexane/ethyl acetate (20/1, 700 mL). Among the 25 mL fractions collected, fractions 84 through 129 contained the desired product and were concentrated by rotary evaporation (40 °C bath, 20 mmHg), and then dried under vacuum (0.6 mmHg) at

25 °C with stirring for 20 h until a constant weight (6.48–6.61 g) was obtained.

23. The physical properties of *N*-(3-phenyl-2-propynyl)aniline (**5**) follow: R$_f$ = 0.40 (TLC analysis performed on glass-backed silica gel TLC plates with a UV254 indicator, obtained from Sorbent Technologies; 10:1 hexane/ethyl acetate is used as the eluent; the product is visualized with a 254 nm UV lamp); IR (thin film): 3388, 3051, 2924, 1601, 1499, 1442, 1252, 752, 690 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 4.01 (s, br, 1 H), 4.19 (s, 2 H), 6.75 – 6.80 (m, 2 H), 6.82 (tt, *J* = 7.3, 1.0 Hz, 1 H), 7.23 – 7.34 (m, 5 H), 7.39 – 7.47 (m, 2 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 34.6, 83.3, 86.3, 113.6, 118.5, 122.9, 128.2, 128.3, 129.2, 131.7, 147.1; HRMS *m/z* calcd for C$_{15}$H$_{14}$N [M+H]$^+$, 208.1121, found 208.1125; Anal. calcd. for C$_{15}$H$_{13}$N: C, 86.92; H, 6.32; N, 6.76; found: C, 86.82; H, 6.37; N, 6.78.

24. Sodium bicarbonate (NaHCO$_3$, certified A.C.S.) was purchased from Fisher Scientific and used as received. The checkers used sodium hydrogen carbonate (ACS) from Merck.

25. Acetonitrile (CH$_3$CN, 99.8%, anhydrous) was purchased from Aldrich Chemical Co., Inc. and used as received.

26. Iodine (I$_2$, 99.9%, certified A.C.S.) was purchased from Fisher Scientific (submitters) or Aldrich Chemical Co., Inc. (checkers) and was purified by sublimation at 1.5 mmHg, 90 °C. The resublimed iodine was ground into a powder before use.

27. The iodine was dissolved in acetonitrile by heating with a heat gun. The latter was used to keep the iodine solution in the dropping funnel warm, thus preventing crystallization of the iodine and the funnel from plugging up. *Caution! Heat guns contain an electrically-heated filament that pose an ignition and spark hazard. Heat guns should only be used in a fume hood and care must be taken to ensure that no flammable vapors are present when heat guns are in use.*

28. During the addition of iodine to the reaction mixture, the internal temperature of the reaction mixture increased from 25 to 28 °C.

29. Slow addition of the solution of iodine in acetonitrile to the reaction mixture prevents the formation of undesired side products, which cause a significant problem in purification of the desired product.

30. Reaction has been monitored by executing ^{1}H NMR spectrum of ~0.10 mL of the reaction mixture extracted with diethyl ether from a saturated aqueous Na$_2$S$_2$O$_3$ solution. The conversion did not increase after

reaching a maximum of 86% as based on the integrations of the multiplet at 6.90 – 6.70 ppm (3H of **5**) and the doublet at 8.15 ppm (1H of **6**).

31. Sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$, certified A.C.S.) was purchased from Fisher Scientific and used as received.

32. During the addition of the sodium thiosulfate solution to the reaction mixture the internal temperature of the reaction mixture decreased from 25 to 19 °C. The solution turned from purple to slightly pink after the addition.

33. Anhydrous magnesium sulfate was purchased from Fisher Scientific and used as received. To ensure proper dryness, 20 g of $MgSO_4$ were added to the organic phase and the resulting mixture was kept at room temperature for 20 min with occasional stirring.

34. 2-Propanol (ACS) was purchased from Scharlab S.L. and used as received.

