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One-Pot Formation and Derivatization of Di- and Triynes Based on the Fritsch−Buttenberg−Wiechell Rearrangement

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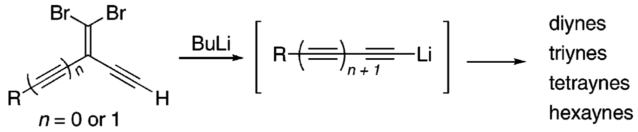

A divergent, one-pot synthesis of functionalized polyynes has been developed. Beginning with the appropriately substituted dibromoolefinic precursor, a carbenoid Fritsch−Buttenberg−Wiechell (FBW) rearrangement is used to generate the lithium acetylide of a conjugated polyyne framework, and subsequent trapping with carbon-based electrophiles provides for in situ formation of a wide range of di- and triynes. The lithium acetylide formed from the FBW reaction can also undergo transmetalation to provide the corresponding zinc, copper, tin, or platinum acetylides, leading to the divergent formation of symmetrical and unsymmetrical conjugated acetylenes, as well as ynones.

Introduction

Conjugated carbon−carbon triple bonds are important building blocks for organic chemistry because they are found in a wide variety of natural products,[1−3] and they can function as carbon-rich scaffolds and organic materials.[4] As well they can be utilized as high-energy precursors for many cyclic and acyclic derivatives.[5] The synthesis of organic compounds containing multiple carbon−carbon triple bonds can be challenging. Over the years, a number of metal-catalyzed hetero- and homocoupling reactions have been developed for the formation of sp−sp^2 and sp−sp bonds, many of which have been refined and applied to the synthesis of structurally diverse derivatives.[6] The use of terminal polyynes in these coupling reactions can, however, be problematic due to the fact that they often show limited stability.[7] Metal acetylides **1** (Scheme 1), on the other hand, are often stable intermediates when kept in solution. Although the most obvious route to an intermediate lithium acetylide might be through a two-step approach consisting of desilylation and lithiation (i.e., Scheme 1A), instability of the terminal polyyne often renders such an approach impossible. Thus, a number of methods have been developed for the in situ generation of the metal acetylide **1**, typically based on one of two strategies. One approach relies on the derivatization of an existing polyyne core through, for example, desilylation/metalation of a 1-(trimethylsilyl)-1,3-butadiyne or -1,3,5-hexatriyne (**2** or **3**) with MeLi−LiBr[8−10] or Si−Sn[11,12] exchange mediated by TBAF (parts B and C, respectively, of Scheme 1). The second approach utilizes an initial elimination reaction using, for example, 1-halo-1-buten-3-ynes **4**[13−17] or (*Z*)-1-methoxy-1-buten-3-ynes **5**[18,19] to construct a conjugated diyne,

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(6) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632−2657.

(7) For stable terminal diynes, see: West, K.; Wang, C.; Batsanov, A. S.; Bryce, M. R. *J. Org. Chem.* **2006**, *71*, 8541−8544.

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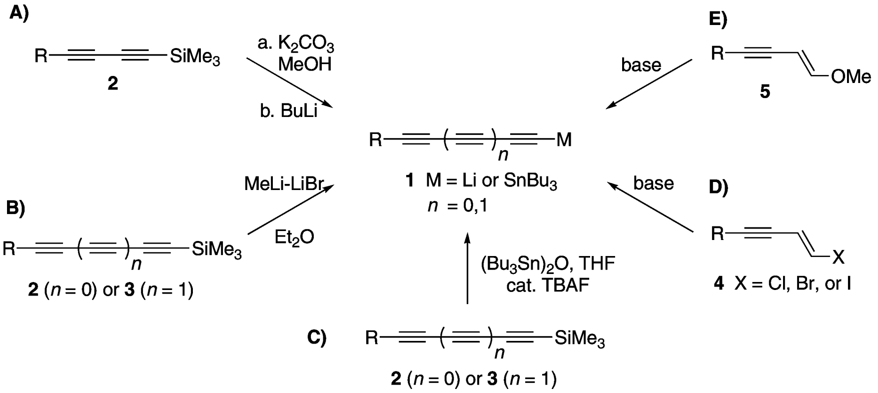
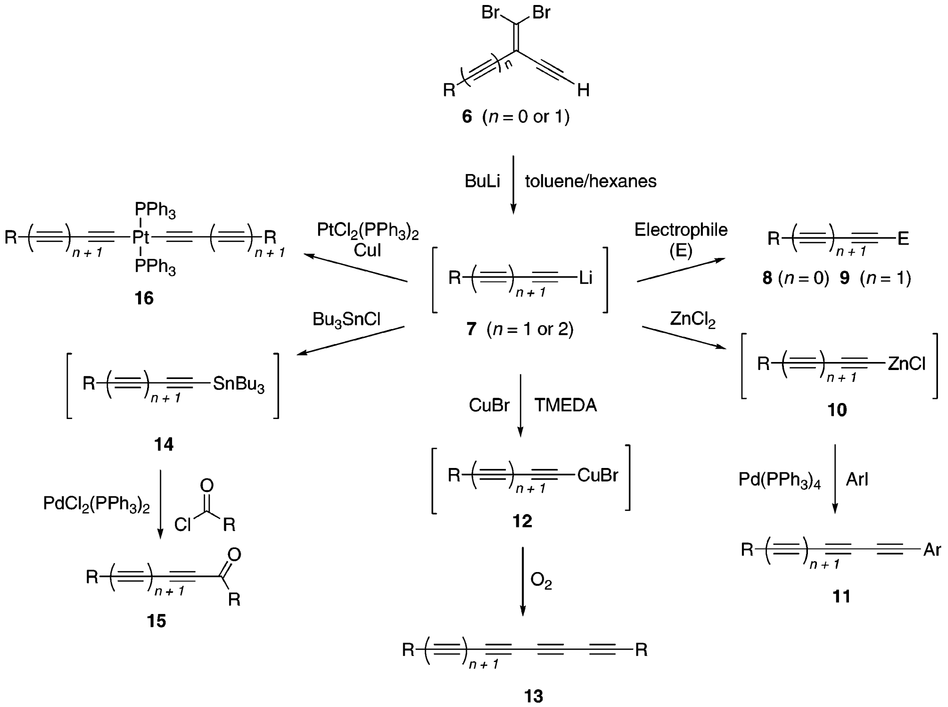
SCHEME 1



