ORGANIC
LETTERS

2006
Vol. 8, No. 4
689−692

A One-Pot Synthesis and Functionalization of Polyynes

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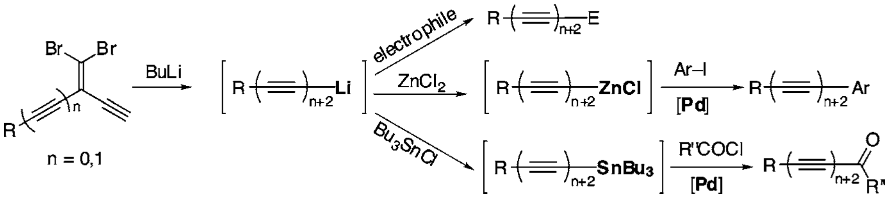
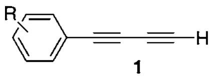
Received November 29, 2005

ABSTRACT



A one-pot synthesis and derivatization of diynes and triynes is reported. The polyyne framework is formed from a dibromoolefin precursor based on a carbenoid rearrangement, and the resulting Li–acetylide is then trapped in situ with an electrophile to provide functionalized di- and triynes. Alternatively, transmetalation of the Li–acetylide intermediate provides either the Zn– or Sn–acetylide, which then allows for the divergent preparation of diaryl polyynes or aryl ynones via palladium-catalyzed cross-coupling reactions.

The development of general methods for the introduction of carbon−carbon triple bonds into organic compounds is an important subject in synthetic organic chemistry.[1] The significance of the carbon−carbon triple bond as a functional group is due to (a) the presence of this moiety in a wide variety of naturally occurring compounds,[2] (b) its ubiquitous role as a rigid-rod constituent of π-conjugated scaffolding,[1] and (c) its versatility as a high energy precursor to many cyclic and acyclic derivatives.[1] Metal-catalyzed hetero- and homocoupling reactions for effecting sp−sp^2 and sp−sp bond formation have been developed and refined as powerful tools for the construction of polyynyl frameworks.[3] The essential use of terminal alkynes for these coupling reactions can be limiting, however, because kinetic stability of terminal alkynes decreases dramatically as the number of conjugated carbon−carbon triple bonds increases.



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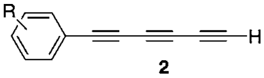

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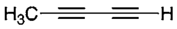

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For example, aryl butadiynes (**1**) are unstable to isolation, which has necessitated the development of in situ techniques for elaboration, while the next higher homologue, phenylhexatriyne (**2**, R = H), reportedly "...exploded at 0 °C in the absence of air" upon attempted isolation.[4] Alkyl polyynes can be equally problematic, and even simple precursors, such as pentadiyne (**3**), a common structural unit of polyyne natural products, can pose a synthetic challenge.[5] In contrast to terminal polyynes, metal acetylides are typically stable intermediates when kept in solution, albeit they are difficult or impossible to generate directly from precursors such as **1**−**3** via deprotonation and metalation. We have thus designed a one-pot method for the construction and derivatization of polyynes, based on the in situ formation of a

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(1) *Acetylene Chemistry: Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(2) (a) Bohlmann, F.; Burkhardt, H.; Zdero, C. *Naturally Occurring Acetylenes*; Academic Press: New York, 1973. (b) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* In press.

(3) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2633−2657. (b) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-VCH: New York, 2002; pp 493−529. (c) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(4) Armitage, J. B.; Entwistle, N.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 147−154.

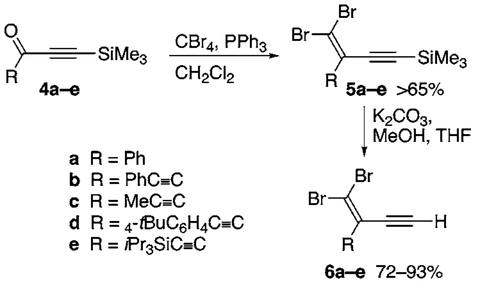
(5) According to Brandsma, "...it is difficult to obtain very pure 1,3-pentadiyne in a good yield using a safe isolation procedure." Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 45.

10.1021/ol0528888 CCC: $33.50

lithium−acetylide intermediate directly from a dibromoolefin precursor via a Fritsch−Buttenburg−Wiechell (FBW) rearrangement.[6,7] The intermediate can either be trapped directly with electrophiles or subjected to transmetalation providing nucleophilic coupling partners suitable for elaboration via Pd-catalyzed cross-coupling reactions. This overall process circumvents the need for terminal polyynes as precursors, while providing functional derivatives difficult to prepare in a stepwise process.

