Removable Linkers for the Hexadehydro-Diels-Alder Reaction

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Abstract

In the hexadehydro-Diels-Alder (HDDA) reaction, a diyne and an alkyne react in a formal [4 + 2] cycloaddition to produce an *o*-benzyne intermediate, which can be trapped to produce a wide variety of substituted arenes. For reasons of kinetics, the HDDA reaction is only practical as an intramolecular reaction with a linker between the two reacting groups. To date, only a small number of viable linker classes are known. Because the linker remains in the product after the reaction, this limits the types of compounds the HDDA reaction can produce. In the current work, sulfur-based linkers were developed which can be removed by reductive desulfurization after the HDDA reaction. These linkers were constructed using alkyne thiolate chemistry, enabling them to be directly synthesized from terminal alkynes or diynes in a one-pot reaction. Silicon-linked compounds were also investigated, but they were found to be unreactive under both thermal and photochemical HDDA conditions. Overall, these results help to delineate which linkers are feasible for the HDDA reaction, and also provide a new synthetic strategy that broadens the set of compounds accessible via this reaction.

Table of Contents

Introduction and Background

o-Benzynes are versatile reactive intermediates with many uses in organic synthesis. Most notably, their electrophilic character means that they can be trapped with a wide variety of nucleophiles in order to form substituted aromatic compounds. They can also participate in cycloaddition reactions (such as by serving as the dienophile in a Diels-Alder reaction), Alder-ene reactions, and C-H insertions.[1,2] For these reasons, *o*-benzynes are starting points for a wide variety of other compounds, and thus they are highly useful in synthetic chemistry.

There are many methods of forming *o*-benzynes, but most involve the 1,2-elimination of two groups positioned *ortho* to each other on a benzene ring. This elimination usually requires the use of additional reagents, and often under strongly basic conditions. Furthermore, the requirement for a preformed 1,2-disubstituted arene limits the practical utility of this method, since in many cases the starting material is difficult to synthesize.

In recent years, an alternative method for o-benzyne generation has been developed: the hexadehydro-Diels-Alder (HDDA) reaction. Early studies of this reaction investigated the flash vacuum pyrolysis of 1,3,8-nonatriyne and the synthesis of fluorenol derivatives.[3,4] More recently, the Hoye group has undertaken a broader exploration of the possibilities of using the HDDA reaction in organic synthesis.[5]

The HDDA reaction involves the formal [4+2] cycloaddition of a diyne and an alkyne, which forms an *o*-benzyne. Importantly, this requires only thermal activation, and no additional reagents which could interfere in the process. Once the *o*-benzyne is formed, it can be trapped as usual, and the simpler conditions permit a wider variety of trapping

agents: for example, dichlorination can be performed using dilithium tetrachlorocuprate,[6] or cycloalkanes can be donors for 2H transfer. The versatility of the HDDA reaction holds great promise for the synthesis of a wide variety of substituted aromatic compounds.

Despite its similar name to the Diels-Alder reaction, which follows a concerted mechanism, recent computational studies have revealed that the HDDA reaction most likely follows a stepwise mechanism involving diradicals (Figure 1).[7,8] The rate-limiting step is *o*-benzyne formation, with trapping proceeding quickly afterwards. Notably, the *o*-benzyne formation has a relatively high activation energy (roughly 100 kJ/mol, depending on substrate) but is exergonic once this barrier is overcome, with a free energy change of roughly -240 kJ/mol. Besides having a large energetic barrier, benzyne formation also has a substantial entropic barrier since the diyne and diynophile must adopt a precise relative position.[7] The required positioning is best provided by the *gauche* conformation of a three-atom linker.

Although an intermolecular HDDA reaction could be possible in some cases with especially reactive diynes, the high concentrations required for the reaction to proceed (given second-order kinetics and a generally high activation energy) would lead to reaction of the benzyne with additional diyne starting material, causing oligomerization. One

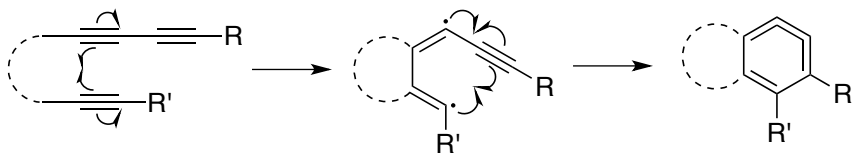


Figure 1: Mechanism of the HDDA reaction. A triyne forms a diradical intermediate, which then closes to a benzyne (shown here as the cumulene resonance structure).

example of this is the explosive polymerization of neat 1,3-butadiyne.[9,10] While carefully controlled HDDA cascades can be useful under certain conditions for producing polycyclic aromatic hydrocarbons, uncontrolled oligomerization is generally not desired. Therefore, for all practical purposes the HDDA reaction must occur intramolecularly, requiring a linker between the diyne and alkyne.

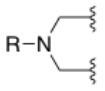
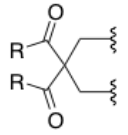
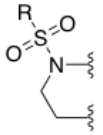
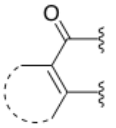
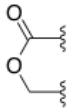
In contrast to the wide variety of benzyne traps employed with the HDDA reaction, only a few classes of linkers have been studied. A review of the literature showed only thirteen unique linker classes out of 746 published examples of triynes and tetraynes (Figure 2). Notably, only four new classes have been published in the past five years since the Hoye group's first publication on the reaction.[2,11–13] Since these linkers all remain in the product after the reaction, the small number of known linker classes limits the diversity of compounds that can be produced using the HDDA reaction. Thus, developing new linkers is an important area of research.

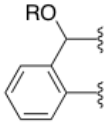
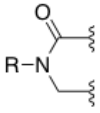
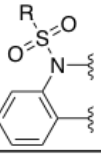
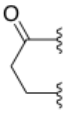
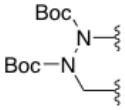
Among previously published linkers, all but one contain exactly three atoms. The sole exception is a five-atom linker that requires substantially harsher conditions (195 °C and 32 hr) for the reaction and gives somewhat lower yields than the equivalent three-atom linkers.[5] While there are some literature examples of four-atom linkers in metal-catalyzed formal cycloadditions of diynes and alkynes, this is not the HDDA reaction and does not proceed through a benzyne.[14] It is likely, although not completely certain, that the geometry of four-atom linkers is unsuitable for the HDDA reactions. This is probably because the more relaxed geometry of a four-atom linker permits the diradical formed at the start of the HDDA reaction to close into a strained cyclobutadiene. Although this is much less stable than an *o*-benzyne, it is likely favored kinetically with a four-atom linker.

Although a three-atom linker is necessary for an efficient HDDA reaction, not every linker with three atoms will work well. A recent investigation found that varying the linker structure could greatly alter the reaction rate constant, with the best linker eight orders of magnitude faster than the worst linker with a measureable rate.[11] Some linkers simply failed to give any observable HDDA product; others gave product only with tetraynes, and not with the less reactive triynes. Linkers with smaller angles between the diyne and the diynophile led to faster rates, likely because of less strain in the transition state. Sterics played an additional role in controlling the proportion of molecules in the reactive *gauche* conformation. In general, linkers containing heteroatoms within the three-atom chain led to faster reaction rates than their methylene analogs did. Furthermore, electron-withdrawing groups in the linker resulted in greater rates. These complex requirements for linker structure further limit the possible substrates that can be used for the HDDA reaction.

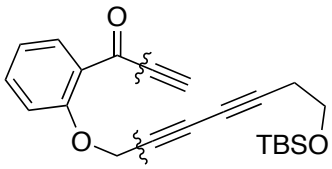
For the atoms in the linker, all previously published examples have combinations of carbon, nitrogen, and oxygen. However, this shared characteristic does not represent a strict requirement. Previous research involving a metal-templated linker formed by coordination of a bis(phosphanyl)diyne with platinum and tungsten suggests the possibility of incorporating larger atoms.[15] The HDDA reaction proceeds with the P-Pt-P linker, but only after the additional coordination to tungsten forces the diynes into the proper conformation. Thus, the P-Pt-P linker alone is insufficient to drive the HDDA reaction, and thus it cannot be considered a true HDDA linker.[15] Although the metal-templated P-Pt-P linker does not work well by itself, it provided inspiration for this study, which involved incorporating larger heteroatoms such as sulfur and silicon into linkers.

A: Three-atom linkers

Structure	Number of Examples	Year First Published
	185	2013[2]
	162	2012[5]
	115	2012[5]
	75	2012[5]
	58	2012[5]
	43	2012[5]

Structure	Number of Examples	Year First Published
	38	1997[4]
	36	2012[5]
	22	2016[13]
	6	2014[11]
	5	1997[3]
	1	2016[12]

B: Sole example of an HDDA substrate with a five-atom linker



1 example, published 2012[5]

Figure 2: List of all previously published HDDA linkers found in the Reaxys database, annotated with the number of examples and publication year of the first example. There are 746 total examples of three-atom linkers and one example of a five-atom linker.

Besides developing new linker structures, another way to diversify the possible products of the HDDA reaction is through the development of cleavable and functionalizable linkers. If the linker need not remain unchanged in the final product, then the linker structure does not limit the product structure. A cleavable linker serves to temporarily connect a diyne with an alkyne so that the HDDA reaction can proceed; afterwards, the linker is removed. Like the metal-templated linker, this makes what would otherwise be an intermolecular reaction intramolecular.

Sulfur compounds are promising for cleavable linkers. Carbon-sulfur bonds can be reductively cleaved through the use of transition metal catalysts, most notably Raney nickel. This is the basis for many important transformations in synthetic chemistry. For example, the Mozingo reduction, in which an aldehyde or ketone is converted to a dithioacetal (or dithioketal) and then reduced to the alkane with Raney nickel, has been widely used in organic synthesis. Likewise, a linker with sulfur as first and third atoms can be reductively cleaved to remove it entirely.

The most promising strategies to synthesize sulfur-based linkers involve the use of alkynethiolate anions as intermediates. These can be produced by reaction of alkynyllithium compounds with elemental sulfur; although the analogous alkynethiols rapidly tautomerize to thioketenes, the lithium alkynethiolates are stable enough to be trapped by reaction with electrophiles.[16] When a geminal bis-electrophile, such as diiodomethane, is used for this purpose, a three-atom linker is formed (Figure 3).

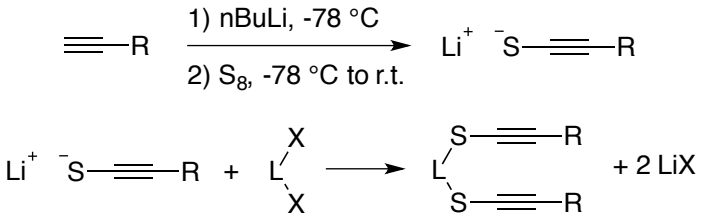


Figure 3: Formation of a generic sulfur-based three-atom linker from an alkyne. Here, L represents a linking atom and X represents a leaving group.

This linker can then be used in the HDDA reaction. Afterwards, the carbon-sulfur bonds can be reductively desulfurized to carbon-hydrogen bonds. This desulfurization can happen under a variety of conditions, most notably with Raney nickel or nickel boride. More selective desulfurization conditions have been developed for aryl sulfides,[17] but these were not investigated in the present study.

One drawback of sulfur-based linkers is the propensity for sulfur to act as a nucleophile and trap benzynes. Although this trapping can be useful in some cases for organic synthesis,[12] in this context it is problematic. However, it can be mitigated by adding electron-withdrawing groups to the linker, adding steric bulk around the sulfur, or simply using a higher concentration of external trapping agent to trap the benzyne before it reacts with the linker in another molecule.

Besides sulfur, silicon is also promising for the creation of cleavable linkers. Silyl chlorides readily react with alkyne anions to form alkynylsilanes, and this reaction can be used to synthesize the linkers. Assuming the HDDA reaction proceeds, the product could be treated with fluoride to cleave the linker. This would likely be more tolerant of other functional groups than reductive desulfurization of a sulfur-based linker, although it would be incompatible with other silicon-based protecting groups. In some cases, additional functionalization beyond simple deprotection would be possible, such as with the Hiyama

coupling. For benzoxadisiloles formed from disiloxane linkers, iodination and elimination would yield another *o*-benzyne,[18] which could subsequently be trapped. Silicon-based linkers have been successfully used for normal intramolecular Diels-Alder reactions,[19] but so far it is unclear whether they could be used for the more sterically sensitive HDDA reaction.

In the present study, tetraynes containing sulfur- and silicon-based three atom linkers were synthesized from alkyne starting materials. For the sulfur-based linkers, screening was conducted to determine the various possibilities for substitution at the central atom. For dithioacetal and dithioorthoformate linkers, the HDDA reaction proceeded smoothly, and various strategies were developed to decrease unwanted trapping by sulfur. Furthermore, a sulfur-linked tetrayne was straightforwardly synthesized in a one-pot reaction from the diyne. Silicon-linked tetraynes were also synthesized and investigated, but cyclization to *o*-benzynes was unsuccessful, likely due to steric effects.