35. The crude material was charged in a 100-mL pear-shaped flask equipped with a 25-mm magnetic stirring bar and a reflux condenser and suspended in 2-propanol (65 mL). The mixture was then heated on an oil bath (80 °C) for 10 min until all the solids dissolved. The oil bath was removed. The mixture was allowed to slowly cool to room temperature with stirring and then placed in a freezer (–20 °C) for 12 h to complete crystallization. The solids were then filtered using a sintered glass Büchner funnel and washed with ice-cold 2-propanol (10 mL). The collected solids were dried under vacuum ((0.6 mmHg) at 25 °C with stirring for 20 h until a constant weight (5.46 g) was obtained.

36. Recrystallization may also be performed from an ethanol (170 mL):water (120 mL) mixture with similar results.

37. The submitters provide conditions for purifying the crude compound by chromatography: Column chromatography was performed on a 7 cm diameter column, wet-packed with 367 g of silica gel (230-400 mesh) in hexanes. The length of silica gel was 24 cm. Dichloromethane (25 mL) was used to ensure the complete transfer of the crude material onto the column. The following solvent systems were used: chloroform/hexane (1/2, 3.5 L), chloroform/hexane (1/1, 9 L). Among the 50 mL fractions collected, fractions 111 through 250 contained the desired product and were concentrated by rotary evaporation (40 °C bath, 20 mmHg), and then dried under vacuum ((0.6 mmHg) at 25 °C for 20 h until a constant weight (5.43 g) was obtained. Fractions 80 through 110 contained the mixture of

the desired product and unreacted *N*-(3-phenyl-2-propynyl)aniline (yields by crude ^{1}H NMR are 13 and 20%, respectively).

38. On smaller scale (13.0 mmol) the checkers obtained a higher yield (71 %) after chromatographic purification.

39. The physical properties of 3-iodo-4-phenylquinoline (**6**) follow: R_f = 0.34 (TLC analysis performed on glass-backed silica gel TLC plates with a UV254 indicator, obtained from Sorbent Technologies; 10:1 hexane/ethyl acetate is used as the eluent; the product is visualized with a 254 nm UV lamp); mp 130–132 °C; IR (thin film) cm^{-1}: 3063, 1679, 1566, 1483, 1437, 1375, 1230, 1095, 845, 758, 698, 668; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.27 – 7.32 (m, 2 H), 7.41 – 7.51 (m, 2 H), 7.52 – 7.61 (m, 3 H), 7.74 (ddd, *J* = 8.4, 6.6, 1.7 Hz, 1 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 9.27 (s, 1 H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 96.30, 126.71, 127.38, 128.64, 128.66, 128.95, 129.05, 129.47, 129.70, 140.33, 147.16, 152.35, 156.59; HRMS *m/z* calcd for C$_{15}$H$_{10}$IN [M]$^+$, 330.9858, found 330.9854; Anal. calcd for C$_{15}$H$_{10}$IN: C, 54.41; H, 3.04; N, 4.23; found: C, 54.13; H, 3.14; N, 4.13.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.
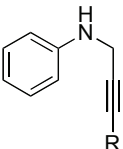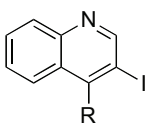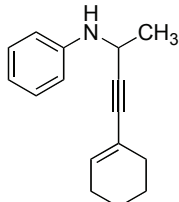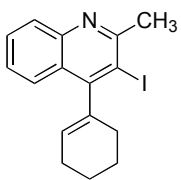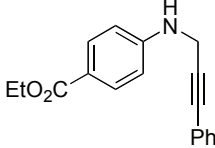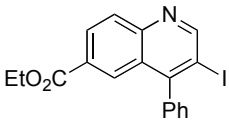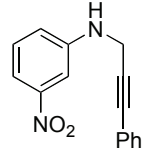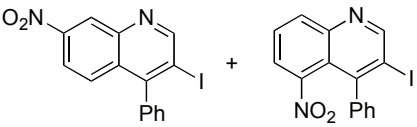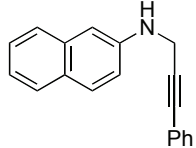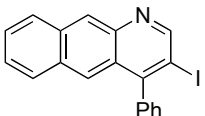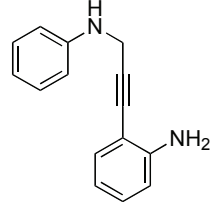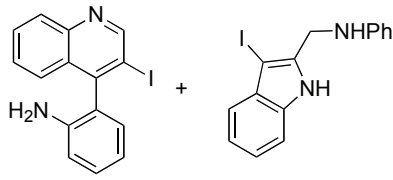
3. Discussion

