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Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled through a Low Energy Barrier Concerted Mechanism

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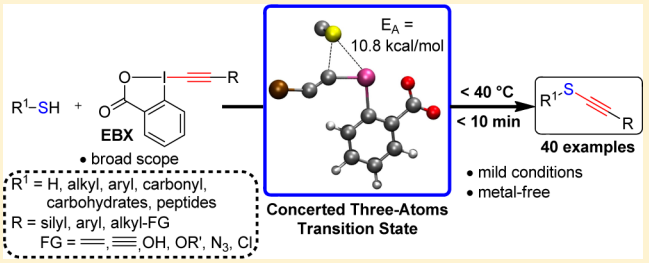
Supporting Information

ABSTRACT: Among all functional groups, alkynes occupy a privileged position in synthetic and medicinal chemistry, chemical biology, and materials science. Thioalkynes, in particular, are highly useful, as they combine the enhanced reactivity of the triple bond with a sulfur atom frequently encountered in bioactive compounds and materials. Nevertheless, general methods to access these compounds are lacking. In this article, we describe the mechanism and full scope of the alkynylation of thiols using ethynyl benziodoxolone (EBX) hypervalent iodine reagents. Computations led to the discovery of a new, three-atom concerted transition state with a very low energy barrier, which rationalizes the high reaction rate. On the basis of this result, the scope of the reaction was extended to the synthesis of aryl- and alkyl-substituted alkynes containing a broad range of functional groups. New sulfur nucleophiles such as thioglycosides, thioacids, and sodium hydrogen sulfide were also alkynylated successfully to lead to the most general and practical method yet reported for the synthesis of thioalkynes.



INTRODUCTION

One of the most important tasks of organic chemistry is discovering practical and general methods for introducing functional groups into molecules to modify their properties and to serve as a platform for further modifications. At a time when research in neighboring fields such as medicine, biology, or materials science is becoming increasingly molecular, easy-to-perform transformative reactions that do not require highly specialized synthetic skills have a particularly broad impact. Among all functional groups in organic chemistry, alkynes occupy a privileged position in this respect.[1] Despite being one of the simplest functional groups with only two carbon atoms, the reactivity of the triple bond makes alkynes exceptionally useful in organic chemistry. They have found applications in bulk chemical synthesis based on acetylene gas[2] as well as in fine chemistry for the stereoselective construction of the carbon backbone of complex natural products[3] and in a myriad of complexity-enhancing metal-catalyzed cyclization reactions to access carbo- and heterocycles.[4] Most importantly, the utility of alkynes has now crossed the boundaries of organic chemistry: their electronic properties have led to widespread applications in organic materials and dyes[5] and the [3 + 2] cycloaddition with azides is now recognized as one of the best biorthogonal conjugation method to modify biomolecules and polymers.[6] The latter transformation is particularly representative of how discoveries in fundamental organic reactivity can strongly impact neighboring research areas. When considering the importance of alkynes for progress in numerous fields of molecular sciences, the development of new methods to access them efficiently under user-friendly conditions is highly desirable.

Among the different classes of alkynes, those directly substituted by a heteroatom are especially interesting for two reasons:[7] (1) the electron-rich heteroatom makes the triple bond more reactive, allowing new chemical transformations and (2) they constitute value-added building blocks, as heteroatoms are essential for the physical and biological properties of small molecules. In short, they bring together the new properties conferred by heteroatoms with the exceptionally rich chemistry of alkynes (Scheme 1). Nevertheless, the synthetic potential of heteroatom-substituted alkynes has long remained underdeveloped due to the absence of convenient methods to access these often sensitive compounds. The coupling of heteroatoms with acetylides is indeed not favorable, as both fragments are inherently nucleophilic and an Umpolung of the reactivity is required.

In the specific case of nitrogen-substituted alkynes (ynamines and ynamides), however, the situation has changed dramatically in the last two decades, when new synthetic methods for the

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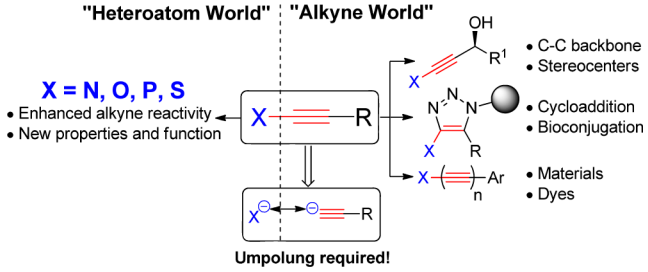
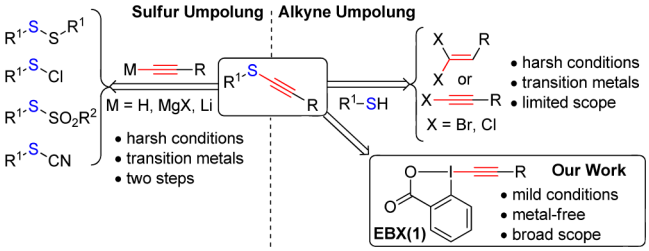
Scheme 1. Heteroatoms-Substituted Alkynes: The Best of Two Worlds, but How To Access Them?



alkynylation of nitrogen with either hypervalent iodine reagents or terminal and halogeno alkynes in the presence of copper catalysts were developed.[8] Ynamides in particular are now intensively used in modern synthetic chemistry.[7c,d] In contrast, the chemistry of thioalkynes is still underdeveloped. This is surprising considering the importance of sulfur in drugs, materials and biomolecules.[9] In fact, the high nucleophilicity of thiols has led to the development of very efficient methods for the formation of S−S (oxidative disulfide formation), S−C(sp^3) (alkylation, thiol−ene) and S−C(sp^2) (thiol−yne) bonds.[10] All of these reactions are routinely used for important transformations in chemical biology and materials science. Until very recently, the direct synthesis of thioalkynes from thiols, on the other hand, has been limited to addition−elimination reactions on alkynyl or alkenyl halides under strongly basic conditions (Scheme 2).[11] The most commonly used methods permitting

Scheme 2. Method To Access Thioalkynes Based on Umpolung of Sulfur or Alkyne



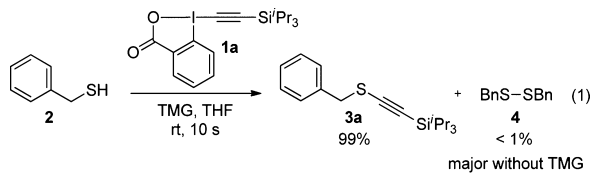
access have been based on the reaction of terminal alkynes with activated sulfur derivatives bearing a leaving group, such as chloride, tosyl or cyano, or disulfides.[12] This lack of efficient synthetic methods under mild conditions has clearly limited the applications of potentially very useful thioalkynes in synthetic and medicinal chemistry.

In 2013, the first efficient metal-catalyzed examples of alkynylation of thiols appeared using copper, palladium or nickel catalysts.[13] Nevertheless, these transformations still required the use of a transition metal catalyst, and the scope of thiols described in these works remained limited to very simple thiophenols and aliphatic thiols[13a] or to thioglycosides,[13b,c] respectively. The same year, our group reported the first method for the alkynylation of thiols using 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **1a**, R = Si^iPr_3).[14] In contrast to previously published methods, the reaction was efficient and user-friendly, leading to the complete alkynylation of aromatic and aliphatic thiols in less than 1 min at room temperature in an open flask. Furthermore, selective alkynylation of thiols was possible in the presence of numerous functional groups such as halogens, alcohols, carboxylic acids, electron-rich aromatic groups or free amines. Nevertheless, two aspects of the developed methodology were not fully satisfying: (1) The mechanistic basis of the extreme efficiency of the reaction could not be rationalized. An in-depth understanding of the alkynylation would be highly useful for further development. (2) The reaction was limited to the transfer of silyl acetylenes on thiols as nucleophiles. Although we demonstrated that the obtained products could easily be deprotected and functionalized, this made our approach less convergent and attractive if the introduction of functionalized alkyne groups is desired. Furthermore, the alkynylation of other sulfur nucleophiles such as thioacetals, thioacids or sulfides salts would also be important in extending the range of accessible thioalkynes.

In this article, we address both issues. On the basis of the isolated side products and computational studies, we propose a mechanism for the reaction. In particular, computations showed that a concerted transition state between the deprotonated thiol and the iodine reagent was possible, leading to an exceptionally low (10.8 kcal/mol) activation energy for the alkynylation using silylated EBX reagents. This type of mechanism has never been proposed for the alkynylation of nucleophiles using hypervalent iodine reagents and is expected to change the way many researchers think about these transformations. We then report an extension of the alkynylation reaction to the use of aryl and functionalized alkyl acetylenes and further extend the scope of thiols to thioglycosides, thioacids and sufide salts, resulting in the most general and practical thiol alkynylation method reported to date.

RESULTS AND DISCUSSION

Mechanism and Computational Studies. Investigating the reaction mechanism of the alkynylation with TIPS-EBX (**1a**) is particularly challenging because of the fast rate: even 10 s after addition of the reagent, full conversion of thiol **2** was already observed when using 1,1,3,3-tetramethyl guanidine (TMG) as a base (eq 1). Furthermore, low-temperature



experiments are difficult because of low solubility of the hypervalent iodine reagent below 0 °C. Nevertheless, control experiments showed that no or very little alkynylation was observed in the absence of a base. In this case, oxidative dimerization to form disulfide **4** was the major process. In addition, no reaction or interaction was observed by NMR between reagent **1a** and TMG. These results permit the reasonable assumption that deprotonation of thiol **2** to form thiolate **2′** is required for the reaction to occur (Scheme 3).

From this point forward, a first possible mechanism would be substitution on iodine to give intermediate $\mathbf{a_1}$, followed by reductive elimination (pathway **a**, blue in Scheme 3). This mechanism is well-established in hypervalent iodine chemistry, especially with aryliodonium salts.[15]

Alternatively, a single electron transfer mechanism (SET) has also been proposed.[16] Nevertheless, in the case of the alkynylation reaction, no radical intermediate could be trapped when using TEMPO as a reagent and the reaction occurred

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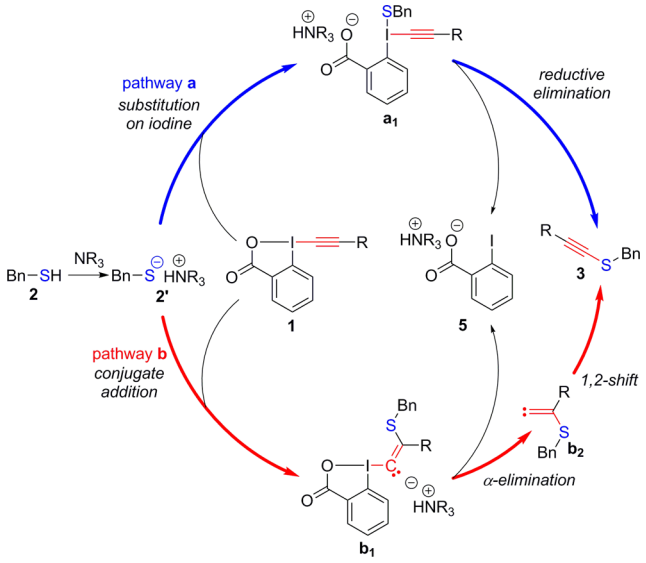
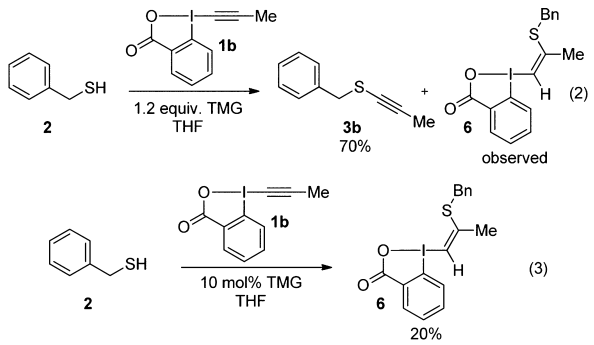
Scheme 3. Initial Speculative Mechanism for the Alkynylation Reaction



with the same yield and reaction time. Although this experiment is naturally not sufficient to exclude a SET pathway, it is also important to note that most reactions of hypervalent iodine reagents occurring via a SET pathway require activation of the reagent by a Lewis or Brønsted acid to accelerate electron transfer,[16] and the alkynylation reaction occurs only under basic conditions.

Nevertheless, alkynyliodonium salts constitute a unique class of hypervalent iodine reagents, as the β-carbon of the alkyne has very strong electrophilic character.[17] In this case, an alternative mechanism is possible: conjugate addition of the thiolate **2**′ on EBX **1** to give a vinyl benziodoxolone intermediate $\mathbf{b_1}$ (pathway **b**, red in Scheme 3). From $\mathbf{b_1}$, α-elimination of iodobenzoate **5** followed by a 1,2-shift of either the sulfur or silicium substituent gave thioalkyne **3**. In fact, this type of mechanism was proposed by Ochiai and co-workers in the case of carbon nucleophiles based on the isolation of C−H insertion products originating from carbene intermediate $\mathbf{b_2}$.[18] Importantly, such insertion products could be observed only when carbon-substituted alkynyliodonium salts were used in the reaction, as the 1,2-shift of silyl groups was faster than insertion reactions.

To establish if Ochiai's mechanism was also correct in the case of sulfur nucleophiles, we decided to investigate Me-EBX (**1b**) as a reagent, as the methyl group was expected to have a very low migrating aptitude. This reagent was easily synthesized using the one-step protocol recently developed by Olofsson and co-workers.[19] Surprisingly, the desired alkynylation product **3b** could still be isolated in 70% yield, although the reaction was less clean than usual (eq 2). In particular, a polar side product with NMR signals in accordance with vinyl benziodoxolone **6** could be observed, although the small quantities of **6** formed did not allow us to isolate this product in pure form at this stage. Compound **6** most likely originated from protonation of intermediate $\mathbf{b_1}$. Consequently, we hypothesized that its formation could be favored if only a catalytic amount of base was used. Indeed, this was the case and we were pleased to see that **6** precipitated directly from the reaction mixture in 20% yield as a single *Z* isomer when only 10 mol % of TMG was used (eq 3). The isolation of **6** constituted



strong support for the conjugate-addition/α-elimination/1,2-shift mechanism. Furthermore, the relatively good yield of isolated alkynylation product was in accordance with a shift of the sulfur atom, as the migration of the methyl group was expected to be too slow to be productive.

Nevertheless, no intermediate could be observed in the case of TIPS-EBX (**1a**). To gain a more comprehensive understanding of the mechanistic details leading to thioalkyne formation, density functional theory (DFT) computations were undertaken using benzyl thiol (**2**) as a substrate. As described above, in the most likely scenario, a deprotonated thiol directly attacks TIPS-EBX (**1a**). This occurs either by direct attack onto the hypervalent iodine atom (pathway **a** in Scheme 3) or through a conjugate addition (pathway **b** in Scheme 3). Computations (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP theoretical level, see Computational Details for additional information) designed to probe the potential energy surface revealed two low-energy van der Waals complexes that roughly correspond to the entry points into the two mechanistic pathways **a** and **b**. The first, $\mathbf{a_0}$ in Figure 1, is a lower energy

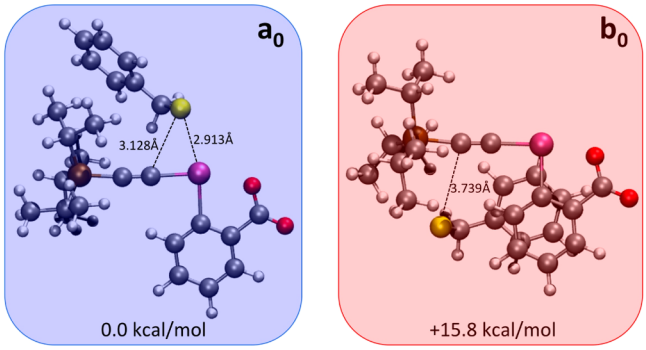


Figure 1. Computed geometries (M06-2X/def2-SVP level) of the van der Waals complexes $\mathbf{a_0}$ and $\mathbf{b_0}$ for TIPS-EBX (**1c**) and thiolate **2**′. Free energies computed at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level and include solvation correction in THF determined using COSMO-RS.

conformation in which the sulfur atom and the iodine atom are in close proximity (2.913 Å). However, the sulfur atom is not exactly opposite to the aryl ring as generally expected for interaction of nucleophiles with hypervalent iodine reagents, but instead lies in a position roughly equidistant between the iodine (2.913 Å) and α-carbon (3.128 Å) atoms of the acetylene. A second complex ($\mathbf{b_0}$ in Figure 1), lying ~15.8 kcal/mol higher in energy, was found to correspond to the aforementioned conjugate addition pathway **b**. Here, the sulfur atom of the deprotonated thiol can clearly participate in a direct attack on the β-carbon of the acetylene unit.

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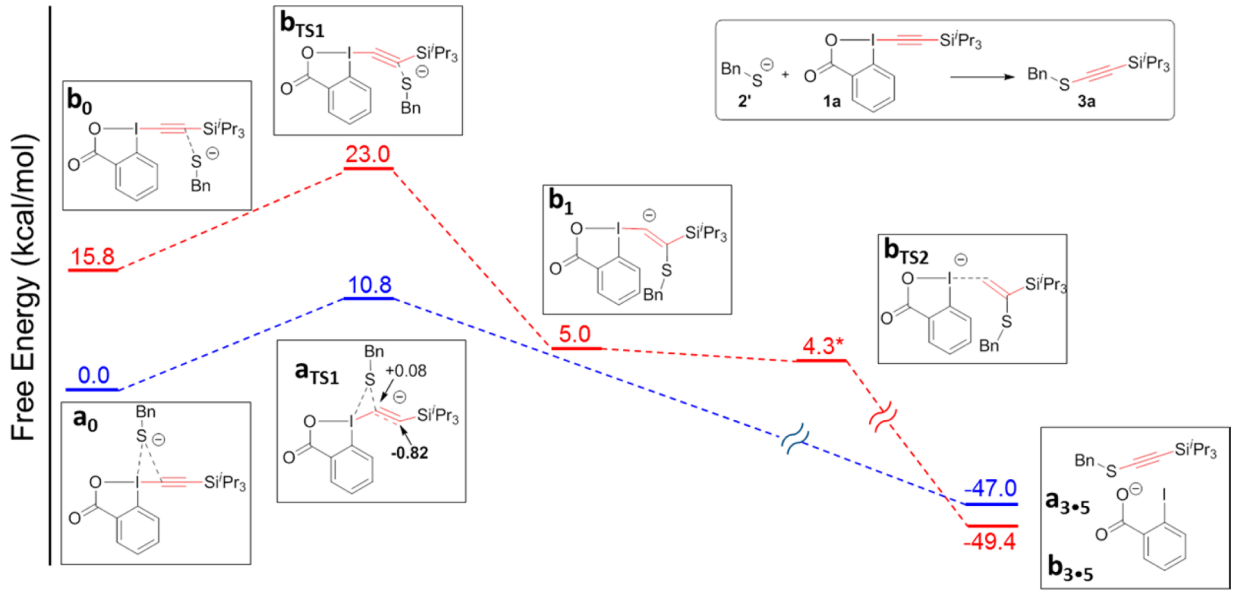

Figure 2. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways **a** (blue) and **b** (red) for the reaction of TIPS-EBX (**1a**) with thiolate **2′**. *Positive deltaE at the M06-2X/def2-SVP level.

Our initial assumption was that complex $\mathbf{a_0}$ (depicted in blue) is the reactant species leading to formation of a S−I bond, as represented by intermediate $\mathbf{a_1}$. To our surprise, no minima containing a formal S−I bond could be located on the potential energy surface (Figure 2, blue pathway). Instead, the quasi-triangular atomic arrangement between the sulfur, iodine, and α-carbon atoms results in a direct addition of the sulfur onto the α-carbon atom of the acetylene unit with simultaneous breaking of the C−I bond.[20] This process is associated with a quite modest $\mathbf{a_{TS1}}$ barrier height of only 10.8 kcal/mol.[21] Upon formation of the new S−C bond (Figure 3, $\mathbf{a_{TS1}}$ in blue), the thioalkyne-iodobenzoic acid complex $\mathbf{a_{3•5}}$ is spontaneously formed in a highly exergonic process. Importantly, we find no computational evidence predicting formation of a stable intermediate, which is in agreement with of our failure to isolate any side products with TIPS-EBX (**1a**) as reagent.

The conjugate addition pathway **b** (Figure 2, red pathway), begins from the higher energy (+15.8 kcal/mol, red) van der Waals complex $\mathbf{b_0}$. Here, the reaction proceeds as originally proposed by Ochiai.[18] Formation of the new S−C bond occurs in a facile process, requiring only ∼7.2 kcal/mol of energy ($\mathbf{b_{TS1}}$). In contrast to the previously discussed pathway, the β-carbon conjugate addition route **b** does lead to the formation of the expected intermediate species $\mathbf{b_1}$. However, the TS barrier associated with cleavage of the I−C bond ($\mathbf{b_{TS2}}$, Figure 3) is negligible (ΔG = −0.7 kcal/mol at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP level, ΔE = +0.3 kcal/mol at the M06-2X/def2-TZVP//M06-2X/def2-SVP level), meaning the species is likely short-lived, making experimental characterization, observation or even protonation highly unlikely. As in pathway **a**, formation of the final product complex is highly exergonic, proceeding via a 1,2-shift of the silicium atom. No minima corresponding to a free carbene $\mathbf{b_2}$ could be located on the potential energy surface.

From the reaction free energy profile in Figure 2, it is clear that both the **a** (blue) and **b** pathway (red) mechanisms are easily accessible at room temperature. While the β-conjugate addition pathway **b** involves a slightly lower TS barrier $\mathbf{b_{TS1}}$ corresponding to S−C bond formation, the lower relative

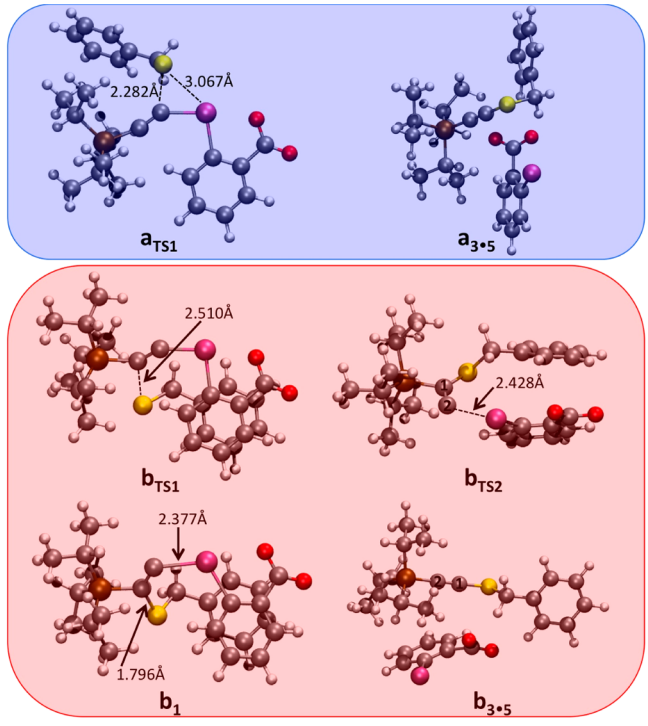

Figure 3. Computed geometries (M06-2X/def2-SVP level) of the relevant structures.

energy of the α-addition van der Waals complex $\mathbf{a_0}$ (blue, Figure 1) results in pathway **a** being the overall energetically preferred reaction mechanism by 12.2 kcal/mol. This is highly interesting, considering that a mechanism involving addition to the α-carbon atom concerted with elimination of the iodine has never seriously been considered for alkynyl hypervalent iodine reagents.

To ensure that other mechanisms that include either direct attack by a protonated thiol or explicit involvement of the base (TMG) are not more energetically favorable, we computed a number of additional pathways (see SI for details). However,

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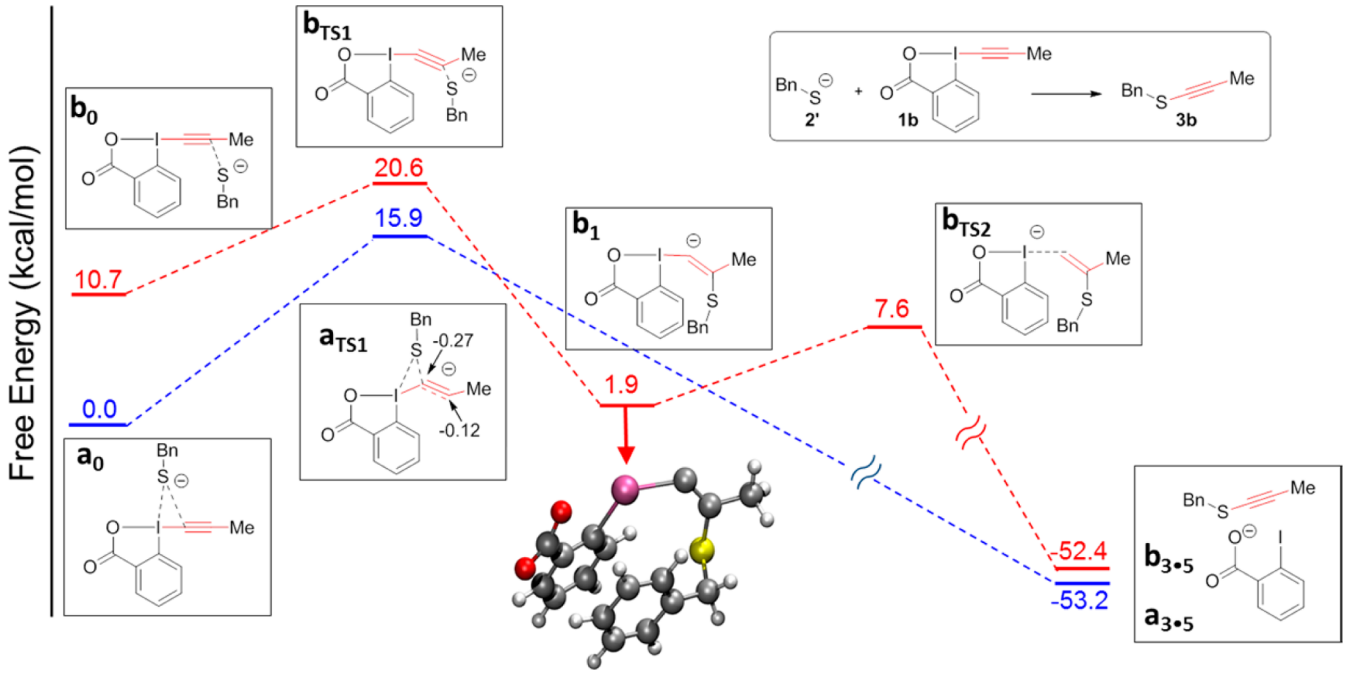

Figure 4. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways **a** (blue) and **b** (red) for the reaction of Me-EBX (**1b**) with thiolate **2′**.

none were found to be energetically competitive with the direct attack of thiolate mechanism described above. As an example, direct attack by the protonated thiol species involves a TS barrier of 32.6 kcal/mol for S−C bond formation. This compares quite unfavorably to the 10.8 kcal/mol barrier seen when the deprotonated thiol is involved in a direct attack type mechanism.[22]

The computational results obtained for the reaction of TIPS-EBX (**1a**) are highly interesting. Nevertheless, they seemed to be in contradiction with the isolation of side product **6** when Me-EBX (**1b**) was used (eq 3), as **6** would be generated from very short-lived intermediate $\mathbf{b}_1$ via the least favored pathway **b**. To see if this result could be rationalized by computation, we also examined the reaction free energy profile for Me-EBX (**1b**) (Figure 4). Like for TIPS-EBX (**1a**) (Figure 2), a mechanism featuring attack on the α-carbon is favored based on enhanced stability of the prereaction van der Waals complex $\mathbf{a}_0$ and $\mathbf{b}_0$. In contrast, however, the TS barrier associated with formation of the S−C bond ($\mathbf{a}_{TS1}$ and $\mathbf{b}_{TS1}$, Figure 4) lie relatively close to each other (within 5 kcal/mol at the PBE0-dDsC/TZ2P level and within 2 kcal/mol at the M06-2X/def2-TZVP level).[23] Since this first transition state represents the highest point along the reaction pathway for both mechanisms, it can be envisaged that a small percentage of reactions proceed via the red pathway **a**, as opposed to the more energetically favorable blue pathway **b**. Furthermore, a significant $\mathbf{b}_{TS2}$ barrier height (+5.7 kcal/mol) is obtained, in contrast to the reaction with silylated reagent **1c**. This enhanced barrier, probably due to the less favorable shift of the sulfur group in this case, likely equates to a longer-lived intermediate that can be protonated and observed as **6** (eq 3).