Results and Discussion

Dithioacetal and dithioorthoformate linkers

The simplest sulfur-based cleavable linker is a formaldehyde dithioacetal, and this was a logical starting point for the investigation. Tetraynes having this linker can be accessed from the Cadiot-Chodkiewicz coupling of bis(ethynylthio)methane (**1**) with bromoalkynes. Starting material **1** was obtained from the deprotection of the TMS derivative. Initially, a preparation was attempted from dithiocyanatomethane and lithiated TMS-acetylene according to a literature procedure,[20] but this gave only trace amounts of the desired product. A more satisfactory procedure was developed, in which lithiated TMS-acetylene was first reacted with elemental sulfur to form the alkynethiolate. The alkynethiolate was then trapped with dibromo- or diiodomethane to give **1a**, which was deprotected to **1** (Figure 4). The use of diiodomethane gave somewhat higher yields (72% vs. 61%), as expected given its higher reactivity toward nucleophiles.

Diyne **1** was next coupled with bromoalkyne **4**, which was prepared from 2-iodoanisole by the sequence of Sonogashira coupling with TMS-acetylene, desilylation,

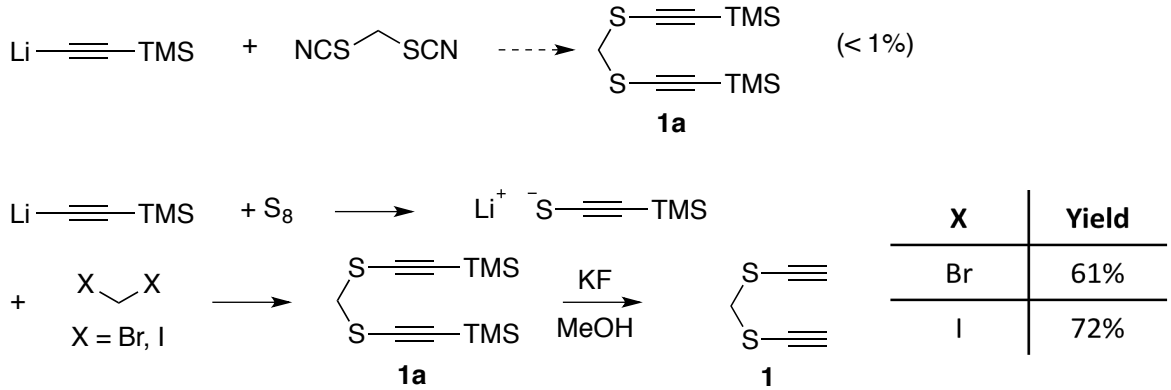


Figure 4: Synthesis of sulfur-linked diyne **1** via its protected derivative **1a**. First, a literature procedure was attempted for producing **1a** from dithiocyanatomethane, with unsatisfactory results. Next, **1a** was successfully prepared using alkynethiolate chemistry with dibromo- or diiodomethane. **1a** was subsequently deprotected to yield **1**.

and bromination with NBS and catalytic $AgNO_3$. Under Cadiot-Chodkiewicz conditions, **1** and **4** were coupled to give the tetrayne **5**. When heated in chloroform solution (3.3 mM), the tetrayne **5** cyclized to the HDDA product **8** in moderate (42%) yield (Figure 5).

I hypothesized that this relatively low yield was due to the use of the *o*-methoxy group as a benzyne trap. First, since thioethers are more nucleophilic than ethers, the linker itself was a better trap than the *o*-methoxy group. Ideally, a trapping reaction will be faster than the rates of undesired benzyne engagement of a sulfur atom in either the substrate **5** or the product **8**. Each of these undesired reactions is bimolecular in nature, whereas capture by the *o*-methoxy group is intramolecular. When more concentrated solutions were used for the reaction, the yield was lower, decreasing to roughly 20% at 10 mM and nearly zero at 25 mM (notably, 25 mM works well for non-sulfur-linked tetraynes). This is consistent with the hypothesis that intermolecular side reactions decrease yield.

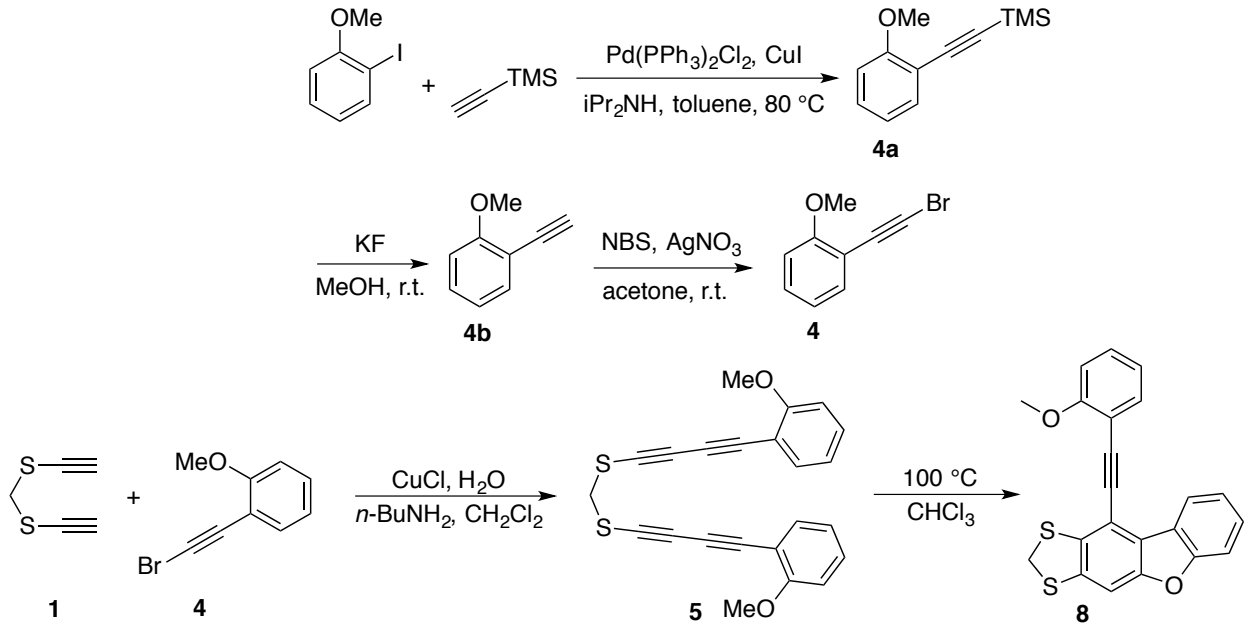


Figure 5: Synthesis and HDDA cyclization of sulfur-linked tetrayne. First, bromoalkyne **4** was prepared in a sequence of reactions from 2-iodoanisole. Diyne **1** was coupled with **4** to form tetrayne **5**, which was heated to form benzofuran **8** via the HDDA reaction.

Second, the initial product of the intended trapping was a methyl oxonium zwitterion. Although this intermediate could be quenched by transfer of the methyl group to the chloroform solvent, a competing reaction I envisioned was methylation of the thioether to form a sulfonium ion, a process that would also diminish the yield of product **8**. The addition of *t*-butanol to the reaction mixture increased the yield of the desired product, perhaps by intercepting the methylated oxonium ion intermediate to form methyl *t*-butyl ether. Use of diisopropylamine with a similar intent was also explored, but this additive was sufficiently nucleophilic that it trapped the benzyne faster than the methoxy oxygen.

In order to investigate sulfur-based linkers that were less reactive towards benzynes and oxonium ions, a screening protocol was performed using various geminal bis-electrophiles containing bulkier or electron-withdrawing substituents. In these experiments, a solution of lithium TMS-acetylenethiolate in THF was added to the candidate compounds. Diiodomethane was used as a positive control. The reaction mixtures were analyzed by GCMS and TLC. Of the thirteen electrophiles tested (Figure 6), only three (α,α-dibromotoluene, dichloromethyl methyl ether, and the diiodomethane control) gave the corresponding desired products **1a**, **2a**, and **3a**.

For the other electrophiles, some were likely too sterically bulky to allow for substitution (for example, 2,2-dibromopropane). Although alkynethiolates can be trapped by trityl chloride in an S_N1 reaction, the reaction is slow and low-yielding.[21] In the case of a larger-scale reaction using 9,9-dibromofluorene, bifluorenylidene was detected as the major product by GCMS and TLC and was isolated in 79% yield. A possible mechanism for the formation of bifluorenylidene involves alkynethiolate attack at bromine instead of

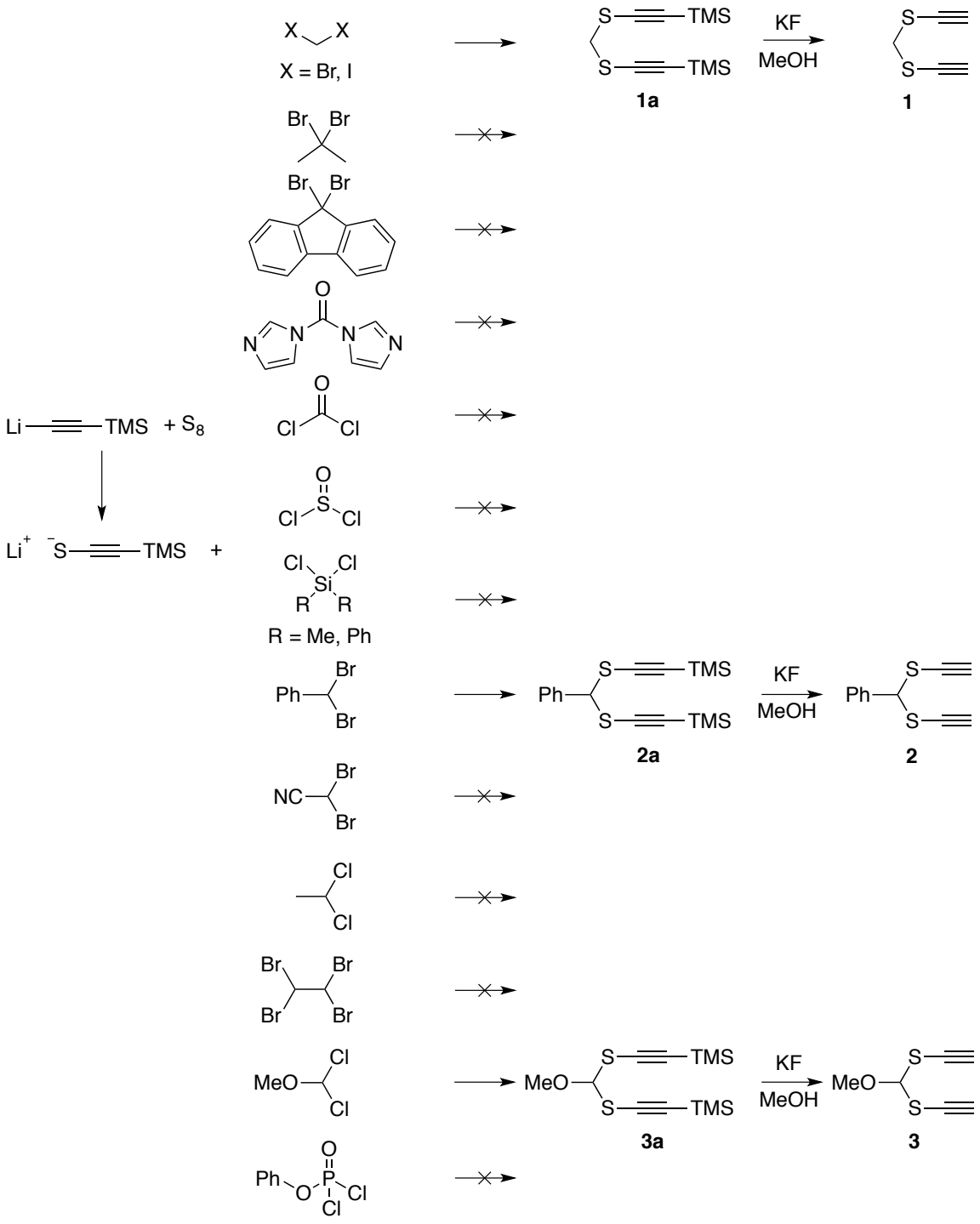


Figure 6: Screening reactions for linker formation. A solution of lithium (trimethylsilyl)ethynethiolate was mixed with various electrophiles. The products were analyzed by TLC and GCMS. In the cases where the desired products were formed, the reactions were verified by running them on a larger scale and isolating the products. After deprotection, this gave **1**, **2**, and **3**.

