152.0828, calcd for $C_9H_{12}O_2$ 152.0837. In the ^1H NMR spectrum of **2c**, the two absorptions of 5.36 (dt, J = 11, 7) and 5.54 (dq, J = 11, 7) may be assigned to the two olefinic protons of the disubstituted olefinic moiety of the minor component (*Z*)-**2c** although they are not clearly separated from those of (*E*)-**2c**. Product **2c'**: IR (neat, cm^{-1}) 3090, 1800, 1700, 1640, 1300, 1120, 1005, 910, 850; ^1H NMR 1.14 (d, J = 7.0, 3 H), 2.69 (t, J = 8.5, 2 H), 2.82–2.94 (m, 3 H), 4.97 (d, J = 10.1, 1 H), 5.02 (d, J = 17.1, 1 H), 5.12 (d, J = 9.9, 1 H); MS, m/e (relative intensity) 152 (M^+, 19), 129 (47), 101 (100), 69 (47), 55 (41); HRMS, m/e 152.0816, calcd for $C_9H_{12}O_2$ 152.0837. Product **2e** (PLC, ether:hexane = 6:5 v/v): IR (neat, cm^{-1}) 3025, 1790, 1690, 1590, 1490, 1300, 1100, 960, 830, 740, 680; ^1H NMR 2.65–2.72 (m, 4 H), 2.84 (t, J = 7.3, 2 H), 5.34 (tt, J = 8.0, 2.3, 1 H), 6.18 (dt, J = 15.8, 6.2, 1 H), 6.42 (d, J = 15.7, 1 H), 7.15–7.40 (m, 5 H); MS, m/e (relative intensity) 214 (M^+, 100), 130 (33), 129 (34), 95 (41), 91 (49); HRMS, m/e 214.0972, calcd for $C_{14}H_{14}O_2$ 214.0994.

Palladium(0)-Catalyzed Reaction of Lithium 4-Hexynoate (3b) and Allyl Acetate. The reaction was carried out under nitrogen. The palladium(0) catalyst solution was prepared separately by the reaction of *n*-BuLi hexane solution (0.15 mmol) and $Pd(OAc)_2$ (0.017 g, 0.075 mmol) in THF (8 mL) containing $P(OCH_2)_3CEt$ (0.086 mL, 0.30 mmol) at room temperature for 15 min. To a stirred suspension of **3b** (0.177 g, 1.50 mmol) in MeCN (12 mL) in an 80-mL glass tube was added the above-prepared palladium(0) catalyst solution followed by allyl acetate (0.162 mL, 1.50 mmol). The glass tube was sealed by flame and was heated at 120 °C for 3 h under magnetic stirring. The reaction mixture was concentrated to give the residue which was purified twice by PLC (ether:hexane = 1:1 v/v) to give **4b** (0.087 g, 38%): IR (neat, cm^{-1}) 3075, 1790, 1700, 1640, 1300, 1120, 990, 910; ^1H NMR 1.71 (s, 3 H), 2.64–2.70 (m, 4 H), 2.82 (t, J = 8.2, 2 H), 5.02–5.09 (m, 2 H), 5.73 (ddt, J = 17.0, 10.1, 6.5, 1 H); MS, m/e (relative intensity) 152 (M^+, 100), 137 (19), 124 (23), 110 (39), 109 (82), 97 (77), 95 (54), 68 (47), 56 (50), 43 (32); HRMS, m/e 152.0809, calcd for $C_9H_{12}O_2$ 152.0837.

The reaction of lithium 4-pentynoate (**3a**) and cinnamyl acetate was carried out as described above. The product **4c** was identified as follows. Product **4c**: IR (neat, cm^{-1}) 1750, 1650, 1310, 1180, 960; ^1H NMR 1.45 (d, J = 6.6, 3 H), 3.02 (dd, J = 17.2, 7.0, 1 H), 3.16 (dd, J = 17.3, 6.5, 1 H), 4.97 (q, J = 6.8, 1 H), 5.22 (dq, J = 16.8, 1.3, 1 H), 5.24 (dq, J = 10.3, 1.2, 1H), 5.81 (s, 1 H), 5.84 (ddt, J = 17.4, 10.3, 6.6, 1 H); MS, m/e (relative intensity) 138 (M^+, 23), 95 (100), 67 (27), 68 (27), 43 (22); HRMS, m/e 138.0696, calcd for $C_8H_{10}O_2$ 138.0681.

