Published in final edited form as:

Org Lett. 2018 November 02; 20(21): 6845–6849. doi:10.1021/acs.orglett.8b02975.

Synthesis of 1,3-Diynes Via Cadiot-Chodkiewicz Coupling of Volatile, in Situ-Generated Bromoalkynes

Phil C. Knutson, Haleigh E. Fredericks[†], and Eric M. Ferreira^{*}

Department of Chemistry, University of Georgia, Athens, Georgia 30602, United States

Abstract

A convenient Cadiot-Chodkiewicz protocol that facilitates the use of low molecular weight alkyne coupling partners is described. The method entails an in situ elimination from a dibromoolefin precursor and immediately subjecting to copper-catalyzed conditions, circumventing the hazards of volatile brominated alkynes. The scope of this method is described, and the internal 1,3-diyne products are preliminarily evaluated in ruthenium-catalyzed azide alkyne cycloadditions.

Graphical Abstract

In organic synthesis, 1,3-diynes have been attractive targets for several decades.¹ The structural motif appears in many natural products,^{1b} bioactive molecules,² intriguing materials³ and supra-molecular tools,^{1a,4} and it has been exploited as a central functionality in several complexity-generating hexahydro-Diels-Alder cycloadditions.^{5,6} The Glaser-Eglinton-Hay coupling represents a straightforward synthesis of homo-coupled 1,3-diynes,⁷ but producing cross-coupled diynes is more complicated. Among methods for accessing the cross-coupled variant, the Cadiot-Chodkiewicz coupling⁸ stands out as the most widely employed, exemplified by its use in a number of natural product syntheses.⁹ Recent examples utilizing this coupling include polyyne natural products ivorenolide A^{9a,b} and 4,8-dihydroxy-3,4-dihydrovernoniynone (Figure 1).^{9c} This coupling strategy has also been employed to provide important intermediates en route to natural products, such as toward the selaginpulvilins^{9d} and the dictyodendrins.^{9e}

^{*}Corresponding Author: emferr@uga.edu.

[†]Present Addresses: Medical College of Georgia, Augusta University, Augusta, GA 30912, United States

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, and spectra (PDF)

The authors declare no competing financial interest.

During the course of our synthesis of gelsenicine,¹⁰ our strategy evolved to utilize a diene-diyne as a key precursor (Figure 2). The Cadiot-Chodkiewicz reaction appeared ideal for accessing this unsymmetrical diyne, although we were wary of potential issues. Namely, it is well appreciated that homocoupling can complicate these transformations, particularly in cases where the reactants have similar electronic characteristics (e.g., aryl-aryl, alkyl-alkyl).^{1a,b,11} We considered two possible sets of coupling precursors (Figure 2a). In Case 1, a bromoalkyne would be coupled with propyne, but we anticipated this strategy would be complicated by the latter's low boiling point (−23 °C).¹² Case 2, where we switch the bromination of the coupling partners, appeared more attractive from this perspective. Indeed, 1-bromopropyne is known, but previous reports¹³ indicated serious hazardous properties.¹⁴ To circumvent the handling of this compound, we conceived of an in situ approach involving direct elimination from a dibromoolefin and immediate coupling (Figure 2b). In several copper- and palladium-catalyzed reactions, 1,1-dibromo-1-alkenes have been used to generate alkynyl electrophiles, suggesting promise for this strategy.^{15,16} Herein, we report the development of this elimination/coupling procedure, used successfully in our total synthesis effort,¹⁰ and we demonstrate its viability as a method to directly couple volatile alkyne substrates. We also describe preliminary reactivity of these diyne compounds in Ru-catalyzed azide-alkyne cycloadditions, highlighting that 1,2,3-triazoles can be obtained from these diynes in a chemo- and regioselective fashion.