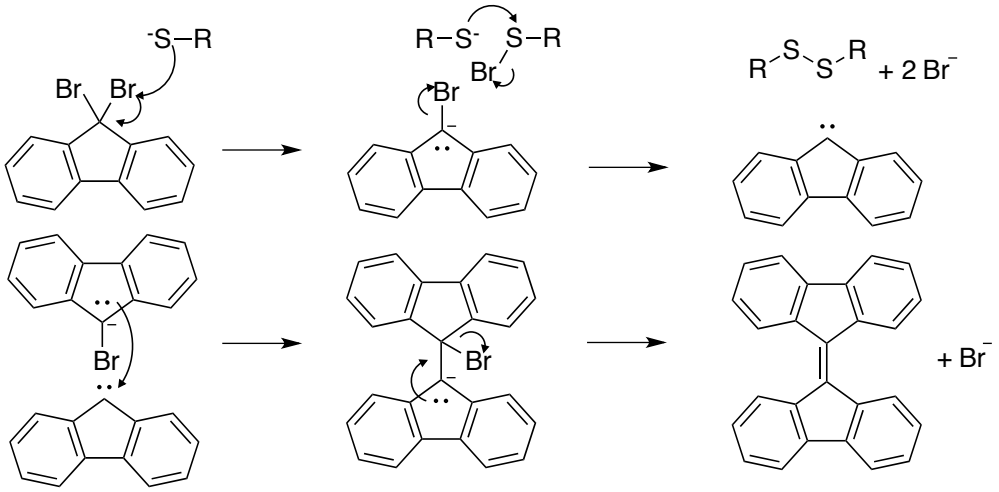


Figure 7: Possible mechanism of bifluorenylidine formation from 9,9-dibromofluorene and thiolate. First, the thiolate attacks at bromine, forming a sulfenyl bromide and a resonance-stabilized fluorenyl anion. The sulfenyl bromide reacts with another equivalent of thiolate to form a disulfide. Meanwhile, some of the fluorenyl anion eliminates bromide to form a singlet carbene. This carbene then acts as an electrophile in reaction with additonal carbanion. The adduct formed subsequently eliminates bromide to form bifluorenylidine. Direct carbene dimerization would also be possible, but less likely given the lower concentration of carbene than carbanion.

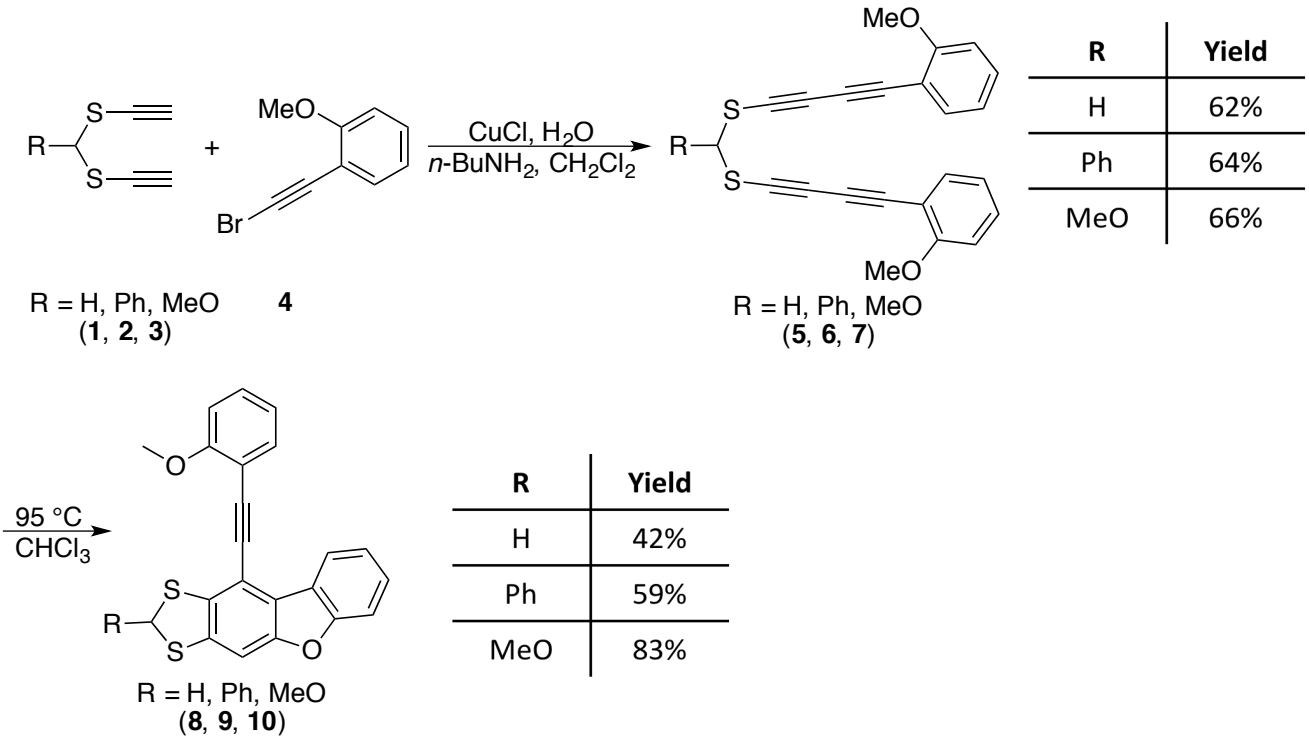
carbon, eventually leading to carbene formation (Figure 7). Addition of the intermediate carbanion to the carbene gives an adduct from which bromide elimination would give bifluorenylidene. Additional experiments to confirm or refute this mechanism could include a carbene trap, such as an olefin.

Other electrophiles likely reacted with the alkynethiolate, but not to form the desired product. A previous study suggests that silyl chloride electrophiles may have formed a bond with carbon instead of sulfur, leading to thioketene formation, an undesirable side reaction in this case.[22] Although formation of a dithiocarbonate linker was unsuccessful, an *S*-alkynyl thiocarbonate was formed by reaction of the lithium alkynethiolate with methyl chloroformate. This result suggests that in the case of the reaction with phosgene, either the intermediate *S*-alkynyl thiochloroformate, or the

dithiocarbonate itself, was unstable and decomposed. Dithiosulfite and dithiophosphate linkers likely failed for similar reasons. Notably, there are no literature examples of isolable *S,S*-dialkynyl dithiocarbonates, dithiosulfites, or dithiophosphates. *S,S*-divinyl dithiocarbonate is known, but it is unstable and readily polymerizes.[23]

After this screening, **2** and **3** were synthesized on a larger scale using a method analogous to the synthesis of **1**. These compounds were then coupled with **4** to form the tetraynes **6** and **7**. The yield of these coupling reactions was roughly equivalent to that of **5.** Upon heating in chloroform, **6** and **7** underwent the HDDA reaction to form cyclized products **9** and **10** (Figure 8).

The higher yields of the reactions of **6** and **7** to **9** and **10** support the idea that the relatively low yield of the reaction of **5** to **8** was caused by interference from the thioether



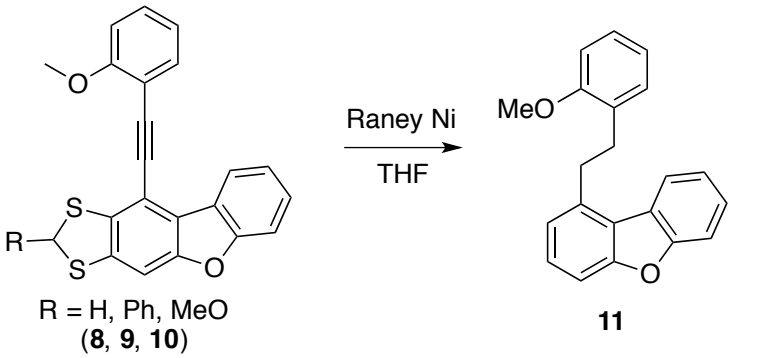
R	Yield
H	62%
Ph	64%
MeO	66%

R	Yield
H	42%
Ph	59%
MeO	83%

Figure 8: Synthesis of tetraynes **5**, **6**, and **7**, and subsequent HDDA cyclizations to benzofurans **8**, **9**, and **10**. The procedures were analogous to those described in Figure 5.

groups in the linker. Compound **6** contains a bulky phenyl substituent that likely lowers the linker reactivity via steric effects. Compound **7** has a methoxy substituent, and although the methoxy group provides less of a steric barrier than the phenyl group of **6**, the electron-withdrawing character diminishes the nucleophilicity of the sulfur atoms. In general, dithioorthoformates are less nucleophilic than the equivalent dithioacetals, and this is no exception. The Thorpe-Ingold effect may also play an additional role; bulky substituents should increase the proportion of molecules in the reactive conformation, leading to increased HDDA reaction rates. If the rate of the desired reaction increases relative to the rate of side reactions, then yield increases. In particular, a previous kinetics study found increased yield with faster-reacting HDDA linkers.[11] Of course, extremely bulky linkers may be unfeasible to prepare (for example, the fluorene-based linker), so there is a limit to the improvements possible from increasing the bulk.

After the HDDA products **8**, **9**, and **10** were isolated and characterized, the compounds were reductively desulfurized to cleave the linker. Two different desulfurization reagents were investigated: nickel boride and Raney nickel. The first of these was prepared *in situ* by addition of sodium borohydride to a solution of nickel(II) chloride hexahydrate in methanol/THF. When tested on **8**, nickel boride was able to cleave the linker, but the conversion was incomplete and a variety of products resulted. Although careful optimization of the reaction conditions may enable nickel boride to be more useful, Raney nickel was found to be a more reliable reagent. Compounds **8**, **9**, and **10** were all successfully desulfurized with excess Raney nickel in THF (Figure 9). The excess Raney



R	Yield
H	90%
Ph	77%
MeO	94%

Figure 9: Synthesis and HDDA cyclization of sulfur-linked tetraynes. Tetraynes **5**, **6**, and **7** were prepared by Cadiot-Chodkiewicz coupling of bromoalkyne **4** with sulfur-linked diynes **1**, **2**, and **3**. Thermal cyclization afforded HDDA products **8**, **9**, and **10**. These could all be reductively desulfurized using Raney nickel to yield the common product **11**.

nickel also reduced the alkyne to the alkane. If the reaction was stopped early, the main product was the desulfurized compound where the alkyne was reduced to the alkene, but substantial amounts of starting material still remained. The yield was best with compounds **8** and **10**. Although the reaction was only performed once with compound **9**, and the lower yield may merely represent experimental variance, it is also possible that the bulky phenyl substituent somewhat hinders the desulfurization process.

Direct one-pot linker construction from a diyne

In some cases, it may be more advantageous to directly construct a three-atom linker between two diynes. In order to prove the possibility of direct linker construction, a dithioacetal linker was made using phenylbutadiyne **12**. This was converted to the alkynyllithium, and then elemental sulfur was added to convert this into the alkynethiolate. The lithium alkynethiolate was trapped with diiodomethane, forming a dithioacetal-linked tetrayne **13**. The overall yield for this process was 61%, which is roughly equivalent to the yields for the analogous reactions forming **5**, **6**, and **7** using TMS-acetylene. This shows that

diynes can also be used to form alkynethiolates which can react with electrophiles to form linkers (Figure 10).

The tetrayne **13** was then heated in chloroform, with furan as an external HDDA trap. The high furan concentration limited unwanted trapping of the benzyne with the linker by quickly reacting with the benzyne to form the adduct **14**. In comparison with the internal methoxy trapping with the equivalent linker, the yield for this reaction was considerably greater (86% vs 42%). This supports the hypothesis that eliminating unwanted trapping can increase the yield of the reaction. Furthermore, with the furan trap higher tetrayne concentrations could be used without sacrificing much yield, and this is beneficial because it requires less solvent for the same amount of product. Overall, the results of this reaction showed that the dithioacetal linker works better with high concentrations of an efficient benzyne trap.