A New Synthesis of 4-Substituted Isoquinolines

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Although 4-substituted isoquinolines are relatively rare in nature, considerable interest in the syntheses of these molecules has been generated by reports of their significant pharmacological activity.[1-4] In particular, analogues of papaverine in which the benzyl substituent is transposed from C-1 to C-4 have been attractive as synthetic targets. A strategy that has proven very effective introduces the C-4 substituent by the reaction of a 1,2-dihydroisoquinoline, which behaves as an enamine, with an aldehyde or alkyl halide.[5] Appropriate 1,2-dihydroisoquinolines can be generated in situ from 1,2,3,4-tetrahydroisoquinolines,[6] the Bobbit modification[7,8] of the Pomerantz–Fritsch reaction, or the $LiAlH_4$ reduction of isoquinoline and its salts;[9-11] but none of these appears to be as effective as the boron-activated enamine **3**, prepared by the reduction of isoquinoline (**1**) with sodium triethylborohydride (**2**). The reactions of **3** with aryl aldehydes produce superior yields of **6** (R = Ar) and can be carried out as "one-pot" operations. Aliphatic aldehydes can also be used, but the yields of **6** (R = alkyl, H) are not as high.

Scheme I

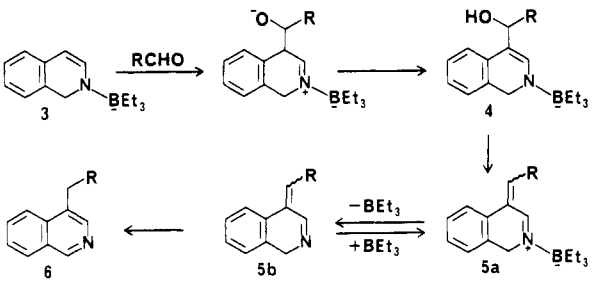
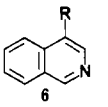
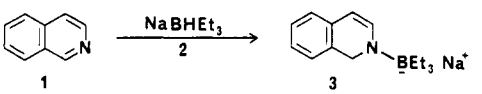


Table I. Yields and Physical Constants for Compounds 6



compd	R	% yield	mp, °C	bp, °C (mmHg)
6a	benzyl	65	117.5–118.5	
6b	2-furylmethyl	60	53.0–53.5	
6c	3,4-dimethoxybenzyl	58	83.5–84.0	
6d	4-quinolylmethyl	65	181.0–182.0	
6e	methyl	25		54–55 (0.03)
6f	*n*-propyl	28		60–61 (0.025)
6g	β-phenethyl	38		120–122 (0.03)



The formation of **3** can be followed by the disappearance of the doublet for **2** at δ −12.6 in the ^{11}B NMR spectrum and the appearance of a broad singlet for **3** at δ −6.1 as isoquinoline is added to a sample tube containing **2** (1 M in THF). The reaction is virtually instantaneous at room temperature and provides a solution of **3** that can be used directly.

Presumably, the overall mechanistic pathway leading to **6** involves electrophilic attack of the aldehyde at C-4 followed by proton transfer, conjugate loss of hydroxide, and rearomatization (Scheme I). However, it does not appear that these processes are complete prior to quenching since the workup procedure affects product

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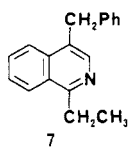
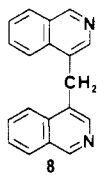
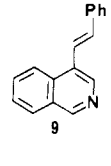
distribution. When aqueous acid is added first[12] and followed by basic peroxide, the yield of **6** decreases and a larger amount of **1** is recovered. This suggests the possibility of an acid-catalyzed retro hydroxyalkylation, which could occur by protonation at C-4 of **4** and loss of R^+CHOH. These workup conditions also lead to a small amount of a rather unexpected product having an ethyl group at C-1.[13] When benzaldehyde is used as the electrophile, the crude product mixture consists of **7** (11%),



7



8



9

1 (11%), and **6a** (78%), from which pure **6a** can be isolated in 46% yield by column chromatography and recrystallization. Under the best conditions, when the reaction is quenched directly with basic peroxide, only **1** (6%) and **6a** (94%) are present and the yield of isolated **6a** rises to 65%. In the reactions of **3** with other aromatic aldehydes (see Table I), the compositions of the crude product mixtures are similar and the yields of isolated products range from 58 to 65%.