SCHEME 2



followed by metal acetylide formation (parts D and E, respectively, of Scheme 1). In either case, the result is a nucleophilic acetylide that can be subsequently derivatized, and both approaches have been quite successful for the formation of diynes. Much less has been done to generalize these protocols to triynes, although a recent report by Negishi and co-workers provides a viable route to not only triynes, but tetra- and pentaynes as well.[20]

We envisioned a one-pot, divergent route for the formation and substitution of di- and triynes based on the α-elimination of a 1,1-dibromoolefin, **6** (Scheme 2), to initiate a sequence consisting of a Fritsch−Buttenberg−Wiechell (FBW) rearrangement[21−24] and deprotonation. The result would be a lithium acetylide intermediate **7** that could then be trapped directly with electrophiles to give diynes **8** or triynes **9**. Alternatively, the lithium acetylide could be subjected to transmetalation to give (a) zinc acetylides **10** for Negishi coupling to provide α,*ω*-tolans **11**, (b) copper acetylides **12** for Glaser−Hay homocoupling to polyynes **13**, (c) alkynylstannanes **14** for Stille coupling to ynones **15**, and (d) the stable platinum *σ*-acetylide complexes **16**. We report herein the successful development of this

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(14) Negishi, E. I.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629−2632.

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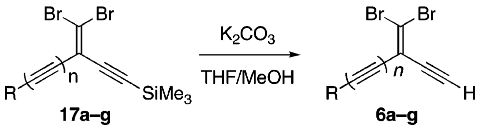
SCHEME 3



17a–g **6a–g**

a R = Ph $n = 0$ (93%)
b R = p-tBuC$_6$H$_4$ $n = 0$ (97%)
c R = Ph $n = 1$ (77%)
d R = p-tBuC$_6$H$_4$ $n = 1$ (93%)
e R = Me $n = 1$ (77%)
f R = Bu $n = 1$ (76%)
g R = iPr$_3$Si $n = 1$ (72%)

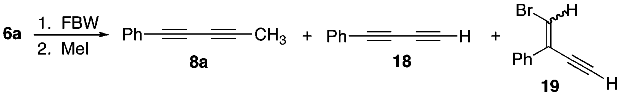
divergent process for the one-pot formation of polyynes and describe its scope for the construction of substituted derivatives.[25]

Results and Discussion

The requisite precursors, terminal alkynes **6a**−**g**, were synthesized in good yield from the corresponding TMS-protected enynes **17a**−**g**[11,22] (Scheme 3) via desilylation with K_2CO_3 in methanol/THF. The most important aspect in the preparation of compounds **6a**−**g** is the purification process, which must ensure that the terminal alkyne products are absolutely anhydrous before being carried on to the deprotonation−rearrangement step to follow (vide infra). Typically, this can be accomplished by passing the terminal alkyne product through a short column of unactivated alumina before proceeding to the FBW reaction.

Initial studies were aimed at optimizing the FBW/deprotonation and trapping sequence. It is known that the successful formation of polyynes using an FBW reaction requires an apolar solvent such as hexanes.[22] In the present case, however, the dibromoolefins **6a**−**g** showed only minimal solubility in hexanes, especially upon cooling to the desired reaction temperature. Optimization studies determined that this problem could be circumvented if the dibromoolefin **6** (ca. 0.5−1 mmol) was initially dissolved in ca. 2 mL of toluene and this solution then diluted with ca. 10 mL of hexanes.[26] In the second step of the reaction, it was quickly discovered that addition of an electrophile directly to the solution of intermediate **7** in hexanes/toluene typically gave a low yield of the desired products **8** or **9** (Scheme 2). It was surmised that the nonpolar reaction medium that favored the FBW rearrangement concurrently disfavored the subsequent reaction with an electrophile. This problem was easily solved by adding the electrophile as an ethereal solution to the intermediate **7**.