There have been a few reports using 1,1-dibromoalkenes to generate 1-bromo-1-alkynes in situ as precursors for 1,3-diynes.^{16a–c} Unfortunately, these strategies require excess terminal alkyne or elevated temperature (70–100 °C), and none utilized a volatile haloalkyne intermediate. These cases contrasted with conditional stipulations in our desired coupling. First, the terminal alkyne needed to be used as the limiting reagent, chiefly because that coupling component had already been advanced multiple steps in our total synthesis campaign. Second, the temperature needed to be kept low so as to maximize the quantity of volatile alkyne in solution. Although we would consider all options, we felt that in general we wanted to steer away from Pd-based conditions that could result in byproduct formation from enyne reactivity.

Our optimization studies are presented in Table 1. Our strategy here involved first testing with hydrocinnamaldehyde-based dibromoolefin **2a**, whose in situ elimination would be more straightforward to monitor by conventional methods (i.e., TLC). NaH¹⁷ did not induce the elimination (entry 1), while TBAF•3H₂O in DMF¹⁸ was incompatible with the coupling. We found that LiHMDS in THF¹⁹ could induce the elimination at the desired lower temperature, and the desired 1,3-diyne product was observed in low yield when this was subjected to Cu(I) coupling conditions (CuCl, NH₂ OH•HCl, DMF,²⁰ entry 3). Palladium/copper mixed systems^{11c,21} were not as effective (entries 4, 5). However, we found that using aqueous conditions with Cu(I)^{1d} in the coupling process were ultimately the most promising (entries 7, 8).

With this lead, we then switched to the volatile 1-bromopropyne (Table 1, entries 9–13). Because the dibromoolefin is also relatively volatile, we found that the simplest protocol was to synthesize this directly from acetaldehyde using the zinc-based dibromoolefination conditions originally described by Corey and Fuchs (eq 1).^{22,23}

Simply passing the reaction mixture through a plug of silica gel to remove the phosphine byproducts and removing the volatiles afforded the crude dibromoolefin in sufficient purity to be advanced directly. Testing this compound in the above optimized conditions showed they were not as effective. We hypothesized that using a significant excess of the in situ generated bromopropyne was not advantageous, and eventually we found that 1.5 equiv was the optimal amount to employ with an increased loading of CuCl/NH₂OH•HCl, to ensure efficient reaction completion.

(1)

With this protocol fully optimized, we proceed to evaluate this coupling of in situ generated 1-bromopropyne with a range of terminal alkynes (Scheme 1). Aryl alkynes were generally effective. Electron-neutral aryl alkyne coupling partners afforded the 1,3-diyne product in good yields (**7a,b**). Comparatively, terminal alkynes with more electron-rich arenes were lower yielding (**7d,e**), while electron-deficient arenes were tolerated unless the withdrawing functionality was sensitive to reduction (i.e., **7f**). Ortho-substituted aryl bromide **7j** could be obtained, a compound with a convenient coupling handle for potential further manipulations.

Pyridine **7k** was formed in 69% yield, and enynes were also effective (**7l**). Alcohols and ethers were successful alkyne coupling partners, where the products could be formed in generally good yields. Notably, the transformation also performs reasonably consistent upon scaleup; ether **7p** was formed in 76% yield on gram-scale.²⁴ Propiolates and silylalkynes were ineffective in this coupling procedure (**7t,u**).²⁵

We also evaluated our coupling procedure using in situ generated 1-bromobutynes. 1-Bromobutynes is relatively volatile (bp = 90–91 °C), but it is not reported to have similar hazardous properties as those of 1-bromopropyne. However, the method can serve as a useful strategy to circumvent handling 1-butyne (bp = 8 °C). Scheme 2 illustrates examples of couplings originating from 1,1-dibromobutene. Aryl and heteroaryl alkynes were again successful. Propargylic alcohols were coupled effectively to afford products **8d-f** in excellent yields. Benzyl ether **8g** was also formed, albeit in diminished yield compared to the related propynyl example.