The electrophile-promoted intramolecular cyclization of alkynes containing proximate nucleophilic functional groups is an efficient synthetic method for the construction of a wide variety of carbocycles and heterocycles.[3] This synthetic method provides a facile protocol for the synthesis of functionalized cyclic compounds by regioselective addition of the nucleophile and the electrophile across the alkyne carbon-carbon triple bond. The preparation of 3-iodo-4-phenylquinoline described here illustrates a general protocol for the iodine promoted *6-endo-dig* electrophilic cyclization of *N*-(2-alkynyl)anilines.[4] The present protocol for the synthesis of substituted quinolines includes three steps, (1) monoalkylation of the aniline amine functional group, (2) Sonogashira coupling of the *N*-propargylaniline with an aryl iodide and (3) iodine-promoted intramolecular cyclization. The monoalkylation of aniline has employed a literature

procedure with a slight modification.[5] A traditional Sonogashira coupling protocol has been used for the second step.[6] The third step is based on the protocol developed by the Larock group with a slight modification of the reaction conditions.[4]

The present procedure provides a convenient approach for the synthesis of 3-iodoquinolines under mild reaction conditions. It's noteworthy that the iodo functional group offers considerable potential for further structure elaboration, using well-known, palladium-catalyzed coupling protocols, such as Suzuki-Miyaura coupling[7] and Buchwald-Hartwig amination.[8] Besides iodine, other electrophiles have also been successfully employed in the present cyclization protocol, including iodine monochloride (Table 1, entries 2 and 4) and phenylselenyl bromide (Table 1, entry 5). A variety of functional groups are readily accommodated under the present conditions, including ester, nitro, and amino groups. (Table 1, entries 10, 11 and 13).

Table 1. Synthesis of quinolines by electrophilic cyclization of *N*-(2-alkynyl)anilines.

entry	propargylic aniline	electrophile	product(s)	% yield
1	R = Ph	I₂[a]	R = Ph	76
2		ICl[b]		83
3	R = *p*-MeOC₆H₄	I₂[a]	R = *p*-MeOC₆H₄	71
4		ICl[b]		73
5	R = *p*-MeOC₆H₄	PhSeBr[c]	R = *p*-MeOC₆H₄	74
6	R = *p*-FC₆H₄	I₂[a]	R = *p*-FC₆H₄	78
7	R = *p*-MeCOC₆H₄	I₂[a]	R = *p*-MeCOC₆H₄	57
8	R = *n*-Bu	I₂[a]	R = *n*-Bu	43
9		I₂[a]		80
10		I₂[a]		88
11		I₂[a]		8+71
12		I₂[a]		75
13		I₂[a]		55+0

[a] Reactions were run under the following conditions: 0.3 mmol of the propargylic aniline, 3 equiv of I₂, and 2 equiv of NaHCO₃ in 3 mL of CH₃CN were stirred at room temperature. [b] To 0.3 mmol of propargylic aniline and 2 equiv of NaHCO₃ in 2 mL of CH₃CN was added 2 equiv of ICl in 1 mL of CH₃CN dropwise at room temperature. [c] To 0.3 mmol of propargylic aniline and 2 equiv of NaHCO₃ in 2 mL of CH₃CN was added 2 equiv of PhSeBr in 1 mL of CH₃CN dropwise at room temperature.

This quinoline synthesis presumably proceeds by the mechanism illustrated in Scheme 1: (1) the carbon-carbon triple bond of the propargylic aniline coordinates to an iodine cation generating an iodonium intermediate **A**, (2) intramolecular electrophilic aromatic substitution by the activated alkyne at the *ortho* position of the aniline forms dihydroquinoline **B**, and (3) in the presence of I_2 or air, the dihydroquinoline **B** is oxidized to the corresponding quinoline.