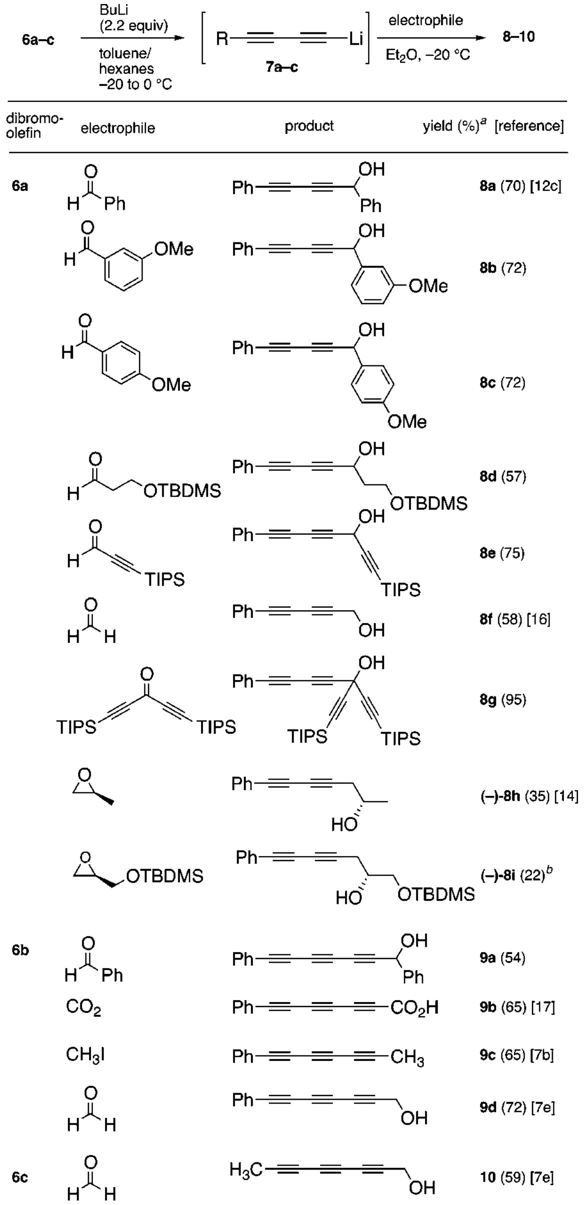
Beginning with readily available ketones **4**, a sequence of dibromoolefination to **5**, followed by proteodesilylation with methanoic K_2CO_3 gave the necessary carbenoid precursors **6a**−**e**.[8] Products **6a** and **6d** were obtained as stable solids, whereas **6b**,**c** and **6e** were oils that slowly discolored over time (days) in their neat form, but could be stored in a solution of hexanes without decomposition.

Scheme 1. Synthesis of Dibromoolefinic Precursors **6a**−**e**



As a model system, dibromoolefin **6a** was chosen to probe the viability of the proposed approach (Table 1). It is well established that the success of a typical FBW rearrangement is solvent dependent, with the best results for polyynes normally obtained in an apolar medium, such as hexanes.[7c] Compound **6a**, however, precipitated from pure hexanes upon cooling. Thus, **6a** (0.5−1 mmol) was first dissolved in toluene (ca. 2 mL) and then diluted with hexanes (ca. 10 mL) to give a mixture that remained homogeneous at low temperature.[9] The FBW rearrangement−deprotonation sequence was then initiated at −20 °C using a slight excess of BuLi (2.2 equiv) and the reaction warmed slowly to 0 °C to ensure complete rearrangement to intermediate **7a**.[10] Direct addition of the electrophile to this reaction mixture after recooling to −20 °C afforded only low yields of the desired products. Better results were obtained when the reaction mixture was first diluted with an equal amount of Et_2O, followed by addition of the electrophile (dissolved in Et_2O). Under these conditions, decent yields could be achieved in the formation of 2° alcohols resulting from reaction of intermediate **7a** with aryl (**8a**−**c**), alkyl (**8d**), and alkynyl (**8e**) aldehydes, as well as paraformaldehyde to give diynol **8f**. The reaction of **7a** with a ketone allowed for the formation of the highly unsaturated **8g** in excellent yield.[11,12]

Table 1. One-Pot Synthesis of Functionalized Polyynes **8**−**10**



[a] Isolated yield based on dibromoolefin. [b] HMPA added.