When comparing the lowest energy pathway **a** for the reaction of TIPS-EBX (**1a**) and Me-EBX (**1b**), a strong accelerating effect of the silicium atom (about 5 kcal/mol) is apparent. Although understanding fully this effect will require more in-depth studies, some insights can already be gained by looking closely at the unsymmetrical structure of transition state $\mathbf{a}_{TS1}$. Indeed, the sulfur atom is already in close proximity to the α carbon atom of the alkyne, and the geometry around the β carbon is strongly distorted from sp to sp^2. This would lead to the formation of a partial charge on the β carbon. Indeed, calculations indicated an iterative Hirshfeld charge of −0.82 at this position in the case of TIPS-EBX (**1a**) (Figure 2). In contrast, no strong charge transfer was observed in the case of Me-EBX (**1b**) (charges of −0.27 and −0.12 at the α and β positions, respectively, Figure 4). Silicium is well-known to stabilize negative charges on adjacent carbons (α-silicium effect).[24] Consequently, a lower activation barrier could be expected in this case through transition state stabilization.

SCOPE EXTENSION

The previous method developed in our group was very efficient using TIPS-EBX (**1a**) as a reagent. However, to introduce a fluorophore or other functional groups on the alkyne, two further steps were required (silyl deprotection and cycloaddition), making the approach less convergent.[14a] Furthermore, sensitive substrates could potentially not resist in the desilylation step using basic TBAF. Consequently, it would be highly desirable to install the desired functionality on the alkyne on the cyclic hypervalent iodine reagent before carrying out the thioalkynylation reaction. On the basis of the side reactions observed by Ochiai and co-workers with alkyl-substituted alkynyliodonium salts and carbon nucleophiles,[18] a generalization of the scope appeared highly challenging to us when we started this project. However, the surprisingly good results obtained with Me-EBX (**1b**) during our mechanistic investigations and the very low activation energies obtained by computation indicated that sulfur nucleophiles should behave differently and have a much broader scope in the alkynylation reaction. To test this hypothesis, benziodoxolone hypervalent iodine reagents were first synthesized via Olofsson's one-step method starting from alkynyl boronic esters (eq 4).[19] This

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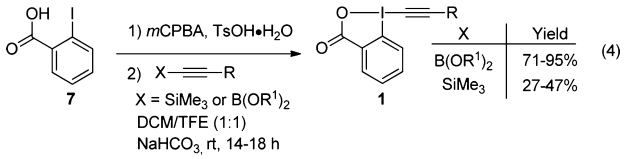
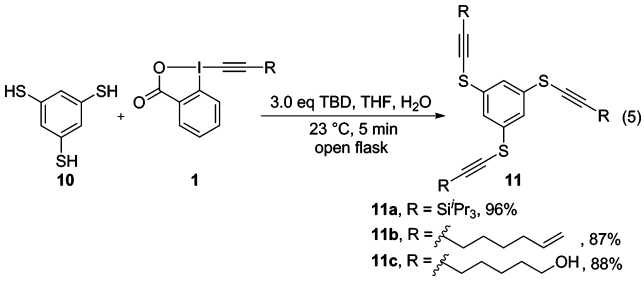


protocol turned out to be very efficient and easily scalable giving the EBX reagents in 71−95% yield in up to 9 g scale in the case of Me-EBX (**1b**). Nevertheless, in case of more functionalized alkynes, it was not possible to access the very sensitive alkynyl boronic esters. In this case, the use of more stable silylated alkynes gave the desired products in 27−47% yield. Importantly, EBX reagents bearing functional groups such as alkenes, alkynes, halogens, azides or alcohols were synthesized for the first time. Although the yield was moderate, the procedure was easily scalable to the multigram scale and the enhanced stability of benziodoxolone compared to alkynyliodonium salts allowed easy purification by column chromatography to obtain pure reagents **1**. A significant amount of silyl acetylenes could also be recovered.[25]

Due to the significance of aromatic thiols as important structural motifs in the synthesis of pharmaceutical, natural, and medicinal compounds and the excellent results obtained in our previous work, we decided to start our investigation with this class of substrates. *o*-Bromo thiophenol **8** was chosen as a substrate for studying the different EBX reagents, as the bromo group constitutes an ideal handle for further functionalization. In the case of aliphatic EBX reagents, we found that TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) was superior to TMG as a base and THF was still the optimal solvent. When EBX reagent **1b** was added to the mixture consisting of *o*-bromo thiophenol (**8**), TBD, and THF at room temperature and stirred for 5 min in an open flask, the corresponding thioalkynylated product **9a** was obtained in 93% yield (Table 1, entry 1). Noteworthy, the reaction was not affected by the water which was added to increase the solubility of the formed thiolate salts in certain cases. The alkynylation with longer alkyl chains (entries 2 and 3) or a *tert*-butyl group (entry 4) proceeded in quantitative yields. At this point, the use of functionalized alkyl-EBX reagents was investigated for the first time (entries 5−9).

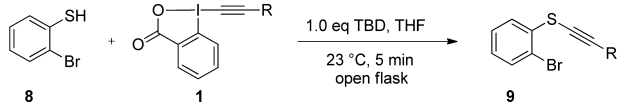
We were pleased to see that the alkynylation with reagents bearing an alkene, an alkyne, a chloride, an azide or a free alcohol proceeded in 87−98% yield. The fact that functional groups are tolerated both on the thiol and alkyne reagent makes the method more attractive for the synthesis of thioalkynes. Finally, the alkynylation was not limited to the transfer of aliphatic alkynes: mesityl-substituted product **9j** was also obtained in quantitative yield (entry 10).

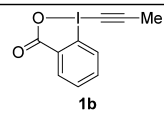
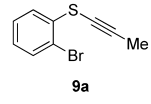
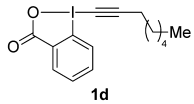
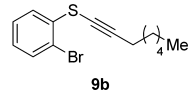
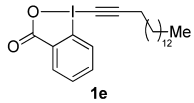
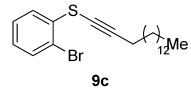
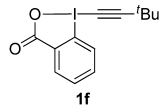
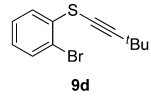
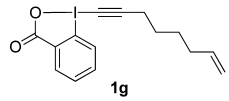
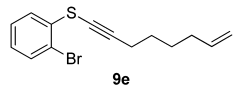
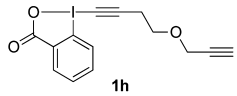
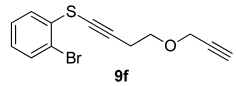
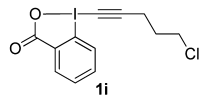
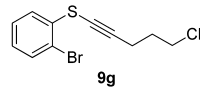
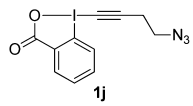
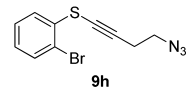
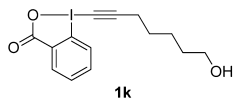
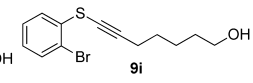
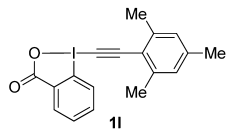
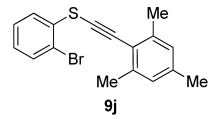
Inspired by the efficiency of the thioalkynylation reaction (Table 1), we further studied the use of EBX reagents for the multiple alkynylation of benzene-1,3,5-trithiol (**10**) (eq 5). In this context, TIPS-EBX (**1a**) and EBX reagents **1g** and **1k** were examined. We were able to isolate the corresponding triple-alkynylated products **11a−c** in 96%, 87% and 88% yield, respectively. Due to the efficiency of the reaction and the versatility of the introduced functional groups, the method is highly useful for the synthesis of dendrimers with potential applications in materials science or drug delivery.



To further demonstrate the utility of the synthesized thioalkyne products, we investigated their transformation into other useful building blocks. We first examined the transformation of thioalkyne **9b** into the corresponding benzothio-

Table 1. Scope of EBX Reagents with *o*-Bromo Thiophenol[a]



Entry	R-EBX	Product	Yield[b]
1	 1b	 9a	93%
2	 1d	 9b	98%
3	 1e	 9c	98%
4	 1f	 9d	quant.
5	 1g	 9e	93%
6	 1h	 9f	95%
7	 1i	 9g	87%
8	 1j	 9h	90%
9	 1k	 9i	98%
10	 1l	 9j	quant.

[a] *O*-Bromo thiophenol (**8**, 0.30−0.80 mmol), alkyne transfer reagent (**1**, 0.33−0.88 mmol), base (0.30−0.80 mmol), THF (3.75−10.0 mL), 23 °C, 5 min, open flask. [b] Isolated yield after purification by column chromatography.

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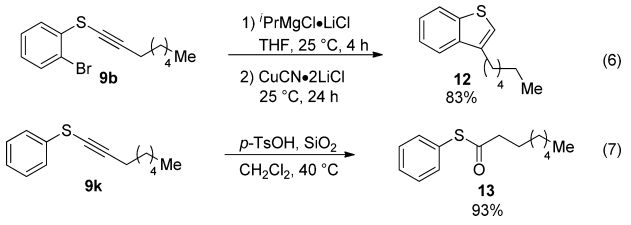
phene **12** using a protocol developed by Knochel and co-workers (eq 6).[26] The addition of ^{i}PrMgCl·LiCl in THF to **9b**



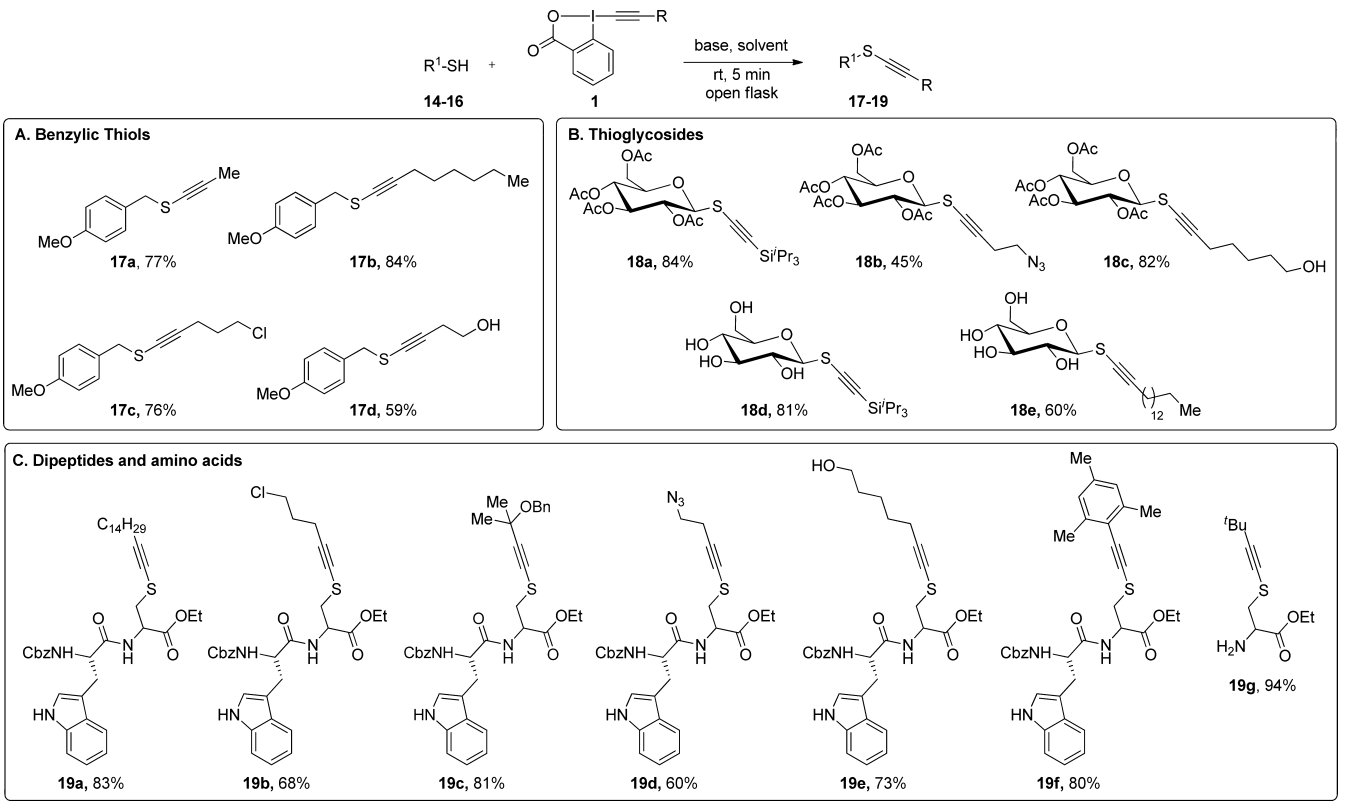
followed by CuCN·2LiCl afforded the 3-alkyl benzothiophene **12** in 83% yield after 24 h. Thiolakyne **9k**, easily obtained from the alkynylation of thiophenol with reagent **1d**, was subjected to acid hydrolysis to furnish the corresponding thioester **13** in 93% yield (eq 7).[27]

After having successfully extended the scope of the alkynylation to alkyl- and aryl-substituted EBX reagents in the case of thiophenols, we turned to aliphatic thiols (Scheme 4). (4-Methoxyphenyl)methanethiol (**14**) was alkynylated successfully, furnishing alkynylation products **17a–d** in 59–84% yield (Scheme 4A).[28] Again, long and short alkyl chains, as well as a chloride and an alcohol, were well tolerated on the reagent, although the yields were lower than in the case of thiophenols. As a second important class of aliphatic thiols, we decided to turn to thioglycosides (Scheme 4B). These compounds are key building blocks in carbohydrate synthesis and exhibit important biological activities.[29] Recently, Messaoudi and co-workers reported the alkynylation of protected and unprotected thioglycosides using transition metal catalysts.[13b,c] Our metal free thioalkynylation method provides a valuable alternative that avoids the use of expensive or toxic metal catalysts, ligands, base and higher temperature. Furthermore, only the synthesis of aromatic alkynes had been reported to date. Using our method, protected thioglycoside **15a** was alkynylated with TIPS-EBX (**1b**) and reagents **1j** and **1k** in a few minutes at room temperature to afford the corresponding products **18a–c** in 45–84% yield. Protection of the hydroxy groups of the carbohydrate was not required: products **18d** and **18e** bearing four free hydroxy groups were also obtained in 81% and 60% yields, respectively.

After demonstrating that the reaction protocol worked well with simple aliphatic thiols and thioglycosides, we studied the alkynylation of a cysteine containing dipeptide **16a** (TrpCys). In fact, cysteine is one of the natural amino acids and plays a key role in the activity and structure of proteins. It is also an ideal entry for bioconjugation reactions.[9,30] As shown in Scheme 4C, the reaction worked efficiently for a variety of EBX reagents. Substituents containing an alkyl chain without (product **19a**) or with additional functional groups (products **19b–e**) were tolerated including a chloro, an ether,[31] an azido and a hydroxy group. Finally, a mesityl-substituted alkyne group could also be introduced in 80% yield (product **19f**). The selective alkynylation of dipeptide **16a** with different functionalized alkynes is an important preliminary result in view of the modification of more complex molecules, such as peptides and proteins. In addition, the alkynylation of N-unprotected cysteine ester **16b** with ^{t}Bu-EBX (**1f**) gave exclusively thiol alkynylation in 94% yield.

As a last example of more complex aliphatic thiol, angiotensin-converting enzyme (ACE) inhibitor Captopril (**20**), which is used as a drug to treat hypertension,[32] was

Scheme 4. Scope of the Alkynylation for Benzylic Thiol 14 (A), Thioglycosides 15 (B), and Amino Acid Derivative 16 (C)[a]



[a]See Supporting Information for experimental details (solvents, base).

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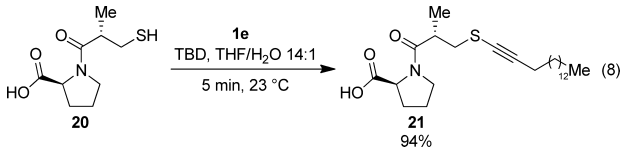
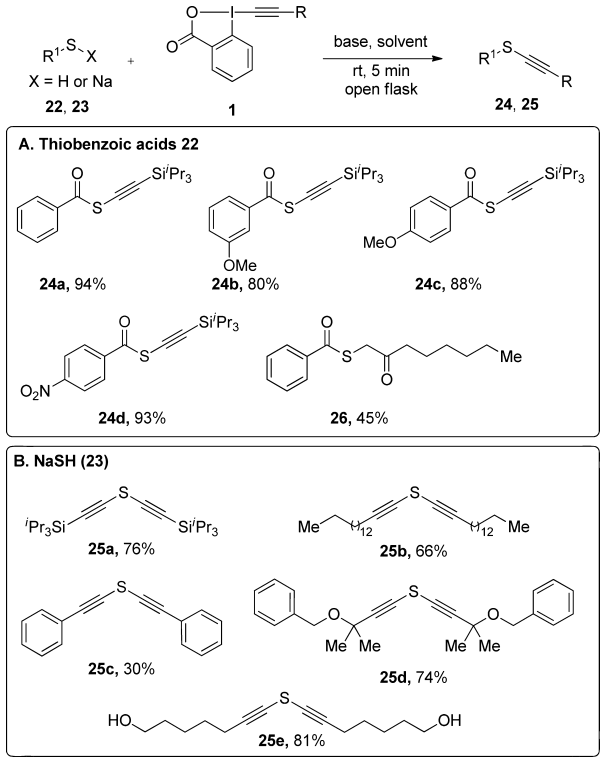
successfully alkynylated with **1e** to give the corresponding thioalkyne **21** in 94% yield (eq 8). This result demonstrated that free carboxylic acid groups were tolerated in the alkynylation reaction.



To further demonstrate the generality of the alkynylation reaction, we studied two classes of sulfur nucleophiles which were not included in our previous studies: thiocarboxylic acids and sodium hydrogen sulfide, the simplest of all sulfur nucleophiles (Scheme 5). Thiocarboxylates are less nucleophilic

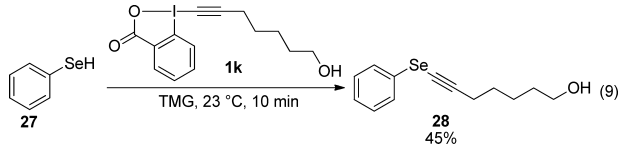
Scheme 5. Alkynylation of Thioacids 22 (A) and Sodium Hydrogen Sulfide (23) (B)



than thiolates. Nevertheless, TIPS-EBX (**1a**) was again an excellent reagent for the alkynylation of thiobenzoic acid (**22a**) giving the desired product **24a** in 94% yield. Electron-donating and -withdrawing groups were well tolerated on the benzene ring (products **24b–d**). On the other hand, thioesters derived from aliphatic alkynes were unstable under the reaction conditions, and ketone product **26**, probably resulting from the hydration of the triple bond, was instead isolated in 45% yield. Only very low yields were obtained in the case of aliphatic thioacids (results not shown). Unlike other thiols, the alkynylation of thioacids did not require the use of base, probably due to the higher acidity of these substrates.

Due to the significant properties of diethynyl sulfides in material and interstellar chemistry,[33] we then attempted their synthesis through the alkynylation of sodium hydrogen sulfide. The resulting one-step protocol would be unprecedentedly fast to access this class of compounds. The double alkynylation worked for all three classes of alkynes: silyl (product **25a**), alkyl (product **25b**) and aryl (product **25c**). The lower yield of the latter is probably due to the low solubility of the reagent Ph-EBX (**1o**). The reaction also worked for the introduction of a propargylic ether (product **25d**) or an alcohol (product **25e**).[34]

We then examined if the alkynylation method could be extended to selenium nucleophiles. In fact, alkynyl selenium compound **28** was obtained in 45% yield from phenylselenol (**27**) without further optimization of the reaction conditions. This preliminary result is promising for the development of a more general method for the alkynylation of selenols.



CONCLUSION

In summary, in this manuscript we described the first computational studies of the alkynylation of thiols using ethynyl benziodoxolone (EBX) reagents. An unprecedented concerted mechanism involving the sulfur, iodine and α-carbon atoms of the alkyne was discovered by computation, leading directly to the alkynylation products with a low activation barrier. In case of silyl-substituted EBX reagents, the activation energy was exceptionally low (10.8 kcal/mol), which made this pathway the most favorable according to the computations and may explain the high rate observed for the reaction. For the case of alkyl-substituted reagents, a second mechanism involving conjugate addition, followed by simultaneous α elimination of iodobenzoic acid and sulfur 1,2-shift was also found to be competitive. This latter result rationalizes the isolation of small amounts of vinyl benziodoxolone intermediate **6** resulting from conjugate addition of benzylthiol (**2**) on Me-EBX (**1b**) followed by protonation.

The unique properties of thiolates in reaction with EBX reagents led us to anticipate that the transformation may have a broader scope than reactions involving carbon nucleophiles. This was indeed the case, and we could use, for the first time, functionalized alkyl- and aryl-substituted EBX reagents for the alkynylation of both aromatic and aliphatic thiols. Functional groups such as alkenes, alkynes, ethers, chlorides, azides and alcohols were tolerated on the alkynes. In addition to simple thiophenols and benzylic thiols, the alkynylation of cysteine in a dipeptide, thioglycosides, thiobenzoic acid derivatives and sodium hydrogen sulfide was also successful. The practical and user-friendly character of the method (5 min reaction time, open-flask, water tolerance, room temperature) and a deeper understanding of the reaction mechanism have set the stage for a broader application in the functionalization of materials and biomolecules in the future.

COMPUTATIONAL DETAILS

All geometries were optimized using Truhlar's M06-2X[35] density functional with the def2-SVP basis set in Gaussian09.[36] M06-2X computations employed the "Ultrafine" grid to remove known problems with the size of the integration grid for this functional family.[37] To obtain refined energy estimations that explicitly account for nonbonded interactions, a density dependent dispersion correction[38] was used appended to the PBE0[39] functional (PBE0-dDsC). PBE0-dDsC single point computations made use of the slater-

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type orbital 3-ζ basis set, TZ2P, as implemented in ADF.[40] To confirm the accuracy of the PBE0-dDsC computations, a second set of single point energies was obtained at the M06-2X/def2-TZVP level. All reported free energies include the effects of solvation (in THF) using the implicit continuum model for realistic solvents[41] (COSMO-RS), also as implemented in ADF, as well as free energy correction derived from M06-2X/def2-SVP computations. Iterative Hirshfeld charges[42] were computed using Q-Chem[43] at the M06-2X/def2-SVP level.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. Additional computational, data including Cartesian coordinates of relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) Computed free energies at the M06-2X/def2-TZVP//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS) yielded the same trends, albeit with a slightly lower energy difference between the two pathways (Energy a_{TS1}, 11.8 kcal/mol; b_{TS1}, 20.1 kcal/mol; difference, 8.3 kcal/mol. See Supporting Information for details.

(22) Computation of the transition state a_{TS1} for other nucleophiles was also done in order to better understand the observed chemioselectivity. With methanol and dimethyl phosphite, no transition state could be located. Higher energies were observed for methylamine and acetate as nucleophiles (+30.8 and +18.1 kcal/mol, respectively). In contrast, a low energy transition state (+12.2 kcal/mol) was observed in the case of deprotonated dimethyl phosphite. Indeed, the facile alkynylation of this class of nucleophiles was recently reported by our group (ref 14h). See Supporting Information for details.

(23) Computed free energies at the M06-2X/def2-TZVP//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS): a_{TS1}, 18.9 kcal/mol; b_{TS1}, 20.8 kcal/mol; difference, 1.9 kcal/mol. In addition, the difference in free energies obtained using B3LYP-dDsC and B3LYP-D3 methods was situated in between the other results (4.3 and 3.3 kcal/mol, respectively). Nevertheless, the importance of the three-atom concerted pathway should not be overestimated at this stage. See Supporting Information for details.

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Supporting Information for

Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled Through a Low Energy Barrier Concerted Mechanism

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1. Computational Details

Figure S1. Electronic energies along the intrinsic reaction coordinate for the **a** pathway. Computations at the M06-2X/def2-SVP level.

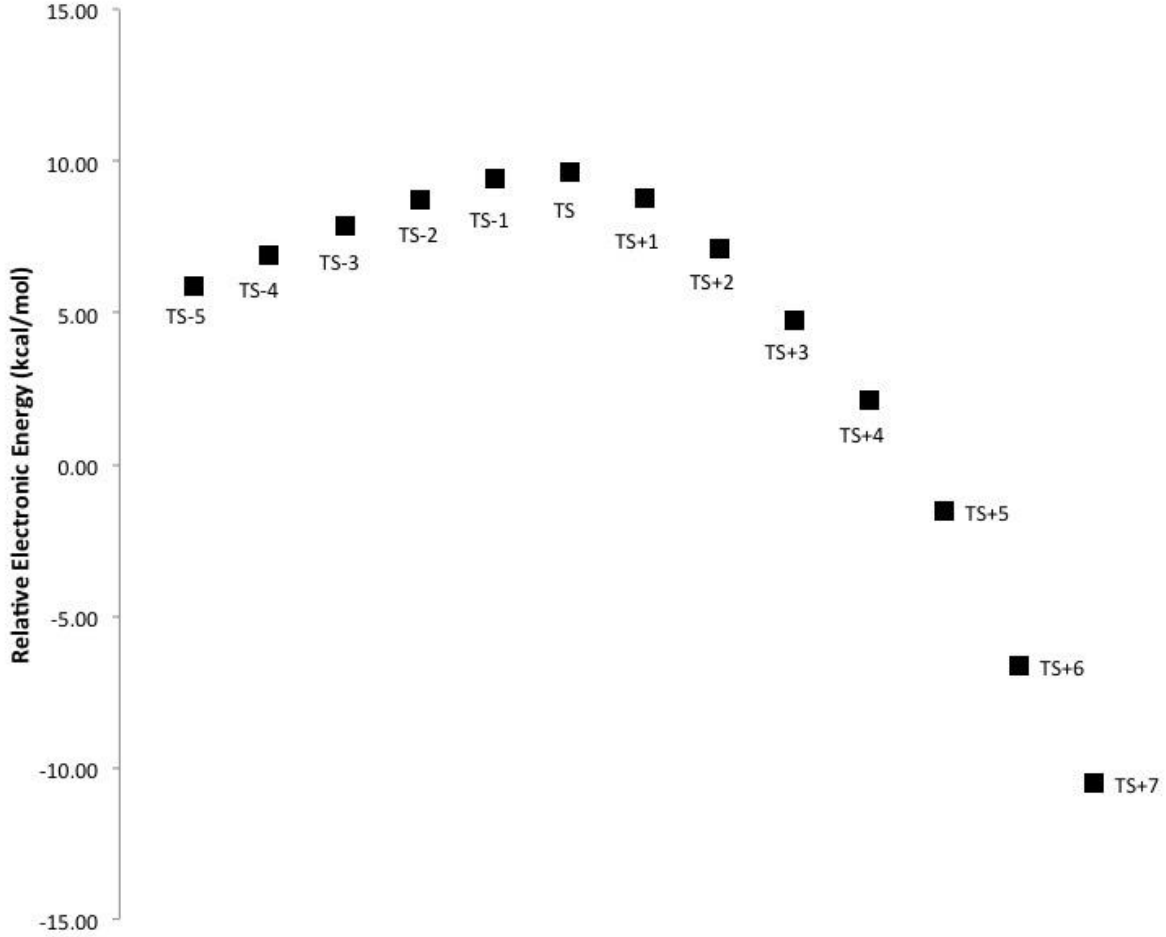

Figure S2. Selected geometries along the IRC for the **a** pathway. Structures correspond to labels from figure S1.