1,3-Diynes have been shown to be precursors to thiophenes and pyrroles, among other transformations.^{1c} Toward further expanding the potential applications of these compounds, we sought to investigate 1,3-diyne reactivity in metal-catalyzed azide-alkyne cycloadditions.²⁶ While a few cases using other catalyst systems for intermolecular azide-alkyne cycloadditions with internal alkynes have been reported,²⁷ ruthenium-catalyzed systems have been by far the most prominent.²⁸ Internal 1,3-diynes can pose intriguing questions regarding cycloaddition reactivity, with respect to both chemoselectivity and regioselectivity.²⁹ In a standard 1,3-diyne cycloaddition, there can be up to eight possible products. Selective reactivity has been successfully addressed to some extent with terminal 1,3-diynes using Cu

catalysis via acetylide formation,³⁰ but that mechanistic strategy cannot be extended to internal alkynes. Other selectivity modes, however, may be achievable.³¹

When propargylic alcohol **7o** was subjected to Ru-catalyzed conditions as described by Fokin, an approx. 5:1 ratio of triazole products **9** and **10** were observed (Scheme 3). Cu-catalyzed cycloaddition attempts using this diyne were unsuccessful.^{29a} Interestingly, in the Ru case only the alcohol-adjacent alkyne was reactive; the other alkyne remained intact. Our observation matched hypotheses regarding cycloaddition regioselectivity for internal alkynes with Ru catalysis,^{32,33} where hydrogen bond donors are presumed to enable catalyst coordination with the ligating chloride to favor the regioselectivity outcome for the observed triazole isomer (intermediate **11**). Notably, the alcohol imparting chemoselectivity between two alkynes has not been observed in this transformation. When benzyl ether diyne **7q** was utilized, which lacks this hydrogen bond donor, even better regioselectivity was observed (**12**). The alkyne chemoselectivity was somewhat compromised, however, in that the second alkyne became competitive in cycloaddition as triazole **12** was being formed. Regioselectivities for both additions were excellent (>19:1); origins of these effects are presently unclear. Mechanistically, the most nucleophilic carbon of an alkyne precursor is expected to become C-4 in the triazole,³⁴ but assessments of relative nucleophilicities of the alkyne carbons were inconclusive.³⁵ To our knowledge, ethereal groups have not been invoked as catalyst directing moieties in these cycloadditions, but they could be influential here. In this preliminary study, it appears that synthetically useful levels of selectivity can be attained; factors that impact chemo- and regioselectivity in these azide-alkyne cycloadditions appear to be somewhat interconnected and merit further investigation.

In summary, we have developed a useful addition to the Cadiot-Chodkiewicz alkyne-alkyne cross coupling. The in situ generation of the reportedly hazardous 1-bromo-1-propyne intermediate allows an efficient and convenient workaround to using volatile unit alkynes as coupling partners. We have also showed that this method can be readily scaled for applications in complex molecule synthesis. Preliminary studies in azide-alkyne cycloadditions demonstrate that synthetically useful chemo- and regioselectivities can be achieved. Further investigations of the synthetic utility of these 1,3-diynes are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The National Institutes of Health (NIGMS, R01GM110560) is gratefully acknowledged. H.E.F. was supported by the National Science Foundation and Environmental Protection Agency (CHE-1339674: NSMDS). Mass spectrometry data was acquired on an instrument supported by the NIH (S10RR028859).

REFERENCES

- (1). (a)Siemsen P; Livingston RC; Diederich F *Angew. Chem. Int. Ed* 2000, 39, 2632.(b)Shi Shun ALK; Tykwinski RR *Angew. Chem. Int. Ed* 2006, 45, 1034.(c)Shi W; Lei A *Tetrahedron Lett*

2014, 55, 2763.(d)Cadiot P; Chodkiewicz W In Chemistry of Acetylenes; Viehe HG, Ed.; Marcel Dekker: New York, 1969; Ch. 9.