Attempts to extend this in situ protocol to epoxides were also conducted, but yields were consistently lower. For

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(6) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795−3849.

(7) (a) Eisler, S.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 10736−10737. (b) Shi Shun, A. L. K.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 6810−6813. (c) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem.*−*Eur. J.* **2003**, *9*, 2542−2550. (d) Eisler, S.; Slepkov, A. D.; Elliott, E.; Luu, T.; McDonald, R.; Hegmann, F. A.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2005**, *127*, 2666−2676. (e) Luu, T.; Shi, W.; Lowary, T. L.; Tykwinski, R. R. *Synthesis* **2005**, 3167−3178.

(8) The ketones **4a**−**c**,**e** and dibromides **5b**,**c**,**e** have been previously reported, others were synthesized by analogous routes. See Supporting Information for references as well as synthetic and spectroscopic details for all new compounds.

(9) The FBW rearrangement can be successfully accomplished in pure toluene, but product isolation is more difficult due to its higher boiling point. This is an issue in cases were the triyne product is not particularly stable to heating; a mixture of hexanes and toluene is procedurally the easiest.

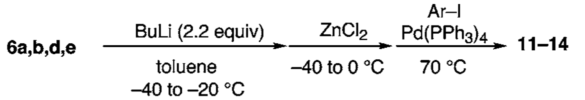
(10) It is has not yet been established if deprotonation precedes the FBW rearrangement, or vice versa. Given the good yields of the reactions, however, the former seems more likely because the latter should lead to byproduct formation resulting from protonation of the carbenoid intermediate by the terminal acetylene.

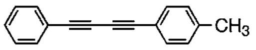
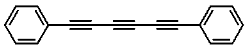
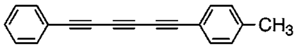
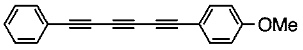
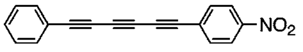
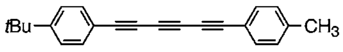
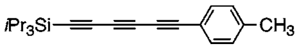
example, reaction of intermediate **7a** with (*S*)-propylene oxide gave the desired product (−)-**8h** in 35% yield ($[\alpha]^{20}_{D}$ = −9.3, MeOH). Use of $BF_3{\cdot}Et_2O$ as an additive[13] gave slightly higher overall yield, but regioselectivity decreased, with approximately equal substitution at the more and less hindered site of the epoxide. The other enantiomer of this alcohol, (+)-**8h** (pilosol A), has been recently isolated from *Bidens pilosa* ($[\alpha]^{26}_{D}$ = +6, MeOH),[14] and the *R*-configuration can thus tentatively be set for the natural product based on the known configuration of the (*S*)-propylene oxide precursor to (−)-**8h**. In a similar vein, the formation of (−)-**8i** via addition of **7a** to commercially available TBDMS (*R*)-(+)-glycidyl ether also proceeded in low yield.

Unsymmetrically substituted triynes are both desirable and challenging synthetic targets, with many such molecules occurring naturally in fungi, plants, and marine organisms.[2] Thus, the one-pot formation of triyne derivatives was explored starting from enediyne **6b**. Using the protocol established with **6a**, reaction of **6b** with BuLi afforded acetylide **7b**, which was then reacted with aldehydes, carbon dioxide, and methyl iodide to give triyne products **9a**−**d**. An analogous reaction initiated with **6c** and trapping with paraformaldehyde gave triynol **10**, a natural product isolated from neutral fractions of the fungus *Kuehneromyces mutabilis*.[15]

Metal-mediated cross-coupling of acetylenes is a powerful technique for the formation of carbon-rich scaffolds and organic materials.[3] The formation of aryl di- and triynes via cross-coupling reactions can, however, be a challenging task due to instability of deprotected triynes.[18,19] The ease with which the polyyne framework of intermediate acetylides **7** could be formed in situ suggested an extension of this protocol to the formation of unsymmetrical aryl polyynes using the Negishi coupling reaction (Table 2).[20] BuLi (2.2 equiv) was added to the respective dibromoolefinic precursor **6** at −40 °C in toluene, and the reaction mixture was slowly warmed to ca. −20 °C to complete the generation of the lithium−acetylide intermediate. The reaction mixture was recooled to −40 °C, and $ZnCl_2$ (1.2 equiv, 0.5 M in THF) was added dropwise to effect transmetalation to zinc. The zinc−acetylide was then reacted with the desired aryl iodide in the presence of a catalytic amount of $Pd(PPh_3)_4$ (5 mol %) at 70 °C in toluene[21] to give the corresponding diaryl diyne **11** and triynes **12**−**14** in good yield. These reactions were uniformly successful without regard for either the nature of the aryl iodide (i.e., electron-rich or electron-poor) or the reacting acetylide.[22]