Linker removal for HDDA product **14** proceeded under the same desulfurization conditions used for **8**, **9**, and **10**. The use of excess Raney nickel resulted in the reduction of

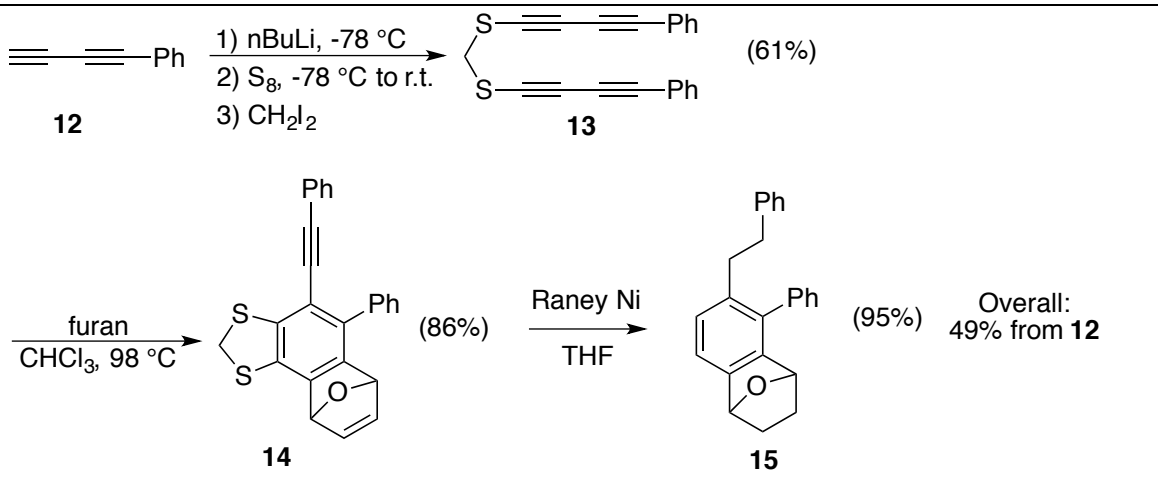


Figure 10: Synthetic route from **12** to **15**. A dithioacetal-linked tetrayne was constructed directly from **12** via the alkynethiolate. Next, HDDA cyclization with external furan trap afforded **14**. Finally, this was desulfurized using Raney nickel to yield the product **15**.

not only the alkyne; additionally, the dihydro-1,4-epoxynaphthalene was reduced to the tetrahydro form in the product **15**. However, the bridging oxygen atom remained in place. The overall yield, with purifications included, of **15** from phenylbutadiyne was 49%. Although this value could likely be improved with additional optimization of reaction, workup, and purification conditions, even now it is not bad, given that the structural complexity of the product would make synthesis by other methods challenging.

Silicon linkers

The possibility of silicon-based removable linkers was also investigated. In a manner analogous to the synthesis of **13**, tetraynes **16** and **17** were also directly synthesized from diyne **12** by lithiation followed by reaction with a bis(chlorosilane) (Figure 11). However, unlike the sulfur-linked tetraynes, these silicon-linked ones were unreactive. Even when heated to 215 °C in cyclooctane, they remained unchanged. Although no benzyne formed, neither did the compounds decompose. Based on a recent report of a photochemical HDDA reaction activated by UV light,[24] tetraynes **16** and **17** were

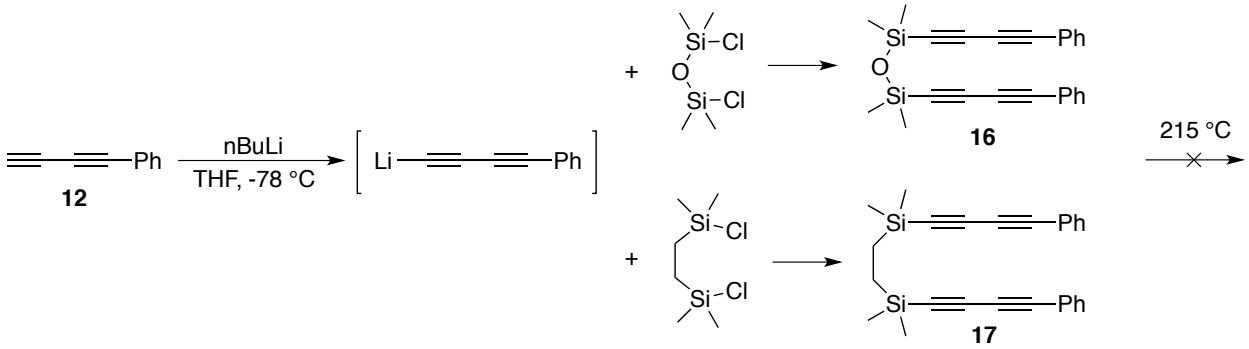


Figure 11: Preparation of silicon-linked tetraynes. Tetraynes **16** and **17** were synthesized from **12** by lithiation followed by reaction of the alkynyllithium with bis(chlorosilanes). Upon heating, even to 215 °C, these tetraynes remained unchanged and did not undergo the HDDA reaction. Neither did they react when irradiated by UV light.

irradiated in solution, but neither 254 nor 300 nm light caused any detectable changes besides a slight orange discoloration.

The remarkable stability of these tetraynes stands in contrast to the analogous sulfur-linked tetraynes, and to the parent phenylbutadiyne. This could be due to steric effects; in particular, the methyl groups on the silicon atoms likely force the diyne units away from each other. It is known that terminal silyl groups greatly stabilize polyynes,[25] and a similar effect might happen in this situation. Unlike with polyynes, in this context this stability is undesirable. Although having hydrogen atoms in place of the methyl groups might lead to a more reactive linker, these compounds would be considerably more difficult to synthesize and handle due to instability towards oxygen and water. Therefore, silicon-based cleavable linkers are likely impractical.

Conclusions and Future Directions

In conclusion, this study has expanded the scope of the HDDA reaction by developing new sulfur-based removable linkers. In the case of compounds **1**, **2**, and **3**, these linkers were pre-formed, and tetraynes could be produced by Cadiot-Chodkiewicz coupling with a bromoalkyne. In contrast, the linkers could also be produced in a one-pot reaction starting from a diyne, as in the case of compound **13**. Various factors influencing the yield of HDDA reactions using these linkers were examined, and minimizing unwanted trapping was found to be necessary for improving the yield. A dithioorthoformate linker performed best in this respect.

These experiments also showed that the sulfur-based linkers can be cleaved by reductive desulfurization, leaving only hydrogen atoms in their place. Thus, the overall process of linker formation, HDDA reaction, and desulfurization is equivalent to an intermolecular HDDA reaction between terminal diynes. Since true intermolecular HDDA reactions are unfeasible, this removable linker method opens up new synthetic pathways that previously were inaccessible and expands the set of compounds that the HDDA reaction can produce.

In addition, this study explored the properties of silicon-linked tetraynes. These compounds, which were prepared from the reaction of lithiated diynes with bis(silyl chlorides), proved to be remarkably stable both thermally and photochemically. Although the compounds will be less useful for the purposes of synthesis because they do not undergo the HDDA reaction, this negative result helps to define the boundaries of feasible HDDA linkers.

This study was mainly a proof-of-concept for the sulfur-based removable linkers, and it now opens many worthwhile future directions of research. First, the method could be adapted for the synthesis of triynes and asymmetrical tetraynes. This could be done through use of chloromethyl alkynyl sulfanes (which can be prepared using bromochloromethane and alkynethiolates)[26] or similar compounds. Reaction with an additional equivalent of a different alkynethiolate would produce a triyne or asymmetrical tetrayne, depending on the particular compound used. This would be useful for producing a wider set of compounds using this method.

Second, more selective desulfurization conditions could be investigated to improve the range of functional groups possible in the final product. With the current Raney nickel desulfurization method, alkenes and alkynes are reduced to the corresponding alkanes. While this may be acceptable in some cases, it still limits the possible compounds that can be produced by the method. A more selective desulfurization, such as by use of bis(cyclooctadiene)nickel(0) and triethylsilane,[17] could be more useful in this respect. In the case of dithioorthoformate linkers, it may be possible to hydrolyze the linker to the free thiols, which would allow the use of milder, and thus more selective, desulfurization conditions.

Finally, functionalizable linkers could be developed instead of merely cleavable ones. An example of this could be a carboxylic acid anhydride linker, which could be converted into a variety of carboxylic acid derivatives or further functionalized via decarboxylative cross-coupling. This would enable the production of an even broader set of products using the HDDA reaction.

Experimental Section:

General Notes:

TLC was performed on plastic-backed silica gel plates. Visualization was by UV light, or for compounds not absorbing UV, by ceric ammonium molybdate stain. For flash chromatography, the stationary phase was E. Merck silica gel (230-400 mesh).

GCMS data were obtained using an Agilent 6890N chromatograph with EI detection (electron energy 70 eV). Samples were ethyl acetate solutions of the analytes. HRMS data were obtained using a Bruker BioTOF II (ESI-TOF) spectrometer. Samples were dissolved in methanol/CH_2Cl_2, with sodium formate as a sodium ion source and polyethylene glycol as an internal standard. Reported *m/z* values are the median of five independent measurements.

IR spectra were measured with a Midac Prospect 4000 FT-IR instrument, using ATR of thin film samples on a germanium window. The spectral resolution was 4 cm^{-1}. NMR spectra were obtained with a Bruker Avance 400 MHz spectrometer. ^{1}H spectra are referenced to TMS = 0 ppm, and ^{13}C spectra are referenced to $CDCl_3$ = 77.16 ppm.

Melting points were measured on a Bristoline Bristolscope heated stage microscope. Reported reaction temperatures are external oil bath temperatures. Compounds were stored at -20 °C. This was particularly important for compounds **7** and **11**, which decomposed at room temperature.

Caution: compounds **2**, **3**, and especially **1** are quite malodorous. Additionally, many of the electrophiles tested (most notably phosgene) are highly toxic, and all procedures must be performed with proper training and safety equipment.

General procedure for alkyne thiolate preparation:

The alkyne was dissolved in anhydrous THF (1.2 mL/mmol) under N_2 and the solution was chilled to -78 °C. A solution of n-butyllithium (2.5 M in hexanes, 1 eq.) was added slowly with stirring. The solution was stirred for 15 min., and then elemental sulfur (1 eq.) was added. To accomplish this step, the reaction flask was briefly uncapped. After reestablishing the N_2 atmosphere, the stirred reaction mixture was allowed to warm to r.t. over a period of 1 hr. During this time, the sulfur dissolved to give an orange solution. At this point, the solution was ready for the addition of the electrophile.

General procedure for deprotection of trimethylsilyl alkynes:

The protected alkyne was added to a solution of potassium fluoride dihydrate in methanol (0.8 M KF, 2 eq. per TMS group). If necessary, small amounts of THF (generally <5 mL) were added to help the alkyne dissolve. The solution was stirred under N_2 and the reaction was monitored by TLC and/or GC-MS. After completion (usually 15 min. to 2 hr.), the methanol was removed by rotary evaporation, and water and ethyl acetate were added (1 mL each per mmol alkyne). The organic layer was removed, washed with brine, dried ($MgSO_4$), and concentrated to yield the deprotected product.

General procedure for Cadiot-Chodkiewicz coupling:

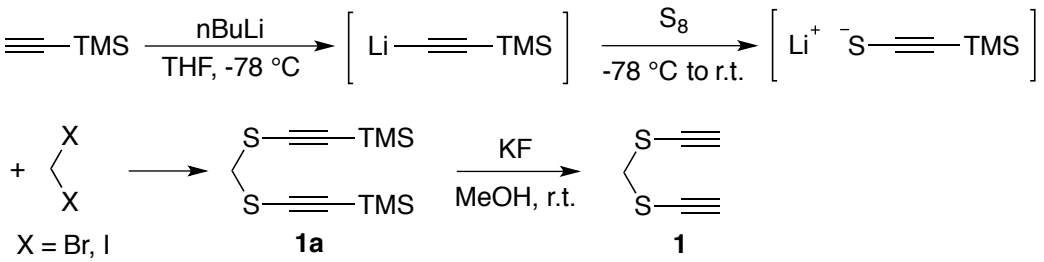
Copper(I) chloride was dissolved in a 4:6 mixture of n-butylamine:water (5 mL/mmol alkyne). Hydroxylamine hydrochloride was added to reduce trace copper(II) and change the color from blue to colorless. This solution was cooled to 0 °C in an ice bath. The substrates to be coupled were dissolved in dichloromethane (5 mL/mmol alkyne), and this solution was added to the reaction flask all at once. The biphasic mixture was vigorously

stirred under N_2, and the reaction was monitored by TLC. Upon completion (typically 1 - 4 hr.), the organic layer was removed and washed with portions of sat. aq. NH_4Cl until these portions no longer took on a blue color. The organic layer was dried ($MgSO_4$) and concentrated by rotary evaporation to yield the crude product.

General procedure for desulfurization with Raney nickel:

Raney nickel wet with water (approx. 2 g wet per mmol sulfur in reactant) was stirred with THF to exchange the solvents. During the washing, care was taken to ensure that the Raney nickel was never dry. The excess THF was decanted, and a THF solution of the compound to be desulfurized (approx. 0.2 M) was added. The resulting suspension was stirred under N_2 atmosphere and the reaction was monitored by TLC and/or GCMS. Upon completion, the Raney nickel was removed by filtration with glass wool, and washed with additional THF. During this process, the Raney nickel was never allowed to dry. The filtrate and washings were combined and evaporated to yield the crude product.

Preparation of methanebis(ethynylsulfane) (**1**)



An alkyne thiolate solution was formed using TMS-acetylene (3.5 mL, 2.45 g, 25 mmol) according to the general procedure. To this solution, diiodomethane (0.97 mL, 3.2 g, 12 mmol) was added. The reaction mixture was stirred overnight, and then saturated NH_4Cl (5 mL) and water (5 mL) were added. The organic layer was removed, washed with

brine (5 mL), dried ($MgSO_4$), and evaporated to yield the crude product as a brown oil (3.3012 g). This product was deprotected according to the general procedure to yield the deprotected product (1.102 g, 8.593 mmol, 72%). The reaction could also be performed with dibromomethane, although the yields were lower (61% instead of 72%).