- (2). For select examples, see:Ladika M; Fisk TE; Wu WW; Jons SD J. Am. Chem. Soc 1994, 116, 12093.Gotteland J-P; Brunel I; Gendre F; Désiré J; Delhon A; Junquéro D; Oms P; Halazy S J. Med. Chem 1995, 38, 3207. [PubMed: 7650673] Listunov D; Saffon-Merceron N; Joly E; Fabing I; Génisson Y; Maraval V; Chauvin R Tetrahedron 2016, 72, 6697.Liang X; Gopalaswamy R; Navas F, III; Toone EJ; Zhou P J. Org. Chem 2016, 81, 4393. [PubMed: 27128325] Heydenreuter W; Kunold E; Sieber SA Chem. Commun 2015, 51, 15784.
- (3). For examples, see:Carbon-Rich Compounds: From Molecules to Materials; Haley MM, Tykwinski RR, Eds.; Wiley-VCH: Weinheim, 2006.Egbe DAM; Birckner E; Klemm EJ Polym. Sci., Part A 2002, 40, 2670.Eisler S; Slepko AD; Elliott E; Luu T; McDonald R; Hegmann FA; Tykwinski RR J. Am. Chem. Soc 2005, 127, 2666. [PubMed: 15725024]
- (4). For examples, see:Diederich F Chem. Commun 2001, 219.Bandyopadhyay A; Varghese B; Sankararama SJ Org. Chem 2006, 71, 454.Berná J; Goldup SM; Lee A; Leigh DA; Symes MD; Teobaldi G; Zerbetto F Angew. Chem. Int. Ed 2008, 47, 4392.
- (5). For reviews related to the hexahydro-Diels-Alder reactions, see:Holden C; Greaney MF Angew. Chem. Int. Ed 2014, 53, 5746.Li W; Zhou L; Zhang J Chem. Eur. J 2016, 22, 1558. [PubMed: 26786814] Karmakar R; Lee D Chem. Soc. Rev 2016, 45, 4459. [PubMed: 26811898] Diamond OJ; Marder TB Org. Chem. Front 2017, 4, 891.
- (6). For seminal reports, see:Hoye TR; Baire B; Niu D; Willoughby PH; Woods BP Nature 2012, 490, 208. [PubMed: 23060191] Miyawaki K; Suzuki R; Kawano T; Ueda I Tetrahedron Lett 1997, 38, 3943.Bradley AZ; Johnson RP J. Am. Chem. Soc 1997, 119, 9917.
- (7). (a)Glaser C Ber. Dtsch. Chem. Ges 1869, 2, 422.(b)Eglington G; Galbraith AR Chem. Ind 1956, 737.(c)Hay AS J. Org. Chem 1960, 25, 1275.
- (8). For a seminal report, see:Chodkiewicz W; Cadiot PC R. Hebd. Seances Acad. Sci 1955, 241, 1055.For reviews, see:Sindhu KS; Thankachan AP; Sajitha PS; Anilkumar G Org. Biomol. Chem 2015, 13, 6891. [PubMed: 26008847] Evano G; Blanchard N; Toumi M Chem. Rev 2008, 108, 3054. [PubMed: 18698737] Hua R Copper-Catalyzed Alkynylation and Alkenylation Reactions