During the initial optimization of this procedure, the effect of adventitious water on the reaction was also probed (eq 1). Using dry hexanes and toluene,[27] the reaction of dibromoolefin **6a** with BuLi at −20 °C followed by quenching with methyl iodide gave **8a** in 67% yield.[28] Conversely, when the reaction was repeated using either “wet” toluene or “wet” hexanes, only a trace amount of the desired diyne **8a** was observed.[29] The major product formed in both cases was the terminal diyne **18**,[7] along with a trace of the protonated species **19** that resulted from quenching of the carbenoid intermediate of the reaction.[22] Thus, the presence of water does not completely prevent FBW rearrangement to the diyne, but it does effectively prevent trapping of the intermediate acetylide.



(1)

The scope of this one-pot reaction was then explored, again using precursor **6a** as a model system and diynols as the first targets. Both di- and triynols have been isolated from a range of natural sources and show a vast array of biological activity.[1,3,30−33] They can also be challenging synthetic targets.[34] Thus, dibromoolefin **6a** was subjected to BuLi to generate the lithium acetylide intermediate **7a**, which was subsequently trapped with a variety of carbonyl electrophiles, including formaldehyde, aryl and alkyl aldehydes, ketones, and CO_2. The products **8b**−**i** were isolated typically in good yields (57−95%) following aqueous workup and chromatographic purification (Table 1). The latter three examples (**8g**−**i**) are perhaps the most noteworthy. Compound **8g** represents a substrate that could easily be carried on to the formation of the unsymmetrical tetrayne via a sequence of oxidation, dibromoolefination, and an FBW rearrangement,[35] while **8h** provides an interesting building block for three-dimensional carbon-rich architectures.[36] The formation of **8i** demonstrates the potential of this protocol for reactions with alkyl aldehydes with acidic α-protons.

The successful formation of unsymmetrical diynes then directed efforts to the formation of triynes using an analogous route. Gratifyingly, the reaction of dibromoolefin **6c** with BuLi at −20 °C followed by trapping with a variety of electrophiles gave triyne derivatives **9a**−**e**.[37] While the overall yields of 54−72% for these reactions might only be labeled as moderate, it is worth emphasizing that, in a single step, the triyne core is both constructed and functionalized. Thus, this method is nicely complementary to existing routes of triyne formation such as the Cadiot−Chodkiewicz reaction.[38]

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[25] For a preliminary report of this work, see: Morisaki, Y.; Luu, T.; Tykwinski, R. R. *Org. Lett.* **2006**, *8*, 689−692.

[26] Pure toluene can also be used for the FBW/deprotonation. Due to the higher boiling point of toluene, however, it is more difficult to remove during product isolation, which can cause problems in cases where the di- or triyne product shows limited thermal stability.

[27] Hexanes were dried by distillation from CaH_2, and toluene was dried by distillation from Na/benzophenone ketyl.

[28] Compound **8a** has been isolated from a well-known Chinese folk medicine derived from the shrub Yin Chen Hao; see: Tang, W.; Eisenbrand, G. *Chinese Drugs of Plant Origin*; Springer: Berlin, 1992.

[29] “Wet” toluene and hexanes were arrived at by storing reagent grade solvent over molecular sieves (4 Å) for 24 h.

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[37] Triyne **9c** is a natural product isolated from several species, such as *Bidens pilosus*, *Bidens leucanthus*, and *Dahlia pinnata*; see: (a) Bohlmann, F.; Bornowski, H.; Kleine, K.-M. *Chem. Ber.* **1964**, *97*, 2135−2138. (b) Bohlmann, F.; Arndt, C.; Kleine, K.-M.; Wotschokowsky, M. *Chem. Ber.* **1965**, *98*, 1228−1232. (c) Bendixen, O.; Lam, J.; Kaufmann, F. *Phytochemistry* **1969**, *8*, 1021−1024.

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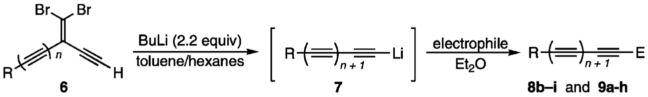
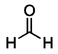
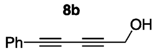
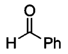
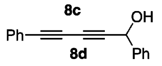
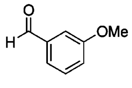
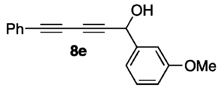
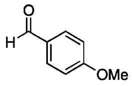
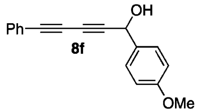
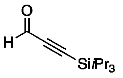
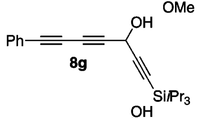
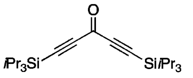
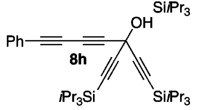
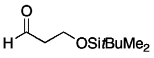
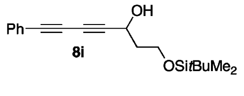
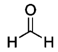
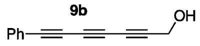
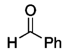
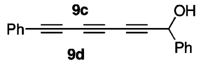
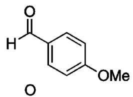
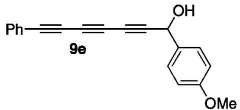
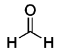
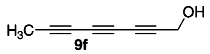
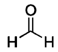
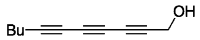
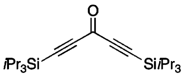
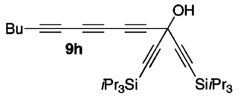
TABLE 1. One-Pot Formation of Di- and Triynes through Trapping with Carbon-Based Electrophiles