Data for TMS-protected compound **1a**:

TLC: (19:1 hexanes/ethyl acetate) R_f 0.44, (9:1 hexanes/ethyl acetate) R_f 0.65

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.19 (s, 12H) and 4.05 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ -0.0, 43.1, 92.1, and 104.3.

GC-MS: t_R = 7.24 min, *m/z* 272 ($M^{+\bullet}$), fragments 226, 211, 143, 121, 97, and 73.

Data for deprotected compound **1**:

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.99 (s, 2H), and 4.06 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 42.1, 72.1, and 85.6.

GC-MS: t_R = 3.20 min, *m/z* 128 ($M^{+\bullet}$), fragments 127, 84, 71, and 57.

Screening reaction:

An alkyne thiolate solution was formed using TMS-acetylene (3.5 mL, 2.45 g, 25 mmol) according to the general procedure. Then, the solution was chilled to 0 °C.

Ten test tubes were flushed with N_2, sealed with septa, and placed in an ice bath at 0 °C. Then, various potential linker compounds were dispensed into the tubes:

Compound	Volume (μL)	Amount (mmol)
Diiodomethane	81	1
Dichloromethane	64	1
1,1-dichloroethane	82	1
Dichloromethyl methyl ether	89	1
α,α-dibromotoluene	166	1
Dibromoacetonitrile	87	1
1,2-dibromoethane	87	1
1,1,2,2-tetrabromoethane	58	0.5
Phenyldichlorophosphate	149	1
Dichlorodimethylsilane	122	1

To each tube, an aliquot (4 mL, approx. 3 mmol) of the alkyne thiolate solution was added. The tubes were removed from the ice bath and the reactions were allowed to proceed overnight. The reactions were stopped by addition of sat. aq. NH_4Cl (2 mL) to each tube, and product presence was detected by GC-MS and TLC. Diiodomethane, dichloromethyl methyl ether, α,α-dibromotoluene, and 1,2-dibromoethane yielded the desired products; the other compounds did not.

Other electrophiles (phosgene in toluene, thionyl chloride, carbonyldiimidazole, 2,2-dibromomethane, 9,9-dibromofluorene, and diphenyldichlorosilane) were tested individually, with procedures analogous to the preparations of **1**, **2**, and **3**. Dibromotoluene and 9,9-dibromofluorene were synthesized using the following procedures:

Preparation of α,α-dibromotoluene

Benzyl bromide (2.5753 g, 15.057 mmol) and *N*-bromosuccinimide (3.1085 g, 17.47 mmol) were added to 25 mL $CHCl_3$. The mixture was heated overnight in a closed glass vessel at 75°C with stirring under strong illumination by a white incandescent light placed above the tube. Then, the reaction mixture was allowed to cool to r.t. and the solvent was evaporated to give a crude slush (6.332 g) containing succinimide and the desired product.

The product was isolated on a short silica plug (eluted with hexanes). Yield 3.4527 g, 13.815 mmol, 91.7%.

TLC (hexanes) Rf 0.51

^{1}H-NMR (400 MHz; $CDCl_3$): δ 6.66 (s, 1H), 7.40-7.32 (m, 3H), and 7.59-7.56 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 41.2, 126.6, 128.8, 130.0, and 142.1.

GC-MS: t_R = 5.33 min, *m/z* 171 and 169 ($M^{+\bullet}$), fragments 90 and 63.

Preparation of 9,9-dibromofluorene:

Fluorene (163 mg, 0.981 mmol), *N*-bromosuccinimide (389 mg, 2.186 mmol), and azobisisobutyronitrile (17 mg, 0.11 mmol) were dissolved in 3 mL $CHCl_3$. The solution was heated to reflux overnight with stirring. Then, the reaction mixture was allowed to cool to r.t., the precipitate was removed by filtration, and the filtrate was evaporated to give the crude product as a slush (394 mg). The product was purified by recrystallization from acetonitrile. Yield 243 mg crystals, 0.749 mmol, 76%

Melting point: 110-114 °C

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.43-7.36 (m, 4H), 7.58-7.56 (m, 2H), 7.87-7.84 (m, 2H).

^{13}C NMR (101 MHz; $CDCl_3$): δ 52.6, 120.3, 126.1, 129.3, 130.4, 135.4, 148.7.

In order to examine the stability of *S*-alkynyl monothiocarbonates, methyl chloroformate was used as an electrophile in the following procedure:

Preparation of *O*-methyl *S*-((trimethylsilyl)ethynyl) thiocarbonate

An alkyne thiolate solution was formed using TMS-acetylene (0.42 mL, 0.29 g, 3.0 mmol) according to the general procedure. To this solution, methyl chloroformate (0.19 mL, 0.23 g, 2.5 mmol) was added. The reaction mixture was stirred for 30 min., and then saturated NH_4Cl (5 mL) was added. The organic layer was removed, washed with brine (5

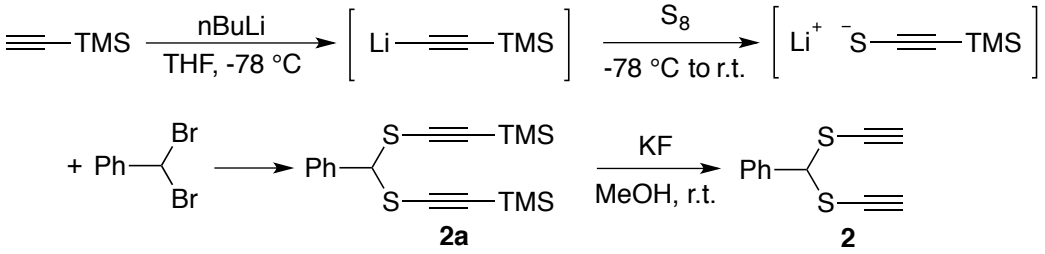
mL), dried ($MgSO_4$), and evaporated to yield the crude product as a red oil (467 mg). NMR integration showed that this crude product contained 343 mg product (1.82 mmol, 73% yield) with the remaining mass being residual solvent.

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.23 (s, 9H), 3.90 (s, 3H).

^{13}C NMR (101 MHz; $CDCl_3$): δ -0.3, 55.9, 84.5, 109.4, 167.2.

GC-MS: t_R = 4.30 min, *m/z* 188 ($M^{+\bullet}$), fragments 173, 145, 129, 114, 99, 89, 73, and 59.

Preparation of (phenylmethylene)bis(ethynylsulfane) (**2**)



An alkyne thiolate solution was formed using TMS-acetylene (3.5 mL, 2.45 g, 25 mmol) according to the general procedure. To this solution, α,α-dibromotoluene (2.959 g, 11.84 mmol) was added. The reaction mixture was stirred overnight, and then saturated NH_4Cl (10 mL) was added. The organic layer was removed, washed with brine (10 mL), dried ($MgSO_4$), and evaporated to yield the crude product as a red oil (4.409 g). This product was deprotected according to the general procedure to yield crude deprotected product (3.088 g), which was purified on a flash column (19:1 hexanes/ethyl acetate).

Yield: 1.627 g, 7.961 mmol, 67%

Data for protected compound **2a**:

GC-MS: t_R = 9.38 min, *m/z* 348 ($M^{+\bullet}$), fragments 219, 179, 121, and 73.

Data for deprotected compound **2**:

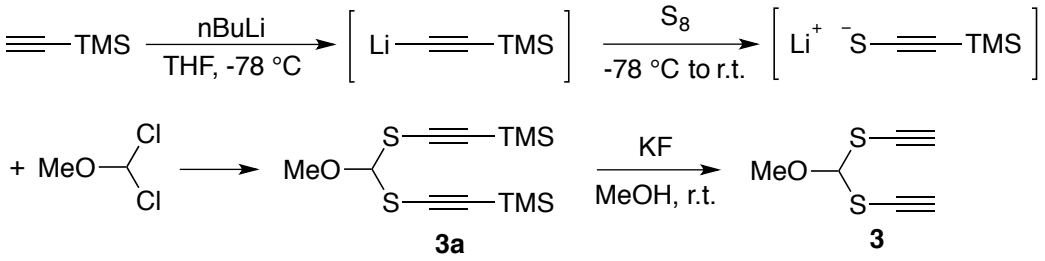
TLC (hexanes) Rf 0.29

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.02 (s, 2H), 5.43 (s, 1H), 7.41-7.35 (m, 3H), and 7.48-7.46 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 58.9, 72.0, 86.9, 127.7, 128.9, 129.5, and 136.6.

GC-MS: t_R = 6.92 min, *m/z* 204 ($M^{+\bullet}$), fragments 203, 147, 121, 103, 89, 77, 63, and 51.

Preparation of (methoxymethylene)bis(ethynylsulfane) (**3**)



An alkyne thiolate solution was formed using TMS-acetylene (3.5 mL, 2.45 g, 25 mmol) according to the general procedure. To this solution, methyl dichloromethyl ether (1.09 mL, 1.39 g, 12.1 mmol) was added. The reaction mixture was stirred overnight, and then saturated NH_4Cl (10 mL) was added. The organic layer was removed, washed with brine (10 mL), dried ($MgSO_4$), and evaporated to yield the crude product as a red oil (3.9468 g). This product was deprotected according to the general procedure to yield crude deprotected product (2.470 g), which was purified on a flash column (9:1 hexanes/ethyl acetate). Yield: 947 mg, 5.99 mmol, 49%

Data for protected compound **3a**:

GC-MS: t_R = 7.48 min, ($M^{+\bullet}$) not observed, fragments *m/z* 173, 115, 89, 73, and 59.

Data for deprotected compound **3**:

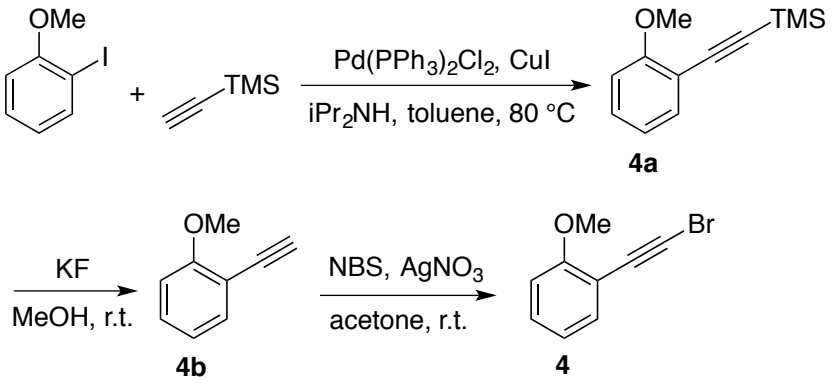
TLC (9:1 hexanes/ethyl acetate) Rf 0.45

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.10 (s, 2H), 3.61 (s, 3H), and 6.09 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 55.7, 70.2, 87.2, and 93.0.

GC-MS: t_R = 4.03 min, *m/z* 158 ($M^{+\bullet}$), fragments 143, 127, 101, 86, 69, and 58.

Preparation of 2-(bromoethynyl)anisole (**4**)



2-iodoanisole (15.96 g, 68.15 mmol), TMS-acetylene (11.3 mL 7.86 g, 80.0 mmol), triphenylphosphine (178 mg, 0.679 mmol), bis(triphenylphosphine)palladium(II) dichloride (144 mg, 0.205 mmol), and copper(I) iodide (130 mg, 0.684 mmol) were all dissolved in diisopropylamine (65 mL) and toluene (130 mL) under N_2. The reaction mixture was heated to 80 °C and stirred overnight. The precipitate which had formed was removed by filtration, and the solids were washed with ethyl acetate (25 mL). The filtrate and washings were combined, extracted with sat. aq. NH_4Cl (2 x 100 mL) and brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent yielded 16.503 g brown oil. This was deprotected according to the general procedure, yielding 2-ethynylanisole (8.448 g, 63.92 mmol, 94%) which was subsequently used without further purification.

2-ethynylanisole (5.737 g, 43.41 mmol) and *N*-bromosuccinimide (8.883 g, 49.91 mmol) were dissolved in acetone (90 mL). Silver nitrate (369 mg, 2.17 mmol) was added, and the reaction mixture was stirred overnight under nitrogen out of direct light. The

precipitate which formed was removed by filtration, and the filtrate concentrated by rotary evaporation. The crude product was passed through a plug of silica gel (eluent 19:1 hexanes/ethyl acetate) to remove remaining succinimide. The solvent was evaporated to yield the product as a pale red oil (8.072 g, 38.24 mmol, 88%).