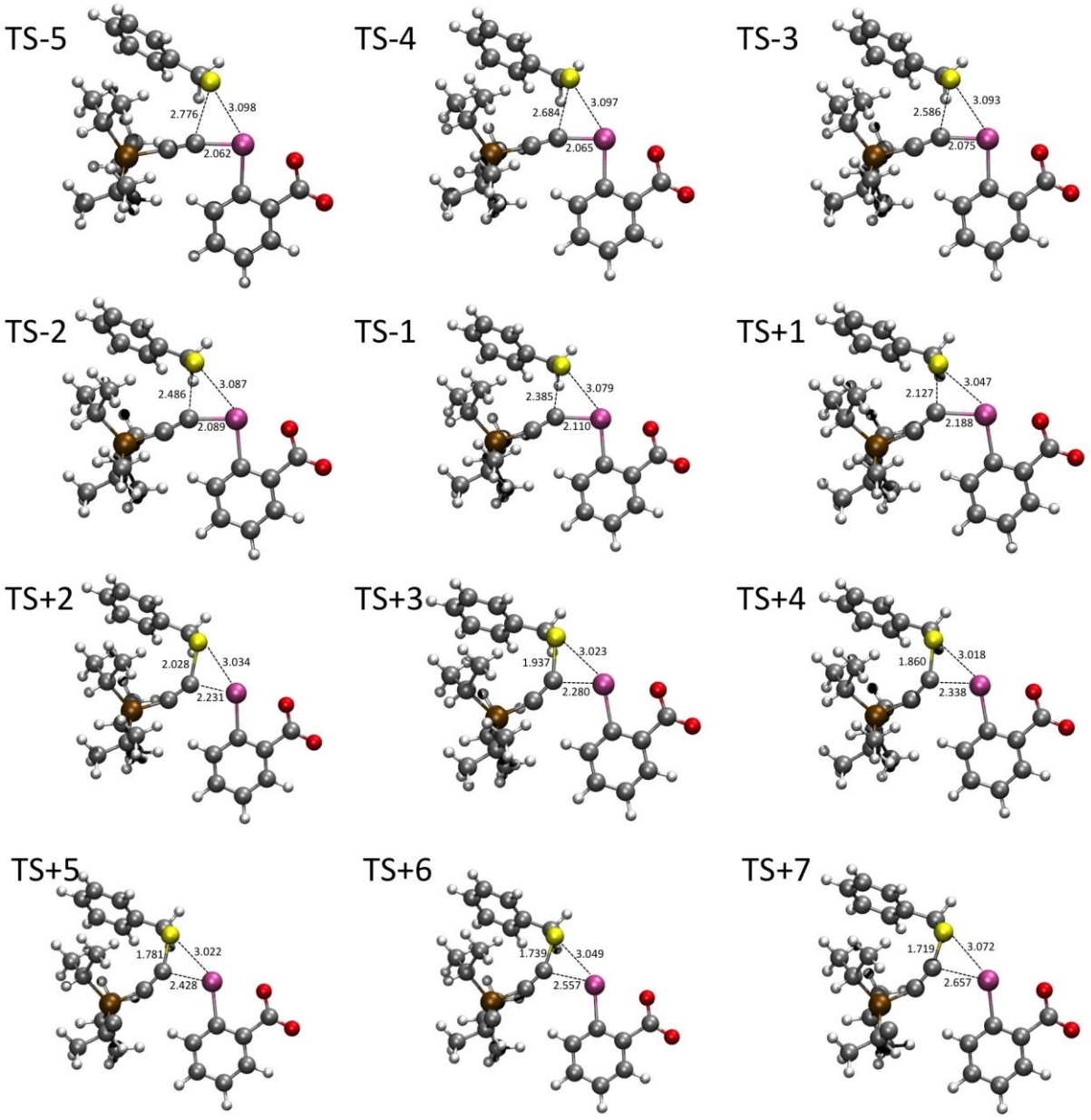

Table S1. Electronic energies, free energy corrections, and solvation corrections for relevant compounds using the TIPS-EBX reagant. PBE0-dDsC/TZ2P and M06-2X/def2-TZVP electronic energies obtained from single point computations on M06-2X/def2-SVP geometries.[1]

Compound	M06-2X/def2-SVP Electronic Energy (hartree)	M06-2X/def2-SVP Free Energy Correction (hartree)	M06-2X/def2-TZVP Electronic Energy (hartree)	PBE0-dDsC/TZ2P Electronic Energy (hartree)	COSMO-RS Solvation Energy (kcal/mol)
$\mathbf{a_0}$	-2106.082266	0.440280	-2107.606383	-16.332255	-52.866
$\mathbf{b_0}$	-2106.074669	0.441889	-2107.598451	-16.315327	-48.750
$\mathbf{a_{TS1}}$	-2106.066858	0.438536	-2107.587790	-16.318528	-49.640
$\mathbf{b_{TS1}}$	-2106.064275	0.443031	-2107.584800	-16.306042	-48.055
$\mathbf{b_1}$	-2106.090006	0.441073	-2107.608545	-16.327049	-51.620
$\mathbf{b_{TS2}}$	-2106.089913	0.442080	-2107.608026	-16.328147	-52.324
$\mathbf{a_{3\text{-}5}}$	-2106.187915	0.442548	-2107.702682	-16.413023	-50.590
$\mathbf{b_{3\text{-}5}}$	-2106.177060	0.438296	-2107.694266	-16.408391	-53.279

Table S2. Reaction free energies (in kcal/mol) for the **a** and **b** pathways using the TIPS-EBX reagent. PBE0-dDsC/TZ2P and M06-2X/def2-TZVP free energies include free energy corrections obtained from M06-2X/def2-SVP computations and solvation corrections (in THF) from COSMO-RS (at the PBE0-dDsC/TZ2P theoretical level).

Reaction	PBE0-dDsC Free Energy	M06-2X Free Energy
$\mathbf{a_0 \rightarrow a_{TS1}}$	10.75	13.80
$\mathbf{a_{TS1} \rightarrow a_{3\text{-}5}}$	-57.73	-70.53
$\mathbf{b_0 \rightarrow b_{TS1}}$	7.24	9.98
$\mathbf{b_{TS1} \rightarrow b_1}$	-17.98	-19.69
$\mathbf{b_1 \rightarrow b_{TS2}}$	-0.76	0.25
$\mathbf{b_{TS2} \rightarrow b_{3\text{-}5}}$	-53.68	-57.45
$\mathbf{a_0 \rightarrow b_0}$	15.75	10.10
$\mathbf{a_{TS1} \rightarrow b_{TS1}}$	11.04	6.28

Table S3. Electronic energies, free energy corrections, and solvation corrections for relevant compounds using the Methyl-EBX reagant.[1]

Compound	M06-2X/def2-SVP Electronic Energy (hartree)	M06-2X/def2-SVP Free Energy Correction (hartree)	M06-2X/def2-TZVP Electronic Energy (hartree)	PBE0-dDsC/TZ2P Electronic Energy (hartree)	COSMO-RS Solvation Energy (kcal/mol)
$\mathbf{a_0}$	-1501.355114	0.209054	-1502.419519	-9.927595	-51.671
$\mathbf{b_0}$	-1501.348373	0.210347	-1502.413181	-9.916865	-48.546
$\mathbf{a_{TS1}}$	-1501.330293	0.208068	-1502.393028	-9.905776	-48.827
$\mathbf{b_{TS1}}$	-1501.332390	0.211039	-1502.395983	-9.904429	-46.844
$\mathbf{b_1}$	-1501.364149	0.212440	-1502.424548	-9.930714	-49.940
$\mathbf{b_{TS2}}$	-1501.351776	0.208410	-1502.411644	-9.909202	-55.178

[1] ADF computes energies relative to basic atom fragments, rather than to separated particles (e.g., nuclei and electrons), as is done in Gaussian. This gives rise to the magnitude difference in the reported M06-2X (computed in Gaussian) and PBE0-dDsC (computed in ADF) electronic energies. Note that absolute electronic energies computed using different density functionals cannot be directly compared with one another.

$\mathbf{a}_{3\cdot5}$	-1501.452165	0.210268	-1502.509091	-10.005636	-51.947
$\mathbf{b}_{3\cdot5}$	-1501.445995	0.208701	-1502.504574	-10.003114	-51.747

Table S4. Reaction free energies (in kcal/mol) for the **a** and **b** pathways using the Methyl-EBX reagent. PBE0-dDsC/TZ2P and M06-2X/def2-TZVP free energies include free energy corrections obtained from M06-2X/def2-SVP computations and solvation corrections (in THF) from COSMO-RS (at the PBE0-dDsC/TZ2P theoretical level).

Reaction	PBE0-dDsC Free Energy	M06-2X Free Energy
$\mathbf{a}_0 \rightarrow \mathbf{a}_{TS1}$	15.92	18.85
$\mathbf{a}_{TS1} \rightarrow \mathbf{a}_{3\cdot5}$	-64.40	-74.57
$\mathbf{b}_0 \rightarrow \mathbf{b}_{TS1}$	9.94	12.93
$\mathbf{b}_{TS1} \rightarrow \mathbf{b}_1$	-18.71	-20.14
$\mathbf{b}_1 \rightarrow \mathbf{b}_{TS2}$	5.73	0.33
$\mathbf{b}_{TS2} \rightarrow \mathbf{b}_{3\cdot5}$	-55.32	-54.70
$\mathbf{a}_0 \rightarrow \mathbf{b}_0$	10.67	7.91
$\mathbf{a}_{TS1} \rightarrow \mathbf{b}_{TS1}$[a]	4.69	1.99

[a] In addition calculation at the B3LYP-dDsC and B3LYP-D3 level gave energies of 4.33 and 3.28 kcal/mol respectively.

Table S5. Reaction free energies (in kcal/mol) for the **a** pathways using the TIPS-EBX reagent and different nucleophiles. PBE0-dDsC/TZ2P free energies include free energy corrections obtained from M06-2X/def2-SVP computations and solvation corrections (in THF) from COSMO-RS (at the PBE0-dDsC/TZ2P theoretical level).

Reaction	Nucleophile	PBE0-dDsC Free Energy
$\mathbf{a}_0 \rightarrow \mathbf{a}_{TS1}$	MeOH	Not located
$\mathbf{a}_0 \rightarrow \mathbf{a}_{TS1}$	$MeNH_2$	+30.8
$\mathbf{a}_0 \rightarrow \mathbf{a}_{TS1}$	Acetate	+18.1
$\mathbf{a}_0 \rightarrow \mathbf{a}_{TS1}$	$HP(O)(OMe)_2$	Not located
$\mathbf{a}_0 \rightarrow \mathbf{a}_{TS1}$	$^{-}P(O)(OMe)_2$	+12.2

Scheme S1. Alternative mechanistic pathways involving participation of the base.

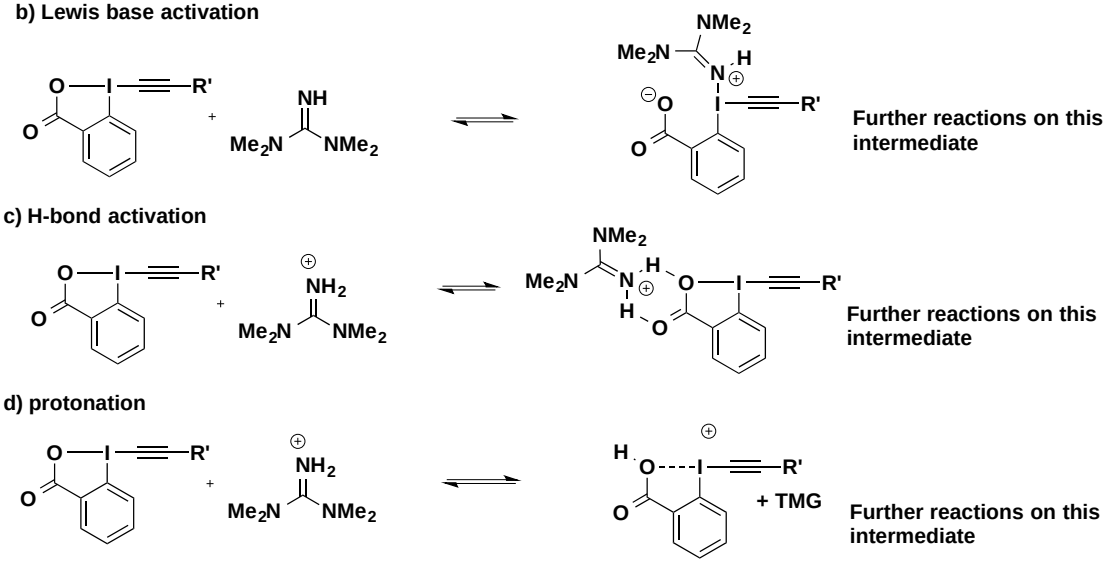

Table S6. Highest energy points on potential energy surface leading to formation of thioalkynes with TMS-EBX.

Mechanistic Pathway	**Highest Energy Value on PES (kcal/mol)**
Direct Attack (discussed in manuscript)	9.4
Lewis Base Activation	14.9
H-bond Activation	13.1
Protonation	47.2

Cartesian Coordinates of Relevant Compounds

62
A0 - TIPS

C	0.00761	-0.50119	-0.12839
S	-1.54444	2.11166	0.81379
C	-1.58265	2.36457	-0.98721
I	1.11052	0.91818	0.91545
C	4.03583	0.16549	1.26576
C	5.22483	-0.56318	1.18742
C	2.87919	-0.36166	0.70101
C	5.24830	-1.80161	0.55221
H	6.11038	-0.11520	1.64231
C	2.88171	-1.59918	0.06270
C	4.07735	-2.31724	-0.00823
H	6.17801	-2.37086	0.49123
H	1.96761	-2.00409	-0.37454
H	4.08989	-3.28884	-0.50676
C	4.01459	1.52706	1.96834
O	5.05014	1.95513	2.44925
O	2.86190	2.07694	1.96759
C	-0.65855	-1.30664	-0.76087
Si	-1.80244	-2.45433	-1.64628
C	-1.40363	-2.30970	-3.50183
C	-1.39408	-0.84972	-3.96938
H	-2.19784	-2.85271	-4.04723
C	-0.05426	-2.96912	-3.81116
C	-3.59806	-2.02718	-1.17690
C	-3.65991	-1.33812	0.19409
H	-4.09876	-3.01177	-1.09709
C	-4.35237	-1.20329	-2.22500
C	-1.40573	-4.22089	-1.05749
H	-0.32442	-4.35803	-1.23633
C	-2.17146	-5.26800	-1.87223
C	-1.66478	-4.39045	0.44178
C	-2.95046	2.31355	-1.64282
H	-1.13245	3.33982	-1.24238
H	-0.96221	1.60070	-1.49048
C	-4.14115	2.27659	-0.91056
C	-5.37773	2.23690	-1.55810
C	-5.44945	2.23046	-2.94986
C	-3.03696	2.31732	-3.04361
C	-4.26830	2.27215	-3.69381
H	-4.06773	2.26647	0.17870
H	-6.29489	2.20308	-0.96576
H	-6.41702	2.19014	-3.45403
H	-2.11368	2.34631	-3.62966
H	-4.30731	2.26508	-4.78536
H	-5.41149	-1.09391	-1.93925
H	-3.94052	-0.18537	-2.29802
H	-4.31940	-1.66031	-3.22695
H	-4.70798	-1.14493	0.47823
H	-3.20166	-1.94898	0.98680
H	-3.12510	-0.37319	0.19027
H	-1.15272	-0.78431	-5.04356
H	-2.35746	-0.34757	-3.80744
H	-0.63015	-0.27729	-3.41859
H	0.20743	-2.84981	-4.87543
H	0.74942	-2.49773	-3.22124
H	-0.04773	-4.04547	-3.58308
H	-1.92205	-6.29052	-1.54333
H	-3.26015	-5.14499	-1.74942
H	-1.95247	-5.20080	-2.94916
H	-1.35946	-5.39190	0.78772
H	-1.11737	-3.64248	1.03458
H	-2.73716	-4.27754	0.67013

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A_TS1 - TIPS
C 0.12497 -0.37979 -0.59944
S -0.78602 -2.35245 -1.29791
C -1.45144 -2.74401 0.34942
I 2.00638 -1.38546 -0.47819
C 4.56173 -0.03758 0.40668
C 5.40473 0.99182 0.83065
C 3.22651 0.25834 0.16582
C 4.91103 2.28216 1.00284
H 6.44819 0.72764 1.01255
C 2.70409 1.53978 0.32121
C 3.56489 2.55333 0.74651
H 5.57411 3.08314 1.33561
H 1.64992 1.73278 0.11766
H 3.17112 3.56357 0.87713
C 5.10734 -1.45772 0.20422
O 6.28781 -1.66304 0.43913
O 4.22323 -2.27484 -0.20298
C -0.44761 0.70311 -0.35193
Si -1.64593 2.05563 -0.16394
C -1.81917 2.40209 1.70928
C -2.03777 1.10873 2.50253
H -2.70359 3.05332 1.84189
C -0.58599 3.13555 2.24901
C -3.32941 1.67792 -0.99469
C -3.12573 0.74384 -2.19463
H -3.71489 2.64902 -1.36044
C -4.36999 1.08320 -0.04232
C -0.91804 3.61931 -0.98889
H 0.05951 3.76831 -0.49542
C -1.77750 4.86227 -0.74289
C -0.66180 3.41591 -2.48389
C -2.93542 -2.50811 0.53668
H -1.24216 -3.80573 0.56228
H -0.90488 -2.15701 1.10609
C -3.84536 -2.63046 -0.52014
C -5.21382 -2.47005 -0.30712
C -5.70095 -2.17464 0.96608
C -3.43705 -2.21034 1.81040
C -4.80463 -2.04210 2.02621
H -3.45399 -2.83568 -1.51844
H -5.90515 -2.56415 -1.14714
H -6.77133 -2.03607 1.12918
H -2.73810 -2.09836 2.64335
H -5.16969 -1.79721 3.02578
H -5.33110 0.92270 -0.56036
H -4.04172 0.09937 0.32798
H -4.56176 1.72826 0.82984
H -4.08664 0.53308 -2.69562
H -2.43971 1.16786 -2.94336
H -2.68572 -0.21337 -1.87054
H -2.10968 1.31534 3.58428
H -2.94883 0.57640 2.19694
H -1.18970 0.42203 2.34542
H -0.66731 3.29831 3.33703
H 0.32441 2.53861 2.07423
H -0.43685 4.11740 1.77502
H -1.31236 5.76522 -1.17385
H -2.76931 4.75449 -1.21158
H -1.94148 5.05078 0.32971
H -0.13185 4.27856 -2.92235
H -0.06004 2.51332 -2.67024
H -1.61184 3.30410 -3.03171

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A_35 - TIPS
C -1.95407 -0.33338 -1.12674
S -2.15209 -1.63564 -2.18561
C -1.24705 -2.96589 -1.28118
I 1.57604 -0.62852 -3.03131
C 2.32633 0.58242 -0.28609
C 3.04163 1.47393 0.52519
C 2.66784 0.53420 -1.64006
C 4.07090 2.26444 0.02374
H 2.74384 1.52883 1.57417
C 3.68593 1.33374 -2.16593
C 4.39671 2.19251 -1.33068
H 4.61327 2.94288 0.68527
H 3.91344 1.28874 -3.23160
H 5.19526 2.81104 -1.74526
C 1.22731 -0.26745 0.39644
O 0.60799 0.31570 1.31073
O 1.10768 -1.43176 -0.00464
C -1.83718 0.62675 -0.37775
Si -1.72633 2.16098 0.65193
C -1.88399 1.82821 2.52788
C -2.23563 0.36323 2.80587
H -2.73272 2.46449 2.84468
C -0.65284 2.23899 3.34315
C -3.31118 3.12140 0.15674
C -3.33374 3.50651 -1.32409
H -3.30239 4.04765 0.76301
C -4.56551 2.31916 0.51717
C -0.18311 3.17902 0.21447
H 0.59089 2.71955 0.85045
C -0.33554 4.65674 0.58878
C 0.26506 3.02317 -1.24190
C -1.94355 -3.36580 -0.01409
H -1.21957 -3.78912 -2.00990
H -0.23427 -2.58790 -1.07950
C -3.02051 -4.26084 -0.02956
C -3.67827 -4.60027 1.14963
C -3.26850 -4.03780 2.36045
C -1.53447 -2.80376 1.20111
C -2.20094 -3.14156 2.38057
H -3.34758 -4.68772 -0.98181
H -4.51480 -5.30193 1.12576
H -3.78508 -4.29796 3.28673
H -0.68563 -2.11036 1.19426
H -1.88110 -2.69092 3.32217
H -5.48492 2.88025 0.27546
H -4.59002 1.37413 -0.04896
H -4.60119 2.06171 1.58680
H -4.27715 4.01261 -1.59396
H -2.50539 4.18023 -1.58792
H -3.24316 2.60911 -1.95760
H -2.41811 0.19991 3.88268
H -3.12617 0.02818 2.25129
H -1.38971 -0.26312 2.48694
H -0.83574 2.07644 4.41948
H 0.20782 1.62886 3.03652
H -0.39392 3.30072 3.20890
H 0.61425 5.19910 0.44415
H -1.09284 5.15211 -0.04150
H -0.64143 4.79852 1.63748
H 1.28750 3.41601 -1.38245
H 0.26619 1.96996 -1.55630
H -0.40211 3.56952 -1.92870

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B0 - TIPS

I	-0.74217	-1.90481	-0.83210
C	1.12019	-1.32012	-0.12438
C	-1.73856	-0.42079	0.32873
O	-2.92346	-2.26360	-1.31049
C	-3.77680	-1.52320	-0.68582
O	-4.98621	-1.57813	-0.76550
C	-3.11736	-0.49470	0.22205
C	-3.85821	0.42878	0.96011
H	-4.94548	0.37426	0.88060
C	-3.20506	1.37720	1.74930
H	-3.78994	2.10245	2.31824
C	-1.81086	1.42174	1.79569
H	-1.25427	2.18398	2.34839
C	-1.04064	0.50427	1.07388
H	0.05271	0.61184	1.09135
C	2.19618	-0.98724	0.35239
S	1.65664	2.50882	1.56335
C	1.33193	3.52311	0.06674
H	1.01380	4.53753	0.35793
H	2.25982	3.63493	-0.52164
C	0.27677	2.91448	-0.81680
C	0.60046	1.88442	-1.71311
H	1.63929	1.55274	-1.78014
C	-0.37872	1.27582	-2.49469
H	-0.09832	0.48389	-3.19356
C	-1.71674	1.66350	-2.38219
H	-2.48875	1.16789	-2.97451
C	-2.05345	2.68413	-1.49422
H	-3.09658	2.99012	-1.38683
C	-1.06440	3.30611	-0.73078
H	-1.33617	4.09677	-0.02613
Si	3.85751	-0.80967	1.18469
C	3.59965	-0.94628	3.06240
C	2.72799	0.16046	3.66220
H	4.61638	-0.86461	3.49311
C	3.03341	-2.32495	3.42496
C	4.75087	-2.40278	0.60390
H	4.06454	-3.23575	0.83528
C	6.06144	-2.62594	1.36378
C	4.98541	-2.39321	-0.90906
C	4.92767	0.64443	0.58628
C	5.22473	1.71267	1.64453
C	4.35601	1.28705	-0.68109
H	5.88260	0.14795	0.32634
H	5.04273	2.05590	-1.07290
H	4.17507	0.55044	-1.48060
H	3.39899	1.76470	-0.42127
H	6.00095	2.40376	1.27404
H	4.31063	2.29476	1.84788
H	5.59107	1.27734	2.58848
H	2.63697	0.02225	4.75315
H	3.12318	1.16584	3.46527
H	1.71623	0.14401	3.22750
H	2.87594	-2.40542	4.51307
H	2.05676	-2.48011	2.93847
H	3.69383	-3.15078	3.11979
H	6.57108	-3.54344	1.02375
H	6.76180	-1.78918	1.20431
H	5.90008	-2.71645	2.44900
H	5.45203	-3.33364	-1.24821
H	4.04273	-2.26321	-1.46182
H	5.65900	-1.57098	-1.20182

62
B_TS1 - TIPS

I	-1.19629	-1.49772	-1.23452
C	0.77703	-1.32884	-0.65939
C	-2.09693	-0.44846	0.40392
O	-3.49378	-1.41574	-1.75113
C	-4.23673	-0.79992	-0.91514
O	-5.43239	-0.57362	-0.99254
C	-3.47003	-0.30740	0.31312
C	-4.12713	0.30820	1.38040
H	-5.20917	0.42374	1.29349
C	-3.40535	0.75629	2.48309
H	-3.92235	1.24266	3.31261
C	-2.01807	0.59554	2.53061
H	-1.44812	0.96300	3.38579
C	-1.33606	-0.02210	1.48127
H	-0.25235	-0.13010	1.48672
C	1.66216	-0.51430	-0.27576
S	1.11084	1.90687	0.08968
C	0.18470	2.03073	-1.47347
H	0.60471	2.86325	-2.06507
H	0.35875	1.11748	-2.06968
C	-1.31223	2.24790	-1.36142
C	-2.16815	1.75603	-2.35579
H	-1.74601	1.18798	-3.18950
C	-3.54790	1.94219	-2.28121
H	-4.19988	1.49727	-3.03459
C	-4.09811	2.64563	-1.21162
H	-5.18071	2.75786	-1.13349
C	-3.25577	3.15360	-0.22206
H	-3.67891	3.68858	0.63140
C	-1.87836	2.94938	-0.29087
H	-1.21427	3.29812	0.50282
Si	3.45944	-0.33475	0.16255
C	3.66693	-0.03520	2.03714
C	3.02114	1.23405	2.60129
H	4.76260	0.04502	2.17802
C	3.17071	-1.25620	2.82303
C	4.21699	-2.06329	-0.18507
H	3.55883	-2.77406	0.34422
C	5.64012	-2.20687	0.36192
C	4.17047	-2.41571	-1.67415
C	4.41875	0.89701	-0.93587
C	4.73808	2.24873	-0.29204
C	3.73679	1.10407	-2.29287
H	5.37749	0.37080	-1.11143
H	4.38175	1.69119	-2.96866
H	3.49393	0.15459	-2.79306
H	2.79683	1.65504	-2.14494
H	5.38274	2.84981	-0.95628
H	3.80368	2.80485	-0.12004
H	5.26214	2.13829	0.67053
H	3.29561	1.36222	3.66270
H	3.31239	2.13975	2.05349
H	1.92398	1.17339	2.53878
H	3.28491	-1.09650	3.90837
H	2.10086	-1.43240	2.62417
H	3.70927	-2.17869	2.56123
H	6.04931	-3.21063	0.15431
H	6.32282	-1.47882	-0.10783
H	5.68942	-2.04678	1.44992
H	4.52941	-3.44425	-1.85121
H	3.14550	-2.33921	-2.06644
H	4.81540	-1.74132	-2.26214

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B1 - TIPS

I	-1.07411	-1.57971	-0.97560
C	1.26957	-1.40123	-0.61846
C	-2.28292	-0.98836	0.68816
O	-3.70774	-1.08371	-1.80713
C	-4.38440	-0.69125	-0.83727
O	-5.54726	-0.27526	-0.79640
C	-3.62898	-0.68241	0.52638
C	-4.33857	-0.32304	1.67969
H	-5.38951	-0.07052	1.52685
C	-3.72964	-0.28353	2.92936
H	-4.30670	0.00150	3.81188
C	-2.37711	-0.60766	3.05507
H	-1.88572	-0.58076	4.02970
C	-1.64314	-0.96625	1.92719
H	-0.58408	-1.21626	2.00571
C	1.67685	-0.30485	0.02358
S	0.83784	1.08679	0.78812
C	-0.04333	1.85990	-0.63480
H	0.48565	2.79624	-0.87182
H	0.06562	1.18381	-1.49187
C	-1.49867	2.14562	-0.35834
C	-2.46527	1.88958	-1.33686
H	-2.18084	1.39894	-2.27017
C	-3.80674	2.19339	-1.10792
H	-4.55777	1.91978	-1.84878
C	-4.19838	2.74764	0.10792
H	-5.25534	2.94011	0.29802
C	-3.24451	2.99548	1.09483
H	-3.54772	3.40288	2.06150
C	-1.90385	2.69690	0.86292
H	-1.16340	2.87196	1.64796
Si	3.56203	-0.36760	0.23180
C	3.88832	-0.93633	2.03050
C	3.03748	-0.18646	3.06234
H	4.95619	-0.74049	2.24437
C	3.62479	-2.44196	2.15870
C	4.37393	-1.64615	-0.92633
H	3.82490	-2.58369	-0.73807
C	5.85327	-1.85530	-0.58342
C	4.20926	-1.30521	-2.40921
C	4.35539	1.33616	-0.13688
C	4.48407	2.27137	1.06888
C	3.64656	2.05941	-1.28821
H	5.37775	1.07858	-0.47368
H	4.21588	2.94922	-1.60598
H	3.50044	1.41722	-2.16864
H	2.65327	2.39810	-0.95981
H	5.01845	3.19612	0.79150
H	3.48649	2.55941	1.43588
H	5.03257	1.80540	1.90169
H	3.28841	-0.51170	4.08611
H	3.16182	0.90398	3.01176
H	1.96729	-0.39898	2.90544
H	3.73157	-2.77285	3.20541
H	2.59777	-2.67954	1.83525
H	4.30888	-3.04529	1.54459
H	6.29859	-2.63876	-1.21938
H	6.43653	-0.93498	-0.75324
H	6.00650	-2.15148	0.46551
H	4.60868	-2.11365	-3.04449
H	3.14976	-1.16267	-2.66657
H	4.76150	-0.38677	-2.66929