These workup-dependent variations in product composition and the observation of **8** described below indicate that **4** and/or **5** are long-lived intermediates. The aqueous base may facilitate the conversion of **4** into **5** as well as the proton transfers required to aromatize **5**; but the peroxide is also necessary to destroy triethylborane, which otherwise interferes with product purification.

The reactions of **3** with aliphatic aldehydes are much less efficient and generate byproducts that are not chromatographically mobile. When gaseous formaldehyde (from pyrolysis of paraformaldehyde) is used, the major product is the expected 4-methylisoquinoline (**6e**), isolable by column chromatography as part of a practically inseparable binary mixture with **1**. The reaction with propanal is slightly better, but the yield of isolated pure **6f** is only 28%. The lower yields in these two cases reflect an incomplete reaction of **3** with the aldehyde as well as the difficulty in separating products from recovered isoquinoline.

Additional evidence for the mechanism in Scheme I is manifest in the observation of **8** in approximately 14% yield from the reaction of **3** with formaldehyde. This compound is formally a result of the trapping of **5** (R = H) by **3**.[14] The aromatization reaction leading to **8** in this case must involve hydrogen peroxide or atmospheric oxygen during the workup procedure.

In the reaction of **3** with phenylacetaldehyde, two major products (**6g** and **9**[15] in a 1:1 molar ratio) are obtained. The latter can be explained by a competing dehydration reaction of the intermediate **4** (R = CH_2Ph) and subsequent oxidation to the isoquinoline during workup. Catalytic hydrogenation of the mixture in 4:1 CH_3OH/EtOAc (5% Pd/C, H_2, 30 psi, 3 h) gives a reasonable yield (38%) of **6g**.

This study indicates that the reactions of **3** with aryl aldehydes should be considered a method of choice for preparing 4-substituted isoquinolines **6** (R = Ar). Although this process is not as efficient when aliphatic aldehydes are used, the method might yet be preferable in some cases to preparing complex substituted phenethylamine precursors for Pictet–Gams and similar cyclizations.

Experimental Section

All reactions were carried out by using degassed solvents under an argon atmosphere. Anhydrous tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer using $CDCl_3$ solutions with Me_4Si as an internal standard. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Mass spectra were recorded on a Finnigin OWA 1020 mass spectrometer using GC injection. Column chromatography was performed on neutral aluminum oxide (W200, activity grade Super 1) from ICN Pharmaceuticals. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

4-Benzylisoquinoline (6a). A solution of enamine **3** was prepared by dropwise addition over 1–2 min of 5.0 mL (5.0 mmol) of 1.0 M $NaBHEt_3$ in THF (Aldrich) to 0.64 g (5.0 mmol) of isoquinoline in 10 mL of THF at room temperature. The resulting yellow-brown solution was stirred for approximately 30 min at room temperature after which 0.58 g (5.5 mmol) of freshly distilled benzaldehyde was added in one portion via syringe. The color of the solution became almost black but faded to a chalky yellow over 2 h, at which time the solution was cooled to 0° C and 10 mL of 0.5 N NaOH was added. This was followed by the addition of 5.0 mL of 30% H_2O_2, and the ice bath was removed. After 3 h (rapid stirring), the colorless solution was poured into a separatory funnel containing 50 mL of water. The product was extracted with CH_2Cl_2 (1 × 30 mL and 2 × 10 mL), dried over Na_2SO_4, and isolated as a pale yellow oil after removal of solvents by rotary evaporation. The crude product was purified by column chromatography (neutral alumina, 7:3 hexane/ether) to afford 0.78 g of material, which was recrystallized from cyclohexane to give 0.72 g (65%, two crops) of pure **6a**: colorless needles, mp 117.5–118.5 °C (lit.[6] mp 119.5–120.0 °C); ^1H NMR δ 4.36 (2 H, s, CH_2), 7.14–7.28 (5 H, m, Ph), 7.54 (1 H, ddd, J = 8.1, 6.8, 1.3 Hz, H-7), 7.61 (1 H, ddd, J = 8.3, 6.8, 1.5 Hz, H-6), 7.89 (1 H, dd, J = 8.3, 1.3 Hz, H-5), 7.95 (1 H, dd, J = 8.1, 1.5 Hz, H-8), 8.41 (1 H, s, H-3), 9.17 (1 H, s, H-1); ^{13}C NMR δ 36.2 (CH_2), 123.4 (C-5), 126.3 (C-4′), 126.9 (C-7), 128.2 (C-8), 128.5 (C-2′, C-3′, C-9), 129.6 (C-4), 130.3 (C-6), 134.7 (C-10), 139.6 (C-1′), 143.7 (C-3), 151.9 (C-1).