Scheme 1. Proposed mechanism for the iodine-promoted, electrophilic cyclization of *N*-(2-alkynyl)anilines.
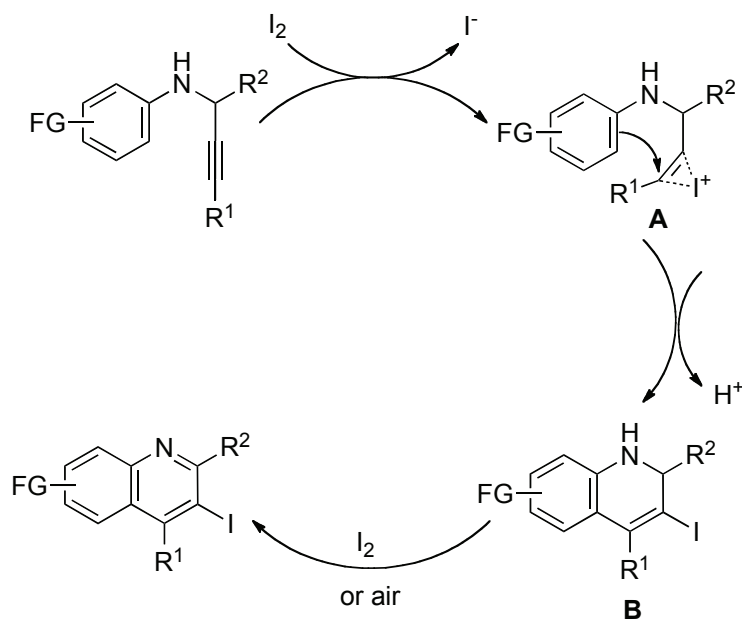
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2. The non-corresponding authors' names are in alphabetical order.
3. For reviews, see: (a) Larock, R. C. In *Acetylene Chemistry. Chemistry, Biology, and Material Science;* Diederich, F.; Stang, P. J.; Tykwinski, R. R. Eds.; Wiley-VCH: New York, NY, 2005; Vol. 2, pp 51–99. (b) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980.
4. (a) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766. (b) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177–1187.
5. Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238–3239.

6. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions;* Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 5, pp 203–229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

7. (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. (b) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

8. (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970. For reviews, see: (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Aniline; (62-53-3)

Propargyl bromide; (106-96-7)

Triethylamine; (121-44-8)

Iodobenzene; (591-50-4)

Bis(triphenylphosphine)palladium dichloride; (13965-03-2)

Copper iodide; (1335-23-5)

Iodine; (7553-56-2)

Sodium thiosulfate pentahydrate; (10102-17-7)

