Organic Letters
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

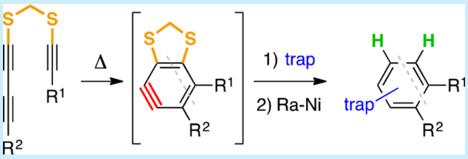
A Traceless Tether Strategy for Achieving Formal Intermolecular Hexadehydro-Diels−Alder Reactions

Merrick Pierson Smela and Thomas R. Hoye*

Department of Chemistry, University of Minnesota, 207 Pleasant Street SE, Minneapolis, Minnesota 55455, United States

Supporting Information

ABSTRACT: A synthetic strategy formally equivalent to an intermolecular hexadehydro-Diels−Alder (HDDA) reaction is described. Sulfur-based linkers were designed and constructed by joining terminal alkynes or diynes using alkyne thiolate chemistry. The resulting tetraynes and triynes successfully underwent HDDA cyclization and benzyne trapping. Linker removal by reductive desulfurization was uneventful. The strategy was also found suitable for the tetradehydro-Diels−Alder (TDDA) reaction.



The cyclization of a 1,3-diyne with a diynophile to generate a benzyne intermediate[1] in a practical and controlled manner, a process now known as the hexadehydro-Diels−Alder (HDDA) reaction,[2] requires that the reacting alkynes be tethered so as to render the process intramolecular in nature (cf. **1** to **2**, Figure 1). To date, the tethers in the vast majority of reported HDDA substrates have been a three-atom linker (cf. ABC in **1**−**3**).[3] In particular, bimolecular HDDA reactions of a pair such as **4a** and **4b** to produce **5** are currently unknown and would pose considerable difficulties with kinetics[4] and selectivity.

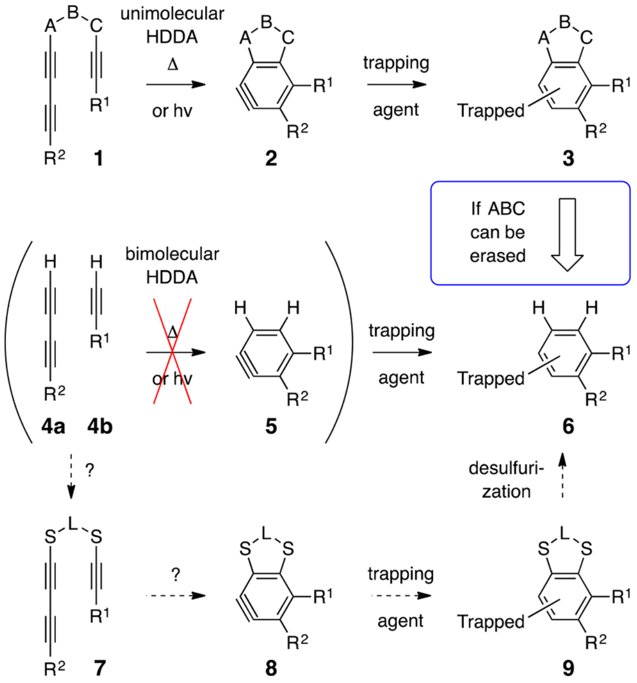


Figure 1. Hypothesis driving this study: Temporary tethering of a 1,3-diyne to a diynophile (cf. **7**) to support intramolecular HDDA cyclization (**1** to **3** via **2**, or **7** to **9** via **8**), and removal of the tether (**3** or **9** to **6**), allows for an otherwise infeasible intermolecular HDDA reaction (cf. **4a** + **4b** to **6** via **5**).

Our current work was motivated by our interest in identifying a tether that, once finished with its primary purpose of holding the reacting groups proximal, could be cleaved to give a product identical to that of a bimolecular HDDA reaction (cf. **3** to **6**). One apparent strategy for accomplishing this is to link the diyne and diynophile through a terminal sulfur atom on each (cf. **7**), since hydrogenolytic removal of the sulfide moieties would introduce a pair of *ortho*-hydrogen atoms in place of the earlier connecting atoms (cf. **9** to **6**). This plan raised, at least, the following questions: could sufficiently efficient chemistry be found to construct substrates such as **7**, and would the bis-sulfide linkage be compatible with the HDDA cyclization (**7** to **8**)? We were optimistic that benzyne trapping reactions of species such as **8** and final desulfurization of **9** would proceed well.