The procedure for preparing **6a** was used to synthesize **6b–d**.

4-(2′-Furylmethyl)isoquinoline (6b). The reaction of 4.9 mmol of **3** with 5.4 mmol of furfural gave 0.94 g of crude **6b**. Column chromatography (neutral alumina, 7:3 hexane/ether) afforded 0.77 g of material, which was recrystallized from cyclohexane to give 0.62 g (60%, two crops) of **6b**: colorless needles, mp 53.0–53.5 °C; ^1H NMR δ 4.33 (2 H, br s, CH_2), 5.92 (1 H, dq, J = 3.2, 1.0 Hz, H-3′), 6.24, (1 H, dd, J = 3.2, 1.9 Hz, H-4′), 7.31 (1 H, dd, J = 1.9, 1.0 Hz, H-5′), 7.56 (1 H, ddd, J = 8.4, 6.9, 1.2 Hz, H-7), 7.67 (1 H, ddd, J = 8.7, 6.9, 1.3 Hz, H-6), 7.95 (1 H, dd,

(12) On a 5.0-mmol scale, the reaction was quenched at 0 °C by the addition of 10 mL of 3 N HCl, and the ice bath was removed. After 6 h (rapid stirring), the mixture was cooled again to 0 °C and 20 mL of 2.0 N NaOH was added. This was followed by 5 mL of 30% H_2O_2, at which point the procedure intercepted the one described for the synthesis of **6a** in the Experimental Section.

(13) Isoquinoline **7** eluted first from the column followed by recovered **1** and **6a**. **7**: ^1H NMR δ 1.44 (3 H, t, J = 7.6 Hz, CH_3), 3.30 (2 H, q, J = 7.6 Hz, CH_2CH_3), 4.30 (2 H, s, CH_2), 7.14–7.26 (5 H, m, Ph), 7.50 (1 H, ddd, J = 8.2, 6.8, 1.4 Hz, H-7), 7.55 (1 H, ddd, J = 8.3, 6.8, 1.5 Hz, H-6), 7.87 (1 H, ddd, J = 8.3, 1.4, 0.7 Hz, H-5), 8.13 (1 H, ddd, J = 8.2, 1.5, 0.7, Hz, H-8), 8.32 (1 H, s, H-3); ^{13}C NMR δ 13.5 (CH_3), 28.3 (CH_2CH_3), 36.2 (CH_2), 124.2 (C-5), 125.7 (C-8), 126.2 (C-4′), 126.4 (C-7), 126.5 (C-9), 127.8 (C-4), 128.4 (C-2′, C-3′), 129.7 (C-6), 135.1 (C-10), 139.9 (C-1′), 142.5 (C-3), 162.1 (C-1). An analogous product, 1-ethyl-4-(2′-furylmethyl)isoquinoline, was isolated from the reaction of **3** with furfural when the acidic quenching procedure[12] was used. The mechanistic origin of these products has not been elucidated.

(14) No products analogous to **8** were seen in any other reactions. The production of **8** may be a consequence of the method for introducing the electrophile. Formaldehyde was bubbled slowly through a solution of **3** while in the other cases, the electrophile was added rapidly all at once.

(15) The ^1H NMR signals for H-1 and H-3 of **9** are reported to appear at δ 8.41 and 7.15 ($CDCl_3$), respectively, in: Konno, S.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1981**, *29*, 3554. These values are incorrect and should be δ 9.11 (H-1) and 8.72 (H-3). In the same reference, the ^1H NMR signal for H-3 of **6g** is reported to be δ 8.83. The actual value is δ 8.31.