62
B_TS2 - TIPS

I	-0.89562	-2.00565	-0.27064
C	1.46123	-1.42644	-0.18543
C	-2.16541	-0.87469	1.02682
O	-3.58220	-2.02442	-1.21197
C	-4.28524	-1.34519	-0.44109
O	-5.48343	-1.04787	-0.51321
C	-3.52611	-0.73302	0.77790
C	-4.25577	0.04542	1.68654
H	-5.31764	0.15886	1.46117
C	-3.65409	0.63878	2.79085
H	-4.24779	1.24499	3.47860
C	-2.28830	0.45987	3.01907
H	-1.80190	0.91887	3.88205
C	-1.53438	-0.30392	2.13235
H	-0.46324	-0.44265	2.28676
C	1.71371	-0.12598	-0.06472
S	0.69443	1.33340	0.13789
C	-0.26099	1.37100	-1.43871
H	0.23461	2.08431	-2.11501
H	-0.19757	0.37270	-1.88719
C	-1.69965	1.76607	-1.22239
C	-2.73127	1.04159	-1.82814
H	-2.50933	0.12889	-2.38623
C	-4.06246	1.42832	-1.66314
H	-4.85670	0.81385	-2.08718
C	-4.37273	2.53797	-0.88074
H	-5.41581	2.82160	-0.72976
C	-3.35157	3.25857	-0.26018
H	-3.59035	4.11676	0.37137
C	-2.02389	2.87586	-0.43181
H	-1.22649	3.43595	0.06446
Si	3.59610	0.10403	0.06821
C	3.97558	0.30440	1.93300
C	3.02711	1.28357	2.63510
H	5.00813	0.69429	2.01275
C	3.90444	-1.05798	2.63370
C	4.56002	-1.41864	-0.55373
H	4.13299	-2.26800	0.00492
C	6.05379	-1.30804	-0.22752
C	4.35378	-1.69590	-2.04466
C	4.17721	1.61956	-0.94694
C	4.18427	2.94900	-0.18681
C	3.39259	1.76854	-2.25543
H	5.22514	1.37180	-1.20255
H	3.85250	2.53003	-2.90753
H	3.32725	0.82917	-2.82292
H	2.36516	2.09267	-2.03618
H	4.60716	3.75402	-0.81178
H	3.15666	3.24001	0.08181
H	4.77730	2.89773	0.73900
H	3.30793	1.40781	3.69451
H	3.01295	2.27811	2.16832
H	1.99402	0.89972	2.61386
H	4.04396	-0.94841	3.72220
H	2.91864	-1.52319	2.46743
H	4.66507	-1.76235	2.26708
H	6.59221	-2.22134	-0.53140
H	6.51943	-0.46692	-0.76746
H	6.24166	-1.15287	0.84587
H	4.84851	-2.63610	-2.34090
H	3.28490	-1.78345	-2.28748
H	4.78945	-0.89271	-2.66198

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B_35 - TIPS

I	0.82404	-3.12097	-2.07083
C	1.23190	1.31448	0.75103
C	0.46955	-2.81227	-0.00279
O	-1.06323	-0.59719	-1.39694
C	-1.54508	-1.17118	-0.40529
O	-2.70454	-1.13160	0.03833
C	-0.56003	-1.99349	0.46065
C	-0.72690	-1.89751	1.85060
H	-1.55539	-1.27590	2.19535
C	0.11001	-2.56275	2.73964
H	-0.03443	-2.45062	3.81620
C	1.12478	-3.38629	2.24940
H	1.78489	-3.92599	2.93167
C	1.29568	-3.52276	0.87421
H	2.07538	-4.17463	0.47769
C	0.04905	1.50251	1.00187
S	-1.57138	1.76574	1.39027
C	-2.28033	2.07704	-0.28869
H	-1.75529	2.94877	-0.70085
H	-2.07419	1.18042	-0.89456
C	-3.74916	2.34601	-0.12404
C	-4.64643	1.27137	-0.05411
H	-4.23542	0.25730	-0.12832
C	-6.00837	1.51798	0.11490
H	-6.70393	0.67777	0.16428
C	-6.48730	2.82495	0.22036
H	-7.55569	3.01004	0.35066
C	-5.59537	3.89544	0.16047
H	-5.96152	4.92075	0.24456
C	-4.23229	3.65391	-0.00663
H	-3.52855	4.48925	-0.05009
Si	2.99246	1.08256	0.27262
C	3.91296	0.11602	1.64632
C	3.13385	0.13957	2.96670
H	4.86712	0.65673	1.79213
C	4.23735	-1.32655	1.24910
C	3.07980	0.18517	-1.39455
H	2.97358	-0.88579	-1.14445
C	4.44644	0.38876	-2.05899
C	1.92169	0.53883	-2.33441
C	3.77329	2.82208	0.17918
C	3.73664	3.50104	1.55185
C	3.10147	3.70481	-0.87534
H	4.83088	2.66841	-0.10718
H	3.52638	4.72318	-0.87247
H	3.21638	3.29542	-1.88941
H	2.02115	3.79100	-0.67503
H	4.18944	4.50631	1.51238
H	2.69557	3.61620	1.89508
H	4.27683	2.92089	2.31565
H	3.70729	-0.35142	3.77134
H	2.89356	1.16328	3.29166
H	2.17796	-0.39638	2.85387
H	4.77430	-1.84476	2.06192
H	3.31380	-1.89196	1.05316
H	4.86102	-1.38312	0.34420
H	4.53978	-0.23669	-2.96195
H	4.58174	1.43733	-2.37238
H	5.28688	0.13672	-1.39076
H	2.04191	0.01091	-3.29593
H	0.94936	0.23656	-1.91263
H	1.88729	1.61893	-2.55299

35

a_0 – R=Methyl

I	0.88458	-0.73501	-0.08159
C	-0.49172	0.79511	-0.31004
S	-1.57801	-2.26922	-0.14014
C	-2.49773	-1.33418	1.11799
C	3.77113	0.22788	0.11812
C	4.86901	1.09082	0.15239
C	2.49517	0.75910	-0.04543
C	4.68784	2.46505	0.02391
H	5.85177	0.63348	0.28240
C	2.29493	2.13093	-0.17565
C	3.40085	2.98275	-0.13980
H	5.54715	3.13837	0.05056
H	1.28929	2.53407	-0.30299
H	3.25242	4.06016	-0.24128
C	3.98291	-1.28484	0.26030
O	5.12141	-1.70276	0.40240
O	2.89922	-1.95354	0.21076
C	-1.34784	1.65275	-0.38041
C	-3.64429	-0.46402	0.63053
H	-2.92226	-2.04352	1.84993
H	-1.81642	-0.68464	1.69599
C	-4.14749	-0.54713	-0.67139
C	-5.23694	0.23140	-1.06790
C	-5.84176	1.11518	-0.17375
C	-4.25479	0.43570	1.51732
C	-5.33991	1.21749	1.12544
H	-3.64571	-1.23287	-1.35730
H	-5.61551	0.14807	-2.08936
H	-6.69276	1.72384	-0.48628
H	-3.86483	0.51936	2.53605
H	-5.79615	1.91112	1.83552
C	-2.40219	2.65881	-0.47774
H	-3.35361	2.17637	-0.74799
H	-2.54688	3.17077	0.48431
H	-2.15972	3.41255	-1.24090

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b_0 – R=Methyl

I	-1.49657	1.73626	0.57577
C	0.56754	1.69702	0.60080
C	-1.61749	0.20840	-0.91549
O	-3.73307	1.50235	0.25784
C	-4.09855	0.63955	-0.62694
O	-5.23441	0.37174	-0.96247
C	-2.92384	-0.08082	-1.27563
C	-3.11028	-1.07027	-2.24149
H	-4.13858	-1.29958	-2.52661
C	-2.00902	-1.72800	-2.78998
H	-2.16162	-2.51029	-3.53598
C	-0.71540	-1.40886	-2.37488
H	0.17190	-1.93485	-2.73729
C	-0.49367	-0.41270	-1.41862
H	0.54100	-0.22289	-1.10186
C	1.78005	1.60575	0.57150
S	2.76305	-1.60426	-1.05641
C	2.34458	-1.99174	0.68550
H	2.92421	-2.87109	1.01981
H	2.63081	-1.16154	1.35859
C	0.87844	-2.27768	0.90063
C	0.09635	-1.52340	1.78250
H	0.57190	-0.72155	2.35433
C	-1.27607	-1.75787	1.91523
H	-1.87143	-1.14222	2.59444
C	-1.89113	-2.75997	1.16927
H	-2.96632	-2.92943	1.25286
C	-1.11588	-3.53724	0.30248
H	-1.59007	-4.32110	-0.29302
C	0.24722	-3.29600	0.17056
H	0.85256	-3.85075	-0.55064
C	3.22392	1.44128	0.49324
H	3.40912	0.51454	-0.10417
H	3.69217	2.29903	-0.00984
H	3.66239	1.32991	1.49501

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a_{TS1} – R=Methyl

I	1.02859	-0.90253	-0.50778
C	-0.64767	0.20721	-1.10224
S	-1.82399	-1.77012	-1.32441
C	-2.47434	-1.58012	0.37167
C	3.59260	0.35460	0.47549
C	4.48455	1.36603	0.83721
C	2.33173	0.71838	0.01991
C	4.10967	2.70335	0.74008
H	5.46746	1.04995	1.19170
C	1.92441	2.04528	-0.08921
C	2.83440	3.03849	0.27864
H	4.81055	3.49111	1.02397
H	0.92264	2.28364	-0.45515
H	2.53696	4.08622	0.20079
C	4.00198	-1.12073	0.58452
O	5.12430	-1.38151	0.99047
O	3.08117	-1.91801	0.22367
C	-1.12348	1.35233	-1.30130
C	-3.45707	-0.44759	0.53003
H	-2.96744	-2.52706	0.64539
H	-1.64308	-1.43701	1.08154
C	-4.61721	-0.39647	-0.25421
C	-5.53782	0.63646	-0.10388
C	-5.31086	1.65117	0.82916
C	-3.23510	0.57939	1.45234
C	-4.15258	1.62075	1.60339
H	-4.76527	-1.17184	-1.00974
H	-6.43504	0.65894	-0.72619
H	-6.02801	2.46659	0.94178
H	-2.31803	0.56864	2.04601
H	-3.95382	2.41730	2.32340
C	-2.39221	1.95555	-1.75759
H	-3.03560	1.19232	-2.23526
H	-2.94694	2.36318	-0.89642
H	-2.23427	2.78551	-2.46381

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b_{TS1} – R=Methyl

I	-1.15410	1.69528	0.37074
C	0.85083	1.53231	0.38078
C	-1.64179	0.13152	-1.01683
O	-3.53047	1.64621	0.25820
C	-4.04485	0.77388	-0.51685
O	-5.22512	0.55396	-0.73413
C	-2.99267	-0.07323	-1.23909
C	-3.34762	-1.08032	-2.13833
H	-4.41424	-1.23969	-2.30848
C	-2.35945	-1.83241	-2.77296
H	-2.64209	-2.62175	-3.47267
C	-1.00911	-1.58804	-2.51148
H	-0.22702	-2.18686	-2.98334
C	-0.62327	-0.58687	-1.61655
H	0.43650	-0.42483	-1.38277
C	2.04719	1.17761	0.31718
S	2.76752	-0.97687	-0.69177
C	2.35131	-1.85082	0.86360
H	2.97012	-2.76061	0.92886
H	2.61191	-1.21964	1.73085
C	0.89686	-2.23177	0.95043
C	-0.00432	-1.50956	1.74001
H	0.37020	-0.67213	2.33471
C	-1.36638	-1.81820	1.74352
H	-2.05900	-1.21885	2.33944
C	-1.85009	-2.86721	0.96450
H	-2.91771	-3.09285	0.94736
C	-0.95635	-3.61170	0.19114
H	-1.32712	-4.42981	-0.43062
C	0.39825	-3.29363	0.18326
H	1.09203	-3.84400	-0.45772
C	3.43585	1.54644	0.68516
H	3.90210	0.75376	1.28586
H	4.05229	1.66130	-0.21562
H	3.42364	2.49111	1.25264

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b_2 – R=Methyl

I	-0.09943	1.36403	-1.08330
C	1.51888	2.49163	-0.18443
C	-0.16703	-0.79712	-1.26989
O	-2.74067	0.46544	-1.15609
C	-2.75898	-0.76984	-0.99241
O	-3.69181	-1.51874	-0.67607
C	-1.38517	-1.46812	-1.20184
C	-1.36045	-2.86342	-1.32014
H	-2.32723	-3.36431	-1.23874
C	-0.16936	-3.55639	-1.50729
H	-0.17537	-4.64515	-1.59831
C	1.03672	-2.85578	-1.57884
H	1.98000	-3.38609	-1.72639
C	1.04107	-1.46710	-1.46062
H	1.97934	-0.91481	-1.50015
C	2.52182	1.98737	0.54637
S	3.00833	0.28111	0.82313
C	2.20665	-0.05892	2.44625
H	2.83639	-0.82406	2.92231
H	2.27691	0.86112	3.04393
C	0.78706	-0.53677	2.32607
C	-0.27534	0.37029	2.27055
H	-0.06527	1.44120	2.34123
C	-1.58047	-0.07568	2.05695
H	-2.39185	0.64397	1.93764
C	-1.84576	-1.43865	1.93334
H	-2.85483	-1.77441	1.69088
C	-0.79295	-2.35193	2.01252
H	-0.98818	-3.41847	1.88567
C	0.51202	-1.90414	2.19754
H	1.33806	-2.62045	2.21812
C	3.44624	2.99041	1.21106
H	3.47021	2.83469	2.30302
H	4.47756	2.87114	0.84360
H	3.10746	4.01558	1.01125

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b_{TS2} – R=Methyl

I	-0.31561	1.23805	-1.65068
C	1.87787	2.95373	0.07141
C	-0.37692	-0.87855	-1.48847
O	-3.07752	0.19961	-0.94477
C	-2.96139	-1.03031	-0.88686
O	-3.78614	-1.89406	-0.54128
C	-1.53803	-1.60897	-1.22630
C	-1.40954	-3.00669	-1.18924
H	-2.33147	-3.55029	-0.97609
C	-0.19272	-3.65041	-1.37842
H	-0.13481	-4.74091	-1.33849
C	0.95702	-2.89305	-1.60876
H	1.92715	-3.37550	-1.74866
C	0.86316	-1.50604	-1.66644
H	1.75149	-0.90010	-1.84879
C	2.79355	2.35814	0.80163
S	2.92583	0.59587	0.57967
C	2.21358	-0.01138	2.17066
H	2.87572	-0.83111	2.48334
H	2.32830	0.80638	2.89649
C	0.79092	-0.48713	2.08547
C	-0.26166	0.41776	1.90449
H	-0.04251	1.48345	1.79777
C	-1.57451	-0.03600	1.80006
H	-2.38085	0.65985	1.56657
C	-1.85521	-1.39981	1.90989
H	-2.87536	-1.75398	1.75584
C	-0.81197	-2.30512	2.09334
H	-1.02131	-3.37557	2.13637
C	0.50435	-1.85293	2.16925
H	1.32298	-2.56880	2.28383
C	3.74091	3.10280	1.70436
H	3.63964	2.73975	2.73840
H	4.77547	2.92705	1.37726
H	3.53416	4.18192	1.69403

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$a_{3\text{-}5}$ – R=Methyl

I	-1.73195	0.11662	-2.13224
C	1.97592	0.19127	-1.42058
S	1.83021	1.81727	-1.86988
C	1.21000	2.53548	-0.28668
C	-1.02942	-1.89475	0.13844
C	-1.00678	-3.19013	0.67847
C	-1.62261	-1.73867	-1.11709
C	-1.55274	-4.28239	0.01430
H	-0.51605	-3.29254	1.64783
C	-2.15577	-2.83144	-1.81114
C	-2.12805	-4.10222	-1.24421
H	-1.52250	-5.27453	0.46982
H	-2.59347	-2.67988	-2.79857
H	-2.55289	-4.94705	-1.79057
C	-0.37716	-0.77347	0.99927
O	0.48789	-1.18317	1.79893
O	-0.78128	0.38104	0.80810
C	2.08110	-0.97501	-1.09792
C	2.26109	2.55423	0.78456
H	0.90457	3.55291	-0.57222
H	0.33497	1.94209	0.02267
C	3.24518	3.55106	0.80933
C	4.23330	3.55425	1.79017
C	4.25195	2.54873	2.75919
C	2.28170	1.54650	1.75726
C	3.27878	1.55104	2.73525
H	3.23526	4.32899	0.04051
H	4.99153	4.34048	1.79930
H	5.02616	2.54560	3.52974
H	1.52075	0.75707	1.75523
H	3.28436	0.75787	3.48540
C	2.16494	-2.36131	-0.64862
H	3.19249	-2.74915	-0.71435
H	1.82412	-2.38359	0.39946
H	1.49708	-3.00987	-1.23615

35

$b_{3•5}$ – R=Methyl

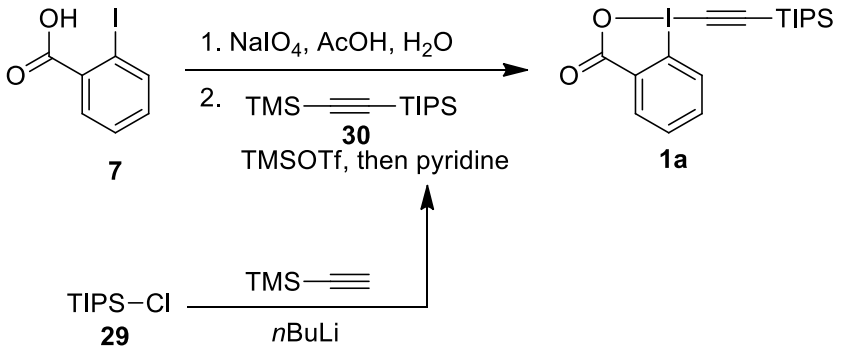
I	-2.89563	-2.25129	0.90395
C	3.32814	-0.37016	1.21630
C	-2.66233	-0.29794	1.70312
O	-1.30214	-0.33225	-0.94034
C	-1.74567	0.76027	-0.54082
O	-1.80085	1.85008	-1.12763
C	-2.22311	0.78920	0.94414
C	-2.15096	2.03077	1.59303
H	-1.83274	2.87008	0.97291
C	-2.46572	2.18358	2.93875
H	-2.38071	3.16276	3.41467
C	-2.89499	1.07894	3.67510
H	-3.15117	1.17726	4.73208
C	-3.00480	-0.16164	3.05249
H	-3.35473	-1.02947	3.61299
C	2.16443	-0.66736	1.40408
S	4.90057	0.13551	0.84144
C	4.73238	0.40635	-0.98745
H	5.67017	0.91465	-1.25438
H	4.71302	-0.58109	-1.46703
C	3.52276	1.21170	-1.34912
C	2.33476	0.55900	-1.69473
H	2.32036	-0.53224	-1.75524
C	1.15843	1.27452	-1.91003
H	0.21969	0.75224	-2.10811
C	1.16496	2.66366	-1.78530
H	0.21889	3.19315	-1.90747
C	2.35134	3.32845	-1.46708
H	2.36065	4.41641	-1.36913
C	3.52304	2.60687	-1.24343
H	4.44285	3.12385	-0.95560
C	0.75251	-0.98338	1.59586
H	0.19449	-0.83147	0.65216
H	0.60793	-2.02652	1.91202
H	0.29981	-0.32225	2.35040

2. General Methods

Technical grade solvents were used for quantitative flash chromatography. HPLC grade solvents purchased from Sigma-Aldrich or freshly distilled solvents were used for flash chromatography for compounds undergoing full characterization. Reaction solvents were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 30 ppm, Karl-Fischer titration). We note; however, that the thiol-alkynylation reaction gives identical results when using HPLC grade THF purchased from Sigma-Aldrich or dried THF from the solvent system. Commercially available reagents were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used without any further purification. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plates and visualized with UV light and permanganate stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H NMR spectra were measured on a Brucker DPX-400 400 MHz spectrometer, all signals are reported in ppm with the corresponding internal solvent peak or TMS as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation). ^{13}C NMR spectra were carried out with ^{1}H-decoupling on a Brucker DPX-400 100 MHz. All signals are reported in ppm with the corresponding internal solvent signal or TMS as standard. Infrared spectra were obtained on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, sh = shoulder). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API.

3. Preparation of Reagents

1-[(Tri*iso*propyllsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (1a)



Following a reported procedure,[2] $NaIO_4$ (77.2 g, 0.361 mol, 1.0 equiv) and 2-iodobenzoic acid (**7**) (89.5 g, 0.361 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (700 mL) under air in a 4-neck sulfonation flask equipped with a mechanic stirrer, a thermometer and a condenser. The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (500 mL) and allowed to cool to room temperature, protecting it from light. After 45 min, the suspension was added to water (1.5 L) and the crude product was collected by filtration, washed on the filter with ice water (3 x 300 mL) and cold acetone (3 x 300 mL), and air-dried in the dark overnight to give 2-iodosylbenzoic acid (77.3 g, 0.292 mol, 81% yield) as a colorless solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1 H, Ar*H*).^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m). The values of the NMR spectra are in accordance with reported literature data.[2]

Following a modified reported procedure,[3] trimethylsilylacetylene (30.3 ml, 213 mmol, 1 equiv) was charged in a 4-neck 500 mL flask equipped with a thermometer, a dropping funnel, an agitator magnetic and a nitrogen arrival. THF (330 mL) was added via a dropping funnel and the reaction was cooled to -78 °C. ^{n}BuLi (86 mL, 0.21 mmol, 0.98 equiv) was added and the reaction was stirred for 5 minutes at -78 °C, then warmed to 0 °C and stirred for 5 minutes. The reaction was then cooled back to -78 °C and ^{i}Pr$_3$SiCl (**29**) (45.5 mL, 213 mmol, 1 equiv) was added dropwise via a dropping funnel. The mixture was then allowed to warm to r.t. and stirred overnight. A saturated solution of NH_4Cl (300 mL) was added and the

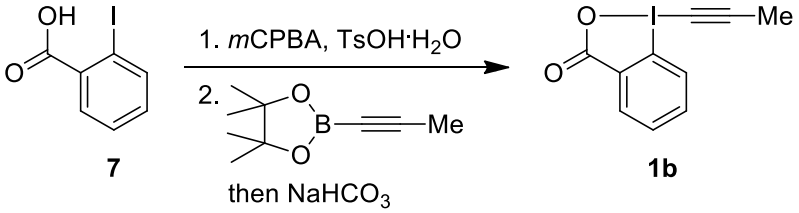
[2] Kraszkiewicz, L.; Skulski, L. *Arkivoc* **2003**, *6*, 120.
[3] Helal, C J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938.

reaction was extracted with Et_2O (2x300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Distillation of the crude product (1.4 mbar, 55°C) afforded trimethylsilyl (triisopropylsilyl) acetylene (**30**) (51.4 g, 203 mmol, 95%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (m, 21 H, TIPS), 0.18 (s, 9 H, TMS). The values of the NMR spectra are in accordance with reported literature data.[3]

Caution: reaction carried out behind a safety shield! Following a modified reported procedure, [4] 2-iodosylbenzoic acid (26.4 g, 100 mmol, 1.0 equiv) was charged in a four-neck flat-bottom flask equipped with a thermometer, a dropping funnel, a mechanic stirrer and a nitrogen arrival. The system was flushed with N_2 by three vacuum/N_2 cycles. Anhydrous acetonitrile (350 mL) was then canulated. The reaction mixture (white suspension) was cooled to 4 °C and then trimethylsilyltriflate (20.0 mL, 110 mol, 1.1 equiv) was added dropwise for 15 min via a dropping funnel. The dropping funnel was rinsed with anhydrous acetonitrile (10 mL). No increase of temperature was observed. The ice bath was removed and the reaction stirred for 15 min. Trimethylsilyl)(tri*iso*propylsilyl)acetylene (**30**) (28.0 g, 110 mmol, 1.1 equiv) was added dropwise via dropping funnel over 15 min (the colorless suspension was converted to a yellow solution). The dropping funnel was rinsed with anhydrous acetonitrile (10 mL) and the reaction was stirred for 30 min. Then pyridine (9.9 mL, 25 mmol, 1.1 equiv) was added dropwise via a dropping funnel over 5 min. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under reduced pressure until a solid was obtained. The solid was dissolved in CH_2Cl_2 (250 mL) and transferred in a 2L separatory funnel. The organic layer was added and washed with 1 M HCl (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (250 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2x250 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting solid (44.8 g) was then recristallized in CH_3CN (110 mL). The colorless solid obtained over cooling down was then filtered over Büchner, washed with hexanes (2x40 mL) and dried for 1 h at 40 °C at 5 mbar. TIPS-EBX (**1a**) (36.2 g, 84.5 mmol, 85%) was obtained as white crystals. Mp 173-177 °C (decomposition). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (m, 1 H, ArH), 8.28 (m, 1 H, ArH), 7.72 (m, 2 H, ArH), 1.13 (m, 21 H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 134.5, 132.3, 131.4, 131.4, 126.1, 115.6, 113.9, 64.7, 18.4, 11.1. The values of the NMR spectra are in accordance with reported literature data.[4]

[4] Brand, J. P.; Waser, J. *Synthesis* **2012**, *44*, 1155.

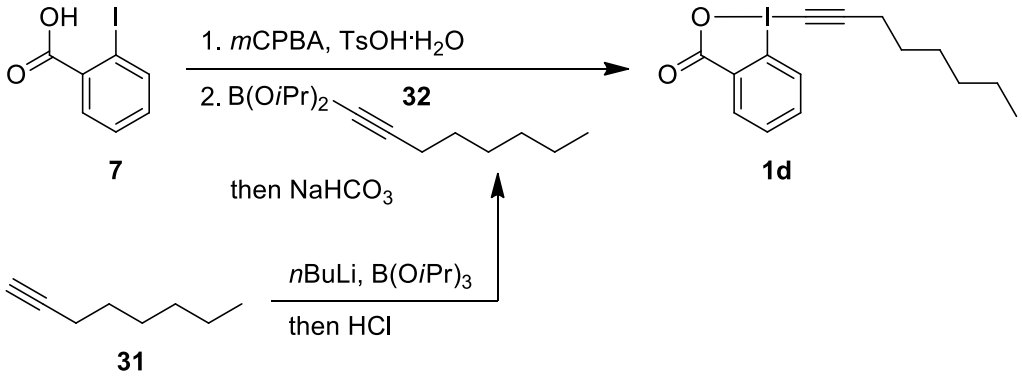
Propynyl-1,2-benziodoxol-3(1*H*)-one (1b)



Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (1.07 g, 4.30 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 818 mg, 4.30 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 1.17 g, 4.73 mmol, 1.10 eq.) were dissolved in dichloromethane (7 mL) and 2,2,2-trifluoroethanol (7 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which propynyl-1-boronic acid pinacol ester (4.85 g, 21.2 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 2.5 hours at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (30 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (30 mL) was added. The mixture was stirred for 15 minutes, the two layers were separated and the aqueous phase was extracted with additional portions of dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1b** (1.03 g, 3.60 mmol, 84%) as a white solid. R_f (EtOAc) = 0.10. Mp 124-150 °C (decomposition). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41-8.35 (m, 1 H, Ar*H*), 8.22-8.14 (m, 1 H, Ar*H*), 7.79-7.68 (m, 2 H, Ar*H*), 2.27 (s, 3 H, CCC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz):[6] δ 166.7, 134.8, 132.5, 131.6, 126.4, 115.6, 105.1, 39.0, 5.7. IR ν 2183 (w), 1607 (s), 1559 (m), 1350 (m), 746 (m), 730 (m). HRMS (ESI) $C_{10}H_8IO_2^+$ $[M+H]^+$ calc. = 286.9564; $[M+H]^+$ obs. = 286.9561.

[5] Bouma, M. J.; Olofsson, B. *Chem. Eur. J.* **2012**, *18*, 14242.
[6] One aromatic carbon signal was not resolved.