One attractive S−L−S tether appeared to be the methylenedithyl moiety (i.e., SCH_2S). This presented the challenge of how one might prepare a structure such as **15** (Figure 2). To demonstrate proof-of-principle, we decided to synthesize this symmetrical tetrayne. More specifically toward that end, alkynyllithium reagents react efficiently with elemental sulfur (0.125 equiv S_8) to generate lithium alkynethiolates (cf. **11**). Moreover, these ambident nucleophiles are known to cleanly alkylate at the soft sulfur atom.[5] Indeed, we found that the diynes **12** and **13** could be efficiently prepared by sequential *in situ* alkylation with either dibromo- or diiodomethane, followed by alkyne desilylation. These bisalkynes are known entities, having been previously prepared by an alternative sequence—namely, sulfenylation of trimethylsilylethynyllithium with $CH_2(SCN)_2$ (11% after deprotection).[6]

Received: August 2, 2018

DOI: 10.1021/acs.orglett.8b02473
Org. Lett. XXXX, XXX, XXX−XXX

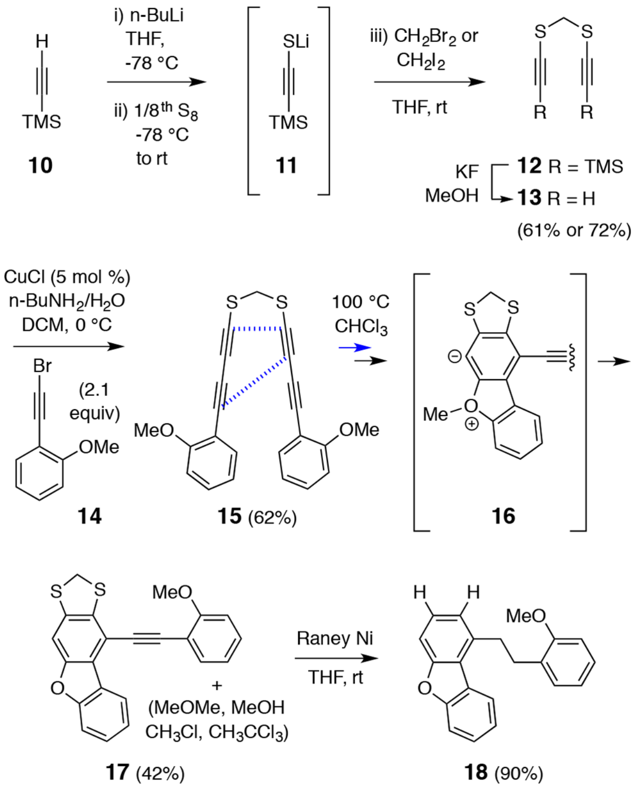


Figure 2. Proof-of-concept: Linker synthesis, Cadiot−Chodkiewicz coupling, HDDA, and desulfurization.

We were then pleased to see that **13** was an acceptable donor partner in Cadiot−Chodkiewicz cross-coupling reactions with 1-bromoalkynes. Accordingly, the symmetrical, SCH_2S-linked tetrayne **15** was produced upon reaction of diyne **13** with the bromoalkyne **14**. Moreover, the alkynylsulfide moieties were compatible with the thermal conditions required to promote HDDA cyclization. More specifically, **15**, containing this new, unique linker, showed a half-life of ca. 40 min at 85 °C (external bath *T*, $CDCl_3$, ^1H NMR monitoring). The benzodithiole derivative **17** was the major product observed (42% yield after purification). We have observed participation by *o*-methoxy groups in other benzyne trapping reactions via what we proposed as analogs of the zwitterion **16**. The fate of the methyl group was identified as methanol (from intervention by water), dimethyl ether, methyl chloride, and 1,1,1-trichloroethane (the last two following protonation of the zwitterion by chloroform) in those experiments.[7] Finally (and to establish feasibility of the last phase of this strategy for traceless tethering), the SCH_2S moiety was reductively cleaved upon exposure of **17** to hydrogen adsorbed on Raney nickel. This reaction also saturated the alkyne to provide **18**, the formal product of a bimolecular HDDA reaction cascade.

To demonstrate an alternative approach for assembling other requisite polyyne substrates, we carried out the experiments summarized in Figure 3. Phenylbutadiyne (**19**)[8] was lithiated, treated with S_8, and exposed to CH_2I_2 to more directly provide the tetrayne **20**. When heated in the presence of furan, this substrate gave rise to adduct **21** in very good yield.