of Alkynyl Derivatives: New Access to Diynes and Enynes In Copper-Mediated Cross-Couplings Reactions; Evano G, Blanchard N, Eds.; John Wiley & Sons, Inc.: New Jersey, 2014, pp 455–483.Donnard M; Blanchard N Copper-Catalyzed C–C Bond Formation in Natural Product Synthesis: Elegant and Efficient Solutions to a Key Bond Disconnection In Copper-Mediated Cross-Couplings Reactions; Evano G, Blanchard N, Eds.; John Wiley & Sons, Inc.: New Jersey, 2014, pp 683–723.
- (9). For select recent examples, see:Zhang B; Wang Y; Yang S-P; Zhou Y; Wu W-B; Tang W; Zuo J-P; Li Y; Yue J-M J. Am. Chem. Soc 2012, 134, 20605. [PubMed: 23214963] Mohapatra DK; Umamaheshwar G; Rao RN; Rao TS; Yadav R,SK, J. S. Org. Lett 2015, 17, 979.Kanikarapu S; Marumudi K; Kunwar AC; Yadav JS; Mohapatra DK Org. Lett 2017, 19, 4167. [PubMed: 28762745] Karmakar R; Lee D Org. Lett 2016, 18, 6105. [PubMed: 27934339] Matsuoka J; Matsuda Y; Kawada Y; Oishi S; Ohno H Angew. Chem. Int. Ed 2017, 56, 7444.Schmidt B; Audörsch SJ Org. Chem 2017, 82, 1743.Schmidt B; Audörsch S Org. Lett 2016, 18, 1162. [PubMed: 26886865] Kuilya TK; Goswami RK Org. Biomol. Chem 2016, 14, 8789. [PubMed: 27714187] Kraus GA; Dong P; Qu Y; Evans A; Carpenter S Tetrahedron Lett 2016, 57, 5185.Galler DJ; Parker KA Org. Lett 2015, 17, 5544. [PubMed: 26509219] Ungeheuer F; Fürstner A Chem. Eur. J 2015, 21, 11387. [PubMed: 26140703] Wang Y; Liu Q-F; Xue J-J; Zhou Y; Yu H-C; Yang S-P; Zhang B; Zuo J-P; Li Y; Yue J-M Org. Lett 2014, 16, 2062. [PubMed: 24666217] Takamura H; Wada H; Lu N; Ohno O; Suenaga K; Kadota IJ Org. Chem 2013, 78, 2443.Takamura H; Wada H; Lu N; Kadota I Org. Lett 2011, 13, 3644. [PubMed: 21688861]
- (10). Newcomb ET; Knutson PC; Pedersen BA; Ferreira EM J. Am. Chem. Soc 2016, 138, 108. [PubMed: 26716762]
- (11). (a)Negishi E; Anastasia L Chem. Rev 2003, 103, 1979. [PubMed: 12744698] (b)Montierth JM; DeMario DR; Kurth MJ; Schore NE Tetrahedron, 1998, 54, 11741.(c)Alami M; Ferri F Tetrahedron Lett 1996, 37, 2763.(d)Barbu E; Tsibouklis J Tetrahedron Lett 1996, 37, 5023. (e)Amatore C; Blart E; Genet JP; Jutand A; Lemaire-Audoire S; Savignac MJ J. Org. Chem 1995, 60, 6829.