dibromoolefin	electrophile	product	yield (%)
6a	CO_2	$Ph{-}C{\equiv}C{-}C{\equiv}C{-}CO_2H$ **8b**	64
		 **8c**	58
		 **8d**	70
		 **8e**	72
		 **8f**	72
		 **8g**	75
		 **8h**	95
		 **8i**	57
6c	CH_3I	$Ph{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}CH_3$ **9a**	65
	CO_2	$Ph{-}C{\equiv}C{-}C{\equiv}C{-}C{\equiv}C{-}COOH$ **9b**	65
		 **9c**	72
		 **9d**	54
		 **9e**	54
6e		 **9f**	59
6f		 **9g**	55
		 **9h**	82

An analogous reaction of alkyl-terminated dibromoolefins **6e** and **6f** with paraformaldehyde produced the triynols **9f** and **9g** in reasonable yields.[39] Compound **9f** was obtained as a white crystalline solid, but slowly turned magenta in color when exposed to light. Triyne **9g**, on the other hand, was isolated as a pale yellow oil that remained unchanged when exposed to light. Finally, the lithium acetylide **7f** generated from **6f** reacted with a highly conjugated diyne ketone to produce tertiary alcohol **9h** as a stable brown oil in an excellent 82% yield.

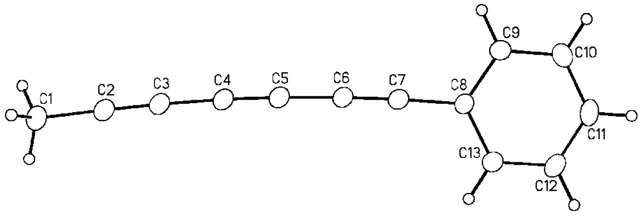


FIGURE 1. ORTEP drawing of **9a** (20% probability level). Selected interatomic distances (Å): C1−C2, 1.4522(17); C2≡C3, 1.1949(17); C3−C4, 1.3685(17); C4≡C5, 1.2067(16); C5−C6, 1.3665(17); C6≡C7, 1.2024(17); C7−C8, 1.4308(17). Selected interatomic angles (Å): C1−C2≡C3, 178.95(13); C2≡C3−C4, 177.58(13); C3−C4≡C5, 178.24(13); C4≡C5−C6, 177.48(13); C5−C6≡C7, 177.57(14); C6≡C7−C8, 178.12(13).

The product **9a** (1-phenylhepta-1,3,5-triyne) is a particularly interesting molecule that has been isolated as a natural product from many plant species such as *Bidens pilosa* (Asteraceae)[40] and several members of the *Coreopsis* family.[3] This triyne has significant insecticidal activity against the larvae of the army worm *Spodoptera frugiperda*, and it has also exhibited antimicrobial and nematicidal activity, as well as phototoxicity toward *Aedes aegypti* larvae.[41] Since single crystals of **9a** were easily grown from a concentrated solution in $CHCl_3$ at 4 °C, the X-ray crystallographic analysis of the molecule was explored. The molecular structure shows a slight bending of the C−C≡C bonds, with angles in the range of 177.6−179.0° (Figure 1).[42] The solid-state packing of **9a** shows no intermolecular close contacts of <4 Å between neighboring triyne segments, which precludes solid-state polymerization and likely contributes to the observed stability of this molecule in the solid state.

Complementary to targeting di- or triynes with an alcohol in the propargylic position through the reaction of an acetylide with a carbonyl compound would be synthesis of the homopropargylic alcohols through addition of an acetylide to an epoxide (Table 2). Thus, the reaction of **6a** with BuLi in pure toluene at −20 °C gave lithium acetylide intermediate **7a**, which was then trapped with (*S*)-propylene oxide to produce (*S*)-**8j** as a light yellow oil in 30% yield ($[\alpha]_D^{20} = -9.3$, *c* 1.3, MeOH). The use of the Lewis acid catalyst $BF_3{\cdot}Et_2O$ did little to improve the yield[43] and provided a 16% yield of (*S*)-**8j** in a ca. 5:1 ratio with (*S*)-**8k**, the product resulting from addition at the more hindered site of the epoxide. Similarly, the addition of (*S*)-propylene oxide dissolved in a combination of DMSO and Et_2O to a solution of **7a** did not improve the yield, giving (*R*)-**8j** in only 20% yield. The product (*R*)-**8j** ($[\alpha]_D^{20}$ +6.4, *c* 0.55, MeOH) shows spectral data and optical rotation identical to those of pilosol A, a diyne isolated from *B. pilosa*, thus confirming both the structure and (*R*)-stereochemistry for this natural product.[44] The reaction of acetylide **7a** with the TBDMS (*R*)-(+)-glycidyl ether was attempted using HMPA as an

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[39] The product **9f** (octa-2,4,6-triynol) has been isolated by Jones and co-workers from the fungus *Kuehneromyces mutabilis*; see: (a) Hearn, M. T. W.; Jones, E. R. H.; Pellatt, M. G.; Thaller, V.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2785−2788. (b) For a previous synthesis, see: Luu, T.; Shi, W.; Lowary, T. L.; Tykwinski, R. R. *Synthesis* **2005**, 3167−3178.