Table 2. Synthesis of Polyynes **11**−**14** via a One-Pot FBW Rearrangement and the Negishi Coupling Reaction

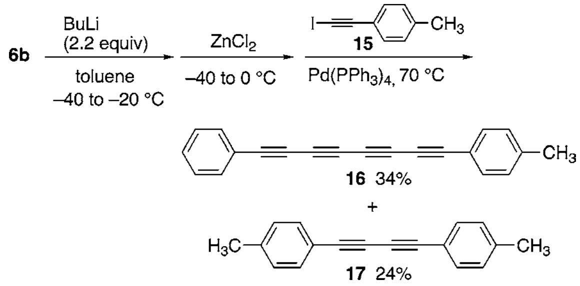


dibromo-olefin	Ar	product	yield (%)[a] [reference]
6a	*p*-Tol		**11** (90) [12d]
6b	Ph		**12a** (70) [22]
	p-Tol		**12b** (81)
	p-MeO-C_6H_4		**12c** (80)
	p-NO_2-C_6H_4		**12d** (84)
6d	*p*-Tol		**13** (60)
6e	*p*-Tol		**14** (69)

[a] Isolated yield based on dibromoolefin.

A preliminary foray into acetylenic chain length extension was attempted using 1-iodoacetylene **15** and an analogous Negishi protocol (Scheme 2). Rearrangement of **6b**, transmetalation to Zn, and Pd-catalyzed cross-coupling with **15** provided the targeted tetrayne **16**. Unfortunately, the con-

Scheme 2. One-Pot Synthesis of Tetrayne **16** via a Modified Negishi Coupling



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(11) A protocol for in situ formation and derivatization of 1-amino-di- and triynes has been reported. See: (a) Faul, D.; Himbert, G. *Chem. Ber.* **1988**, *121*, 1367−1369 and references therein. (b) Bartlome, A.; Stämpfli, U.; Neuenschwander, M. *Helv. Chim. Acta* **1991**, *74*, 1264−1272.

(12) For diynes, protocols exist for in situ acetylide formation and trapping. To our knowledge, these routes have not been generalized for triyne synthesis. For examples, see: (a) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F.-T. *J. Org. Chem.* **1984**, *49*, 2629−2632. (b) Himbert, G.; Umbach, H.; Barz, M. *Z. Naturforsch. B* **1984**, *39*, 661−667. (c) Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 3687−3690. (d) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **2003**, *44*, 9087−9090. (e) Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655−2657. (f) Stracker, E. C.; Zweifel, G. *Tetrahedron Lett.* **1990**, *31*, 6815−6818. (g) Okuhara, K. *J. Org. Chem.* **1976**, *41*, 1487−1494.

(13) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394.

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

(15) 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.

(16) Lee, H. J.; Shim, S. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1420−1422.

(17) Bohlmann, F.; Sucrow, W.; Queck, I. *Chem. Ber.* **1964**, *97*, 2586−2597.

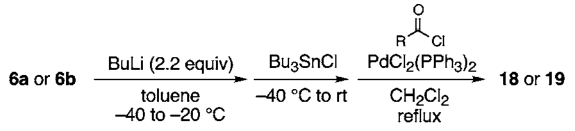
(18) Otera and co-workers reported a double elimination method of β-substituted sulfones that addresses this problem. See: Ye, F.; Orita, A.; Yaruva, J.; Hamada, T.; Otera, J. *Chem. Lett.* **2004**, *33*, 528−529 and references therein.

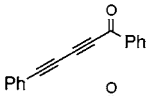
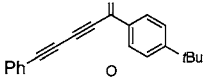
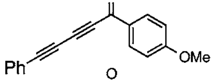
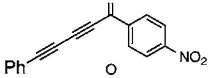
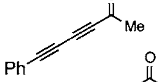
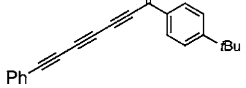
comitant formation of diyne byproduct **17** not only kept the yield of **16** modest but also made purification difficult. This result suggests that the homocoupling reaction of **15** catalyzed by palladium, as has been previously reported by Lee and co-workers,[23] successfully competes with Negishi cross-coupling. To date, this process could not be optimized to a point that minimizes the formation of such side products.