Richard C. Larock received his B.S. at the University of California, Davis in 1967. He then joined the group of Prof. Herbert C. Brown at Purdue University, where he received his Ph.D. in 1972. He worked as an NSF Postdoctoral Fellow at Harvard University in Prof. E. J. Corey's group and joined the Iowa State University faculty in 1972. His current research interests include aryne chemistry, electrophilic cyclization, palladium catalysis, and polymer chemistry based on biorenewable resources.
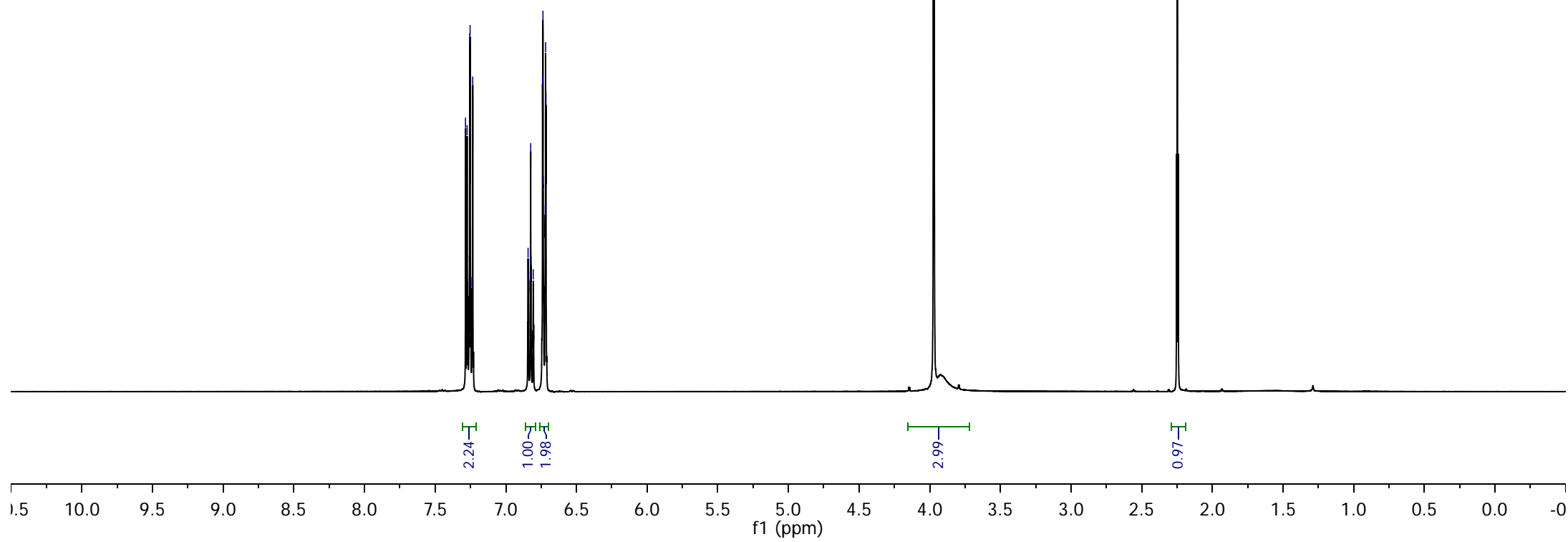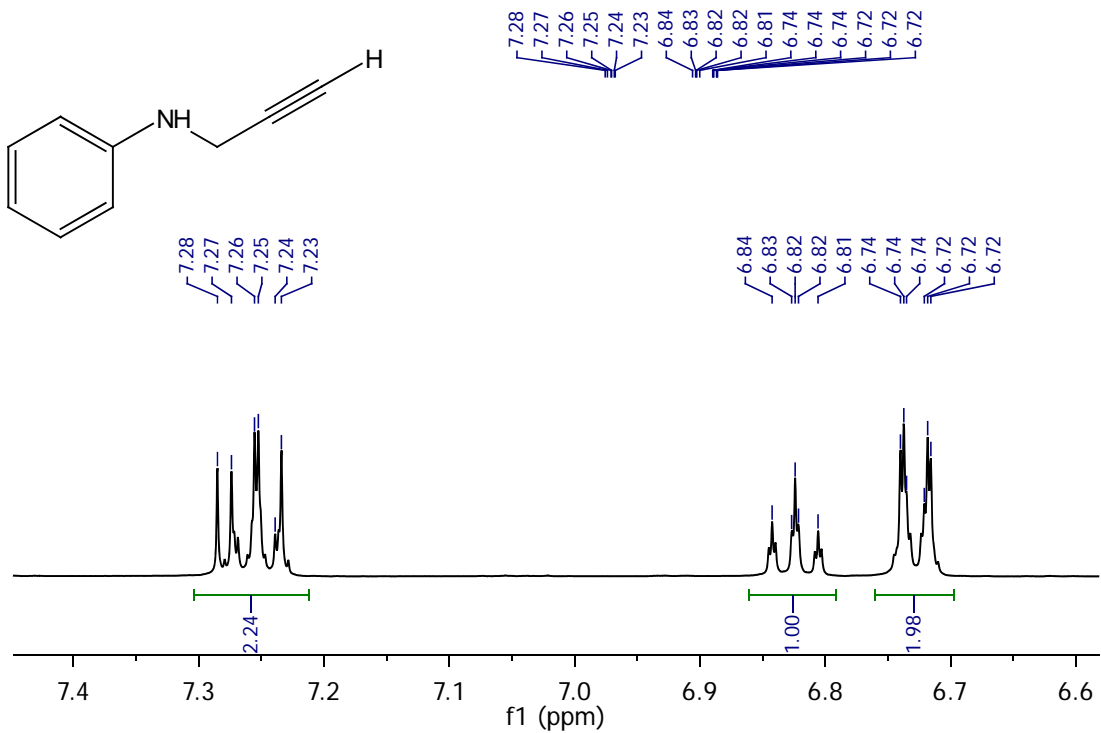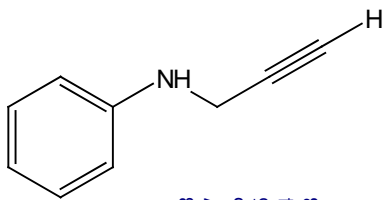