[40] Wat, C.-K.; Biswas, R. K.; Graham, E. A.; Bohm, L.; Towers, G. H. N.; Waygood, E. R. *J. Nat. Prod.* **1979**, *42*, 103−111.

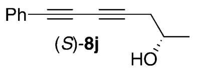
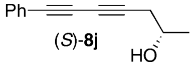
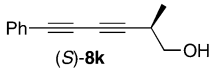
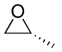
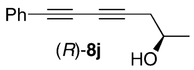
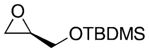
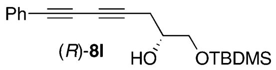
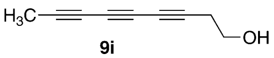
[41] Arnason, T.; Swain, T.; Wat, C.-K.; Graham, E. A.; Parington, S.; Towers, G. H. N. *Biochem. Syst. Ecol.* **1981**, *9*, 63−68.

[42] Crystal data for **9a**: $C_{13}H_8$, $M = 164.19$, monoclinic space group $P2_1/n$ (an alternate setting of $P2_1/c$ [No. 2]), $D_c = 1.158$ g cm^{-3}, $a = 6.1920(8)$ Å, $b = 7.7938(11)$ Å, $c = 19.640(3)$ Å, $\beta = 96.640(2)°$, $V = 941.5(2)$ Å^3, $Z = 4$, $\mu = 0.066$ mm^{-1}. Final $R(F) = 0.0400$, $wR_2(F^2) = 0.1163$ for 119 variables and 1925 data with $F_o^2 \geq -3\sigma(F_o^2)$ (1415 observations [$F_o^2 \geq 2\sigma(F_o^2)$]). CCDC 657101.

[43] Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394.

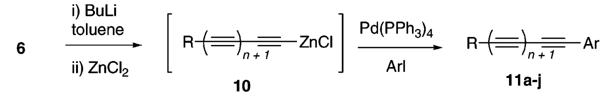
[44] Chang, M.-H.; Wang, G.-J.; Kuo, Y.-H.; Lee, C.-K. *J. Chin. Chem. Soc.* **2000**, *47*, 1131−1136.

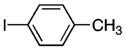
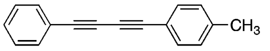
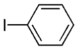
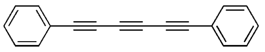
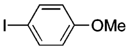
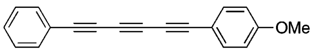
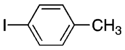
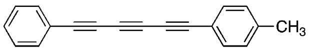
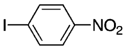
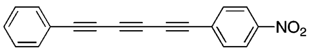
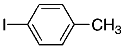
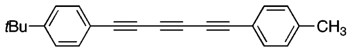
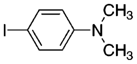
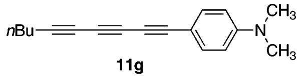
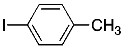
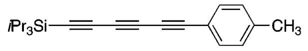
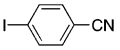
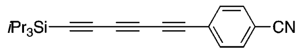
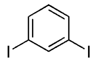
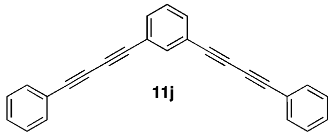
TABLE 2. Acetylide Addition to Epoxides

dibromoolefin	epoxide	product	yield (%)
6a		 (*S*)-**8j**	30
		 (*S*)-**8j**  (*S*)-**8k**	16[a]
		 (*R*)-**8j**	20[b]
		 (*R*)-**8l**	22[c]
6e		 **9i**	58[d]

[a] $BF_3 \cdot OEt_2$ added, ~5:1 ratio of **8j** to **8k** formed, not separated. [b] DMSO added. [c] HMPA added. [d] NH_3 added.

TABLE 3. One-Pot Formation and Negishi Coupling of Di- and Triynes



dibromoolefin	ArI	product	yield (%)
6a		 **11a**	90
6c		 **11b**	70
		 **11c**	80
		 **11d**	81
		 **11e**	84
6d		 **11f**	60
6f		 **11g**	24
6g		 **11h**	69
		 **11i**	78
6a		 **11j**	64

additive,[45] but gave (*R*)-**8l** in only 22% yield. Given the limited success of these addition reactions, only a single attempt was made to form a triyne. Dibromoolefin **6e** was used to provide **7e** in toluene, and to this solution was added a mixture of excess oxirane, ammonia, and THF at −20 °C. This procedure ultimately gave a 58% yield of the triyne product **9i** as a colorless oil.[46] Thus, the last set of conditions may ultimately provide a general path to triyne homopropargylic alcohols, and investigation of this possibility is ongoing.