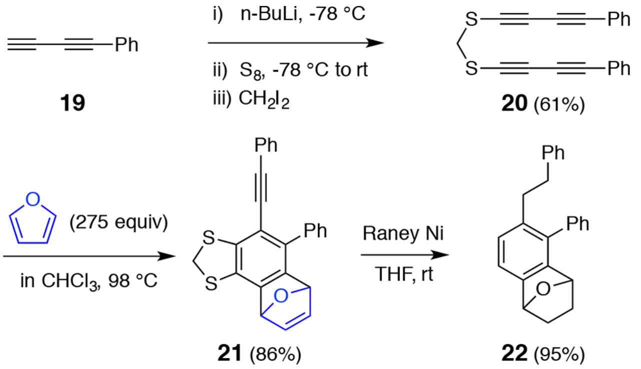


Figure 3. Alternative synthesis of tetrayne substrates and an example of external benzyne trapping.

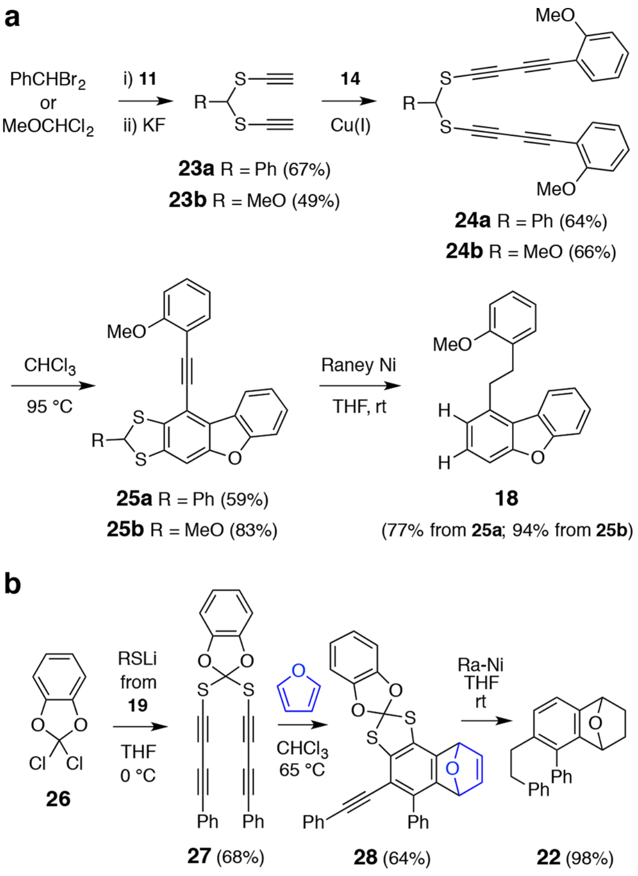
Because furan is such an efficient (fast) benzyne trapping reagent, even though bimolecular, we were curious whether it would outcompete the internal *o*-methoxy group present in substrate **15**. When that tetrayne was heated in the presence of excess furan (47 equiv), the major product formed (i[9]) was a furan-trapped adduct analogous to compound **21**, and only a trace of **17** was observed (<1%, ^1H NMR analysis of the crude product mixture). That is, furan reacted sufficiently quickly with the benzyne to outcompete the intramolecular trapping by the methoxy group.

Side reactions that we suspect diminish the yield of product formation are (i) trapping of the benzyne intermediate by a thioether groups,[10] present in both the substrate and product and/or (ii) methylation of those sulfur atoms by methyl-oxonium ion intermediates. Consistent with this, we observed (i) a diminished yield when the reaction of **15** was performed with a higher initial concentration of tetrayne substrate and (ii) the yield of the product **21** was significantly higher than that of **17**, even though the former reaction was performed at 3-fold higher initial substrate concentration than the latter. To possibly protect against these sorts of processes, we explored modifying the linker with bulky or inductively electron-withdrawing groups.

With this goal in mind, we screened a series of geminal dihalides in a reaction with alkynethiolate **11** to find one(s) suitable for linker construction (Figure 4a). We found that α,α-dibromotoluene and dichloromethyl methyl ether each readily gave the corresponding linked diynes **23a** and **23b**. The tetraynes **24a** and **24b** were easily formed by cross-coupling with **14**. Each successfully underwent the HDDA reaction with trapping by the *o*-methoxy group to provide the dibenzofurans **25a** and **25b**.

While searching to identify a linker having a fully substituted carbon between the bis-sulfide atoms, we found that 2,2-dichlorobenzodioxole **26**, known to engage a simple arylthiolate,[11] reacted with alkynethiolates (Figure 4b). Although the hydrolytic lability of the resulting dithioorthocarbonate precluded use of standard Cadiot−Chodkiewicz coupling conditions, we adapted the strategy used to prepare **20** (i.e., from diyne **19**) to directly produce tetrayne **27**. The HDDA cyclization of this tetrayne in the presence of furan proceeded uneventfully to produce the expected adduct **28** in good yield. Similarly to compound **21**, **28** underwent clean reductive desulfurization upon treatment with Raney nickel to yield **22**.