J = 8.4, 1.3 Hz, H-8), 7.96 (1 H, dd, J = 8.7, 1.2 Hz, H-5), 8.42 (1 H, s, H-3), 9.17 (1 H, s, H-1); ^{13}C NMR δ 29.1 (CH_2), 106.5 (C-3′), 110.2 (C-4′), 122.9 (C-5), 126.8 (C-7), 127.1 (C-4), 128.0 (C-8), 128.2 (C-9), 130.2 (C-6), 134.4 (C-10), 141.2 (C-5′), 143.2 (C-3), 151.9 (C-1), 153.0 (C-2′). Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30. Found: C, 80.18; H, 5.28.

4-(3′,4′-Dimethoxybenzyl)isoquinoline (6c). The reaction of 4.3 mmol of **3** with 4.5 mmol of 3,4-dimethoxybenzaldehyde gave 1.19 g of crude **6c**. Column chromatography (neutral alumina, 7:3 hexane/ether) afforded 0.71 g of material, which was recrystallized from cyclohexane to give 0.68 g (58%, two crops) of pure **6c**: colorless needles, mp 83.5–84.0 °C; ^{1}H NMR δ 3.78 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.33 (2 H, s, CH_2), 6.71 (1 H, dd, J = 8.0, 2.0 Hz, H-5′), 6.73 (1 H, d, J = 2.0 Hz, H-2′), 6.75 (1 H, d, J = 8.0 Hz, H-6′), 7.57 (1 H, ddd, J = 8.0, 6.9, 1.2 Hz, H-7), 7.65 (1 H, ddd, J = 8.4, 6.9, 1.5 Hz, H-6), 7.93 (1 H, dd, J = 8.4, 1.2 Hz, H-5), 7.98 (1 H, dd, J = 8.0, 1.5 Hz, H-8), 8.40 (1 H, s, H-3), 9.18 (1 H, s, H-1); ^{13}C NMR δ 35.8 (CH_2), 55.7 (OCH_3), 111.2 (C-5′), 111.7 (C-2′), 120.4 (C-6′), 123.2 (C-5), 126.7 (C-7), 128.0 (C-8), 128.4 (C-9), 129.6 (C-4), 130.1 (C-6), 132.0 (C-1′), 134.6 (C-10), 143.3 (C-3), 147.4 (C-3′ or C-4′), 148.9 (C-3′ or C-4′), 151.9 (C-1). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.28; H, 6.19.

4-(4′-Quinolylmethyl)isoquinoline (6d). The reaction of 1.2 mmol of **3** with 1.3 mmol of 4-quinolinecarboxaldehyde gave 0.28 g of crude semisolid, which was recrystallized from THF to give 0.21 g (65%, two crops) of pure **6d**: mp 181.0–182.0 °C; ^{1}H NMR δ 4.78 (2 H, s, CH_2), 6.78 (1 H, d, J = 4.5 Hz, H-3′), 7.57–7.64 (3 H, m, H-7, H-6′, H-7′), 7.72–7.77 (2 H, m, H-6, H-5′), 8.01–8.05 (1 H, m, H-8′), 8.15 (1 H, dd, J = 8.5, 1.3 Hz, H-5), 8.18 (1 H, dd, J = 8.6, 1.3 Hz, H-8), 8.33 (1 H, s, H-3), 8.68 (1 H, d, J = 4.5 Hz, H-2′), 9.24 (1 H, s, H-1); ^{13}C NMR δ 32.0 (CH_2), 120.9 (C-3′), 122.7 (C-5′), 122.9 (C-5), 129.1 (C-6), 130.2 (C-8), 134.5 (C-10), 143.8 (C-3), 144.9 (C-4′), 147.9 (C-9′), 150.0 (C-2′), 152.2 (C-1), and signals at δ 126.6, 127.0, 127.1 (2 C), 128.2, and 130.5 that could not be assigned. Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22. Found: C, 84.16; H, 5.34.

4-Methylisoquinoline (6e) and Bis(4′-isoquinolyl)methane (8). Enamine **3** (5.0 mmol) in THF was prepared as described earlier. Paraldehyde was heated in a side-arm test tube equipped with a gas-delivery system, and gaseous formaldehyde was allowed to bubble through the stirred solution of **3** for 10 min at room temperature. After 4 h, the standard oxidation, workup, and column chromatography (neutral alumina, 7:3 hexane/ether) procedures afforded 0.27 g of a mixture containing **6e** (57%) and **1** (43%). The ^{13}C NMR spectrum of a pure sample of **6e**, obtained by repeated column chromatography of the mixture, was in excellent agreement with that reported by Smith:[16] δ15.8 (CH_3), 123.1 (C-5), 126.9 (C-7), 127.3 (C-4), 128.1 (C-8), 128.2 (C-9), 130.2 (C-6), 135.3 (C-10), 142.7 (C-3), 151.0 (C-1).