Polyynes terminated with aryl groups are attractive synthetic targets due to their potential as electronic and optical materials.[35] The ease with which the polyyne framework of intermediate acetylides **7** could be formed in situ suggested their use as nucleophilic coupling partners in the formation of aryl polyynes via the Negishi coupling reaction (Table 3).[47] Thus, the appropriate dibromoolefinic precursor **6** was reacted with BuLi (2.2 equiv) at −40 °C in pure toluene to generate the lithium acetylide **7**. To ensure the rearrangement was complete, the reaction mixture was warmed slowly to ca. −20 °C and then recooled to −40 °C. To this mixture was added $ZnCl_2$ (1.2 equiv, 0.5 M in THF) to effect transmetalation to the zinc acetylide **10**. The appropriate aryl iodide and $Pd(PPh_3)_4$ (5 mol %) were added, and the mixture was heated at 70 °C for 20 h. Workup and column chromatography provided diyne **11a** and triynes **11b−i.** With the exception of **11g**, the desired diaryl polyynes were formed in generally good yields. In the reaction of **10f** with 4-iodo-*N*,*N*-dimethylaniline, the unfortunate low yield of triyne **11g** was not unexpected given the known issues of Pd insertion into electron-rich C−I bonds.[48] Finally, this method could also be extended to multiple couplings, as demonstrated by the Negishi reaction of **10a** with 1,3-diiodobenzene to yield **11j** in 64% yield.

An attempt was made to parlay this methodology toward the cross-coupling of alkynyl iodides using a hybrid of the Negishi and Cadiot−Chodkiewicz protocols (Scheme 4). Zinc acetylide **10c** was formed from **6c** and reacted with iodoalkyne **20** to afford tetrayne **21** in 34% yield, as well as diyne **22** (24% yield), the result of homocoupling of precursor **20**. Competition between the desired heterocoupling and the undesirable homocoupling is a well-known problem in Cadiot−Chodkiewicz-type reactions,[6] and attempts to reduce the byproduct were not successful. Given the difficulty in separating the two products chromatographically due to their similar polarities on common supports, efforts toward optimizing this potentially useful reaction were abandoned.

Transmetalation to Cu(I) was next explored toward effecting oxidative homocoupling under Glaser−Hay conditions (Table 4). Intermediates **7a,b,g** were generated from **6a,b,g** under standard conditions in toluene. To this mixture were added CuBr (1 equiv) and TMEDA (17 equiv) to give copper acetylides **12a,b,g**,[49] and oxygen gas was then bubbled into the mixture for 15 min. After TLC analysis revealed the reaction was

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(45) Xie, X.; Yue, G.; Tang, S.; Huo, X.; Liang, Q.; She, X.; Pan, X. *Org. Lett.* **2005**, *7*, 4057−4059.

(46) Triyne **8d** is a natural product first isolated from the fungus *Collybia peronata* and later from cultures of *Lentinus edodes*; see: (a) Higham, C. A.; Jones, E. R. H.; Keeping, J. W.; Thaller, V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1991−1994. (b) Tokimoto, K.; Fujita, T.; Takeda, Y.; Takaishi, Y. *Proc. Jpn. Acad.* **1987**, *63*, 277−280.

(47) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 15.

(48) Bréfort, J. L.; Corriu, R. J. P.; Gerbier, P.; Guérin, C.; Henner, B. J. L.; Jean, A.; Kuhlmann, T. *Organometallics* **1992**, *11*, 2500−2506.

SCHEME 4

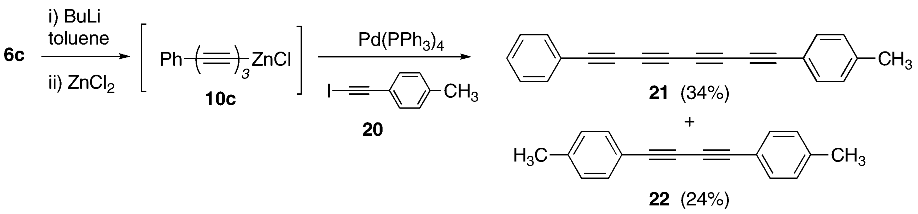
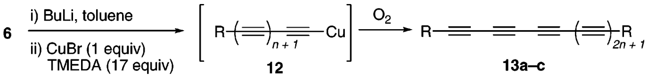
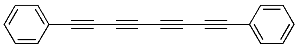
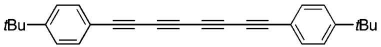
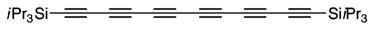


TABLE 4. One-Pot Formation and Oxidative Homocoupling of Di- and Triynes

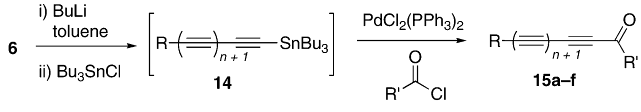


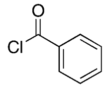
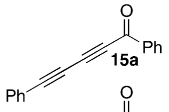
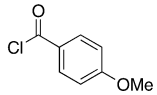
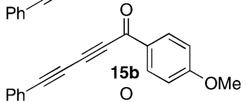
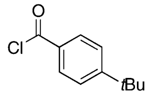
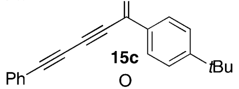
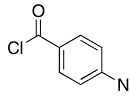
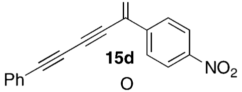
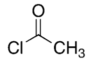
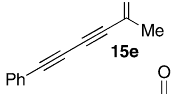
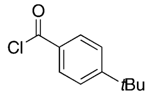
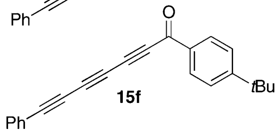
dibromoolefin	product	yield (%)
6a	 **13a**	69
6b	 **13b**	93
6g	 **13c**	68

completed, the mixture was passed through a plug of alumina to remove the insoluble salts, and the crude products were purified by column chromatography to produce tetraynes **13a**[35] and **13b**,[50] as well as hexayne **13c**[24] (Table 4). By way of comparison, the previous synthesis of **13c** was also derived from **6g**, but required two additional steps and provided an overall yield of only 35%, whereas the current procedure provides **13c** in 68% yield and only one step.[24]