Octynyl-1,2-benziodoxol-3(1*H*)-one (1d)



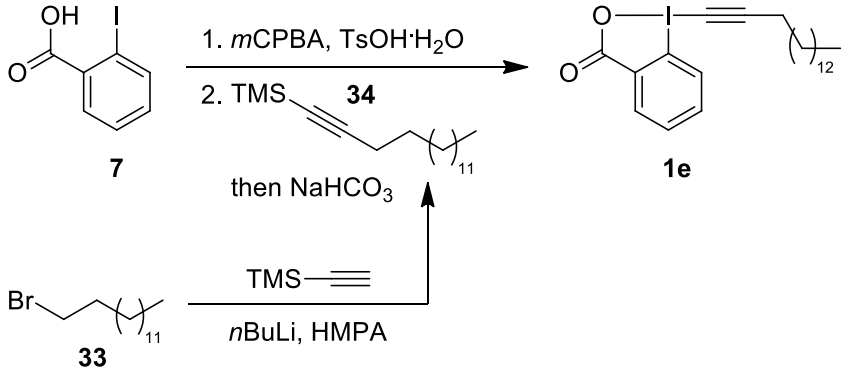
Following a slightly modified procedure,[7] a solution of 1-octyne (**31**) (747 mg, 6.78 mmol, 1.00 eq.) and dry diethyl ether (7.0 mL) was cooled to -78 °C, at which temperature 1.6 M *n*BuLi in hexanes (4.24 mL, 6.78 mmol, 1.00 eq.) was added dropwise. The mixture was stirred at -78 °C for 90 minutes and then canullated into a to -78 °C pre-cooled solution consisting of triisopropyl borate (1.56 mL, 6.78 mmol, 1.00 eq.) and dry diethyl ether (7.0 mL). The reaction mixture was stirred at -78 °C for 2 hours, after which 2.0 M HCl in diethyl ether (3.73 mL, 7.46 mmol, 1.10 eq.) was added. The cooling bath was removed and the mixture was stirred for an additional 60 minutes. After filtration and solvent removal, Kugelrohr distillation (75 °C at 0.6 mbar) furnished pure diisopropyloct-1-ynylboronate (**32**, 940 mg, 3.95 mmol, 58% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.55 (sept, 2 H, J = 6.2 Hz, ^{i}Pr-CH), 2.27 (t, 2 H, J = 7.0 Hz, propargyl CH_2), 1.60-1.48 (m, 2 H, CH_2), 1.45-1.24 (m, 6 H, CH_2), 1.19 (d, 12 H, J = 6.2 Hz, ^{i}Pr-CH_3), 0.89 (t, 3 H, J = 6.9 Hz, alkyl CH_3). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[8]

Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (692 mg, 2.79 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 531 mg, 2.79 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 756 mg, 3.07 mmol, 1.10 eq.) were dissolved in dichloromethane (4.5 mL) and 2,2,2-trifluoroethanol (4.5 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which diisopropyloct-1-ynylboronate (**32**, 930 mg, 3.90 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 2 hours at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (30 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (30 mL) was added. The mixture was stirred for 15 minutes, the two layers were separated and the

[7] Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631.
[8] Morita, R.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Org. Biomol. Chem.* **2005**, *3*, 1263.

aqueous layer was extracted with additional portions of dichloromethane (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1d** (940 mg, 2.64 mmol, 95%) as a white solid. R_f (EtOAc) = 0.25. Mp 50-63 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42-8.35 (m, 1 H, Ar*H*), 8.20-8.13 (m, 1 H, Ar*H*), 7.78-7.69 (m, 2 H, Ar*H*), 2.59 (t, 2 H, *J* = 7.1 Hz, CCC*H*$_2$), 1.70-1.58 (m, 2 H), 1.51-1.39 (m, 2 H), 1.38-1.26 (m, 4 H), 0.94-0.86 (m, 3 H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.7, 134.7, 132.5, 131.7, 131.6, 126.3, 115.7, 109.9, 39.4, 31.3, 28.7, 28.3, 22.6, 20.6, 14.1. IR ν 2930 (w), 2858 (w), 2166 (w), 1619 (s), 1561 (w), 1439 (w), 1331 (m), 1297 (m), 832 (w), 748 (m). HRMS (ESI) $C_{15}H_{18}IO_2^+$ $[M+H]^+$ calc. = 357.0346; $[M+H]^+$ obs. = 357.0339.

Hexadecynyl-1,2-benziodoxol-3(1*H*)-one (1e)



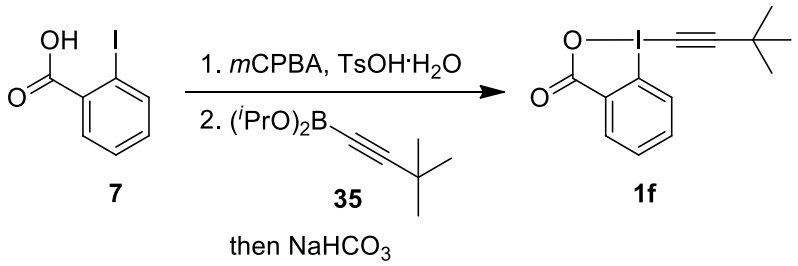
To a mixture of trimethylsilylacetylene (8.33 g, 85.0 mmol, 1.20 eq.) and dry THF (46 mL) was added at -78 °C under nitrogen 2.5 M *n*BuLi in hexanes (33.9 mL, 85.0 mmol, 1.20 eq.) over a 10 minute time period. The resulting light yellow solution was stirred at -78 °C for 60 minutes, after which a mixture consisting of 1-bromotetradecane **33** (19.6 g, 70.7 mmol, 1.00 eq.), hexamethylphosphoramide (HMPA, 14.2 mL, 78.0 mmol, 1.10 eq.) and dry THF (23 mL) was slowly added *via* cannula over a 20 minute time period. The reaction mixture was stirred for 60 minutes at -78 °C, followed by 24 hours of stirring at room temperature. The reaction was quenched at 0 °C with saturated aq. NH_4Cl (50 mL) and diluted with water (10 mL) and EtOAc (50 mL). The two layers were separated and the aq. layer was extracted with additional portions of EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The light brown crude liquid was finally pushed through a small plug of silica gel with pentane as eluent to afford pure hexadec-1-yn-1-yltrimethylsilane (**34**, 19.3 g, 65.5 mmol, 92.7% yield) as a colorless liquid. R_f (pentane) = 0.78. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.19 (t,

2 H, *J* = 7.1 Hz, CCC*H*$_2$), 1.54-1.44 (m, 2 H, CH_2), 1.42-1.18 (m, 22 H, CH_2), 0.87 (t, 3 H, *J* = 6.7 Hz, CH_2C*H*$_3$), 0.13 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$, 100 MHz): [9] δ 107.7, 84.3, 32.2, 29.9, 29.8, 29.7, 29.6, 29.3, 29.0, 28.9, 22.9, 20.0, 14.3, 0.3. IR ν 2924 (m), 2854 (m), 2175 (w), 1461 (w), 1249 (w), 910 (w), 841 (s), 761 (w), 736 (m). HRMS (ESI) $C_{19}H_{38}AgSi^+$ $[M+Ag]^+$ calc. = 401.1794; $[M+Ag]^+$ obs. = 401.1798.

Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (8.00 g, 32.2 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 6.13 g, 32.2 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 8.74 g, 35.5 mmol, 1.10 eq.) were dissolved in dichloromethane (60 mL) and 2,2,2-trifluoroethanol (60 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which hexadec-1-yn-1-yltrimethylsilane (**34**, 13.3 g, 45.1 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 14 hours at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (400 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (400 mL) was added. The mixture was stirred for 60 minutes, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1e** (6.02 g, 12.9 mmol, 40%) as a white solid. R_f (EtOAc) = 0.36. Mp 102.6-105.3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44-8.37 (m, 1 H, Ar*H*), 8.21-8.14 (m, 1 H, Ar*H*), 7.80-7.70 (m, 2 H, Ar*H*), 2.59 (t, 2 H, *J* = 7.1 Hz, CCC*H*$_2$), 1.65 (p, 2 H, *J* = 7.1 Hz, $CCCH_2C$*H*$_2$), 1.52-1.40 (m, 2 H), 1.39-1.19 (m, 20 H, CH_2), 0.86 (t, 3 H, *J* = 6.7 Hz, CH_2C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz):[5] δ 166.6, 134.7, 132.5, 131.7, 131.6, 126.2, 115.7, 109.9, 39.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.2, 29.1, 28.3, 22.8, 20.6, 14.3. IR ν 2924 (s), 2853 (m), 2166 (w), 1649 (m), 1623 (m), 1439 (w), 908 (m), 736 (s). HRMS (ESI) $C_{23}H_{34}IO_2^+$ $[M+H]^+$ calc. = 469.1598; $[M+H]^+$ obs. = 469.1614.

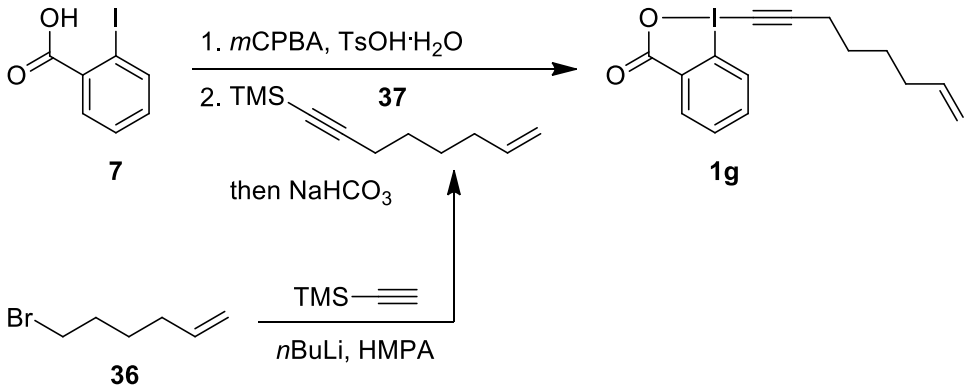
[9] Some signals were not resolved at 100 MHz.

3,3-Dimethylbutynyl-1,2-benziodoxol-3(1*H*)-one (1f)



Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (1.64 g, 6.59 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 1.25 g, 6.59 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 1.79 g, 7.25 mmol, 1.10 eq.) were dissolved in dichloromethane (12 mL) and 2,2,2-trifluoroethanol (12 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which diisopropyl (3,3-dimethylbut-1-yn-1-yl)boronate (**35**, 1.94 g, 9.23 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 1 hour at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (120 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (120 mL) was added. The mixture was stirred for 60 minutes, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1f** (2.06 g, 6.28 mmol, 95%) as a white solid. R_f (EtOAc) = 0.36. Mp 189-192 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.39-8.33 (m, 1 H, Ar*H*), 8.13-8.07 (m, 1 H, Ar*H*), 7.78-7.66 (m, 2 H, Ar*H*), 1.34 (s, 9 H, *t*Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.7, 134.7, 132.4, 131.6, 131.5, 126.0, 117.5, 115.7, 38.2, 30.6, 29.7. IR ν 3463 (w), 2971 (w), 2171 (w), 1646 (s), 1622 (s), 1440 (w), 1332 (m), 1248 (m), 913 (w), 832 (m), 745 (s). HRMS (ESI) $C_{13}H_{14}IO_2^+$ $[M+H]^+$ calc. = 329.0033; $[M+H]^+$ obs. = 329.0023.

(Oct-6-en-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (1g)



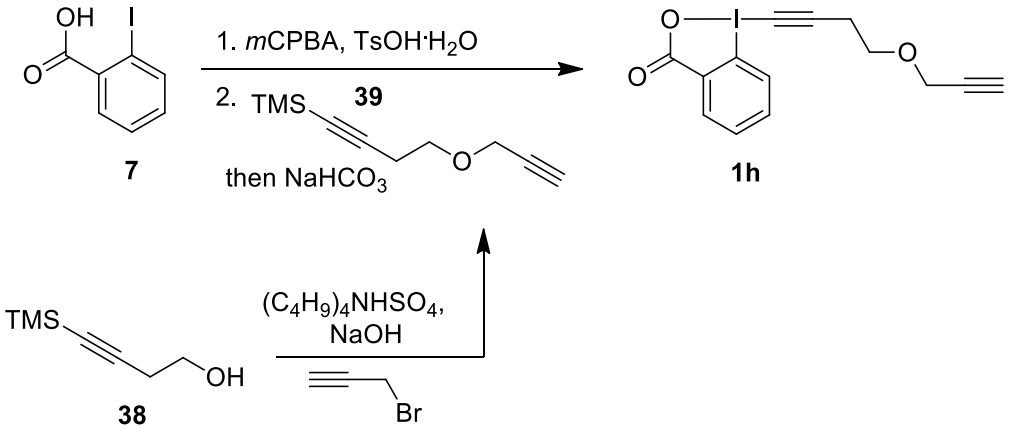
To a mixture of trimethylsilylacetylene (7.23 g, 73.6 mmol, 1.20 eq.) and dry THF (40 mL) was added at -78 °C under nitrogen 2.5 M *n*BuLi in hexanes (31.9 mL, 80.0 mmol, 1.30 eq.) over a 10 minute time period. The resulting light yellow solution was stirred at -78 °C for 60 minutes, after which a mixture consisting of 6-bromohexene (**36**) (10.0 g, 61.3 mmol, 1.00 eq.), hexamethylphosphoramide (HMPA, 12.0 mL, 67.5 mmol, 1.10 eq.) and dry THF (20 mL) was slowly added *via* cannula over a 20 minute time period. The reaction mixture was stirred for 60 minutes at -78 °C, followed by 24 hours of stirring at room temperature. The reaction was quenched at 0 °C with saturated aq. NH_4Cl (50 mL) and diluted with water (5 mL) and EtOAc (50 mL). The two layers were separated and the aq. layer was extracted with additional portions of EtOAc (3 x 50 mL). The combined organic layers were washed with water (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The light brown crude liquid was finally pushed through a small plug of silica gel with pentane as eluent to afford pure trimethyl(oct-7-en-1-yn-1-yl)silane (**37**, 10.6 g, 58.8 mmol, 95.9% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (ddt, 1 H, J = 16.9, 10.2, 6.7 Hz, CH_2CHCH_2), 5.04-4.91 (m, 2 H, CH_2CHCH_2), 2.22 (t, 2 H, J = 6.9 Hz, CH_2), 2.11-2.01 (m, 2 H, CH_2), 1.58-1.43 (m, 4 H, CH_2), 0.14 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.8, 114.7, 107.6, 84.5, 33.3, 28.2, 28.1, 19.9, 0.3. The values of the NMR spectra are in accordance with reported literature data.[10]

Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (9.82 g, 39.6 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate ($TsOH \cdot H_2O$, 7.53 g, 39.6 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 10.7 g, 43.6 mmol, 1.10 eq.) were dissolved in dichloromethane (73 mL) and 2,2,2-trifluoroethanol (73 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which trimethyl(oct-7-en-1-yn-1-yl)silane (**37**, 10.0 g, 55.4 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 14 hours at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (700 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (700 mL) was added. The mixture was stirred for 1 hour, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1g** (2.60

[10] Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 1245.

g, 7.34 mmol, 19%) as a white solid. In addition, starting trimethyl(oct-7-en-1-yn-1-yl)silane (**35**, 3.20 g, 17.7 mmol) was recovered and re-submitted to the above described conditions to afford additional **1g** (1.18 g, 3.33 mmol, 28%) as a white solid, giving an overall yield of 27% brsm. R_f (EtOAc) = 0.34. Mp 48-58 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43-8.36 (m, 1 H, Ar*H*), 8.21-8.13 (m, 1 H, Ar*H*), 7.80-7.69 (m, 2 H, Ar*H*), 5.81 (ddt, 1 H, *J* = 17.0, 10.2, 6.7 Hz, CH_2CHCH_2), 5.10-4.95 (m, 2 H, CH_2CHCH_2), 2.61 (t, 2 H, *J* = 7.0 Hz), 2.17-2.07 (m, 2 H), 1.73-1.51 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.7, 138.1, 134.8, 132.5, 131.6, 131.6, 126.2, 115.7, 115.2, 109.5, 39.7, 33.2, 28.1, 27.7, 20.4. IR ν 3294 (w), 2912 (w), 2869 (w), 1731 (w), 1650 (w), 1625 (w), 1447 (m), 1250 (w), 1101 (s), 1018 (m), 747 (s). HRMS (ESI) $C_{15}H_{16}IO_2^+$ $[M+H]^+$ calc. = 355.0189; $[M+H]^+$ obs. = 355.0182.

4-(Prop-2-yn-1-yloxy- but-1-yn-1-yl)-1,2-benziodoxol-3(1*H*)-one (1h)

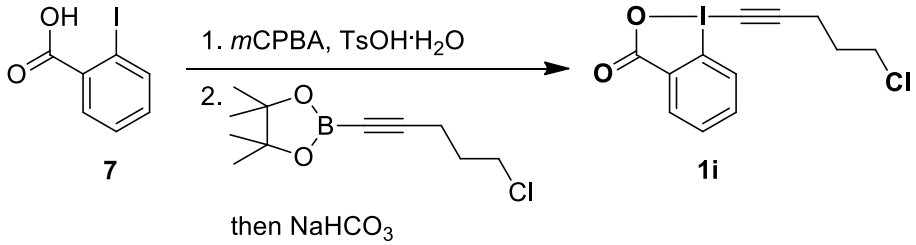


A 50-mL flame-dried two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and a nitrogen inlet adapter was charged with silane **38** (2.00 g, 14.1 mol, 1.00 eq.) and dry DCM (30 mL). The clear colorless solution was cooled to 0 °C and tetrabutylammonium hydrogensulfate (0.239 g, 0.703 mmol, 0.05 eq.) and NaOH (1.12 g, 28.1 mmol, 2.00 eq.) were added to the mixture. After stirring at 0 °C for 5 minutes, propargyl bromide (2.09 g, 14.1 mmol, 1.00 eq.) was added. The resulting yellow reaction mixture was continuously stirred at 0 °C under nitrogen and monitored by TLC (EtOAc:Pentane 30:1, $KMnO_4$ staining). After 2 h, 30 mL of water was added to the reaction mixture at 0 °C and the aqueous layer was extracted with 30 mL of DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude yellow oil was purified by flash chromatography columns using EtOAc:Pentane 1:299 as mobile phase to afford pure trimethyl(4-(prop-2-yn-1-yloxy)but-1-yn-1-yl)silane (**39**, 0.245 g, 1.36 mmol, 10% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.17 (d, 2 H, *J* = 2.3

Hz, CCCH_2O), 3.64 (t, 2 H, J = 7.2 Hz, OCH_2), 2.53 (t, 2 H, J = 7.2 Hz, OCH$_2$CH_2), 2.43 (t, 1 H, J = 2.4 Hz, CCH), 0.14 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 103.3, 86.0, 79.6, 74.7, 68.2, 58.3, 21.2, 0.19. IR ν 3291 (w), 2932 (w), 2859 (w), 2179 (w), 1612 (w), 1511 (m), 1250 (s), 1104 (m), 1036 (w), 843 (s), 761 (w).

Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (0.211 g, 0.832 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate (TsOH·H_2O, 0.160 g, 0.832 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 0.226 g, 0.915 mmol, 1.10 eq.) were dissolved in dichloromethane (1.5 mL) and 2,2,2-trifluoroethanol (1.5 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which trimethyl(4-(prop-2-yn-1-yloxy)but-1-yn-1-yl)silane (**39**, 0.210 g, 1.17 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 14 h at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (15 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (15 mL) was added. The mixture was stirred for 1 h, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1h** (0.177 g, 0.500 mmol, 60%) as a colorless oil. R_f (EtOAc) = 0.1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (dd, 1 H, J = 7.3, 1.8 Hz, ArH), 8.23 (dd, 1 H, J = 8.3, 1.1 Hz, ArH), 7.76-7.69 (m, 1 H, ArH), 7.66 (td, 1 H, J = 7.3, 1.1 Hz, ArH), 4.19 (d, 2 H, J = 2.4 Hz, OCH_2CCH), 3.72 (t, 2 H, J = 6.2 Hz, OCH_2CH$_2$), 2.85 (t, 2 H, J = 6.3 Hz, OCH$_2$CH_2), 2.47 (t, 1 H, J = 2.4 Hz, CCH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.1, 134.8, 132.1, 131.5, 131.3, 126.8, 115.8, 105.6, 79.1, 75.2, 67.3, 58.3, 40.8, 21.8. IR ν 3465 (w), 3253 (w), 2920 (w), 2870 (w), 2175 (w), 1611 (s), 1330 (m), 1298 (m), 1100 (s), 832 (m), 748 (s). HRMS (ESI) $C_{14}H_{12}IO_3^+$ $[M+H]^+$ calc. = 354.9826; $[M+H]^+$ obs. = 354.9824.

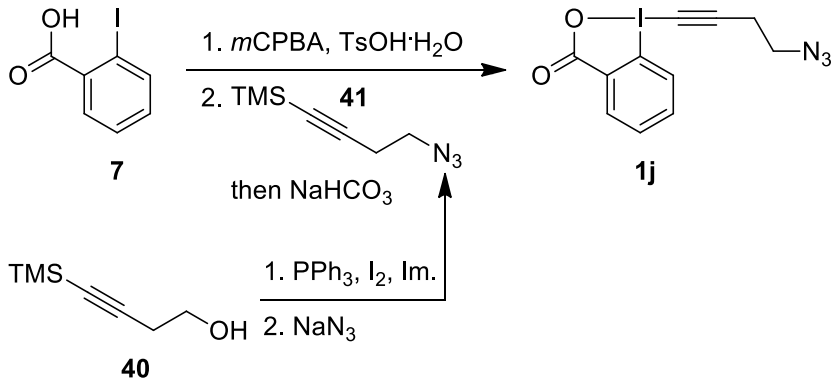
(5-Chloropent-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (1i)



Following a slightly modified procedure,[5] 2-iodobenzoic acid (7) (3.76 g, 15.2 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate (TsOH·H_2O, 2.88 g, 15.2 mmol, 1.00 eq.) and

meta-chloroperoxybenzoic acid (*m*CPBA-70%, 4.11 g, 16.7 mmol, 1.10 eq.) were dissolved in dichloromethane (30 mL) and 2,2,2-trifluoroethanol (30 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which 5-chloro-1-pentynyl-1-boronic acid pinacol ester (4.85 g, 21.2 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 90 minutes at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (15 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (15 mL) was added. The mixture was stirred for 10 minutes, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1i** (3.76 g, 10.8 mmol, 71%) as a white solid. R_f (EtOAc) = 0.15. Mp 138.5-141.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41-8.34 (m, 1 H, Ar*H*), 8.22-8.13 (m, 1 H, Ar*H*), 7.82-7.68 (m, 2 H, Ar*H*), 3.71 (t, 2 H, *J* = 6.1 Hz, ClC*H*$_2$CH$_2$), 2.82 (t, 2 H, *J* = 6.9 Hz, CCC*H*$_2$CH$_2$), 2.18-2.05 (m, 2 H, ClCH$_2$C*H*$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8, 134.9, 132.5, 131.6, 131.6, 126.4, 115.8, 107.1, 43.4, 41.2, 30.7, 18.0. IR ν 2942 (w), 2866 (w), 2171 (w), 2091 (w), 1727 (w), 1617 (s), 1556 (w), 1441 (w), 1339 (m), 1213 (w), 1023 (w), 846 (w), 742 (s). HRMS (ESI) $C_{12}H_{11}ClIO_2^+$ $[M+H]^+$ calc. = 348.9487; $[M+H]^+$ obs. = 348.9484.

(4-Azidobut-1-ynyl)-1,2-benziodoxol-3(1*H*)-one (1j)



Following a slightly modified procedure,[11] triphenylphosphine (27.7 g, 105 mmol, 1.00 eq.) was added at 0 °C to a colorless solution of 4-(trimethylsilyl)but-3-yn-1-ol **40** (15.0 g, 105 mmol, 1.00 eq.) in THF (400 mL). After dissolution, imidazole (7.18 g, 105 mmol, 1.00 eq.) and iodine (26.8 g, 105 mmol, 1.00 eq.) were added to the mixture. The cooling bath was removed after 5 minutes and the reaction mixture was stirred at room temperature for 2 hours. Next, the mixture was diluted with diethyl ether (300 mL) and extracted with 10% aq.

[11] Rodier, F.; Rajzmann, M.; Parrain, J. L.; Chouraqui, G.; Commeiras, L. *Chem. Eur. J.* **2013**, *19*, 2467.

$Na_2S_2O_3$ (300 mL). The aq. layer was washed with additional portions of diethyl ether (2 x 100 mL) and the combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting white suspension was filtered and the filtrate was purified by Kugelrohr distillation (95 °C at 0.5 mbar) to furnish pure (4-iodobut-1-yn-1-yl)trimethylsilane (25.3 g, 100 mmol, 95.2% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.19 (t, 2 H, *J* = 7.5 Hz, CH_2CH_2I), 2.76 (t, 2 H, *J* = 7.5 Hz, CH_2CH_2I), 0.13 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 105.1, 86.8, 25.2, 1.1, 0.1. The values of the NMR spectra are in accordance with reported literature data.[12]

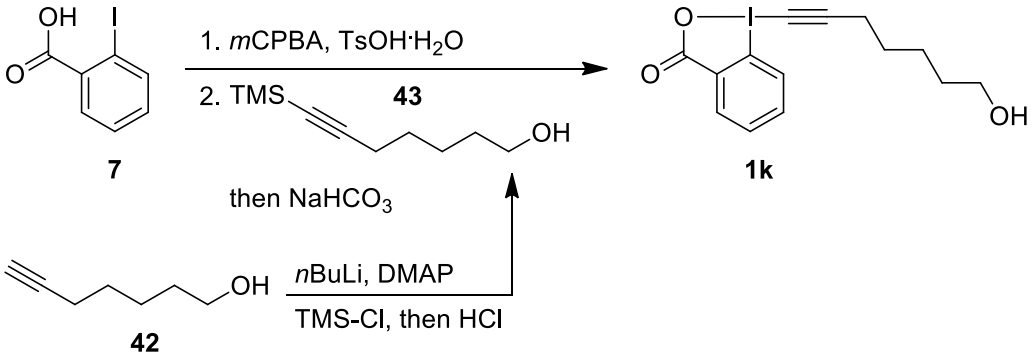
0.5 M sodium azide in DMSO (220 ml, 110 mmol, 1.10 eq.) was added to (4-iodobut-1-yn-1-yl)trimethylsilane (25.2 g, 99.9 mmol, 1.00 eq.) and the reaction mixture was stirred for 24 hours at room temperature. The mixture was next slowly added to ice water (500 mL) and extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with water (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The light yellow crude liquid was finally pushed through a small plug of silica gel with pentane as eluent to afford pure (4-azidobut-1-yn-1-yl)trimethylsilane (**41**, 15.8 g, 94.5 mmol, 94.6% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.36 (t, 2 H, *J* = 6.8 Hz, $CH_2CH_2N_3$), 2.50 (t, 2 H, *J* = 6.9 Hz, $CH_2CH_2N_3$), 0.14 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 102.7, 87.3, 49.8, 21.1, -0.1. The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[13]

Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**, 15.9 g, 64.0 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$, 12.2 g, 64.0 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 17.4 g, 70.5 mmol, 1.10 eq.) were dissolved in dichloromethane (120 mL) and 2,2,2-trifluoroethanol (120 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which (4-azidobut-1-yn-1-yl)trimethylsilane (**41**, 15.0 g, 90.0 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 14 hours at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (750 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (750 mL) was added. The mixture was stirred for 1 hour, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 250 mL). The combined organic layers were dried over $MgSO_4$, filtered

[12] Berkessel, A.; Kramer, J.; Mummy, F.; Neudorfl, J. M.; Haag, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 739.
[13] Diaz, L.; Bujons, J.; Casas, J.; Llebaria, A.; Delgado, A. *J. Med. Chem.* **2010**, *53*, 5248.

and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **1j** (9.20 g, 27.0 mmol, 42%) as a light beige solid. In addition, starting (4-azidobut-1-yn-1-yl)trimethylsilane (**41**, 1.81 g, 10.8 mmol) was recovered and re-submitted to the above described conditions to afford additional **1j** (953 mg, 2.79 mmol, 36%) as a light beige solid, giving an overall yield of 47% brsm. R_f (EtOAc:MeOH 9:1) = 0.47. Mp 114-125 °C (explosive decomposition). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (dd, 1 H, *J* = 7.0, 2.1 Hz, Ar*H*), 8.21 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 7.79-7.63 (m, 2 H, Ar*H*), 3.54 (t, 2 H, *J* = 6.5 Hz, $CH_2CH_2N_3$), 2.85 (t, 2 H, *J* = 6.5 Hz, $CH_2CH_2N_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 134.9, 132.3, 131.5, 131.4, 126.8, 115.8, 104.5, 49.4, 42.7, 21.5. IR ν 3452 (w), 2170 (w), 2112 (s), 1647 (s), 1624 (s), 1439 (w), 1331 (m), 1297 (m), 835 (w), 749 (m). HRMS (ESI) $C_{11}H_9IN_3O_2^+$ $[M+H]^+$ calc. = 341.9734; $[M+H]^+$ obs. = 341.9734.

5-Pentanolethynyl-1,2-benziodoxol-3(1*H*)-one (1k)



Following a slightly modified procedure,[14] 2.5 M *n*BuLi in hexanes (39.2 mL, 98.0 mmol, 2.20 eq.) was added at -78 °C under nitrogen to a mixture of hept-6-yn-1-ol (**42**) (5.00 g, 44.6 mmol, 1.00 eq.) and dry THF (150 mL), followed by 4-dimethylaminopyridine (DMAP, 1.36 g, 11.1 mmol, 0.25 eq.). The mixture was stirred at -78 °C for 60 minutes, after which trimethylsilyl chloride (TMS-Cl, 20.4 mL, 156 mmol, 3.50 eq.) was added dropwise. The cooling bath was removed and the reaction stirred for 2 hours. Next, 1.0 N aq. HCl (50 mL) was added and the solution was stirred vigorously for 30 minutes at room temperature. The mixture was diluted with EtOAc (200 mL) and extracted. The aqueous layer was extracted with additional portions of EtOAc (3 x 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (100 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pentane:EtOAc 4:1) to afford 7-(trimethylsilyl)hept-6-yn-1-ol (**43**, 8.22 g, 43.5 mmol, 97%) as a colorless oil.