- (12). It should be noted that we tried this strategy, but it never afforded the product in greater than 50% yield.
- (13). (a) Brandsma L; Verkruijsse HD *Synthesis* 1990, 984. (b) Nash BW; Thomas DA; Warburton WK; Williams TD J. Chem. Soc 1965, 2983. [PubMed: 14289815] (c) Hatch LF; Kidwell LE J. Am. Chem. Soc 1954, 76, 289. (d) Cleveland FF; Murray MJ J. Chem. Phys 1943, 11, 450. (e) Chodkiewicz W *Ann. Chim* 1957, 2, 861.
- (14). Ref 13d: "The residue, or the pure compound, ignites quickly when it comes in contact with air." Ref 13c: "1-bromo-1-propyne is spontaneously flammable in air." We have had no adverse experiences with this compound using our protocols.
- (15). For a review on metal catalysis-based examples, see: Chelucci G *Chem. Rev* 2012, 112, 1344. [PubMed: 22085400] Legrand F; Jouvin K; Evano G *Isr. J. Chem* 2010, 50, 588.
- (16). For select examples, see: Rao MLN; Islam SS; Dasgupta P *RSC. Adv* 2015, 5, 78090. Rao MLN; Dasgupta P; Ramakrishna BS; Murty VN *Tetrahedron Lett* 2014, 55, 3529. Huang Z; Shang R; Zhang Z; Tan X; Xiao X; Fu YJ *Org. Chem* 2013, 78, 4551. Kiruthika SE; Perumal PT *Org. Lett* 2014, 16, 484. [PubMed: 24378141] Rao MLN; Jadhav DN; Dasgupta P *Org. Lett* 2010, 12, 2048. [PubMed: 20377270] Berciano BP; Lebrequier S; Besselièvre F; Piguel S *Org. Lett* 2010, 12, 4038. [PubMed: 20735077] Coste A; Karthikeyan G; Couty F; Evano G *Angew. Chem. Int. Ed* 2009, 48, 4381. Shen W; Thomas SA *Org. Lett* 2000, 2, 2857. [PubMed: 10964383]
- (17). Durand-Reville T; Gobbi LB; Gray BL; Ley SV; Scott JS *Org. Lett* 2002, 4, 3847. [PubMed: 12599474]
- (18). Okutani M; Mori YJ *Org. Chem* 2009, 74, 442.
- (19). Grandjean D; Pale P; Chuche J *Tetrahedron Lett* 1994, 35, 3529.
- (20). Ghose BN; Walton DR M. *Synthesis* 1974, 890.
- (21). (a) Wityak J; Chan JB *Synth. Commun* 1991, 21, 977. (b) Shi W; Luo Y; Luo X; Chao L; Zhang H; Wang J; Lei AJ *Am. Chem. Soc* 2008, 130, 14713.
- (22). Corey EJ; Fuchs PL *Tetrahedron Lett* 1972, 3769.
- (23). Dibromoolefin 1a had been purified prior to the coupling.
- (24). We also note that diyne 4b was synthesized as part of our total synthesis effort using this procedure in 66% yield on >15 g scale.
- (25). Propiolates are frequently troublesome in Cadiot-Chodkiewicz couplings, likely due to conjugate addition complications with present nucleophilic species (e.g., amine). This may be another reason for the unsuccessful formation of 7f. It is not clear why silylalkyne 7u was not formed, given its prior success in these couplings under similar conditions. See, Marino JP; Nguyen HN *J. Org. Chem* 2002, 67, 6841. Perhaps the byproducts of the in situ elimination suppressed this specific reactivity. [PubMed: 12227823]
- (26). For select reviews, see: Meldal M; Törnøe CW *Chem. Rev* 2008, 108, 2952. [PubMed: 18698735] Hein JE; Fokin VV *Chem. Soc. Rev* 2010, 39, 1302. [PubMed: 20309487] Liang L; Astruc D *Coord. Chem. Rev* 2011, 255, 2933. Haldón E; Nicasio MC; Pérez PJ *Org. Biomol. Chem* 2015, 13, 9528. [PubMed: 26284434]
- (27). [Cu]: Díez-González S; Correa A; Cavallo L; Nolan SP *Chem. Eur. J* 2006, 12, 7558. [PubMed: 16969776] Sau SC; Roy SR; Sen TK; Mullangi D; Mandal SK *Adv. Synth. Catal* 2013, 355, 2982. Shen T; Huang X; Liang Y-F; Jiao, N. *Org. Lett* 2015, 17, 6186. [PubMed: 26646089] [Ni]: Kim WG; Kang ME; Lee JB; Jeon MH; Lee S; Lee J; Choi B; Cal PMSD; Kang S; Kee J-M; Bernardes GJL; Rohde J-U; Choe W; Hong SY *J. Am. Chem. Soc* 2017, 139, 12121. [PubMed: 28814075] [RB(OH)2]: Zheng H; McDonald R; Hall DG *Chem. Eur. J* 2010, 16, 5454. [PubMed: 20373314]
- (28). Johansson JR; Beke-Sofmai T; Stålsmeded AS; Kann N *Chem. Rev* 2016, 116, 14726. [PubMed: 27960271]
- (29). For examples of AAC reactions using internal 1,3-diynes, see: Cu: Mandadapu AK; Sharma SK; Gupta S; Krishna DGV; Kundu B *Org. Lett* 2011, 13, 3162. [PubMed: 21591629] Ru: Zheng J; Chen Q-Y; Sun K; Huang Y; Guo Y *Tetrahedron Lett* 2016, 57, 5757. Cu: Szadkowska A; Zaorska E; Staszko S; Pawlowski R; Trzybinski D; Wozniak K *Eur. J. Org. Chem* 2017, 4074.
- (30). For select examples, see: Luu T; McDonald R; Tykwinski RR *Org. Lett* 2006, 8, 6035. [PubMed: 17165923] Fiandanese V; Bottalico D; Marchese G; Punzi A; Capuzzolo F *Tetrahedron* 2009, 65,