Next, we investigated the effect of central linker atom substitution on the rate of the HDDA cycloisomerization to the corresponding benzyne intermediate (Figure 4c). By heating a solution of each tetrayne in deuterated chloroform, we determined the rates by *in situ* NMR analysis of substrate



c influence of the dithiolane linker structure on the rate of HDDA cyclization

linker subst. substrate	H,H 15‡	H,H 15‡	H,H 20§	Ph,H 24a‡	MeO,H 24b‡	catecholate 27§
temp	85 °C	65 °C	65 °C	65 °C	65 °C	65 °C
k_{rel}	7.3	1.1	1.0	3.0	5.2	9.3
$t_{1/2}$ (min)	36	247	263	87	50	28

Figure 4. Effect of the difference of linker structures on the rates and efficiencies of the HDDA cycloisomerization and product formation.

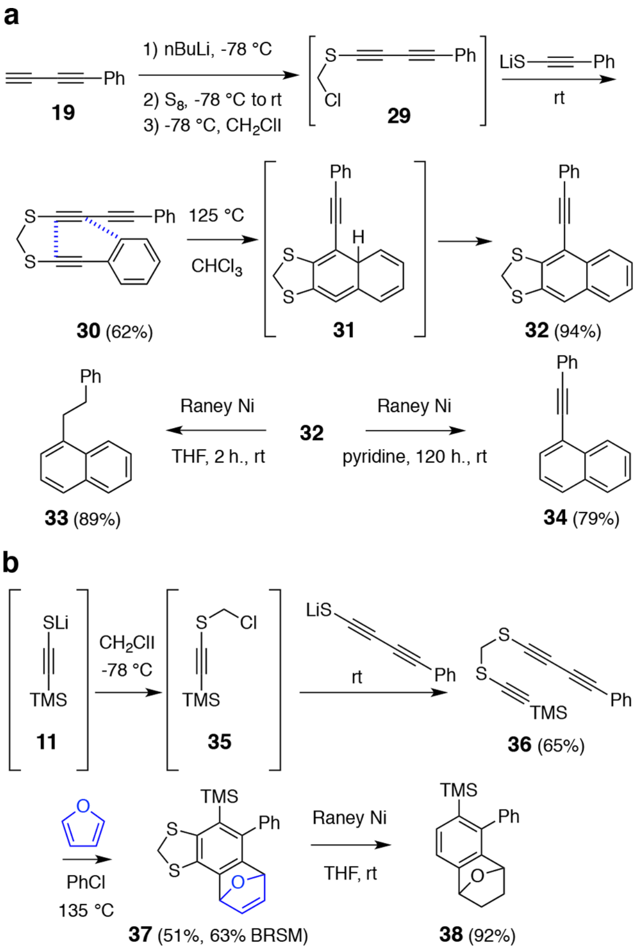


Figure 5. (a) Phenyl-substituted triyne **30** is diverted to a TDDA cycloisomerization pathway. (b) When the TDDA reaction is not possible, triyne **36** undergoes the HDDA reaction in the normal fashion.

consumption relative to an internal standard. In accordance with our expectations, the reactions followed a first-order rate law. The relative rates of conversion are normalized to the slowest reaction—that of the parent tetrayne **20** at 65 °C ($t_{1/2}$ = 263 min). The related substrate **15**, having the same linker, cyclized at a nearly identical rate. Under these conditions, substrates **24a**, **24b**, and **27** reacted at progressively faster rates ($t_{1/2}$'s of 87, 50, and 28 min, respectively), reflecting the effect of greater substitution. Even at ambient temperature, **24b** and **27** slowly cyclized ($t_{1/2}$ approximately 2 days) as observed by NMR. HDDA reactivity at room temperature is unusual but not without precedent.[12] These experiments show that with proper substitution a sulfur-based tether can enable an HDDA cyclization under mild thermal conditions.

To this point, all of the examples involved the synthesis of symmetric compounds having identical diyne units. We next modified our approach to allow for the synthesis of the pair of asymmetrically linked triynes **30** and **36** (Figure 5). Using chloroiodomethane, we were able to selectively displace the iodide ion at −78 °C with 1 equiv of an alkynethiolate; the resulting solution of chloromethyl sulfide intermediate (i.e., **29** or **35**, the latter demonstrated to be isolable, if desired)[13] was then directly treated with a second alkynethiolate and allowed to warm to ambient temperature. Using this procedure, we isolated the asymmetric triynes **30** (62%) and **36** (65%).