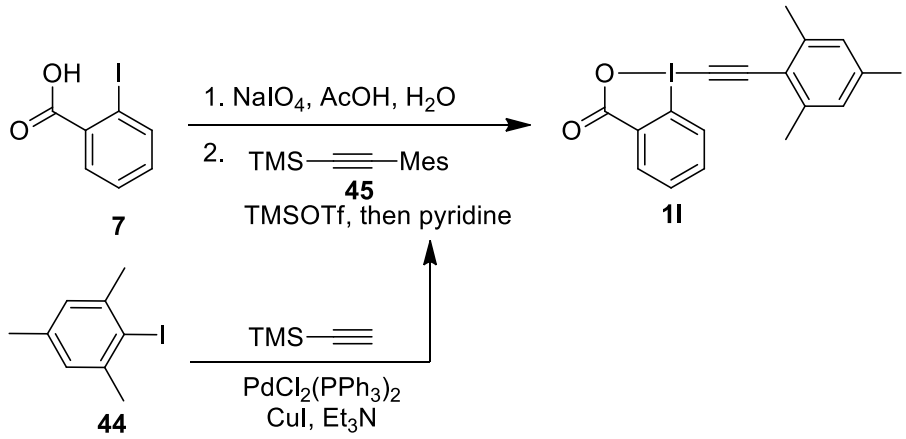
[14] Peixoto, P. A.; Richard, J. A.; Severin, R.; Chen, D. Y. *Org. Lett.* **2011**, *13*, 5724.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.61 (t, 2 H, *J* = 6.5 Hz, C*H*$_2$OH), 2.21 (t, 2 H, *J* = 7.0 Hz, CCC*H*$_2$), 1.73 (bs, 1 H, CH$_2$O*H*), 1.61-1.48 (m, 4 H), 1.48-1.38 (m, 2 H), 0.11 (s, 9 H, TMS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 107.4, 84.6, 62.8, 32.3, 28.5, 25.1, 19.9, 0.3. The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[15]

Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (7.69 g, 31.0 mmol, 1.00 eq.), *para*-toluenesulfonic acid monohydrate (TsOH·H$_2$O, 5.90 g, 31.0 mmol, 1.00 eq.) and *meta*-chloroperoxybenzoic acid (*m*CPBA-70%, 8.41 g, 34.1 mmol, 1.10 eq.) were dissolved in dichloromethane (57 mL) and 2,2,2-trifluoroethanol (57 mL). The mixture was stirred at room temperature under nitrogen for 1 hour, after which 7-(trimethylsilyl)hept-6-yn-1-ol (**43**, 8.00 g, 43.4 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 18 hours at room temperature, filtered and concentrated *in vacuo*. The resulting oil was dissolved in dichloromethane (500 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (500 mL) was added. The mixture was stirred for 60 minutes, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc:MeOH 95:5) to afford **1k** (3.56 g, 9.94 mmol, 32%) as a white solid. R_f (EtOAc:MeOH 9:1) = 0.24. Mp 115-120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (dd, 1 H, *J* = 7.2, 2.0 Hz, Ar*H*), 8.15 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.79-7.64 (m, 2 H, Ar*H*), 3.66 (t, 2 H, *J* = 5.9 Hz, C*H*$_2$OH), 2.59 (t, 2 H, *J* = 6.9 Hz, CCC*H*$_2$), 1.73-1.49 (m, 7 H, CH_2 and OH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.0, 134.8, 132.3, 131.6, 131.5, 126.5, 115.7, 109.7, 62.3, 39.2, 32.1, 28.0, 25.3, 20.6. IR ν 3351 (w), 2934 (w), 2170 (w), 1623 (s), 1585 (m), 1561 (w), 1439 (w), 1333 (m), 1300 (w), 1058 (w), 911 (m), 832 (w), 732 (s), 689 (m). HRMS (ESI) $C_{14}H_{16}IO_3^+$ $[M+H]^+$ calc. = 359.0139; $[M+H]^+$ obs. = 359.0136.

[15] Rodier, F.; Rajzmann, M.; Parrain, J. L.; Chouraqui, G.; Commeiras, L. *Chem. Eur. J.* **2013**, *19*, 2467.

1-[2,4,6-Trimethylphenylethynyl]-1,2-benziodoxol-3(1*H*)-one (1l)



Following a reported procedure,[2] $NaIO_4$ (77.2 g, 0.361 mol, 1.0 equiv) and 2-iodobenzoic acid (**7**) (89.5 g, 0.361 mmol, 1.0 equiv) were suspended in 30% (v:v) aq. AcOH (700 mL) under air in a 4-neck sulfonation flask equipped with a mechanic stirrer, a thermometer and a condenser. The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (500 mL) and allowed to cool to room temperature, protecting it from light. After 45 min, the suspension was added to water (1.5 L) and the crude product was collected by filtration, washed on the filter with ice water (3 x 300 mL) and cold acetone (3 x 300 mL), and air-dried in the dark overnight to give 2-iodosylbenzoic acid (77.3 g, 0.292 mol, 81% yield) as a colorless solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1 H, Ar*H*).^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4. IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m). The values of the NMR spectra are in accordance with reported literature data.[2]

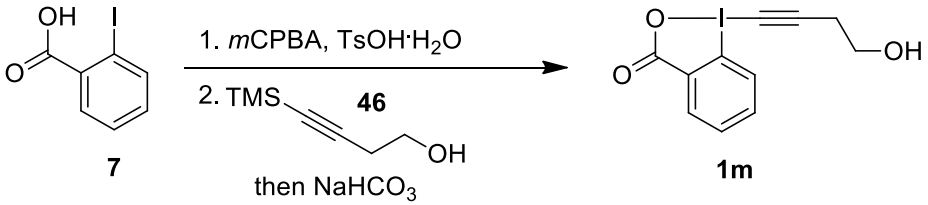
Following a reported procedure,[16] mesityl iodide (**44**) (1.05 g, 4.27 mmol, 1 equiv) was dissolved in Et_3N (10 mL) (without prior drying). After three freeze-thraw-pump cycle, $PdCl_2(PPh_3)_2$ (30 mg, 0.42 mmol, 0.1 equiv) and CuI (16 mg, 0.84 mmol, 0.2 equiv) were added under N_2. After the addition of trimethylsilylacetylene (1.2 mL, 8.5 mmol, 2 equiv), the green suspension was stirred at RT for 1 h. The reaction mixture was reduced under vacuum, dissolved in CH_2Cl_2 (30 mL), washed with 5% EDTA solution (30 mL) and water (30 mL). The organic layers were them dried over $MgSO_4$, filtered and reduced under vacuum. The

[16] Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2012**, *18*, 5655.

resulting oil was purified by column chromatography (PET) to afford **45** (526 mg, 2.43 mmol, 66%) along with 15% of starting material. R_f 0.5 (PET). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 2 H, ArH), 2.41 (s, 6 H, CH_3), 2.29 (s, 3 H, CH_3), 0.28 (s, 9 H, TMS). Used without further purification.

Following a reported procedure,[16] trimethylsilyl triflate (212 μL, 1.15 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (1.00 g, 1.05 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of (mesitylethynyl)trimethylsilane (**45**) (250 mg, 1.15 mmol, 1.1 equiv) dissolved in CH_2Cl_2 (1 mL). The resulting suspension was stirred for 6 h at RT. A saturated solution of $NaHCO_3$ (5 mL) was then added and the mixture was stirred vigorously. The layers were separated and the organic layer was washed with sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was recrystallized in CH_3CN (ca 20 ml). The mother liquors were concentrated and and the obtained solid recrystallized in CH_3CN (4 mL). Both solids were combined, washed with pentane and dried under high vacuum to afford **1l** (120 mg, 0.307 mmol, 30%) as a tan solid. Mp 171-175 °C (decomposition). ^{1}H NMR (400 MHz, $CDCl_3$) (*ca* 0.01 mmol/ml) δ 8.38 (m, 1 H, ArH), 8.28 (m, 1 H, ArH), 7.72 (m, 2 H, ArH), 6.92 (s, 2 H, MesH), 2.45 (s, 6 H, CH_3), 2.31 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 142.1, 140.5, 134.5, 132.2, 131.5, 131.3, 128.0, 126.2, 117.5, 116.5, 105.1, 55.6, 21.4, 21.0. IR 2979 (w), 2916 (w), 2247 (w), 2131 (w), 1650 (m), 1623 (m), 1562 (w), 1439 (w), 1333 (w), 1292 (w), 1212 (w), 1146 (w), 1008 (w), 906 (s), 855 (w), 833 (w), 729 (s), 647 (m). The data are in accordance with reported literature.[16]

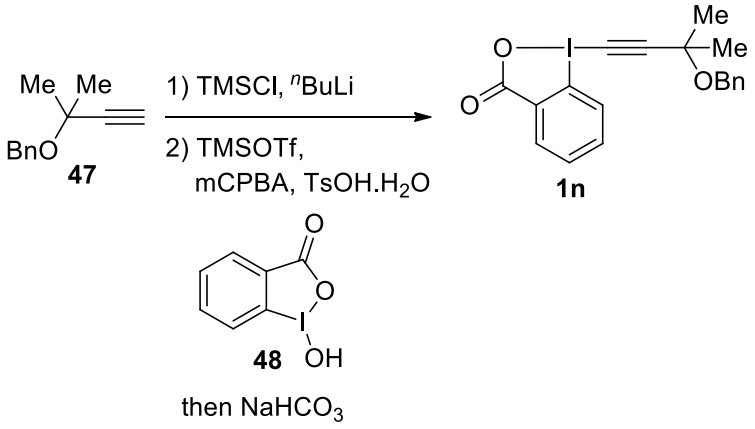
(4-Hydroxybut-1-yn-1-yl)-1,2-benziodoxol-3(1*H*)-one (1m)



Following a slightly modified procedure,[5] 2-iodobenzoic acid (**7**) (10.2 g, 40.2 mmol, 1.00 eq.), para-toluenesulfonic acid monohydrate (TsOH, 7.64 g, 40.2 mmol, 1.00 eq.) and meta-chloroperoxybenzoic acid (mCPBA-70%, 10.9 g, 44.2 mmol, 1.10 eq.) were dissolved in dry dichloromethane (70 mL) and 2,2,2-trifluoroethanol (70 mL). The mixture was stirred at room temperature under nitrogen for 1 h, after which 4-(trimethylsilyl)but-3-yn-1-ol (**46**) (8.00 g,

56.2 mmol, 1.40 eq.) was added in one portion. The reaction mixture was stirred for 17 hours at room temperature, filtered and concentrated in vacuo. The resulting oil was dissolved in dichloromethane (150 mL) and under vigorous stirring, saturated aq. $NaHCO_3$ (150 mL) was added. The mixture was stirred for 15 minutes, the two layers were separated and the aqueous layer was extracted with additional portions of dichloromethane (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (ethyl acetate then flushed with acetone) to afford a white solid, which was further purified by trituration in pentane, filtered, washed twice with pentane and then dried under air to afford **1m** (4.24 g, 40.2 mmol, 33 %) as a white solid. Analytically pure sample was obtained by recrystallization in EtOH/AcOEt (6/4). Mp 165-174 °C (decomposition). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.10 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.85 (ddd, *J* = 8.2, 7.2, 1.8 Hz, 1H), 7.78 (td, *J* = 7.2, 1.0 Hz, 1H), 5.07 (t, *J* = 5.4 Hz, 1H), 3.65 (td, *J* = 6.4, 5.5 Hz, 2H), 2.80 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6):[6] δ 166.1, 134.7, 132.2, 131.1, 127.5, 115.7, 106.2, 59.3, 40.7, 24.2. IR ν 3143 (w), 2983 (w), 2363 (m), 2337 (w), 2166 (w), 1605 (s), 1557 (m), 1436 (w), 1347 (s), 1044 (s), 988 (w), 831 (m), 738 (s). HRMS (ESI) $C_{11}H_{10}IO_3^+$ $[M+H]^+$ calc. = 316.9669; obs. = 316.9679.

3-(Benzyloxy)-3-methyl-but-1-yn-1-yl)-1,2-benziodoxol-3(1H)-one (1n)

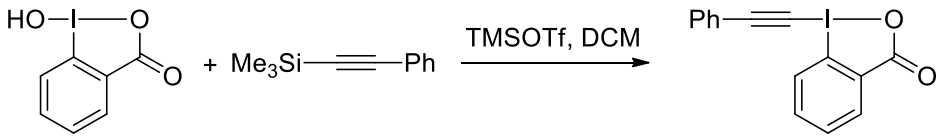


47 (850 mg, 4.90 mmol, 1.00 eq.) was dissolved in 10 mL of dry THF. Next, ^{n}BuLi (2.5 M in hexane, 5.1 mL, 13 mmol, 2.6 eq.) was added through syringe dropwise over 10 minutes and the reaction mixture was stirred for another 10 minutes to get a brownish-red solution. Next, TMSCl (0.70 mL, 5.5 mmol, 1.1 eq.) was added dropwise to get a clear solution and the reaction mixture was stirred for 1.5 h at 0 °C. The resulting reaction mixture was continuously stirred at room temperature for 2.5 h until a white solid precipitated. It was then diluted with

hexane (30 mL), washed with water (3 x 20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using EtOAc:Pentane 1:20 as mobile phase to afford (3-(benzyloxy)-3-methylbut-1-yn-1-yl)trimethylsilane (362 mg, 1.47 mmol, 33%), which was used directly in the next step.

Trimethylsilyltriflate (1.60 mL, 8.56 mmol, 1.1 eq.) was added dropwise to a stirred solution of 2-iodosylbenzoic acid (**48**) (2.12 g, 7.99 mmol, 1.0 eq.) in acetonitrile (40 mL) at 0 °C. After 15 minutes, (3-(benzyloxy)-3-methylbut-1-yn-1-yl)trimethylsilane (2.07 g, 8.89 mmol, 1.05 eq.) was added dropwise, followed, after 30 min, by the addition of pyridine (6 mL). The mixture was stirred for 20 minutes. The solvent was then removed under reduced pressure and the crude oil was dissolved in dichloromethane (100 mL). The organic layer was washed with 0.5 M HCl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from hot EtOAc afforded **1n** (770 mg, 0.183 mmol, 23%) as a light yellow solid. Mp 146.6-148.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.39 (dd, 1 H, *J* = 7.3, 1.8 Hz, Ar*H*), 8.11 (dd, 1 H, *J* = 8.2, 1.1 Hz, Ar*H*), 7.78-7.62 (m, 2 H, Ar*H*), 7.39-7.31 (m, 4 H, Ar*H*), 7.31-7.27 (m, 1H, Ar*H*), 4.70 (s, 2 H, ArCH_2), 1.69 (s, 6 H, 2 x CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 138.3, 135.0, 132.6, 131.7, 131.4, 128.6, 127.9, 127.6, 126.1, 115.8, 110.0, 71.9, 67.2, 45.5, 28.8. IR ν 2986 (w), 2868 (w), 2159 (w), 1618 (s), 1561 (m), 1446 (w), 1330 (m), 1299 (m), 1224 (m), 1159 (m), 1054 (m), 888 (w), 834 (m), 742 (s). HRMS (ESI) $C_{19}H_{18}IO_3^+$ $[M+H]^+$ calc. = 421.0295; $[M+H]^+$ obs. = 421.0305.

1-[Phenylethynyl]-1,2-benziodoxol-3(1*H*)-one (Ph-EBX, 1o)



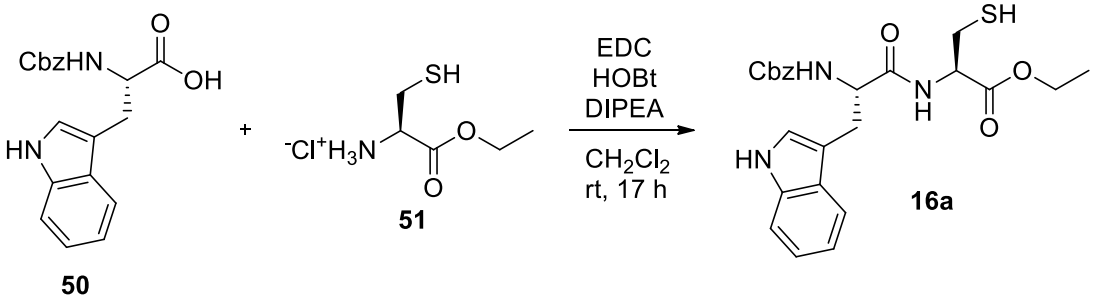
48 **49** **1o**

Following a reported procedure,[16] trimethylsilyltriflate (1.60 mL, 8.56 mmol, 1.1 eq.) was added dropwise to a stirred solution of 2-iodosylbenzoic Trimethylsilyl triflate (7.50 mL, 41.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**48**) (10.0 g, 37.7 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at RT. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (**49**) (8.10 mL, 41.5 mmol, 1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at RT,

during this time a white solid was formed. A saturated solution of $NaHCO_3$ (100 mL) was then added and the mixture was stirred vigorously. The resulting suspension was filtered on a glass filter of porosity 4. The two layers of the mother liquors were separated and the organic layer was washed with sat. $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was combined with the solid obtained by filtration and boiled in CH_3CN (300 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **1o** (6.08 g, 17.4 mmol, 46 %) as a colorless solid. Mp (Dec.) 155 – 160°C (lit 153-155°C). ^{1}H NMR (400 MHz, $CDCl_3$) (*ca* 0.03 mmol/ml) δ 8.46 (m, 1 H, ArH), 8.28 (m, 1 H, ArH), 7.80 (m, 2 H, ArH), 7.63 (m, 2 H, ArH), 7.48 (m, 3 H, ArH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 134.9, 132.9, 132.5, 131.6, 131.3. 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2. Consistent with reported data.[16]

4. Preparation of Substrates

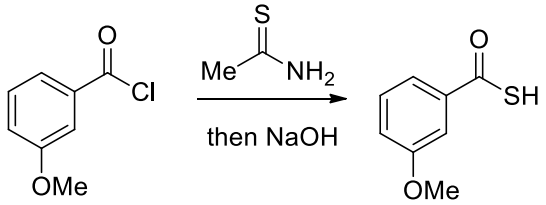
2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)-3-mercaptopropanoate) (16a)



To a mixture of L-cysteine ethyl ester hydrochloride (**51**) (1.90 g, 10.0 mmol, 1.00 eq.), *N*-carbobenzyloxy- L-tryptophan (**50**) (4.06 g, 12.0 mmol, 1.20 eq.) and HOBt hydrate (2.37 g, 15.0 mmol, 1.50 eq.) in CH_2Cl_2 (100 mL) was added at 0 °C EDC hydrochloride (2.30 g, 12.0 mmol, 1.20 eq.) in one portion. The resulting suspension was stirred for 10 minutes at 0 °C, after which DIPEA (5.24 mL, 30.0 mmol, 3.00 eq.) was slowly added. The ice bath was removed and the reaction mixture was stirred at room temperature for 17 h. Next, the solvent was evaporated under reduced pressure. The resulting oil was dissolved in EtOAc (250 mL) and extracted with 5% aq. $KHSO_4$ (3 x 75 mL), 5% aq. $NaHCO_3$ (2 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude white solid was purified by flash chromatography (pentane:EtOAc 2:1 to 3:2) to afford **16a** as a white solid (1.32 g, 2.81 mmol, 28%). Rf (EtOAc:pentane 1:1) = 0.81. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 1 H), 7.65 (d, 1 H, *J* = 7.9 Hz), 7.40 -7.28 (m, 6 H), 7.23-7.17 (m, 1 H), 7.11 (t, 1 H, *J* = 7.5 Hz), 7.07 (d, 1 H, *J* = 2.2 Hz), 6.60 (d, 1 H, *J* = 6.3 Hz), 5.45 (d, 1 H, *J* = 7.5 Hz), 5.13 (s, 2 H), 4.67 (dt, *J* = 7.0, 4.0 Hz, 1H), 4.61-4.51 (m, 1 H), 4.24-4.05 (m, 2 H), 3.42 (dd, 1 H, *J* = 14.7, 5.4 Hz), 3.18 (1 H, *J* = 14.6, 7.0 Hz), 2.96-2.68 (m, 2 H), 1.24 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$) 1.02 (t, 1 H, *J* = 8.8 Hz, S*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 169.5, 156.1, 136.3, 136.1, 128.7, 128.4, 128.3, 127.5, 123.4, 122.6, 120.0, 118.9, 111.4, 110.2, 67.3, 62.1, 55.6, 53.9, 28.4, 26.7, 14.3. The characterization data is in accordance with reported literature values.[17]

[17] Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620.

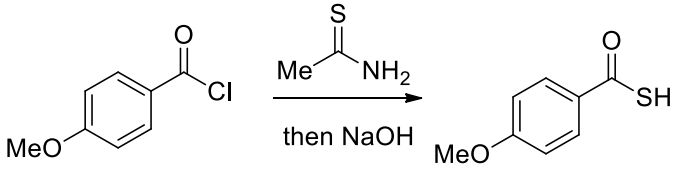
3-Methoxybenzothioic S-acid (22b)



52 **22b**

Following a slightly modified reported procedure, [18] thioacetamide (0.380 g, 5.00 mmol, 1.00 eq.) and chloride **52** (3.54 mL, 5.00 mmol, 1.00 eq.) were dissolved in dry benzene (4 mL). The resulting mixture was stirred for 3 h at 30 °C. Then, 10% NaOH (6 mL) was added to the mixture, the resulting biphasic mixture was stirred for 30 minutes and subsequently acidified by adding 1 M aq. $KHSO_4$. The emulsion was extracted with EtOAc (80 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was finally pushed through a small plug of silica gel (pentane/EtOAc 5:1 to 1:1) to yield a second crude mixture, which was concentrated under reduced pressure and then, dissolved in DCM. The organic layer was extracted with sat. aq. $NaHCO_3$ (2 x 15 mL) and the combined aq. layers were acidified by adding aq. 1 M HCl. The resulting mixture was extracted with EtOAc (3 x 30 mL), after which the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford **22b** (0.270 g, 1.60 mmol, 32%) as a yellow oil. Rf (pentane/EtOAc 1:1, a smear) = 0.57. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1 H, Ar*H*), 7.38 (dd, *J* = 2.6, 1.6 Hz, 1 H, Ar*H*), 7.35 (t, *J* = 7.9 Hz, 1 H, Ar*H*), 7.13 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1 H, Ar*H*), 5.38 (s, 1 H, S*H*), 3.83 (s, 3 H, OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.1, 159.8, 137.9, 129.8, 120.7, 120.4, 111.9, 55.5. IR ν 2963 (w), 2943 (w), 2836 (w), 2565 (w), 2255 (w), 1675 (m), 1584 (m), 1486 (m), 1261 (s), 909 (m), 780 (s), 731 (s), 696 (s). HRMS (ESI) $C_8H_8O_2S^+$ [M+] calc. = 168.0245; [M+] obs. = 167.0180.

4-Methoxybenzothioic S-acid (22c)

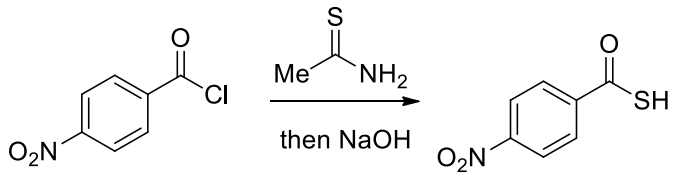


53 **22c**

[18] Toriyama, M.; Kamijo, H.; Motohashi, S.; Takido, T.; Itabashi, K. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 1661.

Following a slightly modified reported procedure,[18] 4-methoxybenzoyl chloride (**53**) (2.08 g, 12.0 mmol, 1.00 eq.) and dry toluene (10.0 mL) were added in an under vacuum flame-dried 25 mL round bottom flask at room temperature. To this clear colorless solution was added thioacetamide (0.924 g, 12.1 mmol, 1.00 eq.) in one portion. The reaction mixture was then stirred at 30 °C for 3 h. The oil bath was then removed and 10 minutes later, 10% (w/w) aq. NaOH (9 mL) was added in one portion. The bi-phasic mixture was stirred for 30 minutes at room temperature and then acidified with 1.0 M aq. $KHSO_4$. The mixture was then extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude yellow oil was then purified by flash column chromatography (Pentane:EtOAc 9:1) to afford **22c** (0.493 g, 2.93 mmol, 25%) as a yellow light crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89-7.83 (m, 2 H, Ar*H*), 6.96-6.88 (m, 2 H, Ar*H*), 4.47 (bs, 1 H, S*H*), 3.86 (s, 3 H, OC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.7, 164.3, 130.3, 129.6, 114.0, 55.7. The ^{13}C NMR data is in accordance with reported literature values.[18]

4-Nitrobenzothioic S-acid (22d)

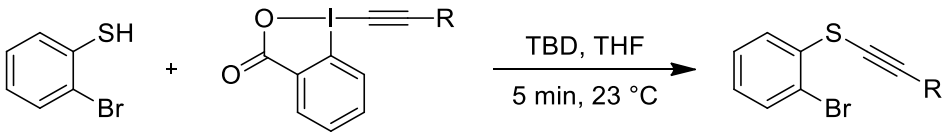


54 **22d**

Following a slightly modified reported procedure,[18] 4-nitrobenzoyl chloride (**54**) (5 g, 26.4 mmol, 1.00 eq.) was added in an under vacuum flame dried 25 mL round bottom flask to a suspension of thioacetamide (2.02 g, 24.4 mmol, 1.00 eq.) and dry toluene (20.0 mL) at room temperature. The light yellow reaction mixture was stirred at 30 °C for 3 h and then cooled to 0 °C. At 0 °C, 10% (w/w) aq. NaOH (14 mL) was added in one portion. The bi-phasic mixture was stirred for 30 minutes at 0 °C and then acidified with 1.0 M aq. $KHSO_4$. The mixture was diluted with water then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude yellow oil was then purified by flash column chromatography using pentane:EtOAc 4:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35-8.30 (m, 2 H, Ar*H*), 8.10-8.04 (m, 2 H, Ar*H*), 4.82 (bs, 1 H, S*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.6, 151.0, 141.1, 129.0, 124.2. The ^{13}C NMR data is in accordance with reported literature values.[18]

5. Alkynylation Reaction

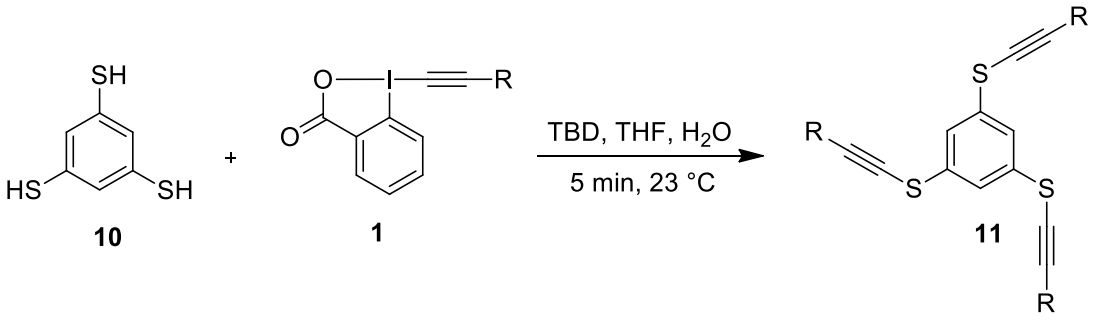
General Procedure A (GPA): 2-Bromothiophenol Alkynylation



8 **1** **9**

The following general procedure was utilized to determine the representative thiophenol scope for the thiol-alkynylation reaction with R-EBX reagents (**1b** to **1l**). A 25 mL round bottom flask was charged with a magnetic stirring bar, 2-bromothiophenol (0.300 to 0.800 mmol, 1.00 eq.) and triazabicyclodecene (TBD, 0.300 to 0.800 mmol, 1.00 eq.). The mixture was dissolved in THF (3.75 to 10.0 mL) to achieve a thiol concentration of 80 mM. Upon dissolution, the corresponding R-EBX reagents (**1b** to **1l**, 0.330 to 0.880 mmol, 1.10 eq.) were added as a solid in one portion. The resulting reaction mixture was stirred with an open flask for 5 minutes at room temperature and worked-up and purified as indicated.