Yu Chen received his B.S. and M.S. degrees at Nankai University in China. He then joined Professor Andrei Yudin's research group at the University of Toronto working in the field of asymmetric catalysis, where he obtained his Ph.D. degree in 2005. After a two-year industrial appointment, he joined Professor Richard Larock's research group at Iowa State University as a postdoctoral fellow in 2007, working on an NIH-funded pilot-scale heterocyclic and carbocyclic library synthesis project. In 2009, he joined Queens College at City University of New York as an assistant professor. His research interests include late transition metal catalysis and asymmetric synthesis.
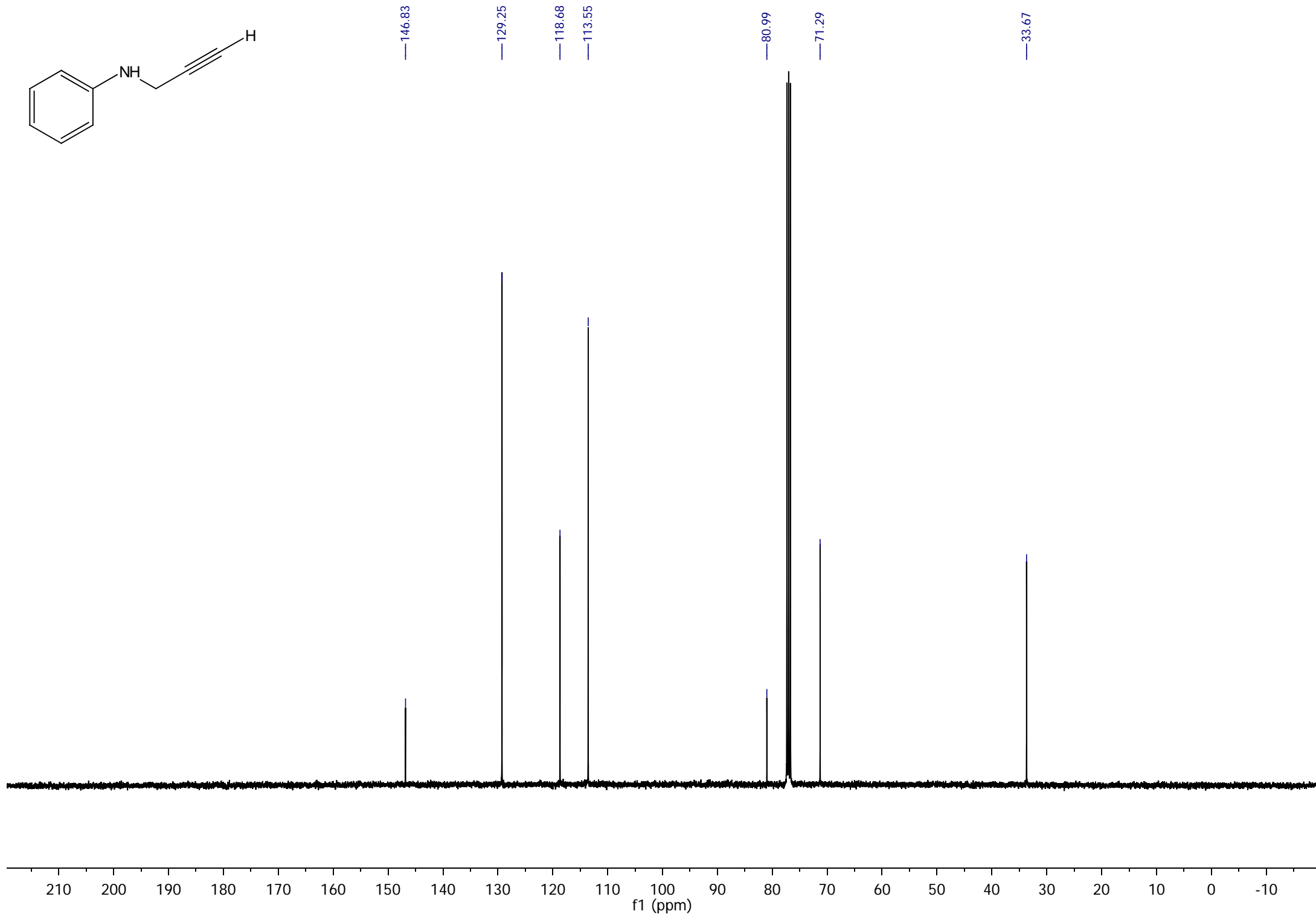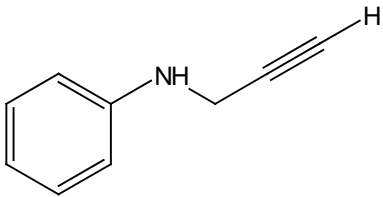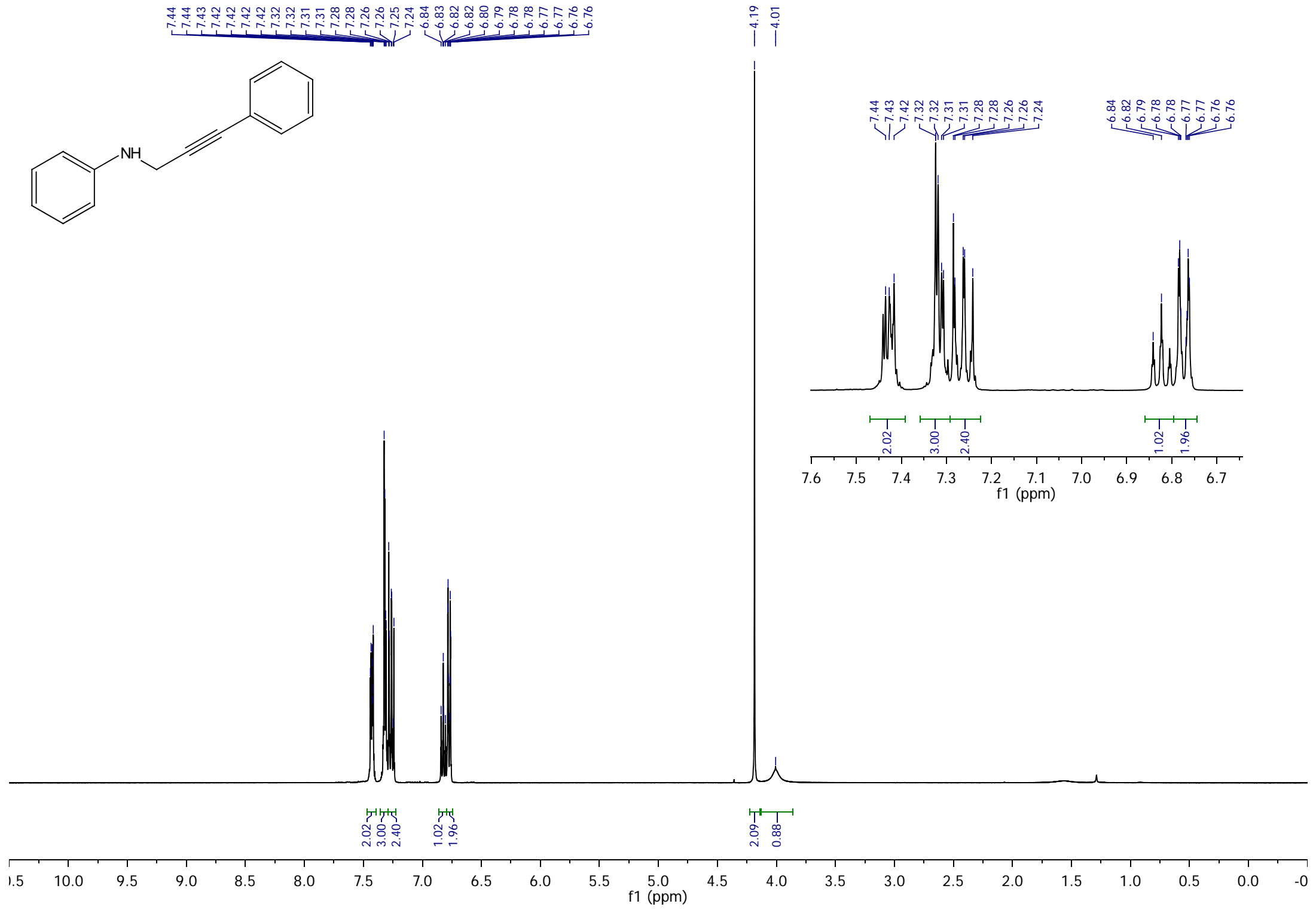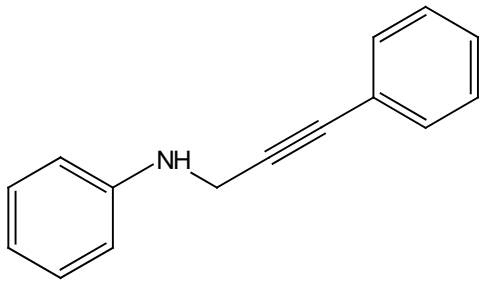
Anton V. Dubrovskiy received his Specialist (B.S./M.S.) degree at the Higher Chemical College of the Russian Academy of Sciences in Moscow, Russia in 2007. He then joined Professor Richard Larock's research group at Iowa State University, where he is currently pursuing his Ph.D. degree. His current research interest is in the development of new synthetic organic methodologies utilizing aryne intermediates.
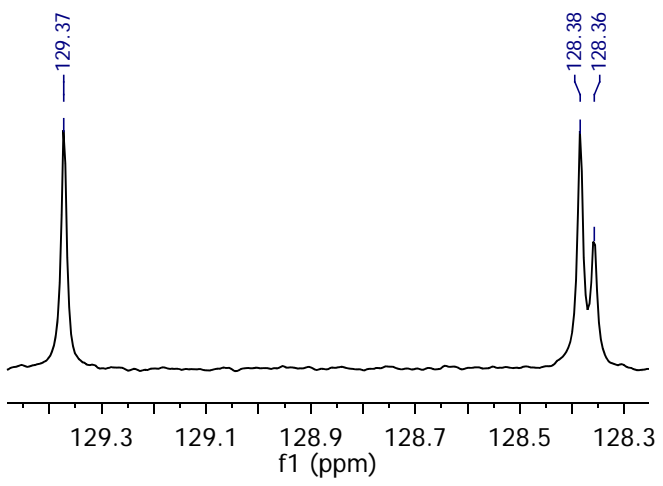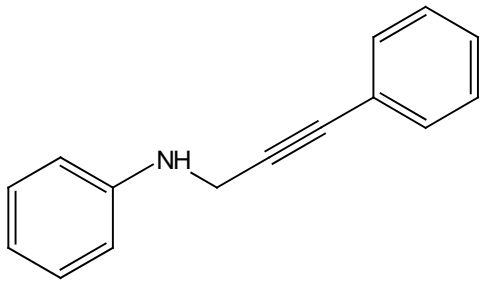
Nicolas Armanino received his B.S. and M.S. degrees at the ETH Zürich, Switzerland in 2009. He then joined Professor Erick M. Carreira's research group at the same institution to pursue his Ph.D. degree. His current research is focused on the development of novel metal-catalyzed reaction cascades for the construction of complex organic molecules.

Inset (7.4–6.6 ppm expansion):

7.28, 7.27, 7.26, 7.25, 7.24, 7.23

6.84, 6.83, 6.82, 6.81, 6.74, 6.74, 6.74, 6.72, 6.72, 6.72

Integrations: 2.24, 1.00, 1.98

Main spectrum peaks: 3.97, 2.25

Integrations: 2.24, 1.00, 1.98, 2.99, 0.97

f1 (ppm)

147.26

131.85
129.37
128.38
128.36
123.01
118.64
113.74

86.48
83.44

34.74

129.37

128.38
128.36