Data for 2-ethynylanisole **4b**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.310 (s, 1H), 3.90 (s, 3H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 7.32 (td, *J* = 7.9, 1.7 Hz, 1H), and 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 55.9, 80.2, 81.2, 110.7, 111.3, 120.5, 130.3, 134.2, and 160.7.

GC-MS: t_R = 4.08 min, *m/z* 132 ($M^{+\bullet}$), fragments 131, 103, 89, and 63.

Data for 2-(bromoethynyl)anisole **4**:

TLC (9:1 hexanes/ethyl acetate) Rf 0.57

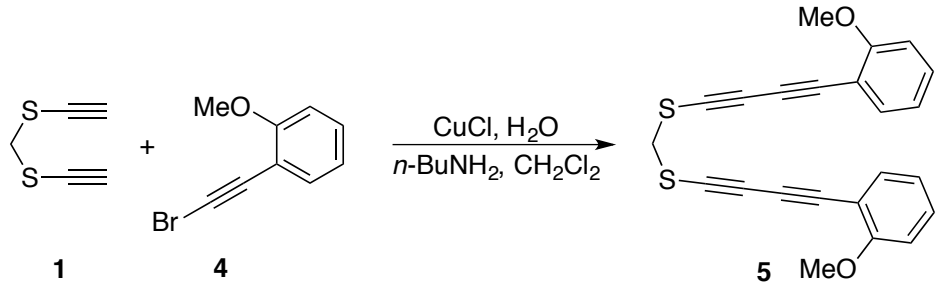
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.86-6.92 (m, 2H), 7.31 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H), and 7.42 (ddd, *J* = 7.6, 1.7, 0.3 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): 53.2, 55.9, 76.6, 110.8, 111.9, 120.5, 130.2, 134.2, and 160.8

GC-MS: t_R = 6.14 min, *m/z* 212 and 210 ($M^{+\bullet}$), fragments 169, 167, 131, 103, 88, and 77.

IR: 3073, 3003, 2959, 2940, 2179, 1595, 1575, 1491, 1462, 1433, 1287, 1279, 1256, 1180, 1162, 1116, 1047, 1023, 936, and 846 cm^{-1}

Preparation of bis(((2-methoxyphenyl)buta-1,3-diyn-1-yl)thio)methane (5)



1 **4** **5**

The general procedure for Cadiot-Chodkiewicz coupling was used to couple compound **1** (102 mg, 0.793 mmol) and compound **4** (363 mg, 1.72 mmol) using CuCl catalyst (17 mg, 0.17 mmol). The crude product after workup was 1.16 g brown oil, still containing some butylamine. Next, this was purified by flash chromatography (19:1 to 6:1 hexanes/ethyl acetate) to yield the product as a red oil (192 mg, .495 mmol, 62%), which solidified into a tan solid upon storage at -20 °C.

TLC (9:1 hexanes/ethyl acetate) Rf 0.22

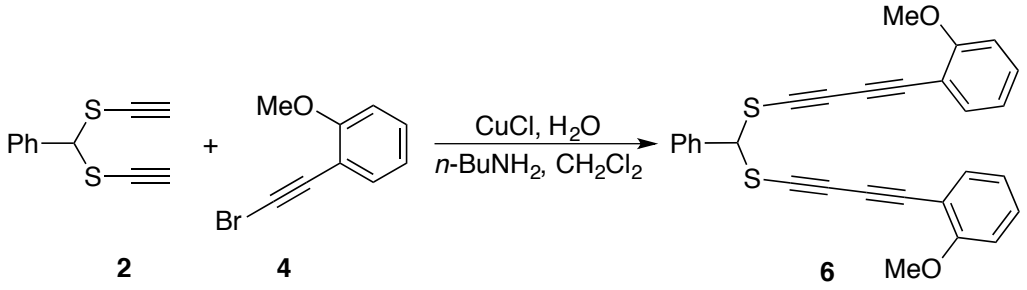
^{1}H-NMR (400 MHz; $CDCl_3$): δ 3.87 (s, 6H), 4.13 (s, 2H), 6.90-6.85 (m, 4H), 7.32 (ddd, *J* = 8.3, 7.6, 1.6 Hz, 2H), and 7.44 (dd, *J* = 7.6, 1.6 Hz, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 43.1, 56.0, 71.5, 77.8, 77.9, 82.9, 110.8, 110.8, 120.7, 131.1, 134.8, and 161.8.

HRMS: Expected $C_{23}H_{16}NaO_2S_2^+$ $[M + Na]^+$ *m/z* 411.0484, found 411.0498

IR: 3072, 3001, 2963, 2943, 2835, 2194, 2103, 1592, 1572, 1489, 1461, 1432, 1274, 1244, 1197, 1181, 1162, 1122, 1056, 1037, 1021, 936, 840, and 804 cm^{-1}

Preparation of bis(((2-methoxyphenyl)buta-1,3-diyn-1-yl)thio)phenylmethane (6)



The general procedure for Cadiot-Chodkiewicz coupling was used to couple compound **2** (619 mg, 3.031 mmol) and compound **4** (1.399 g, 6.630 mmol) using CuCl catalyst (59 mg, 0.60 mmol). The crude product after workup was 1.650 g brown tar. Next,

this was purified by flash chromatography (9:1 to 3:1 hexanes/ethyl acetate) to yield the product as a red oil (901 mg, 1.940 mmol, 64%).

TLC (3:1 hexanes/ethyl acetate) Rf 0.44

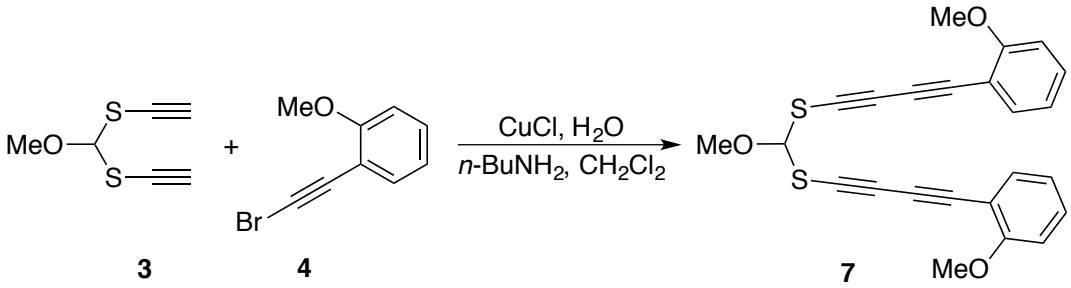
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.86 (s, 6H), 5.51 (s, 1H), 6.90-6.84 (m, 4H), 7.32 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 2H), 7.40-7.37 (m, 3H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 2H), and 7.48 (dd, *J* = 7.9, 1.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 55.9, 60.7, 71.4, 78.0, 78.4, 84.2, 110.8, 110.8, 120.6, 127.8, 129.1, 129.7, 131.0, 134.8, 136.2, and 161.8.

HRMS: Expected $C_{29}H_{20}NaO_2S_2^+$ $[M + Na]^+$ *m/z* 487.0797, found 487.0795

IR: 3062, 3012, 2959, 2934, 2834, 2192, 2101, 1593, 1572, 1490, 1462, 1433, 1275, 1245, 1180, 1162, 1122, 1022, 936, 841, and 805 cm^{-1}

Preparation of bis(((2-methoxyphenyl)buta-1,3-diyn-1-yl)thio)methoxymethane (**7**)



The general procedure for Cadiot-Chodkiewicz coupling was used to couple compound **3** (682 mg, 4.315 mmol) and compound **4** (2.011 g, 9.528 mmol) using CuCl catalyst (85 mg, 0.86 mmol). The crude mass after workup was 2.245 g. This was purified by flash chromatography (4:1 to 1:1 hexanes/ethyl acetate) to yield the product as a red viscous oil (1.198 g, 2.862 mmol, 66%).

TLC (4:1 hexanes/ethyl acetate) Rf 0.32

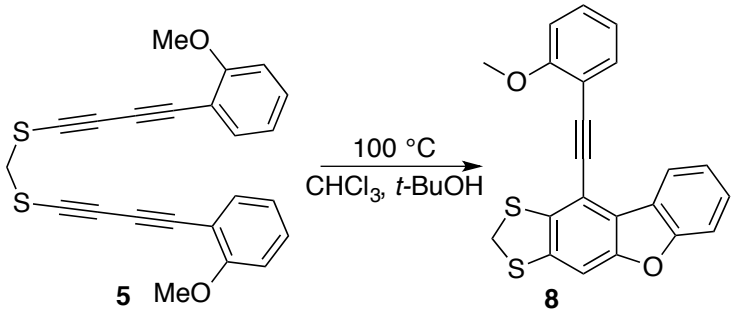
^{1}H NMR (400 MHz; $CDCl_3$): 3.64 (s, 3H), 3.88 (s, 6H), 6.18 (s, 1H), 6.92-6.86 (m, 4H), 7.33 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 2H), and 7.45 (dd, *J* = 7.6, 1.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): 55.8, 56.0, 69.5, 77.8, 78.5, 84.3, 94.4, 110.7, 110.8, 120.7, 131.2, 134.8, and 161.8.

HRMS: Expected $C_{24}H_{18}NaO_3S_2^+$ $[M + Na]^+$ *m/z* 441.0590, found 441.0598

IR: 3007, 2958, 2934, 2834, 2193, 2102, 1593, 1573, 1489, 1461, 1433, 1275, 1245, 1181, 1162, 1123, 1085, 1057, 1021, 938, 906, and 805 cm^{-1}

Preparation of 10-((2-methoxyphenyl)ethynyl)benzo[*b*][1,3]dithiolo [4,5-*f*]benzofuran (8)



5 **8**

Tetrayne **5** (38.3 mg, 0.0986 mmol) was dissolved in $CHCl_3$ (5 mL) and t-BuOH (25 mL) in a sealed tube under nitrogen. The solution was heated to 100 °C for 5 hours, after which time the solvent was evaporated to give a brown tar. The crude product was purified by flash chromatography (9:1 hexanes/ethyl acetate) to yield the desired product as a white crystalline powder (15.6 mg, 0.0417 mmol, 42%).

Melting point: 160-162 °C

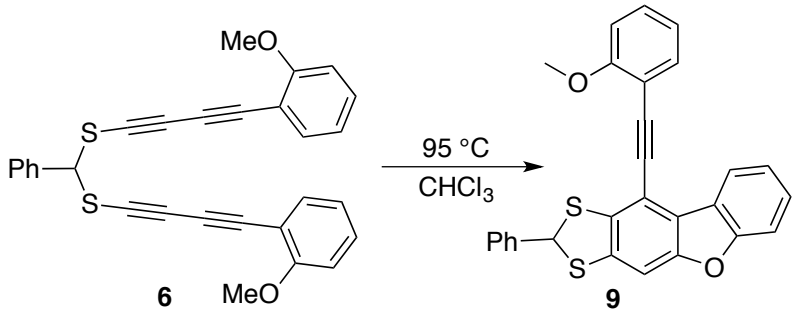
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (s, 3H), 4.63 (s, 2H), 6.98 (d, *J* = 8.79 Hz, 1H), 7.02 (dd, *J* = 7.52, 0.88 Hz, 1H), 7.34-7.41 (m, 3H), 7.45 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 7.5 Hz, 1.7 Hz, 1H), and 8.68 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 36.3, 55.9, 90.0, 95.7, 105.9, 110.9, 111.4, 112.2, 120.8, 122.1, 122.8, 123.0, 123.8, 127.2, 130.6, 133.6, 134.2, 137.1, 137.4, 154.8, 156.7, 160.4.

HRMS: Expected $C_{22}H_{14}NaO_2S_2^+$ $[M + Na]^+$ *m/z* 397.0327, found 397.0311

IR: 2998, 2934, 2832, 2202, 1595, 1574, 1494, 1455, 1434, 1392, 1320, 1301, 1274, 1244, 1197, 1161, 1129, 1021, 935, 901, 849, 824, 810, and 786 cm^{-1}

Preparation of (±)-10-((2-methoxyphenyl)ethynyl)-2-phenylbenzo[*b*][1,3]dithiolo [4,5-*f*]benzofuran (**9**)



Tetrayne **6** (46.5 mg, 0.100 mmol) was dissolved in $CHCl_3$ (30 mL) in a sealed tube under nitrogen. The solution was heated to 95 °C for 13 hours, after which time the solvent was evaporated to give a brown tar. The crude product was purified by flash chromatography (4:1 hexanes/ethyl acetate) to yield the desired product as a white crystalline powder (26.7 mg, 0.0593 mmol, 59%).

The procedure was repeated with a greater starting material concentration (93.2 mg, 0.201 mmol in 40 mL chloroform), leading to a roughly equivalent percent yield of product (50.3 mg, 0.112 mmol, 56%).