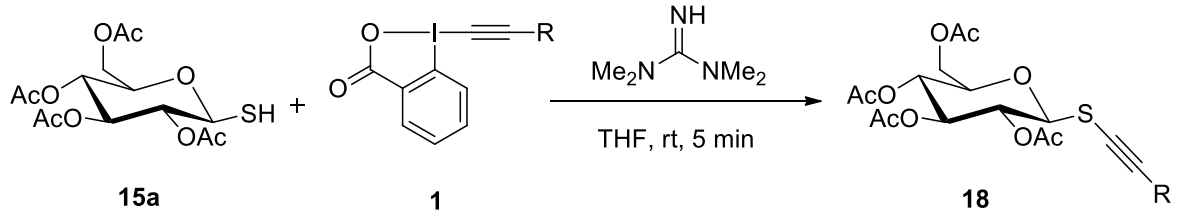
General Procedure B (GPB): Benzene-1,3,5-trithiol Alkynylation



10 **1** **11**

The following general procedure was utilized to alkynylate benzene-1,3,5-trithiol using R-EBX reagents (**1a, 1g,** and **1k**). A 25 mL round bottom flask was charged with a magnetic stirring bar, benzene-1,3,5-trithiol (**10**) (52.3 mg, 0.300 mmol, 1.00 eq.) and triazabicyclodecene (TBD, 125 mg, 0.900 mmol, 3.00 eq.). The mixture was dissolved in THF (5.0 mL) and water (0.5 mL). Upon dissolution, the corresponding R-EBX reagents (**11a-c**, 0.990 mmol, 3.30 eq.) were added as a solid in one portion. The resulting reaction mixture was stirred with an open flask for 5 minutes at room temperature and then quenched by adding water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified as indicated.

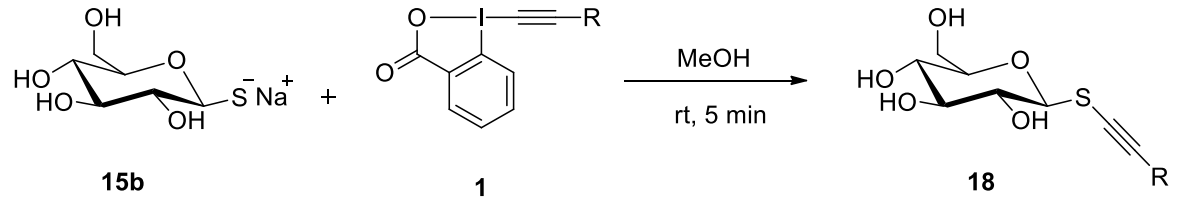
General Procedure C (GPC): Alkynylation of Protected Thioglycosides



15a **1** **18**

A 25 mL round bottom flask was charged with a magnetic stirring bar, thiosugar **15a** (146 mg, 0.400 mmol, 1.00 eq.), TMG (60.0 μL, 0.480 mmol, 1.20 eq.) and THF (5.0 mL). After stirring the resulting solution for 5 minutes at room temperature, R-EBX (**1**) (0.440 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 5 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography.

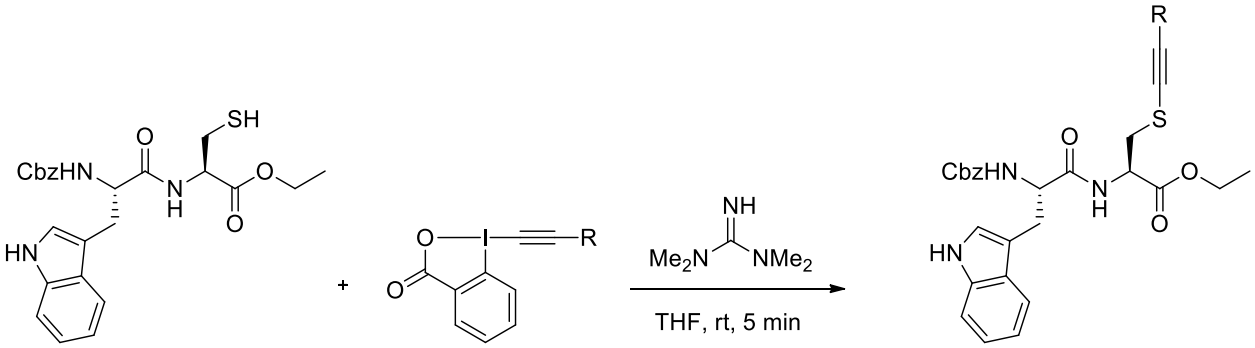
General Procedure D (GPD): Alkynylation of Unprotected Thioglycosides



15b **1** **18**

A 25 mL round bottom flask was charged with a magnetic stirring bar, thiosugar **15b** (87.0 mg, 0.400 mmol, 1.00 eq.) and THF (5.0 mL). After stirring the resulting solution for 5 minutes at room temperature, R-EBX (**1**) (0.440 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 5 minutes at room temperature. Next, the reaction mixture was evaporated under reduced pressure and then crude mixture was washed with 5% aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography.

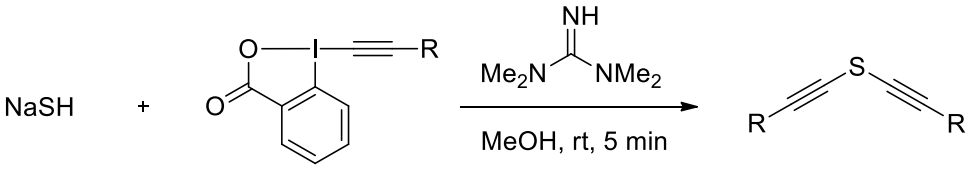
General Procedure E (GPE): Alkynylation of Cysteine Containing Dipeptide 16



16a **1** **19**

A 25 mL round bottom flask was charged with a magnetic stirring bar, TrpCys dipeptide **16** (94.0 mg, 0.200 mmol, 1.00 eq.), TMG (30.0 µL, 0.240 mmol, 1.20 eq.) and THF (5.0 mL). After stirring the resulting solution for 5 minutes at room temperature, R-EBX (**1**) (0.220 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 5 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography.

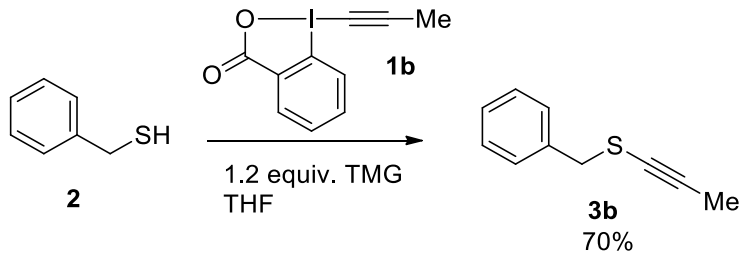
General Procedure F (GPF): Alkynylation of Sodium Hydrogen Sulfide (23)



23 **1** **25**

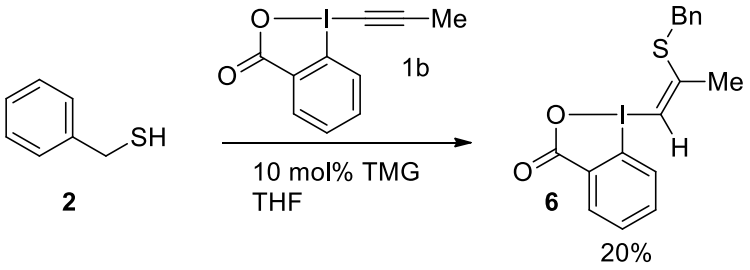
A 25 mL round bottom flask was charged with a magnetic stirring bar, sodium hydrogen sulfide (**23**) (11.2 mg, 0.200 mmol, 1.00 eq.), TMG (60.0 µL, 0.480 mmol, 2.40 eq.) and MeOH (5.0 mL). After stirring the resulting solution for 5 minutes at room temperature, R-EBX (**1**) (0.440 mmol, 2.20 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 5 minutes at room temperature. Next, the reaction mixture was evaporated under reduced pressure and then crude mixture was washed with 5% aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography.

Benzyl(prop-1-yn-1-yl)sulfane (3b)



A 25 mL round bottom flask was charged with a magnetic stirring bar, benzylmercaptane (**2**) (50 mg, 0.40 mmol, 1.00 eq.), TMG (60.0 µL, 0.480 mmol, 1.20 eq.) and THF (5.0 mL). After stirring the resulting solution for 5 minutes at room temperature, Me-EBX (**1b**) (126 mg, 0.440 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 5 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography using pentane as mobile phase affording **3b** (45 mg, 0.28 mmol, 70%) as a colorless oil. Rf (pentane, $KMnO_4$ staining) = 0.47. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.26 (m, 5 H, Ar*H*), 3.90 (s, 2 H, ArCH_2), 1.93 (s, 3 H, CCCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.1, 129.1, 128.6, 127.7, 91.4, 67.4, 40.2, 5.1. IR ν 3062 (w), 3031 (m), 2919 (m), 2850 (w), 1606 (w), 1495 (m), 1450 (s), 1240 (m), 1072 (w), 1028 (w), 768 (s). The characterization data is in accordance with reported literature values.[19]

(*E*)-2-((2-(benzylthio)-2-(triisopropylsilyl)vinyl)iodonio)benzoate (6)

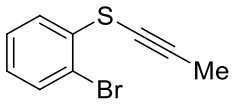


A 25 mL round bottom flask was charged with a magnetic stirring bar, benzylthiol (**2**) (47.0 µL, 0.400 mmol, 1.00 eq.), TMG (5.0 µL, 0.040 mmol, 0.1eq.) and THF (5.0 mL). After stirring the resulting reaction mixture for 5 minutes at room temperature, Me-EBX (126 mg, 0.440 mmol, 1.10 eq.) was added as a solid in one portion. The resulting solution was stirred for 1 h at room temperature. Next, the obtained precipitate was collected and washed several times with hexane and dried under vacuum to afford **6** in 20% yield as a white solid. Melting

[19] Levanova, E. P.; Grabel'nykh, V. A.; Vakhrina, V. S.; Russavskaya, N. V.; Albanov, A. I.; Rozentsveig, I. B.; Korchevin, N. A. *Russ. J. Gen. Chem.* **2014**, *84*, 439.

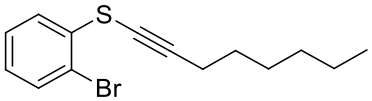
point = 154.1-158.0 °C ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.47 (dd, 1 H, *J* = 7.5, 1.8 Hz, Ar*H*), 7.62 (td, 1 H, *J* = 7.3, 1.0 Hz, Ar*H*), 7.52 (ddd, 1 H, *J* = 8.1, 7.1, 1.8 Hz, Ar*H*), 7.31-7.23 (m, 6 H, Ar*H*), 6.46 (q, 1 H, *J* = 1.3 Hz, alkene H), 4.10 (s, 2 H, ArCH_2), 2.53 (d, 3 H, *J* = 1.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz):[6] δ 166.9, 159.5, 135.9, 133.5, 133.3, 130.8, 129.1, 128.8, 128.1, 125.6, 113.9, 98.1, 37.2, 25.2. IR ν 3430 (w), 3060 (w), 1602 (s), 1550 (m), 1435 (w), 1359 (m), 1227 (w), 1096 (w), 1004 (w), 831 (w), 747 (s). HRMS (ESI) $C_{17}H_{16}IO_2S^+$ $[M+H]^+$ calc. = 410.9910; obs. = 410.9928.

(2-Bromophenyl)(prop-1-yn-1-yl)sulfane (9a)



Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 119 mg, 0.600 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 199:1 as mobile phase affording **9a** (126 mg, 0.555 mmol, 93%) as a clear colorless oil. R_f (pentane) = 0.61. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (dd, 1 H, *J* = 8.0, 1.6 Hz, Ar*H*), 7.47 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.34 (ddd, 1 H, *J* = 8.0, 7.4, 1.3 Hz, Ar*H*), 7.06 (ddd, 1 H, *J* = 7.9, 7.4, 1.6 Hz, Ar*H*), 2.14 (s, 3 H, CCCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.4, 132.6, 128.1, 127.1, 126.8, 119.2, 97.5, 63.7, 5.4. IR ν 3059 (w), 2913 (w), 1563 (w), 1447 (s), 1430 (s), 1104 (w), 1019 (s). HRMS (ESI) $C_9H_8BrS^+$ $[M+H]^+$ calc. = 226.9525; $[M+H]^+$ obs. = 226.9519.

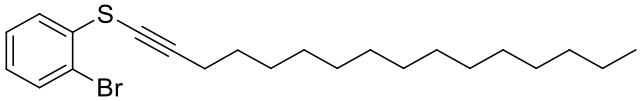
(2-Bromophenyl)(oct-1-yn-1-yl)sulfane (9b)



Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 159 mg, 0.800 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 199:1 as mobile phase affording **9b** (233 mg, 0.784 mmol, 98%) as a clear colorless oil. R_f (pentane) = 0.64. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (dd, 1 H, *J* = 8.0, 1.6 Hz, Ar*H*), 7.48 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.35 (ddd, 1 H, *J* = 8.0, 7.4, 1.3 Hz, Ar*H*), 7.06 (ddd, 1 H, *J* = 7.7, 7.6, 1.6 Hz, Ar*H*), 2.49 (t, 2 H, *J* = 7.1 Hz, CCCH_2), 1.68-1.58 (m, 2 H), 1.52-1.42 (m, 2 H), 1.41-1.26 (m, 4 H), 0.93 (t, 3 H, *J* = 6.9 Hz,

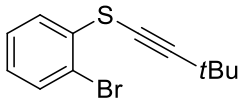
CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.6, 132.6, 128.0, 127.0, 126.7, 119.2, 102.1, 64.5, 31.4, 28.7, 28.6, 22.7, 20.4, 14.2. IR ν 2930 (m), 2858 (w), 1740 (m), 1712 (s), 1447 (s), 1373 (s), 1286 (m), 1253 (m), 1123 (m), 1020 (s), 909 (w). HRMS (ESI) $C_{14}H_{18}BrS^+$ $[M+H]^+$ calc. = 297.0307; $[M+H]^+$ obs. = 297.0297.

(2-Bromophenyl)(hexadec-1-yn-1-yl)sulfane (9c)



Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 100 mg, 0.500 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 499:1 as mobile phase affording **9c** (201 mg, 0.490 mmol, 98%) as a clear colorless oil. R_f (pentane) = 0.71. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (dd, 1 H, *J* = 8.0, 1.6 Hz, Ar*H*), 7.47 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.34 (td, 1 H, *J* = 7.7, 1.4 Hz, Ar*H*), 7.06 (td, 1 H, *J* = 7.7, 1.6 Hz, Ar*H*), 2.48 (t, 2 H, *J* = 7.1 Hz, $CCCH_2CH_2$), 1.63 (p, 2 H, *J* = 7.1 Hz, $CCCH_2CH_2$), 1.51-1.40 (m, 2 H), 1.39-1.20 (m, 20 H), 0.90 (t, 3 H, *J* = 6.8 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz):[9] δ 135.7, 132.6, 128.0, 127.1, 126.8, 119.3, 102.1, 64.5, 32.1, 29.9, 29.8, 29.7, 29.5, 29.3, 29.1, 28.7, 22.9, 20.5, 14.3. IR ν 2923 (s), 2853 (m), 1447 (m), 1429 (w), 1020 (w), 745 (s). HRMS (ESI) $C_{22}H_{34}BrS^+$ $[M+H]^+$ calc. = 409.1559; $[M+H]^+$ obs. = 409.1548.

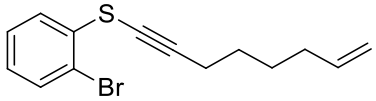
(2-Bromophenyl)(3,3-dimethylbut-1-yn-1-yl)sulfane (9d)



Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 100 mg 0.500 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 499:1 as mobile phase affording **9d** (134 mg, 0.498 mmol, quant.) as a clear colorless oil. R_f (pentane) = 0.85. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (dd, 1 H, *J* = 8.0, 1.6 Hz, Ar*H*), 7.47 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.36 (ddd, 1 H, *J* = 8.0, 7.4, 1.3 Hz, Ar*H*), 7.10-7.02 (m, 1 H, Ar*H*), 1.36 (s, 9 H, *t*Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.7, 132.6, 128.1, 127.1, 126.5, 119.3, 109.7, 63.5, 31.0, 29.2. IR ν 2968 (w), 1575

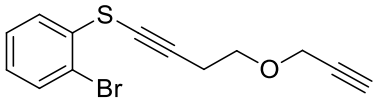
(w), 1446 (s), 1430 (m), 1251 (w), 1019 (m), 745 (s). HRMS (ESI) $C_{12}H_{14}BrS^+$ $[M+H]^+$ calc. = 268.9994; $[M+H]^+$ obs. = 268.9986.

(2-Bromophenyl)(oct-7-en-1-yn-1-yl)sulfane (9e)



Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 100 mg, 0.500 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 299:1 as mobile phase affording **9e** (137 mg, 0.465 mmol, 93%) as a clear colorless oil. R_f (pentane) = 0.69. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (dd, 1 H, *J* = 8.0, 1.6 Hz, Ar*H*), 7.48 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.34 (ddd, 1 H, *J* = 8.0, 7.4, 1.3 Hz, Ar*H*), 7.06 (ddd, 1 H, *J* = 7.7, 7.6, 1.6 Hz, Ar*H*), 5.83 (ddt, 1 H, *J* = 16.9, 10.2, 6.7 Hz, C*H*CH_2), 5.09-4.95 (m, 2 H, CHC*H*$_2$), 2.50 (t, 2 H, *J* = 6.8 Hz, CCC*H*$_2$$CH_2$), 2.16-2.06 (m, 2 H, CH_2), 1.72-1.50 (m, 4 H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.5, 135.6, 132.6, 128.1, 127.1, 126.8, 119.3, 114.9, 101.8, 64.7, 33.3, 28.2, 28.1, 20.3. IR ν 3062 (w), 2859 (w), 1736 (w), 1706 (m), 1447 (m), 1430 (m), 1174 (w), 1019 (m), 912 (m), 745 (s). HRMS (ESI) $C_{14}H_{16}BrS^+$ $[M+H]^+$ calc. = 295.0151; $[M+H]^+$ obs. = 295.0152.

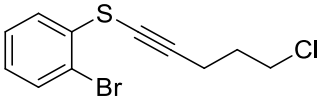
(2-Bromophenyl)(4-(prop-2-yn-1-yloxy)but-1-yn-1-yl)sulfane (9f)



Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 60 mg, 0.30 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 99:1 as mobile phase affording **9f** (84.1 mg, 0.285 mmol, 95%) as a clear colorless oil. R_f (pentane:EtOAc 25:1) = 0.49. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (dd, 1 H, *J* = 8.0, 1.5 Hz, Ar*H*), 7.47 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.35 (ddd, 1 H, *J* = 7.9, 7.4, 1.4 Hz, Ar*H*), 7.06 (ddd, 1 H, *J* = 7.9, 7.4, 1.6 Hz, Ar*H*), 4.22 (d, 2 H, *J* = 2.4 Hz, OC*H*$_2$CCH), 3.74 (t, 2 H, *J* = 6.7 Hz, $CCCH_2C$*H*$_2$O), 2.79 (t, 2 H, *J* = 6.8 Hz, CCC*H*$_2$$CH_2$O), 2.47 (t, 1 H, *J* = 2.4 Hz, OCH_2CC*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.1, 132.6, 128.2, 127.3, 127.0, 119.4, 98.2, 79.5, 74.9, 67.9, 66.3, 58.4, 21.7. IR ν 3294 (w), 2912

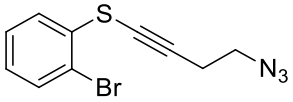
(w), 2869 (w), 1735 (w), 1611 (w), 1447 (m), 1357 (w), 1250 (w), 1102 (s), 1018 (m), 747 (s). HRMS (ESI) $C_{13}H_{12}BrOS^+$ $[M+H]^+$ calc. = 294.9787; $[M+H]^+$ obs. = 294.9783.

(2-Bromophenyl)(5-chloropent-1-yn-1-yl)sulfane (9g)



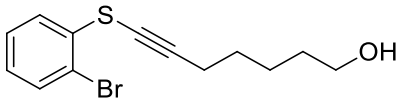
Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 100 mg, 0.500 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 299:1 as mobile phase affording **9g** (126 mg, 0.436 mmol, 87%) as a clear colorless oil. R_f (pentane) = 0.51. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (dd, 1 H, *J* = 8.0, 1.5 Hz, Ar*H*), 7.48 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.36 (ddd, 1 H, *J* = 8.0, 7.4, 1.4 Hz, Ar*H*), 7.07 (ddd, 1 H, *J* = 8.0, 7.4, 1.6 Hz, Ar*H*), 3.70 (t, 2 H, *J* = 6.3 Hz, $CH_2C\mathit{H}_2Cl$), 2.70 (t, 2 H, *J* = 6.8 Hz, $CCC\mathit{H}_2CH_2$), 2.11-2.02 (m, 2 H, $CCCH_2C\mathit{H}_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.1, 132.7, 128.2, 127.3, 126.8, 119.4, 99.7, 66.1, 43.7, 31.2, 17.8. IR ν 2959 (w), 1574 (w), 1446 (s), 1430 (m), 1289 (w), 1019 (m), 746 (s). HRMS (ESI) $C_{11}H_{11}BrClS^+$ $[M+H]^+$ calc. = 288.9448; $[M+H]^+$ obs. = 288.9436.

(4-Azidobut-1-yn-1-yl)(2-bromophenyl)sulfane (9h)



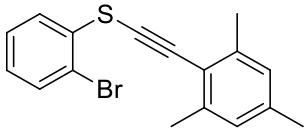
Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 119 mg, 0.600 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 199:1 as mobile phase affording **9h** (153 mg, 0.542 mmol, 90%) as a clear colorless oil. R_f (pentane:EtOAc 30:1) = 0.48. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (dd, 1 H, *J* = 8.0, 1.5 Hz, Ar*H*), 7.49 (dd, 1 H, *J* = 7.9, 1.3 Hz, Ar*H*), 7.36 (ddd, 1 H, *J* = 8.0, 7.4, 1.3 Hz, Ar*H*), 7.08 (ddd, 1 H, *J* = 8.0, 7.4, 1.6 Hz, Ar*H*), 3.51 (t, 2 H, *J* = 6.8 Hz, $CCCH_2C\mathit{H}_2N_3$), 2.77 (t, 2 H, *J* = 6.8 Hz, $CCC\mathit{H}_2CH_2N_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.7, 132.8, 128.2, 127.5, 127.0, 119.5, 97.4, 67.8, 49.9, 21.5. IR ν 2932 (w), 2103 (s), 1574 (w), 1447 (s), 1429 (m), 1301 (w), 1257 (m), 1105 (w), 1018 (m), 744 (s). HRMS (ESI) $C_{10}H_8AgBrN_3S^+$ $[M+Ag]^+$ calc. = 387.8668; $[M+Ag]^+$ obs. = 387.8661.

7-((2-Bromophenyl)thio)hept-6-yn-1-ol (9i)



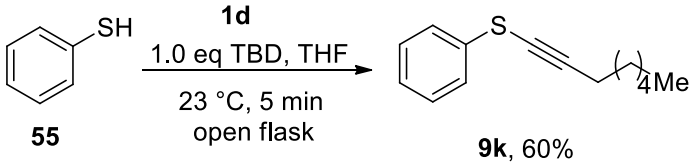
Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 119 mg, 0.600 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 7:2 as mobile phase affording **9i** (175 mg, 0.585 mmol, 98%) as a light yellow oil. R_f (pentane:EtOAc 7:3) = 0.33. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 1 H, *J* = 7.6 Hz, Ar*H*), 7.45 (dd, 1 H, *J* = 7.7 Hz, Ar*H*), 7.33 (t, 1 H, *J* = 7.6 Hz, Ar*H*), 7.04 (td, 1 H, *J* = 7.4 Hz, Ar*H*), 3.65 (t, 2 H, *J* = 5.6 Hz, C*H*$_2$OH), 2.48 (t, 2 H, *J* = 6.7 Hz, CCC*H*$_2$), 1.99 (bs, 1 H, CH_2O*H*), 1.70-1.45 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 132.5, 128.0, 127.1, 126.7, 119.2, 101.7, 64.7, 62.7, 32.2, 28.4, 25.1, 20.4. IR ν 3366 (w), 2938 (w), 2861 (w), 1447 (m), 1430 (w), 1019 (m), 907 (m), 730 (s). HRMS (ESI) $C_{13}H_{15}BrNaOS^+$ $[M+Na]^+$ calc. = 320.9919; $[M+Na]^+$ obs. = 320.9928.

(2-Bromophenyl)(mesitylethynyl)sulfane (9j)



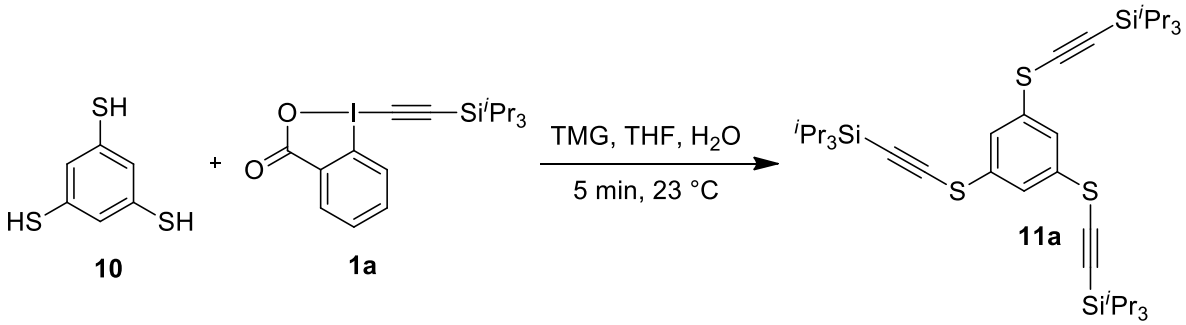
Following general procedure **GPA**, the reaction was carried out using 2-bromothiophenol (**8**, 100 mg, 0.500 mmol). Upon reaction completion, the mixture was concentrated *in vacuo* and purified by flushing the crude oil dissolved in minimum amounts of CH_2Cl_2 through a small plug of silica gel using pentane:EtOAc 499:1 as mobile phase affording **9j** (165 mg, 0.499 mmol, quant.) as a light brown oil. R_f (pentane) = 0.47. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, 1 H, *J* = 7.9 Hz, Ar*H*), 7.55 (d, 1 H, *J* = 7.8 Hz, Ar*H*), 7.39 (t, 1 H, *J* = 7.6 Hz, Ar*H*), 7.18-7.07 (m, 1 H, *J* = 7.4 Hz, Ar*H*), 6.96 (s, 2 H, Ar*H*), 2.52 (s, 6 H, C*H*$_3$), 2.36 (s, 3 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.9, 138.6, 135.4, 132.7, 128.1, 127.8, 127.2, 126.9, 119.4, 119.3, 97.6, 81.2, 21.4, 21.2. IR ν 2914 (w), 2153 (w), 1610 (w), 1574 (w), 1446 (s), 1429 (m), 1019 (s), 852 (m), 744 (s). HRMS (ESI) $C_{17}H_{16}BrS^+$ $[M+H]^+$ calc. = 331.0151; $[M+H]^+$ obs. = 331.0149.

Phenyl(oct-1-yn-1-yl)sulfane (9k)



Benzenethiol (0.522 mL, 5.10 mmol, 1.00 eq.) was dissolved in dry THF (64 mL). Next, TBD (0.700 g, 5.10 mmol, 1.00 eq.) was added and the mixture was stirred for 5 min at room temperature, after which Hex-EBX (**1d**) (2.00 g, 5.61 mmol, 1.10 eq.) was added and the resulting mixture was stirred for 10 min at room temperature. The mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (pentane/EtOAc 1:0 to 100:1) to afford **9k** (0.670 g, 3.08 mmol, 60%) as colorless oil. Rf (pentane/EtOAc 100:1, $KMnO_4$) = 0.98. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.47-7.41 (m, 2 H, Ar*H*), 7.39-7.30 (m, 2 H, Ar*H*), 7.25-7.17 (m, 1 H, Ar*H*), 2.48 (t, *J* = 7.0 Hz, 2 H, CCC*H*$_2$), 1.70-1.57 (m, 2 H, CH_2), 1.55-1.42 (m, 2 H, CH_2), 1.42-1.27 (m, 4 H, CH_2), 0.94 (t, 3 H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.9, 129.1, 126.1, 125.8, 100.2, 64.6, 31.4, 28.7, 28.6, 22.6, 20.4, 14.1. IR ν 2957 (w), 2932 (w), 2859 (w), 2249 (w), 1584 (w), 1479 (w), 1442 (w), 1025 (w), 907 (s), 730 (s), 689 (w). HRMS (ESI) $C_{14}H_{19}S^+$ $[M+H]^+$ calc. = 219.1202; $[M+H]^+$ obs. = 219.1199.