The synthetic potential of other metal-catalyzed cross-coupling reactions was also explored. Conjugated ynones[24−26] are desirable synthetic targets because they are versatile synthetic precursors and are also known to possess interesting biological activity.[27] After experimenting with several transmetalation schemes, it was established that the Stille coupling reaction of a stannylacetylene and an acyl chloride[28] provided good results for the one-pot protocol (Table 3).

Following the FBW rearrangement−deprotonation sequence of **6a** in toluene, Bu_3SnCl was added to the lithium−acetylide at −40 °C, and the mixture was warmed to room temperature to complete formation of the tin−acetylide. To this intermediate were added the acyl chloride (in CH_2Cl_2) and catalytic $PdCl_2(PPh_3)_2$; the reaction was then refluxed. The Stille coupling reaction with aryl acyl chlorides afforded butadiynyl ketones **18a−d** in good yield, while the reaction with acetyl chloride provided only 33% yield of the unstable diynone product **18e**. Attempts to apply this method to triynones, such as **19**, were, unfortunately, not successful. While TLC analysis of the reaction mixture suggested that the formation of **19** would occur, it was not possible to isolate the pure product due to the kinetic instability of **19**. To the best of our knowledge, however, the one-pot procedure combining the FBW rearrangement and Stille coupling reaction is the first example of a straightforward method for the synthesis of diaryl butadiynyl ketones.[29]

Table 3. Synthesis of Ynones **18** via a One-Pot FBW Rearrangement and the Stille Coupling Reaction



dibromo-olefin	R	product	yield (%)[a] [reference]
6a	Ph		**18a** (75) [27]
	p-*t*Bu-C_6H_4		**18b** (71)
	p-OMe-C_6H_4		**18c** (71) [27a]
	p-NO_2-C_6H_4		**18d** (56)
	Me		**18e** (33) [27b]
6b	*p*-*t*Bu-C_6H_4		**19** (–)[b]

[a] Isolated yield based on dibromoolefin. [b] Not isolated because of instability.

In conclusion, we have developed a convenient method for the one-pot syntheses of functionalized polyynyl compounds using a carbenoid rearrangement to generate the polyyne framework. The initially generated lithium−acetylide can be trapped in situ with electrophiles, allowing for the formation of substituted di- and triynes. Optimized protocols have been developed for the preparation of diaryl polyynes via transmetalation to zinc, followed by a Negishi coupling reaction, as well as polyynyl ketones via transmetalation to tin and a subsequent Stille coupling reaction.

Acknowledgment. This work was supported by the University of Alberta and the National Sciences and Engineering Research Council of Canada (NSERC) through the Discovery and Nano Innovation Platform (NanoIP) grant programs. We thank Ms. Nina Cunningham for help with the synthesis of compound **8h**.

Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) In situ deprotection/coupling protocols can be quite effective. See, for example: Bell, M. L.; Chiechi, R. C.; Johnson, C. A.; Kimball, D. B.; Matzger, A. J.; Wan, W. B.; Weakley, T. J. R.; Haley, M. M. *Tetrahedron* **2001**, *57*, 3507−3520.

(20) Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-VCH: New York, 2002; pp 229−247.

(21) The use of toluene rather than hexanes allows for higher reflux temperatures in the subsequent Negishi reaction.

(22) Rubin, Y.; Lin, S. S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 6943−6949.

(23) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085−7087.

(24) (a) Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.* **1984**, *25*, 2411−2414. (b) Yamaguchi, M.; Shibato, K.; Fujiwara, S.; Hirao, I. *Synthesis* **1986**, 421−422.

(25) Palladium-catalyzed alkynylation of acyl halides with metal acetylides. For copper: (a) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777−778. For zinc: (b) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181−5184. (c) Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289−294. For tin: (d) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549−2553. (e) Ackroyd, J.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 338−344. (f) Crisp, G. T.; O'Donoghue, A. I. *Synth. Commun.* **1989**, 1745−1758. For aluminum: (g) Wakamatsu, T.; Okuda, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2425−2426. For indium: (h) Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160.

(26) Palladium-catalyzed alkynylation of acyl halides with terminal alkynes has also been reported. See: Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615−1619 and references therein.

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