Melting point: 205-207 °C (recrystallized from 4:1 hexanes/ethyl acetate)

TLC (9:1 hexanes/ethyl acetate) Rf 0.30, (3:1) Rf 0.64

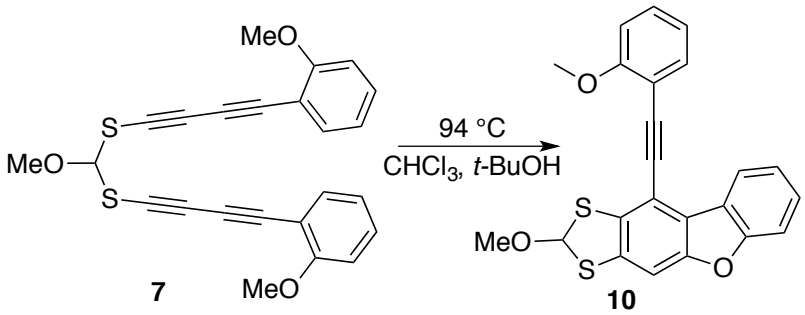
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.00 (s, 3H), 6.39 (s, 1H), 6.99-6.94 (m, 2H), 7.38-7.32 (m, 6H), 7.45 (td, *J* = 7.7, 1.3 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.59 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.8 Hz, 2H), and 8.70 (dd, *J* = 7.7, 0.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 55.9, 57.2, 89.9, 96.0, 105.5, 110.6, 110.9, 111.4, 112.2, 120.8, 122.1, 123.0, 123.1, 123.9, 127.3, 127.5, 128.9, 129.1, 130.6, 133.6, 136.5, 136.7, 139.3, 155.0, 156.6, and 160.4.

HRMS: Expected $C_{28}H_{18}NaO_2S_2^+$ $[M + Na]^+$ *m/z* 473.0640, found 473.0652

IR: 3060, 2936, 2834, 2205, 1594, 1573, 1493, 1454, 1432, 1393, 1320, 1301, 1276, 1247, 1195, 1162, 1130, 1044, 1021, 1002, 937, 905, 848, and 809 cm^{-1}

Preparation of (±)-2-methoxy-10-((2-methoxyphenyl)ethynyl)benzo[*b*][1,3]dithiolo [4,5-*f*]benzofuran (**10**)



Tetrayne **7** (83.5 mg, 0.200 mmol) was dissolved in $CHCl_3$ (5 mL) and t-BuOH (35 mL) in a sealed tube under nitrogen. The solution was heated to 94 °C for 3.5 hours, after which time the solvent was evaporated to give a brown viscous oil. The crude product was purified by flash chromatography (4:1 hexanes/ethyl acetate) to yield the desired product as a colorless amorphous solid (67.2 mg, 0.166 mmol, 83%).

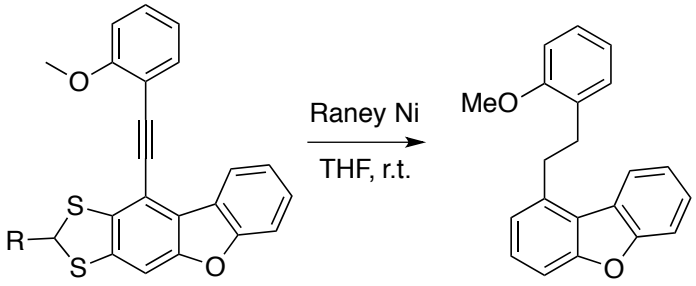
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.29 (s, 3H), 4.00 (s, 3H), 6.89 (s, 1H), 7.01-6.93 (m, 2H), 7.38-7.32 (m, 2H), 7.44 (td, *J* = 7.7, 1.2 Hz, 1H), 7.51-7.49 (m, 2H), 7.64 (dd, *J* = 7.5, 1.6 Hz, 1H), 8.71 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 51.3, 55.8, 89.8, 91.1, 96.2, 105.1, 110.6, 110.8, 111.3, 112.1, 120.7, 122.1, 122.9, 123.0, 123.7, 127.4, 130.7, 133.6, 134.8, 135.1, 154.6, 156.6, and 160.4.

HRMS: Expected $C_{23}H_{16}NaO_3S_2^+$ $[M + Na]^+$ *m/z* 427.0433, found 427.0440

IR: 3070, 3001, 2962, 2933, 2834, 2205, 1596, 1575, 1493, 1455, 1434, 1392, 1369, 1318, 1301, 1276, 1249, 1197, 1162, 1116, 1059, 1021, 928, 900, and 851 cm^{-1}

Preparation of 1-(2-methoxyphenethyl)dibenzofuran (11)



R = H, Ph, MeO
(**8**, **9**, **10**)

11

Compounds **8** (5.79 mg, 0.0155 mmol), **9** (26.9 mg, 0.0597 mmol), and **10** (40.9 mg, 0.101 mmol) were all desulfurized with Raney nickel according to the general procedure. The crude products were purified by MPLC (49:1 hexanes/ethyl acetate) to yield a colorless, viscous oil. From **8**: 4.21 mg, 0.0139 mmol, 90%. From **9**: 13.9 mg, 0.0460 mmol, 77%. From **10**: 28.6 mg, 0.0946 mmol, 94%

TLC (hexanes) Rf 0.09, (49:1 hexanes/ethyl acetate) Rf 0.26,

(19:1 hexanes/ethyl acetate) Rf 0.58

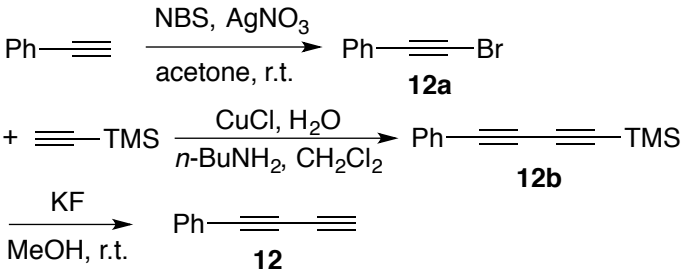
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.10-3.06 (m, 2H), 3.42-3.38 (m, 2H), 3.89 (s, 3H), 6.93-6.89 (m, 2H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.25-7.18 (m, 2H), 7.38-7.34 (m, 2H), 7.47-7.42 (m, 2H), 7.58 (d, *J* = 8.1 Hz, 1H), and 8.24 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 31.6, 34.4, 55.3, 109.4, 110.5, 111.6, 120.7, 122.6, 122.8, 122.9, 123.4, 124.5, 126.7, 127.1, 127.6, 130.1, 130.2, 138.3, 156.2, 156.5, and 157.7.

HRMS: Expected $C_{21}H_{18}NaO_2^+$ $[M + Na]^+$ *m/z* 325.1199, found 325.1203

IR: 3049, 2935, 2834, 1601, 1586, 1493, 1451, 1425, 1323, 1289, 1242, 1226, 1194, 1177, 1109, 1050, 1031, 965, 930, 846, 801, and 790 cm^{-1}

Preparation of phenylbutadiyne (12)



Phenylacetylene (10 mL, 9.3 g, 91 mmol) and *N*-bromosuccinimide (16.82 g, 94.52 mmol) were dissolved in acetone (160 mL). Silver nitrate (155 mg, 0.912 mmol) was added, and the reaction mixture was stirred overnight under nitrogen out of direct light. The precipitate which formed was removed by filtration, and the filtrate concentrated by rotary evaporation. The crude product was passed through a plug of silica gel (eluent hexanes) to remove remaining succinimide. The solvent was evaporated to yield (bromoethynyl)benzene as a pale red oil (16.013 g, 88.5 mmol, 97%).

The general procedure for Cadiot-Chodkiewicz coupling was used to couple (bromoethynyl)benzene (16.013 g, 88.5 mmol) and TMS-acetylene (15.5 mL, 10.8 g, 110

mmol) using CuCl catalyst (450 mg, 4.55 mmol). The reaction was complete within 15 min. at 0 °C. After workup, TMS-phenylbutadiyne was obtained as a pale yellow oil (14.4436 g, 72.8 mmol, 82%), which was sufficiently stable to store at -20 °C indefinitely. At -20 °C the compound formed white waxy crystals. The crude product was sufficient for use in producing **12**, but if needed it could be purified further by flash chromatography (hexanes).

To form **12**, the TMS-derivative was deprotected according to the general procedure. The product quickly polymerized (over the course of minutes) when neat, so typically it was redissolved in hexanes immediately after isolation. Pure samples could also be stored for a few hours under nitrogen at -20 °C, but longer storage resulted in polymerization.

Data for (bromoethynyl)benzene **12a**:

TLC (19:1 hexanes/ethyl acetate) Rf 0.81

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.37-7.31 (m, 3H) and 7.49-7.47 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 49.9, 80.2, 122.8, 128.5, 128.8, and 132.1.

GC-MS: t_R = 4.08 min, *m/z* 182 and 180 ($M^{+\bullet}$), fragments 101, 75, 62, and 51.

Data for TMS-phenylbutadiyne **12b**:

TLC (hexanes): Rf 0.49

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.23 (s, 9H), 7.37-7.28 (m, 3H), and 7.49-7.46 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ -0.3, 74.3, 76.9, 88.0, 90.7, 121.5, 128.6, 129.5, and 132.8.

GC-MS: t_R = 6.94 min, *m/z* 198 ($M^{+\bullet}$), fragments 183, 153, 129, and 77.

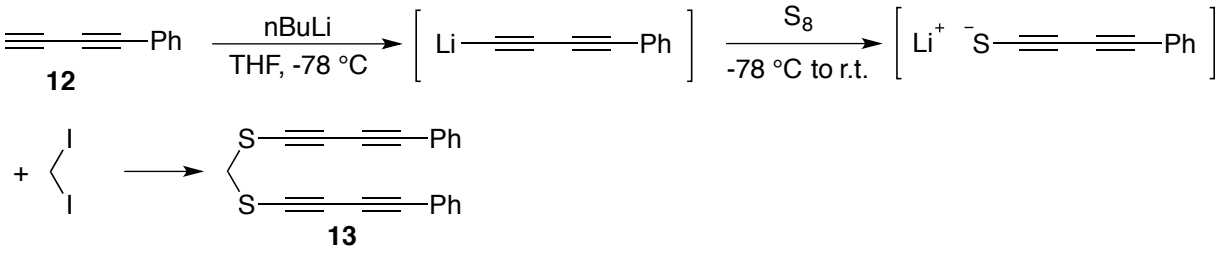
IR: 3059, 2959, 2931, 2873, 2205, 2104, 1655, 1594, 1489, 1455, 1442, 1279, 1251, 1177, 1158, 1069, 1019, 1007, 990, 915, and 845 cm^{-1}

Data for phenylbutadiyne **12**:

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.47 (s, 1H), 7.38-7.30 (m, 3H), 7.54-7.50 (m, 2H).

GC-MS: t_R = 4.31 min, *m/z* 126 ($M^{+\bullet}$), fragments 98 and 74.

Preparation of bis((phenylbuta-1,3-diyn-1-yl)thio)methane (**13**)



An alkyne thiolate solution was formed using Compound **12** (685 mg, 5.43 mmol) according to the general procedure. To this solution, diiodomethane (0.20 mL, 0.67 g, 2.5 mmol) was added. The reaction mixture was stirred overnight, and then saturated NH_4Cl (10 mL) was added. The organic layer was removed, washed with brine (5 mL), dried ($MgSO_4$), and evaporated to yield the crude product as a brown oil (1.9576 g). This was purified by flash chromatography (19:1 hexanes/ethyl acetate) to yield the product as a red oil (496 mg, 1.51 mmol, 61%).

TLC (19:1 hexanes/ethyl acetate) Rf 0.43

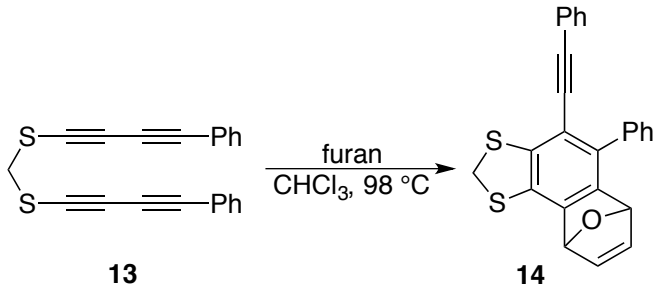
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.14 (s, 2H), 7.37-7.27 (m, 6H), and 7.49-7.46 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 43.0, 70.9, 74.2, 81.3, 82.8, 121.5, 128.6, 129.5, and 132.8.