Conjugated ynones are desirable synthetic targets[51] because they are versatile precursors and are also known to possess interesting biological activity.[52] Thus, a one-pot protocol using the Stille cross-coupling reaction based on transmetalation of lithium acetylide **7** to the tin acetylide **14** was explored (Table 5). The dibromoolefin **6a** or **6c** was rearranged at −40 °C in toluene and converted to the tin acetylide **14** via reaction with Bu$_3$SnCl. The reaction mixture was warmed to room temperature to ensure complete transmetalation, and the acyl chloride (dissolved in a minimal amount of CH$_2$Cl$_2$) was added, followed by a catalytic amount of PdCl$_2$(PPh$_3$)$_2$. After the reaction mixture was refluxed overnight, workup gave the crude ynones **15a**−**d**, which could be isolated pure by column chromatography. Stille coupling of the stannylacetylenes **14** was successful with a variety of aryl acyl chlorides, ranging from electron-donating to electron-withdrawing groups, although the yield for neutral and electron-donating aryl acyl products **15a**−**c** was slightly higher than that with an electron-deficient aryl group, **15d**.[53,54]

TABLE 5. One-Pot Formation, Stannylation, and Stille Coupling of Diynes



dibromoc n	acyl chlodide	product	yield (%)
6a		 **15a**	75
		 **15b**	71
		 **15c**	71
		 **15d**	56
		 **15e**	33
6c		 **15f**	–[a]

[a] Not isolated due to decomposition.

Compound **15e** was derived from the combination of tin species **14a** and acetyl chloride and resulted in an unstable orange oil in low yield. Attempts to extend this method to triynones such as **15f** were unsuccessful, and it was not possible to isolate this product pure due to its instability, although TLC analysis of the reaction mixture did suggest that **15f** had been formed.

Platinum acetylide complexes have recently been designed for the formation of a wide range of carbon-rich oligomers,[55] macrocycles,[56] and supramolecular complexes.[57] Thus, the final transformation explored was the one-pot assembly of platinum acetylides starting from precursors **6a,f,g** (Table 6).[58] The general procedure was used to provide the lithium acetylide **7** in toluene, and to this intermediate was added CuI, followed by PtCl$_2$(PPh$_3$)$_2$. The reaction mixture was stirred at room temperature for 12 h and then at 50 °C for 4 h. Using this

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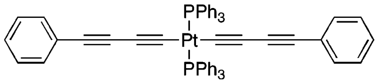
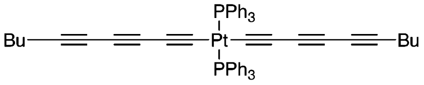
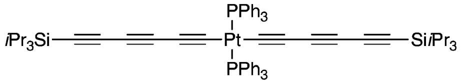
TABLE 6. Platinum Acetylide Formation from Di- and Triynes

$$\mathbf{6} \xrightarrow[\text{ii) CuI, PtCl}_2(\text{PPh}_3)_2]{\text{i) BuLi, toluene}} \mathbf{16a\text{–}c}$$

dibromoolefin	product	yield (%)
6a	 **16a**	91
6f	 **16b**	82
6g	 **16c**	74

procedure, tetrayne **16a** was generated as a marginally soluble, off-white solid in excellent yield. Compound **16b** was synthesized from precursor **6f** as a soluble colorless solid in 82% yield. Formation of the TIPS derivative **16c** was also successful, providing a marginally soluble product in 74% yield, although all attempts to achieve a purity of >90% for this derivative have been unsuccessful. The *trans*-stereochemistry of **16a**−**c** was easily established on the basis of the $^1J_{\text{Pt}-\text{P}}$ coupling constants observed in the ^{31}P NMR spectra (CD_2Cl_2). Values of $^1J_{\text{Pt}-\text{P}}$, 2570, 2525, and 2540 Hz, respectively, indicated formation of the *trans*-isomer, whereas the *cis*-isomer would show a smaller $^1J_{\text{Pt}-\text{P}}$, ∼2300 Hz.[59]

Conclusions

A one-pot protocol for the synthesis and derivatization of di- and triynes has been developed based on an FBW rearrangement−deprotonation sequence. The main advantage of this method is that, from a common dibromoolefinic precursor, a substantial range of polyyne products can be achieved simply through the choice of the electrophile introduced in the second step of the reaction. The efforts to date have shown that carbon-based electrophiles such as aldehydes, ketones, MeI, and CO_2 work quite well, whereas the use of epoxide-based electrophiles results in only low yields of the desired products. Use of an electrophilic transition metal allows for transmetalation from the initial lithium acetylide and the formation of zinc, copper, tin, and platinum acetylides, which greatly increases the range of products that may be achieved. Given the ease with which this one-pot reaction sequence can be effected, the possibility for structure−function analysis of di- and triynes for both materials and medicine has been greatly expanded.