30 as well as **36** was heated in the presence of furan, but quite different courses of reaction occurred. The former underwent a tetradehydro-Diels−Alder (TDDA)[14] reaction to form the naphthalene derivative **32**. When performed in the absence of furan, the reaction (46 h at 125 °C) gave **32** in high yield, establishing that the HDDA process conceivable within **32** is not competitive.[15] This shows that the traceless tether idea is applicable to a second type of cycloisomerization, the TDDA reaction.

On the other hand, when the terminal aryl substituent in **30** was replaced by the trimethylsilyl group in triyne **36** so as to disallow the TDDA pathway, HDDA reactivity reemerged to give furan adduct **37**. It is also notable that the temperature for onset of the TDDA reaction of **30** (to give **32**) was lower than that of the HDDA process in substrate **36** (to give **37**). While the HDDA required 135 °C, the TDDA product was formed, slowly, at 100 °C (see Supporting Information).

Not surprisingly, the sulfur−carbon bonds in both of the product benzodithioles could be cleaved by the action of Raney nickel (in THF) to give adducts **33** and **38**, respectively.

DOI: 10.1021/acs.orglett.8b02473
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Additionally, when the hydrogenolysis of **32** was effected in pyridine,[16] the reaction proceeded considerably more slowly and led to the desulfurized product **34** as the major product, having its alkyne still intact.

In conclusion, we have (i) put forth the concept of a traceless tether for the HDDA reaction (Figure 1), (ii) demonstrated a proof-of-concept example using an SCH_2S linker to support the HDDA reaction, which is then readily removed by treatment with Ra–Ni (Figure 2), (iii) explored the effect of substitution on the methylene linker, which increases the HDDA reactivity (Figure 4), and (iv) extended the concept to a triyne substrate for each of the TDDA and HDDA reactions; these triynes were prepared by one-pot successive alkylation of two different alkynethiolates with CH_2ClI (Figure 5). The HDDA reaction can quickly generate complex substituted arenes, and traceless tethers enable the synthesis of a new structural class of products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02473.

> Experimental procedures, data for characterization of new compounds, and copies of ^1H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hoye@umn.edu.

ORCID

Merrick Pierson Smela: 0000-0001-5816-7098
Thomas R. Hoye: 0000-0001-9318-1477

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this work was provided by the Institute of General Medical Sciences of the U.S. Department of Health and Human Services (R01 GM65597, then R35 GM127097). M.P.S. was supported by a Gleysteen–Heisig summer fellowship and by the University of Minnesota Undergraduate Research Opportunities Program.

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(3) The lone exception to date is one instance of a triyne joined through a five-atom linker, leading to a seven-membered ring fused to the benzyne (and derived benzenoid products).[2a]

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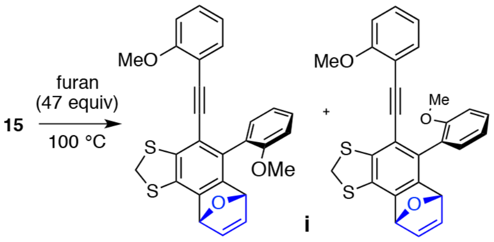
(9) The furan adduct **i** was isolated as a mixture (approximately 2:1) of two coeluting diastereomeric atropisomers: ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 1H), 3.77 (s, 2H), 3.79 (s, 2H), 3.80 (s, 1H), 4.49 (d, J = 9.6 Hz, 0.3H), 4.50 (d, J = 9.6 Hz, 0.7H), 4.58 (d, J = 9.6 Hz, 0.7H), 4.59 (d, J = 9.6 Hz, 0.3H), 5.34 (dd, J = 1.6, 1.0 Hz, 0.7H), 5.43 (dd, J = 1.8, 0.9 Hz, 0.3H), 5.64 (dd, J = 1.7, 1.0 Hz, 0.7H), 5.65 (dd, J = 1.8, 0.9 Hz, 0.3H), 6.84–6.78 (m, 2H), 7.11–6.96 (m, 4.7H), 7.14 (dd, J = 7.5, 1.4 Hz, 0.7H), 7.24–7.18 (m, 1H), 7.41–7.36 (m, 1H), 7.52–7.48 (m, 0.3H), 7.57–7.55 (dd, J = 7.5, 1.6 Hz, 0.7H).



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(12) See ref 2a for an account of a serendipitous room-temperature HDDA reaction.

(13) A small amount of this compound was observed (GC-MS) following chromatographic purification of product **30**. This suggested that it would likely be feasible to isolate intermediates of this sort, if desired. However, due to stench and concerns about toxicity we did not attempt this.

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