Further elution of the column with pure ether afforded 0.10 g of material, which was recrystallized from cyclohexane to give 0.07 g of pure **8**: yellow needles, mp 176.0–177.0 °C; ^{1}H NMR δ 4.76 (2 H, s, CH_2), 7.62 (2 H, ddd, J = 8.0, 6.9, 1.2 Hz, H-7), 7.69 (2 H, ddd, J = 8.3, 6.9, 1.5 Hz, H-6), 7.97 (2 H, br dd, J = 8.3, 1.2 Hz, H-5), 8.01 (2 H, br dd, J = 8.0, 1.5 Hz, H-8), 8.18 (2 H, s, H-3), 9.19 (2 H, s, H-1); ^{13}C NMR δ 30.4 (CH_2), 122.6 (C-5), 126.9 (C-7), 128.0 (C-4 or C-9), 128.1 (C-4 or C-9), 128.2 (C-8), 130.5 (C-6), 134.5 (C-10), 143.3 (C-3), 151.8 (C-1). Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.60; H, 5.23; N, 10.29.

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Registry No. 1, 119-65-3; **3**, 114273-47-1; **6a**, 10166-05-9; **6b**, 114273-40-4; **6c**, 114273-41-5; **6d**, 114273-42-6; **6e**, 1196-39-0; **6f**, 114273-43-7; **6q**, 80998-95-4; **7**, 114273-44-8; **8**, 114273-45-9, 112370-05-5; EtCHO, 123-38-6; $PhCH_2CHO$, 122-78-1; benzaldehyde, 100-52-7; furfural, 98-01-1; 3,4-dimethoxybenzaldehyde, 120-14-9; 4-quinolinecarboxaldehyde, 4363-93-3; 1-ethyl-4-(2′-furylmethyl)isoquinoline, 114273-46-0.

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A Mild Synthesis of 1,3-Diynes

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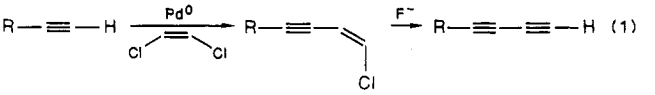
A substantial number of conjugated polyacetylenes, often having antibacterial or antifungal activity, have been isolated from Basidiomycetes fungi and from higher plants of the Compositae family.[1] Despite their frequent occurrence, few methods are available for the synthesis of terminal conjugated polyacetylenes, especially those possessing base-sensitive functionality.[2] The most widely used method is a modification of the Cadiot–Chodkiewicz reaction in which an alkynylcopper is coupled with a 1-bromoacetylene of the type BrC≡CR, where R is $SiMe_3$ or C(OH)R′R″. The resulting diyne can then be deprotected with alkali to liberate the terminal acetylene.[3] However, the yields of this sequence are moderate and byproducts are frequently isolated, although improved yields have been reported employing preformed copper(I) acetylides.[4]

We now report a mild two-step synthesis of 1,3-diynes from terminal acetylenes which is compatible with a wide range of functional groups, including base-sensitive ones. The first step of this synthesis involves a palladium(0)-catalyzed coupling of a terminal alkyne with *cis*-1,2-dichloroethylene to yield a cis chloro enyne.[5] We find that treatment of the chloro enyne with tetra-*n*-butylammonium fluoride then provides the 1,3-diyne in good overall yield (Table I). Our sequence is summarized in eq 1.



Palladium(0)-catalyzed coupling of terminal acetylenes with *trans*-1,2-dichloroethylene, in our hands, also proceeds in good yields, but attempted conversion of the resulting trans chloro enynes to diynes with tetra-*n*-butylammonium fluoride gave only traces of diynes even under vigorous conditions. This is consistent with the finding that the syn elimination of HCl from trans chloro enynes requires a stronger base.[6]

Our method is experimentally simple and can be extended to the synthesis of 1,3,5-triynes by repetition of the procedure. In the course of this investigation an interesting

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