Experimental Section

General Procedure for One-Pot Trapping with Electrophiles. Dibromoolefin **6** (0.5−1.0 mmol) was dissolved in toluene (2 mL), and this mixture was then diluted with hexanes (10 mL) and cooled to −20 °C under an Ar atmosphere. To this solution with stirring was added BuLi (1.6 or 2.5 M in hexanes, 2.2 equiv) via syringe over a period of ca. 1 min. The reaction mixture was allowed to warm slowly to 0 °C and then cooled again to −20 °C. Et_2O (10 mL) was added, followed by the addition of the electrophile (dissolved in 2 mL of Et_2O) via a cannula. The reaction mixture was allowed to warm slowly to rt overnight. Saturated aqueous NH_4Cl (10 mL) and Et_2O (10 mL) were added, and the organic phase was separated, washed with saturated aqueous NaCl (2 × 10 mL), and dried over $MgSO_4$. Solvent removal and purification by column chromatography (silica gel) gave the products **8a**−**i** and **9a**−**h**.

General Procedure for the One-Pot FBW−Negishi Reaction. Dibromoolefin **6** (1.0 mmol) in toluene (10 mL) was cooled to −40 °C under a N_2 atmosphere. To this solution with stirring was added BuLi (2.5 M in hexanes, 0.90 mL, 2.2 mmol) by syringe over a period of ca. 5 min. The reaction mixture was allowed to warm slowly to −20 °C and then cooled again to −40 °C. $ZnCl_2$ (0.50 M in THF, 2.4 mL, 1.2 mmol) was added by syringe over a period of ca. 5 min, the reaction mixture was allowed to warm slowly to 0 °C, the aryl halide (1.1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.050 mmol) were added directly under a flow of N_2, and this mixture was heated to 70 °C. After being heated for 20 h, the reaction mixture was cooled and filtered through a Celite column, the solvent removed under reduced pressure, and the residue purified by column chromatography to give the desired products **11a**−**j** and **21**.

General Procedure for the One-Pot FBW−Hay Reaction. Dibromoolefin **6** (0.70 mmol) in toluene (10 mL) was cooled to −40 °C under a N_2 atmosphere. To this solution with stirring was added BuLi (2.5 M in hexanes, 0.56 mL, 1.40 mmol) by syringe over a period of ca. 5 min. The reaction mixture was allowed to warm slowly to −20 °C. To this mixture with stirring were added CuBr (0.6 mmol) and TMEDA (13 mmol), and oxygen was bubbled through the solution for 15 min. The reaction mixture was allowed to warm slowly to rt overnight, concentrated, filtered through a plug of alumina, and purified by column chromatography to give the desired products **13a**−**c**.

General Procedure for the One-Pot FBW−Stille Reaction. Dibromoolefin **6** (0.70 mmol) in toluene (3.0 mL) was cooled to −40 °C under a N_2 atmosphere. To this solution with stirring was added BuLi (2.5 M in hexanes, 0.65 mL, 1.6 mmol) by syringe over a period of ca. 5 min. The reaction mixture was allowed to warm slowly to −20 °C and then cooled again to −40 °C. Bu_3SnCl (0.45 mL, $d = 1.2$, 0.54 g, ca. 1.2 mmol) was added by syringe over a period of 5 min and the mixture allowed to warm slowly to rt and then stirred for 2 h. The acid chloride (0.70 mmol) and $PdCl_2(PPh_3)_2$ (25 mg, 0.035 mmol), both in CH_2Cl_2 (15 mL), were added to the solution of the tin acetylide, and this mixture was refluxed overnight. The reaction mixture was cooled to rt, aqueous KF solution (30 mL) and ether (30 mL) were added, and the mixture was stirred vigorously for 15 min. This solution was then filtered through a Celite column and the organic phase separated, washed with water, and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography (silica gel) to give the desired products **15a**−**e**.

General Procedure for the One-Pot Formation of Platinum Acetylides. Dibromoolefin **6** (0.50 mmol) in toluene (5.0 mL) was cooled to −40 °C under a N_2 atmosphere. To this solution with stirring was added BuLi (2.5 M in hexanes, 0.45 mL, 1.12 mmol) dropwise by syringe over ca. 5 min. The reaction mixture was allowed to warm slowly to −20 °C and then cooled again to −40 °C. CuI (125 mg, 0.656 mmol) was added directly under a flow of N_2, followed by $PtCl_2(PPh_3)_2$ (199 mg, 0.252 mmol). The reaction mixture was stirred at rt overnight and then at 50 °C for 4 h. After the mixture was cooled, H_2O (5 mL) and CH_2Cl_2 (5 mL) were added, the organic phase was separated, washed with H_2O, and dried over $MgSO_4$, and the solvent was removed under reduced

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[59] Campbell, K.; McDonald, R.; Ferguson, M. J.; Tykwinski, R. R. *J. Organomet. Chem.* **2003**, *683*, 379−387.

pressure. Recrystallization from CH_2Cl_2 by the addition of MeOH or hexanes or column chromatography gave the desired products **16a**−**c**.

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Supporting Information Available: Experimental and spectroscopic data for all new compounds and X-ray crystallographic details for compound **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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