IR: 3060, 2955, 2926, 2196, 2107, 1667, 1595, 1488, 1441, 1196, 1142, 1093, 1069, 1023, 915, and 837 cm^{-1}

HRMS: Expected $C_{21}H_{12}NaS_2^+$ $[M + Na]^+$ *m/z* 351.0273, found 351.0288

Preparation of (±)-5-phenyl-4-(phenylethynyl)-6,9-dihydro-6,9-epoxynaphtho [1,2-*d*][1,3]dithiole (**14**)



13 **14**

Tetrayne **13** (32.8 mg, 0.0999 mmol) was dissolved in chloroform (8 mL) and furan (2 mL) in a sealed tube under N_2. The tube was heated to 98 °C and the reaction proceeded overnight. Next, the solvent was evaporated to a brown tar (45.8 mg) which was purified by MPLC (19:1 hexanes/ethyl acetate) to yield the product (33.9 mg, 0.0855 mmol, 86%).

TLC (9:1 hexanes/ethyl acetate) Rf 0.48

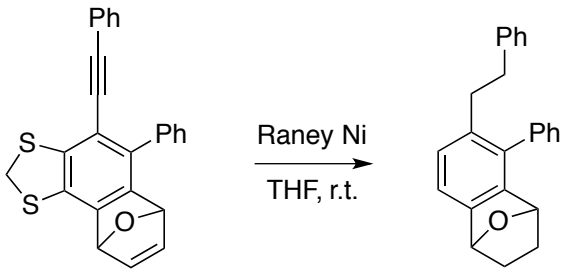
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.51 (d, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 5.55 (dd, *J* = 1.7, 0.9 Hz, 1H), 5.66 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.04 (dd, *J* = 5.5, 1.8 Hz, 1H), 7.08 (dd, *J* = 5.5, 1.8 Hz, 1H), 7.30-7.25 (m, 5H), and 7.49-7.40 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 36.0, 82.2, 82.4, 88.0, 97.0, 113.1, 123.1, 128.0, 128.2, 128.4, 128.5, 129.6, 131.4, 132.2, 134.0, 137.2, 141.6, 142.1, 142.9, 143.1, and 145.8.

HRMS: Expected $C_{25}H_{16}NaOS_2^+$ $[M + Na]^+$ *m/z* 419.0535, found 419.0559

IR: 3060, 3028, 2955, 2928, 2869, 2196, 2107, 1596, 1504, 1486, 1442, 1415, 1276, 1141, 1086, 1069, 1023, 915, 773, and 754 cm^{-1}

Preparation of (±)-6-phenethyl-5-phenyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (**15**)



14 **15**

Compound **14** (19.9 mg, 0.0502 mmol) was desulfurized with Raney nickel according to the general procedure. The crude product was purified by MPLC (19:1) to yield a colorless, viscous oil (15.6 mg, 0.0478 mmol, 95%).

TLC (19:1 hexanes/ethyl acetate) Rf 0.15

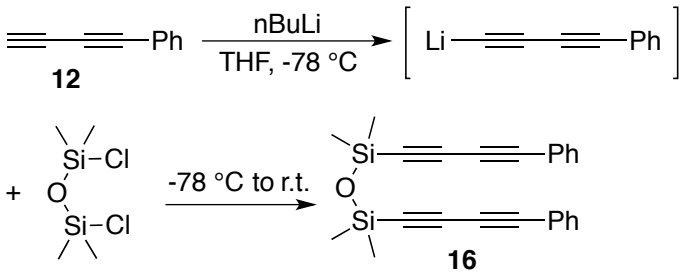
^{1}H NMR (400 MHz; $CDCl_3$): δ 1.36 (ddd, *J* = 11.0, 8.8, 3.3 Hz, 1H), 1.44 (ddd, *J* = 11.0, 8.5, 2.9 Hz, 1H), 1.94 (tdd, *J* = 10.6, 4.9, 3.3 Hz, 1H), 2.05 (tdd, *J* = 10.6, 4.8, 3.4 Hz, 1H), 2.83-2.60 (m, 4H), 5.10 (d, *J* = 4.9 Hz, 1H), 5.42 (d, *J* = 4.9 Hz, 1H), 6.90-6.88 (m, 2H), 7.20-7.09 (m, 6H), 7.45-7.36 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 6.7, 26.9, 35.5, 38.2, 78.3, 79.5, 117.9, 125.9, 127.3, 127.6, 128.4, 128.4, 128.5, 129.3, 133.6, 138.0, 139.0, 142.0, 143.4, and 145.2.

HRMS: Expected $C_{24}H_{22}NaO^+$ $[M + Na]^+$ *m/z* 349.1563, found 349.1582

IR: 3060, 3024, 2999, 2950, 2863, 1601, 1495, 1455, 1443, 1340, 1293, 1243, 1178, 1150, 1111, 1073, 1031, 1018, 988, 927, 869, 829, 815, and 776 cm^{-1}

Preparation of 1,1,3,3-tetramethyl-1,3-bis(phenylbuta-1,3-diyn-1-yl)disiloxane (16)



Diyne **12** (386 mg, 3.06 mmol) was dissolved in anhydrous THF (10 mL) under N_2 and the solution was chilled to -78 °C. nBuLi (2.5 M in hexanes, 1.25 mL, 3.13 mmol) was added, and the reaction mixture was stirred for 15 min. 1,3-dichlorotetramethyldisiloxane (0.29 mL, 0.305 g, 1.5 mmol) was added, and the reaction mixture was allowed to warm to r.t. After 2 hr, the reaction mixture was quenched by addition of sat. aq. NH_4Cl (5 mL) and water (5 mL). The organic layer was evaporated to yield crude product (718.1 mg) as a tan oil. This was purified by flash chromatography (hexanes) to yield **16** as a white waxy solid (301 mg, 0.787 mmol, 52%).

TLC (hexanes): Rf 0.40

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.36 (s, 12H), 7.38-7.27 (m, 6H), and 7.50-7.47 (m, 4H).

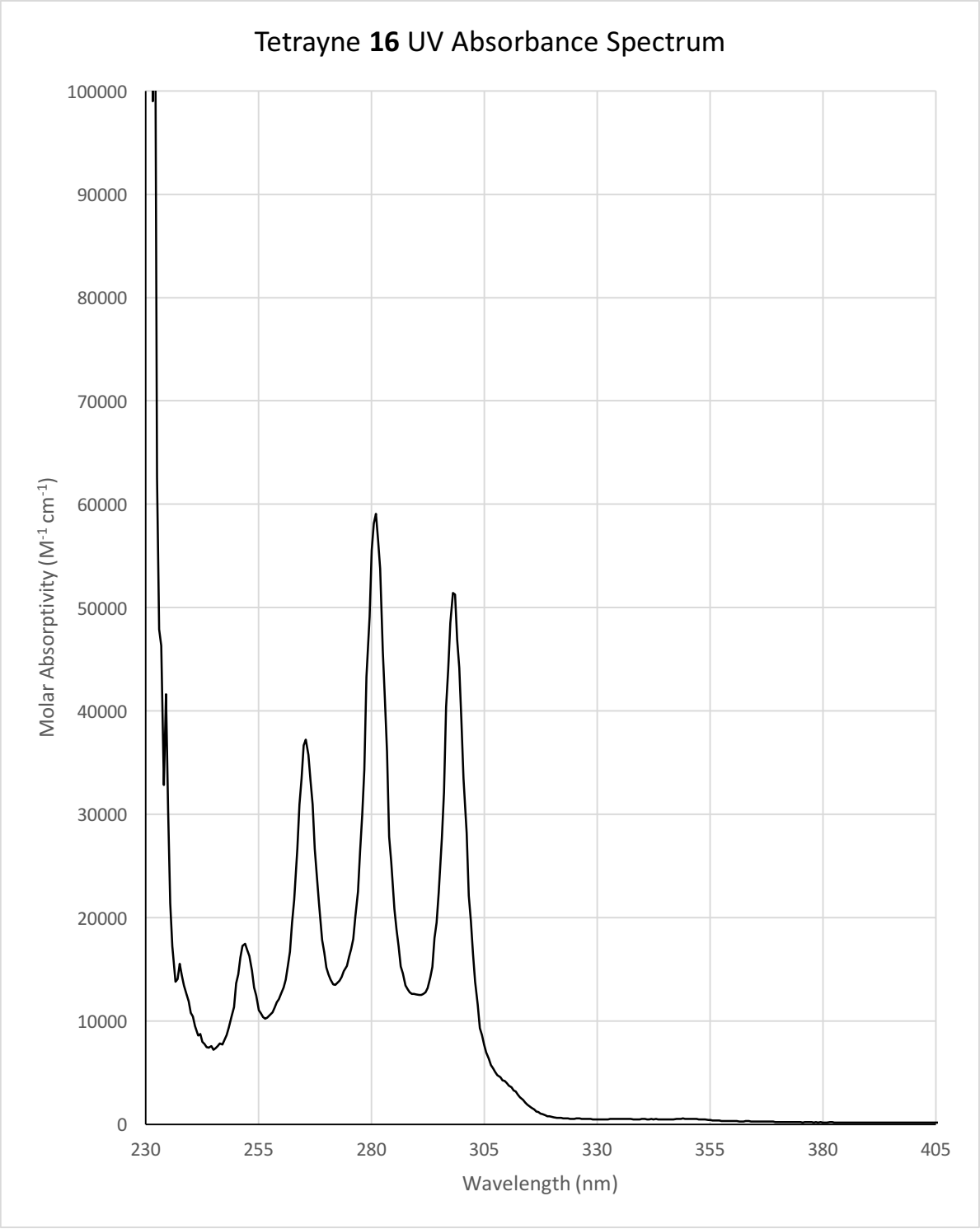
^{13}C NMR (101 MHz; $CDCl_3$) δ 2.1, 74.2, 77.7, 87.3, 88.9, 121.3, 128.6, 129.6, and 132.9.

HRMS: Expected $C_{24}H_{22}NaOSi_2^+$ $[M + Na]^+$ *m/z* 405.1101, found 405.1112

GC-MS: t_R = 12.96 min, *m/z* 382 ($M^{+\bullet}$), fragments 367, 293, 250, 183, and 126.

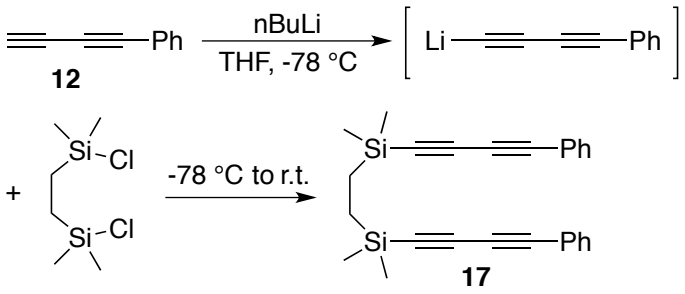
IR: 3059, 2962, 2901, 2205, 2105, 1490, 1442, 1403, 1278, 1258, 1046, 1021, 1009, 992, 965, 944, 912, 834, and 800 cm^{-1}

UV Absorbance: peaks 252.1, 265.4, 281.0, and 298.1 nm



Tetrayne **16** was dissolved in THF at a concentration of $1.017 * 10^{-5}$ M, and the absorbance was measured in a 1 cm path length quartz cuvette over the range 200 - 600 nm. For the photochemical HDDA experiments, irradiation was tested at 254 and 300 nm, wavelengths which roughly correspond to the first and fourth absorption maxima of tetrayne **16**.

Preparation of 1,2-bis(dimethyl(phenylbuta-1,3-diyn-1-yl)silyl)ethane (**17**)



Compound **12** (262 mg, 2.08 mmol) was dissolved in anhydrous THF (5 mL) under N_2 and the solution was chilled to -78 C. nBuLi (2.5 M in hexanes, 0.84 mL, 2.1 mmol) was added, and the reaction mixture was stirred for 15 min. Next, 1,2-bis(chlorodimethylsilyl)ethane (215 mg, 1.00 mmol) in anhydrous THF (0.5 mL) was added, and the reaction mixture was allowed to warm to r.t. After stirring overnight, the reaction mixture was quenched by addition of sat. aq. NH_4Cl (5 mL). The organic layer was evaporated to yield crude product (749 mg) as a brown oil. This was purified by flash chromatography (19:1 hexanes/ethyl acetate) to yield **17** as a white waxy solid (212 mg, 0.538 mmol, 52%).

TLC (19:1 hexanes/ethyl acetate) Rf 0.39

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.23 (s, 12H), 0.68 (s, 4H), 7.36-7.29 (m, 6H), and 7.49 (dd, *J* = 8.1, 1.4 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ -2.4, 8.4, 74.4, 76.8, 88.5, 90.0, 121.5, 128.6, 129.5, and 132.9.

HRMS: Expected $C_{26}H_{26}NaSi_2^+$ $[M + Na]^+$ *m/z* 417.1465, found 417.1468

GC-MS: t_R = 14.19 min, *m/z* 394 ($M^{+\bullet}$), fragments 379, 351, 293, 183, 169, 153, and 126.

IR: 3059, 2958, 2909, 2205, 2103, 1489, 1442, 1405, 1251, 1135, 1056, 1019, 1007, 990, 836, 815, and 784 cm^{-1}

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