10573. Aizpurua JM; Azcune I; Fratila RM; Balentova E; Sagartzazu-Aizpurua M; Miranda JJ *Org. Lett* 2010, 12, 1584. [PubMed: 20196611] Doak BC; Scanlon MJ; Simpson JS *Org. Lett* 2011, 13, 537. [PubMed: 21226513] Kai K; Sogame M; Sakurai F; Nasu N; Fujita M *Org. Lett* 2018, 20, 3536. [PubMed: 29792438]

- (31). Zheng J; Chen Q-Y; Sun K; Huang Y; Guo Y *Tetrahedron Lett* 2016, 57, 5757.
- (32). (a) Boren BC; Narayan S; Rasmussen LK; Zhang L; Zhao H; Lin Z; Jia G; Fokin VV *J. Am. Chem. Soc* 2008, 130, 8923. [PubMed: 18570425] (b) Majireck MM; Weinreb SM *J. Org. Chem* 2006, 71, 8680. [PubMed: 17064059] (c) Zhang C-T; Zhang X; Qing F-L *Tetrahedron Lett* 2008, 49, 3927.
- (33). Reports using propargylic alcohols describe very high regioselectivities (>19:1). For an outlier, see, Neumajer G; Tóth G; Béni S; Noszál B *Cent. Eur. J. Chem* 2014, 12, 115.
- (34). Boren BC; Narayan S; Rasmussen LK; Zhang L; Zhao H; Lin Z; Jia G; Fokin VV *J. Am. Chem. Soc* 2008, 130, 8923. [PubMed: 18570425]
- (35). ¹³C NMR did not give a clear indication of respective carbon nucleophilicity. See the Supporting Information.

Figure 1.
 1,3-Diynes in natural product synthesis.

a) Gelsenicine coupling strategies **b) Elimination/coupling approach**

Figure 2.
1,3-Diynes from volatile bromoalkynes - synthetic strategy.

Scheme 1.

Coupling of in situ-generated 1-bromopropyne. ^a CH₂Cl₂ was added to the coupling reaction to solubilize the reactants. ^b Coupling stirred 4 h at 0 °C and 2 h at 23 °C. ^c Gram scale.

Scheme 2.
Coupling of in situ-generated 1-bromobutyne.

Scheme 3.
1,3-Diynes in Azide-Alkyne Cycloadditions

Reaction optimization.

Table 1.

entry	equiv 1	base (equiv)	catalyst mol%	mol% NH ₂ OH·HCl	equiv <i>n</i> -BuNH ₂	solvent	time (h)	isolated yield (%)
R = -CH ₂ CH ₂ Ph (a)								
1	—	NaH (2.0)	—	—	—	—	—	^b
2	2.0	TBAF·3H ₂ O (10)	CuCl (20)	30	30	DMF	24	0
3	2.0	LiHMDS (2.0)	CuCl (20)	30	2	DMF	24	21
4	2.0	LiHMDS (2.0)	CuCl (2)	0	2 ^c	DMF	24	0
5	2.0	LiHMDS (2.0)	Pd(dba) ₂ (4)	30	2	THF	18	14
6	2.0	LiHMDS (2.0)	CuCl (50)	150	10	THF	18	28
7	2.0	LiHMDS (2.0)	CuCl (20)	30	10	H ₂ O/THF	18	49
8	2.0	LiHMDS (2.0)	CuCl (20)	30	20	H ₂ O/THF	3	80
R = -CH ₃ (b)								
9	2.0	LiHMDS (2.0)	CuCl (20)	30	20	H ₂ O/THF	18	44
10	2.5	LiHMDS (2.5)	CuCl (20)	30	20	H ₂ O/THF	1	27
11	1.0	LiHMDS (1.0)	CuCl (20)	30	20	H ₂ O/THF	1	57
12	1.5	LiHMDS (1.5)	CuCl (20)	30	20	H ₂ O/THF	1	69
13	1.5	LiHMDS (1.5)	CuCl (40)	60	20	H ₂ O/THF	1	72

^a Elimination conditions: NaH: THF, 0 to 23 °C, 24 h; TBAF·3H₂O: DMF, 60 °C, 3 h; LiHMDS: THF, -78 to 0 °C, 1.5 h.

^b Bromoalkyne intermediate **2a** was not observed; coupling was not attempted.

^c Et₃N used as base instead of *n*-BuNH₂.