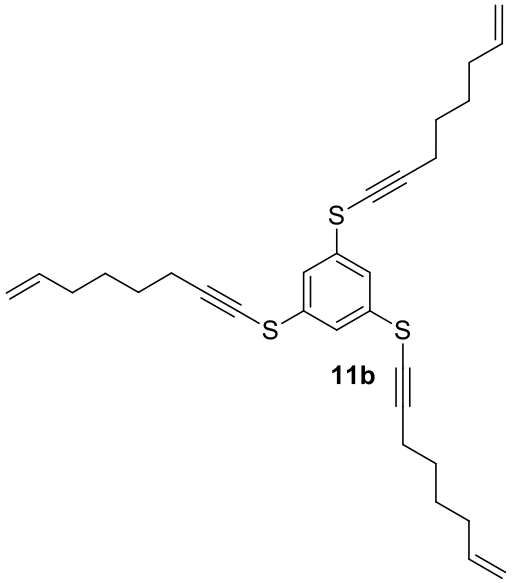
1,3,5-Tris(((triisopropylsilyl)ethynyl)thio)benzene (11a)



Following our recently developed thiol-alkynylation procedure for TIPS-EBX (**1a**),[17] a 25 mL round bottom flask was charged with a magnetic stirring bar, benzene-1,3,5-trithiol (52.3 mg, 0.300 mmol, 1.00 eq.) and 1,1,3,3-tetramethylguanidine (TMG, 137 µL, 1.08 mmol, 3.60 eq.). The mixture was dissolved in THF (5.0 mL) and water (0.5 mL). Upon dissolution, TIPS-EBX (**1a**, 424 mg, 0.990 mmol, 3.30 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred with an open flask for 5 minutes at room temperature and then quenched by adding water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

resulting crude product was purified by column chromatography (pentane) affording **11a** (205 mg, 0.287 mmol, 96%) as a white solid. R_f (pentane) = 0.81. Melting point = 109.1-111.6 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (s, 3 H, Ar*H*), 1.21-1.09 (m, 63 H, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.1, 120.9, 105.5, 89.8, 18.8, 11.5. IR ν 2943 (m), 2865 (m), 2095 (w), 1557 (w), 1463 (w), 996 (w), 882 (s), 858 (s). HRMS (APPI) $C_{39}H_{66}S_3Si_3^+$ $[M]^+$ calc. = 714.3634; $[M]^+$ obs. = 714.3616.

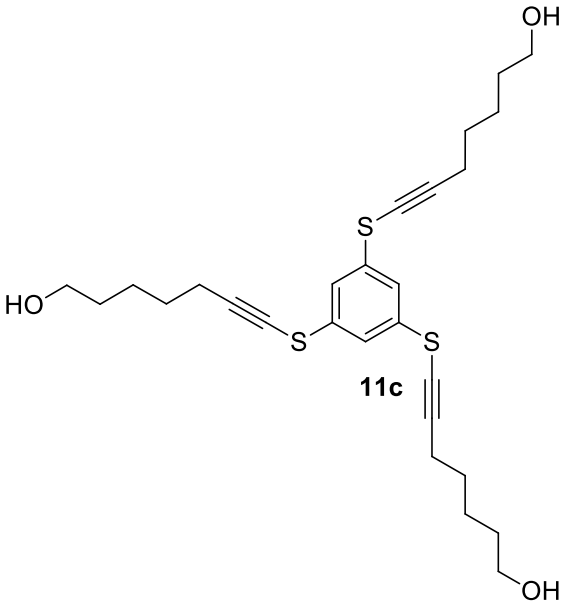
1,3,5-Tris(oct-7-en-1-yn-1-ylthio)benzene (11b)



11b

Following general procedure **GPB**, the crude product was purified by column chromatography (pentane:EtOAc 199:1) affording **11b** (128 mg, 0.260 mmol, 87%) as a colorless oil. R_f (hexane) = 0.79. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (s, 3 H, Ar*H*), 5.81 (ddt, 3 H, *J* = 16.9, 10.2, 6.7 Hz, CH_2CHCH_2), 5.09-4.93 (m, 6 H, CH_2CHCH_2), 2.47 (t, 6 H, *J* = 6.8 Hz, $CCCH_2$), 2.15-2.05 (m, 6 H, CH_2), 1.68-1.49 (m, 12 H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 136.5, 120.2, 114.9, 101.4, 63.9, 33.3, 28.2, 28.1, 20.4. IR ν 3075 (w), 2937 (m), 2862 (m), 2094 (w), 1556 (s), 1411 (m), 994 (m), 912 (s), 840 (m), 786 (m). HRMS (APPI) $C_{30}H_{36}S_3^+$ $[M]^+$ calc. = 492.1979; $[M]^+$ obs. = 492.1977.

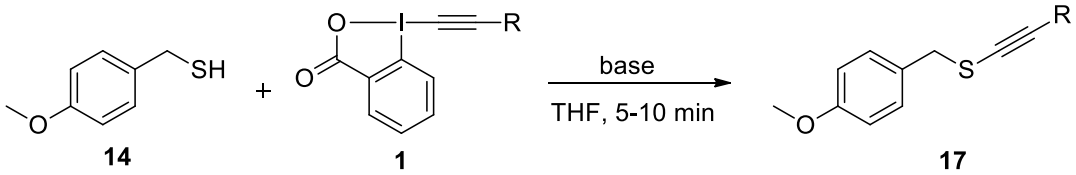
7,7',7''-(Benzene-1,3,5-triyltris(sulfanediyl))tris(hept-6-yn-1-ol) (11c)



11c

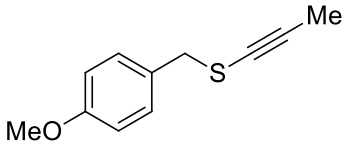
Following general procedure **GPB**, the crude product was purified by column chromatography (EtOAc to EtOAc:MeOH 98:2) affording **11c** (133 mg, 0.264 mmol, 88%) as a colorless oil. R_f (EtOAc) = 0.26. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (s, 3 H, Ar*H*), 3.64 (t, 6 H, *J* = 6.4 Hz, C*H*$_2$OH), 2.46 (t, 6 H, *J* = 7.0 Hz, CCC*H*$_2$), 1.97 (bs, 3 H, O*H*), 1.69-1.44 (m, 18 H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.4, 120.3, 101.4, 63.9, 62.7, 32.3, 28.5, 25.3, 20.5. IR ν 3337 (w), 2937 (w), 2861 (w), 1556 (m), 1411 (w), 1057 (w), 903 (w), 732 (s). HRMS (ESI) $C_{27}H_{36}NaO_3S_3^+$ $[M+Na]^+$ calc. = 527.1719; $[M+H]^+$ obs. = 527.1711.

Alkynylation of (4-methoxyphenyl)methanethiol (14)



14 **1** **17**

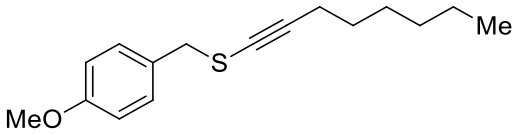
(4-Methoxybenzyl)(prop-1-yn-1-yl)sulfane (17a)



A 25 mL round bottom flask was charged with a magnetic stirring bar, 4-methoxybenzylmercaptane (**14**) (79.0 mg, 0.500 mmol, 1.00 eq.) and dry THF (6.25 mL) at room temperature. The flask was capped with a glass stopper and heated at 40 °C. After 1

minute, the glass stopper was quickly removed and TMG (63.5 μL, 0.500 mmol, 1.00 eq.) was added. The mixture was stirred (capped again) for 30 seconds, after which Me-EBX (**1b**) (157 mg, 0.549 mmol, 1.10 eq.) was added in one portion. The resultant mixture was stirred at 50 °C for exactly 2 minutes. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude was then purified by flash column chromatography using EtOAc:pentane 1:99 as mobile phase affording **17a** (72.8 mg, 0.379 mmol, 77%) as a colorless oil. Rf (EtOAc:pentane 1:24, $KMnO_4$ staining) = 0.24. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.23 (m, 2 H, Ar*H*), 6.93-6.83 (m, 2 H, Ar*H*), 3.88 (s, 2 H, ArC*H*$_2$), 3.81 (s, 3 H, OC*H*$_3$), 1.95 (s, 3 H, CCC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 130.2, 129.1, 114.0, 91.2, 67.6, 55.3, 39.7, 5.1. IR ν 2913 (w), 1610 (m), 1510 (s), 1463 (w), 1302 (w), 1248 (s), 1177 (m), 1034 (m), 832 (m). HRMS (ESI) $C_{11}H_{13}OS^+$ $[M+H]^+$ calc. = 193.0682; $[M+H]^+$ obs. = 193.0684.

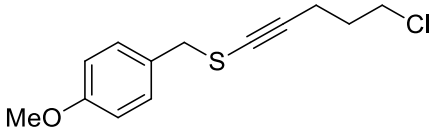
(4-Methoxybenzyl)(oct-1-yn-1-yl)sulfane (17b)



A 25 mL round bottom flask was charged with a magnetic stirring bar, 4-methoxybenzylmercaptane (**44**) (79.0 mg, 0.500 mmol, 1.00 eq.) and dry THF (6.25 mL) at room temperature. The flask was capped with a glass stopper and heated at 40 °C. After 1 minute, the glass stopper was quickly removed and TMG (63.5 μL, 0.500 mmol, 1.00 eq.) was added. The mixture was stirred (capped again) for 30 seconds, after which Hex-EBX (**1d**) (196 mg, 0.550 mmol, 1.10 eq.) was added in one portion. The resultant mixture was stirred at room temperature for 5 minutes. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude was then purified by flash column chromatography using EtOAc:pentane 1:99 as mobile phase affording **17b** (111 mg, 0.422 mmol, 84%) as a colorless oil. Rf (pentane, $KMnO_4$ staining) = 0.31. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26-7.19 (m, 2 H, Ar*H*), 6.87-6.80 (m, 2 H, Ar*H*), 3.84 (s, 2 H, ArC*H*$_2$), 3.77 (s, 3 H, OC*H*$_3$), 2.25 (t, 2 H, *J* = 7.0 Hz, CCC*H*$_2$), 1.50-1.40 (m, 2 H), 1.36-1.18 (m, 6 H), 0.88 (t, 3 H, *J* = 6.9 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 130.2, 129.2, 114.0, 96.0, 68.3, 55.3, 39.9, 31.5, 28.8, 28.6, 22.7, 20.2, 14.2. IR ν 2934 (m), 2857 (w), 1611 (w), 1511

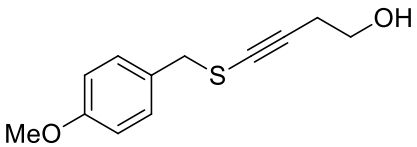
(s), 1463 (w), 1303 (w), 1249 (s), 1176 (w), 1036 (m), 831 (m). HRMS (ESI) $C_{16}H_{23}OS^+$ $[M+H]^+$ calc. = 263.1464; $[M+H]^+$ obs. = 263.1461.

(5-Chloropent-1-yn-1-yl)(4-methoxybenzyl)sulfane (17c)



A 25 mL round bottom flask was charged with a magnetic stirring bar, 4-methoxybenzylmercaptane (**44**) (79.0 mg, 0.500 mmol, 1.0 eq.), DBU (75.0 µL, 0.500 mmol, 1.00 eq.) and dry THF (6.25 mL) at room temperature. After stirring the reaction mixture for 30 seconds at room temperature, ClC_3-EBX (**1j**) (192 mg, 0.550 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 5 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude was then purified by flash column chromatography using EtOAc:pentane 1:99 as mobile phase affording **17c** (97.1 mg, 0.381 mmol, 76%) as a colorless oil. Rf (EtOAc:pentane 1:19, $KMnO_4$ staining) = 0.68. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.21 (m, 2 H, Ar*H*), 6.97-6.82 (m, 2 H, Ar*H*), 3.87 (s, 3 H, OCH_3), 3.82 (s, 2 H, ArCH_2), 3.55 (t, 2 H, *J* = 6.4 Hz, ClCH_2), 2.48 (t, 2 H, *J* = 6.7 Hz, CCCH_2), 1.91 (p, 2 H, *J* = 6.5 Hz, $ClCH_2CH_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 130.2, 128.9, 114.0, 93.8, 69.7, 55.3, 43.7, 39.6, 31.4, 17.6. IR ν 2942 (w), 2865 (w), 2104 (w), 1703 (w), 1600 (m), 1510 (m), 1463 (w), 1255 (s), 1214 (m), 1168 (s), 1032 (m), 886 (s). HRMS (ESI) $C_{13}H_{16}ClOS^+$ $[M+H]^+$ calc. = 255.0605; $[M+H]^+$ obs. = 255.0600.

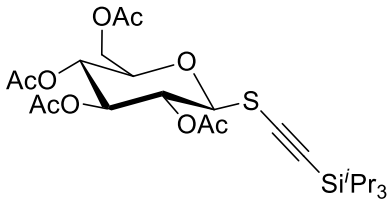
4-((4-Methoxybenzyl)thio)but-3-yn-1-ol (17d)



A 25 mL round bottom flask was charged with a magnetic stirring bar, 4-methoxybenzylmercaptane (**44**) (79.0 mg, 0.500 mmol, 1.00 eq.) and dry THF (6.25 mL) at room temperature. The flask was capped with a glass stopper and heated at 40 °C. After 1 minute, the glass stopper was quickly removed and TMG (63.5 µL, 0.500 mmol, 1.00 eq.) was added. The mixture was stirred (capped again) for 30 seconds, after which OH-ethyl-EBX (**1m**) (174 mg, 0.550 mmol, 1.10 eq.) was added in one portion. It took 10 minutes for

all the OH-ethyl-EBX (**1m**) to dissolve and form a clear reaction mixture. The resultant mixture was stirred at room temperature for 10 minutes. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude was then purified by flash column chromatography using EtOAc:pentane 3:7 as mobile phase affording **17d** (64.8 mg, 0.291 mmol, 59%) as a colorless oil. Rf (EtOAc:pentane 3:7, $KMnO_4$ staining) = 0.45. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.22 (m, 2 H, Ar*H*), 6.91-6.84 (m, 2 H, Ar*H*), 3.88 (s, 2 H, ArC*H*$_2$), 3.81 (s, 3 H, OC*H*$_3$), 3.64 (t, 2 H, *J* = 6.1 Hz, CH_2CH_2OH), 2.54 (t, 2 H, *J* = 6.2 Hz, CCC*H*$_2$), 1.78 (bs, 1 H, CH_2O*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 130.3, 128.9, 114.1, 92.3, 71.0, 61.2, 55.4, 39.6, 24.7. IR ν 3387 (w), 2910 (w), 1610 (m), 1510 (s), 1243 (s), 1177 (m), 1033 (s), 834 (m). HRMS (ESI) $C_{12}H_{15}O_2S^+$ $[M+H]^+$ calc. = 223.0787; $[M+H]^+$ obs. = 223.0784.

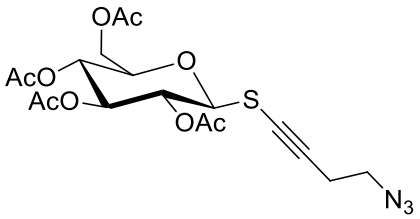
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((trimethylsilyl)ethynyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (18a)



Following general procedure **GPC**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 2:5 as mobile phase affording **18a** (183 mg, 0.336 mmol, 84%) as a white solid. Rf (EtOAc:pentane 2:5, $KMnO_4$ staining) = 0.7. Melting point = 87.2-89.6 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.30-5.17 (m, 2 H, *H*$_2$ & *H*$_3$),[20] 5.09 (dq, 1 H, *J* = 9.6, 5.1, 4.6 Hz, *H*$_4$), 4.61-4.51 (m, 1 H, *H*$_1$), 4.26 (dd, 1 H, *J* = 12.5, 4.8 Hz, *H*$_6$), 4.13 (dd, 1 H, *J* = 12.5, 2.1 Hz, *H*$_6$), 3.76 (ddd, 1 H, *J* = 10.1, 4.7, 2.2 Hz, *H*$_5$), 2.08 (s, 3 H, COC*H*$_3$), 2.07 (s, 3 H, COC*H*$_3$), 2.02 (s, 3 H, COC*H*$_3$), 2.01 (s, 3 H, COC*H*$_3$), 1.12-1.07 (m, 21 H, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.4, 169.4, 169.0, 102.4, 89.0, 85.1, 76.6, 74.0, 70.0, 67.9, 62.1, 20.9, 20.8, 20.8, 20.7, 18.7, 11.4. IR ν 2923 (w), 2863 (w), 2102 (w), 1756 (s), 1742 (s), 1365 (w), 1362 (w), 1231 (s), 1207 (s), 1103 (m), 1053 (s), 914 (w), 884 (w), 860 (w). HRMS (ESI) $C_{25}H_{40}NaO_9SSi^+$ $[M+Na]^+$ calc. = 567.2055; $[M+Na]^+$ obs.= 567.2034.

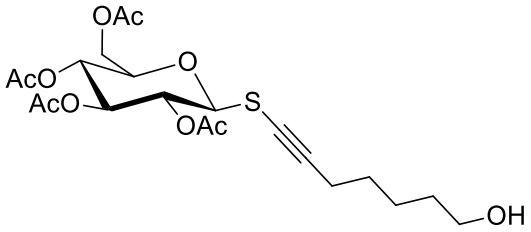
[20] Hydrogens were assigned by analogy with similar compounds reported in the literature : Floyd, N.; Vijayakrishnan, B.; Koeppe, J. R.; Davis, B. G. *Angew. Chem., Int. Ed.***2009**, *48*, 7798.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-azidobut-1-yn-1-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (18b)



Following general procedure **GPC**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 1:2 as mobile phase affording **18b** (81.0 mg, 0.177 mmol, 45%) as a colorless oil. Rf (EtOAc:pentane 1:2, $KMnO_4$ staining) = 0.35. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27-5.18 (m, 2 H, *H*$_3$ & *H*$_2$),[20] 5.15-5.07 (m, 1 H, *H*$_4$), 4.54-4.45 (m, 1 H, *H*$_1$), 4.24 (dd, 1 H, *J* = 12.5, 4.9 Hz, *H*$_6$), 4.13 (dd, 1 H, *J* = 12.5, 2.3 Hz, *H*$_6$), 3.74 (ddd, 1 H, *J* = 10.0, 4.9, 2.3 Hz, *H*$_5$) 3.42 (t, 2 H, *J* = 6.7 Hz, $CH_2CH_2N_3$), 2.62 (t, 2 H *J* = 6.7 Hz, CCC*H*$_2$), 2.07 (s, 3 H, COC*H*$_3$), 2.05 (s, 3 H, COC*H*$_3$), 2.01 (s, 3 H, COC*H*$_3$), 1.99 (s, 3 H, COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.3, 169.4, 169.1, 95.2, 84.1, 76.5, 74.0, 69.6, 67.9, 65.2, 62.1, 49.6, 21.4, 20.8, 20.7, 20.7, 20.7. IR ν 2360 (w), 2111 (w), 1751 (s), 1433 (w), 1370 (m), 1228 (s), 1059 (m), 914 (w). HRMS (ESI) $C_{18}H_{23}N_3NaO_9S^+$ $[M+Na]^+$ calc. = 480.1047; $[M+Na]^+$ obs.= 480.1051.

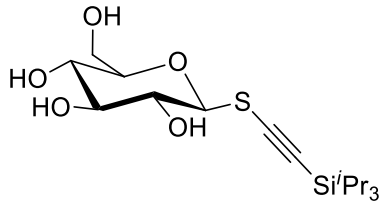
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((7-hydroxyhept-1-yn-1-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (18c)



Following general procedure A, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc: pentane 1:2 as mobile phase affording **18c** (156 mg, 0.328 mmol, 82%) as colorless oil. Rf (EtOAc:pentane 2:1, $KMnO_4$ staining) = 0.5. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.25 (dt, 2 H, *J* = 18.6, 9.3 Hz, *H*$_3$ & *H*$_2$),[20] 5.12 (t,1 H, *J* = 9.6 Hz, *H*$_4$), 4.44 (d, 1 H, *J* = 9.3 Hz, *H*$_1$), 4.26 (dd, 1 H, *J* = 12.4, 4.9 Hz, *H*$_6$), 4.16 (dd, 1 H, *J* = 12.4, 2.2 Hz, *H*$_6$), 3.76 (ddd, 1 H, *J* = 10.0, 4.9, 2.3 Hz, *H*$_5$), 3.67 (t, 2 H, *J* = 6.1 Hz, CH_2CH_2OH), 2.37 (t, 2 H, *J* = 6.4 Hz, CCC*H*$_2$), 2.08 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$), 2.03 (s, 3 H, COC*H*$_3$), 2.01 (s, 3 H, COC*H*$_3$), 1.77 (bs, 1 H, CH_2OH), 1.65-1.46 (m, 6 H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz):[9] δ 170.8, 170.4, 169.7, 169.4, 99.4, 83.9, 76.4, 74.1, 69.7

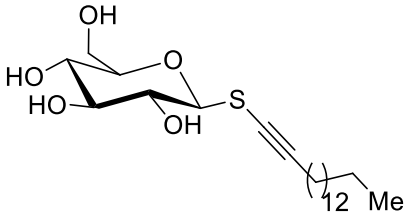
68.0, 62.8, 62.2, 61.9, 32.4, 28.1, 25.1, 20.9, 20.8, 20.8, 20.3. IR ν 2942 (w), 2196 (w), 1756 (s), 1373 (m), 1229 (s), 1053 (m), 915 (w). HRMS (ESI) $C_{21}H_{31}O_{10}S^+$ $[M+H]^+$ calc. = 475.1632; $[M+H]^+$ obs.= 475.1624.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-(((trimethylsilyl)ethynyl)thio)tetrahydro-2H-pyran-3,4,5-triol (18d)



Following general procedure **GPD**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using DCM:methanol 10:1 as mobile phase affording **18d** (122 mg, 0.324 mmol, 81%) as a white solid. Rf (DCM:methanol 10:1, $KMnO_4$ staining) = 0.45. Melting point = 120.1-122.3 °C. ^{1}H NMR (CD_3OD, 400 MHz):[20] δ 4.36 (d, 1 H, *J* = 9.4 Hz, *H*$_1$), 3.87 (dd, 1 H, *J* = 12.1, 2.0 Hz, *H*$_6$), 3.63 (dd, 1 H, *J* = 12.1, 6.1 Hz, *H*$_6$), 3.54 (t, 1 H, *J* = 9.1 Hz, *H*$_2$), 3.40 (t, 1 H, *J* = 8.8 Hz, *H*$_5$), 3.37-3.32 (m , 1 H, *H*$_3$), 3.29-3.22 (m, 1 H, *H*$_4$), 1.17-1.07 (m, 21 H, TIPS). ^{13}C NMR (CD_3OD, 400 MHz): δ 100.9, 93.1, 88.3, 82.8, 79.3, 73.4, 71.3, 63.1, 19.1, 12.6. IR ν 3381 (s), 3256 (m), 2108 (w), 1464 (m), 1367 (w), 1058 (s), 994 (s), 884 (s), 782 (m). HRMS (ESI) $C_{17}H_{32}NaO_5SSi^+$ $[M+Na]^+$ calc. = 399.1632; $[M+Na]^+$ obs.= 399.1632.

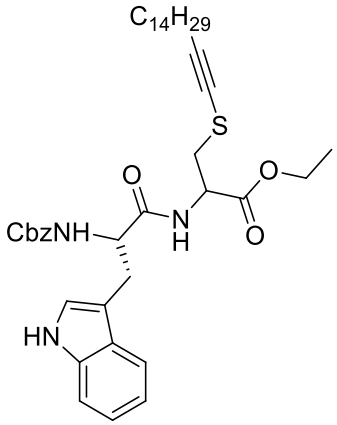
(2*S*,3*R*,4*S*,5*S*,6*R*)-2-(hexadec-1-yn-1-ylthio)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (18e)



Following general procedure GPD, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 10:1 to 20:1 as mobile phase affording **18e** (100 mg, 0.240 mmol, 60%) as a white solid. Rf (EtOAc:pentane 10:1, $KMnO_4$ staining) = 0.22. Melting point = 74.5-77.2 °C. ^{1}H NMR (CD_3OD, 400 MHz): 4.28 (d, 1 H, *J* = 9.2 Hz, *H*$_1$), 3.87 (dd, 1 H, *J* = 12.1, 2.0 Hz, *H*$_6$), 3.66 (dd, 1 H, *J* = 12.1, 5.5 Hz, *H*$_6$), 3.47 (t, 1 H, *J* = 9.0 Hz, *H*$_2$), 3.39 (t, 1 H, *J* = 8.6 Hz, *H*$_5$), 3.36-3.32 (m, 1 H, *H*$_3$), 3.30-3.25 (m, 1

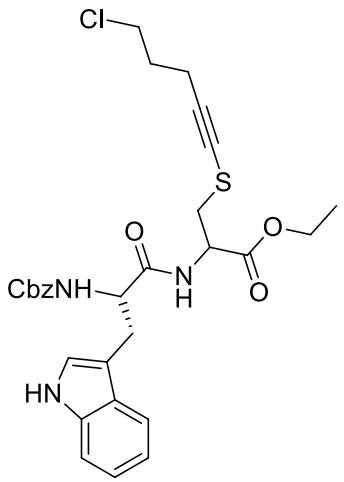
H, H_4)[17], 2.32 (t, J = 6.9 Hz, 2H, CCCH_2CH$_2$), 1.52 (dt, 2 H, J = 14.1, 6.7 Hz, CCCH$_2$CH_2), 1.47-1.34 (m, 2 H), 1.36-1.22 (m, 20 H), 0.90 (t, 3 H, J = 6.8 Hz, CH$_2$CH_3). ^{13}C NMR (CD$_3$OD, 400 MHz):[9] δ 98.2, 88.1, 82.6, 79.4, 73.3, 71.3, 65.0, 62.9, 33.1, 30.8, 30.8, 30.7, 30.5, 30.3, 30.0, 29.8, 23.8, 21.0, 14.4. IR ν 3363 (m), 2937 (s), 2842 (m), 2189 (w), 1636 (w), 1455 (m), 1046 (s), 760 (s). HRMS (ESI) $C_{22}H_{41}O_5S^+$ $[M+H]^+$ calc. = 417.2669; $[M+H]^+$ obs.= 417.2672.

Ethyl 2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)-3-(hexadec-1-yn-1-ylthio)propanoate (19a)



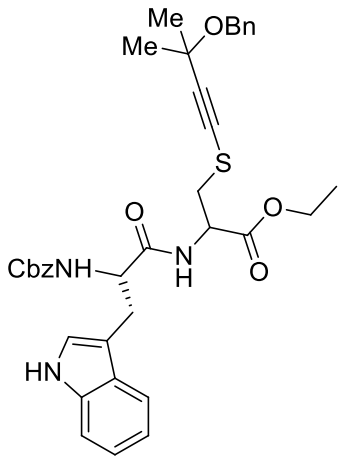
Following general procedure **GPE**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 2:5 as mobile phase affording **19a** (114 mg, 0.165 mmol, 83%) as a white solid. Rf (EtOAc:pentane 2:5, $KMnO_4$ staining) = 0.42. Melting point = 129.0-131.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1 H), 7.68 (d, 1 H, J = 7.9 Hz), 7.42-7.29 (m, 6 H), 7.19 (t, 1 H, J = 7.6 Hz), 7.15-7.01 (m, 2 H), 6.60 (d, 1 H, J = 7.4 Hz), 5.50 (d, 1 H, J = 8.0 Hz), 5.18-5.07 (m, 2 H), 4.80-4.70 (m, 1 H), 4.56 (s, 1 H), 4.28-4.00 (m, 2 H), 3.40 (d, 1 H, J = 13.4 Hz), 3.20 (dd, 1 H, J = 14.6, 7.4 Hz), 3.03 (d, 2 H, J = 4.8 Hz), 2.07 (t, 2 H, J = 7.1 Hz, CCCH_2CH$_2$), 1.44-1.35 (m, 2 H), 1.33-1.19 (m, 25 H), 0.88 (t, 3 H, J = 6.6 Hz, CH$_2$CH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz):[9] δ 171.1, 169.4, 156.0, 136.4, 136.3, 128.7, 128.3, 128.2, 127.6, 123.6, 122.5, 120.0, 118.9, 111.4, 110.4, 95.0, 67.2, 67.0, 62.0, 55.6, 52.4, 37.3, 32.1, 29.8, 29.8, 29.7, 29.5, 29.3, 29.0, 28.8, 28.7, 22.8, 20.0, 14.3, 14.2. IR ν 3300 (m), 2923 (s), 2853 (w), 1724 (m), 1652 (m), 1544 (s), 1461 (w), 1254 (m), 1043 (w). HRMS (ESI) $C_{40}H_{56}N_3O_5S^+$ $[M+H]^+$ calc. = 690.3935; $[M+H]^+$ obs.= 690.3945.

Ethyl 2-((*S*)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)-3-((5-chloropent-1-yn-1-yl)thio)propanoate (19b)



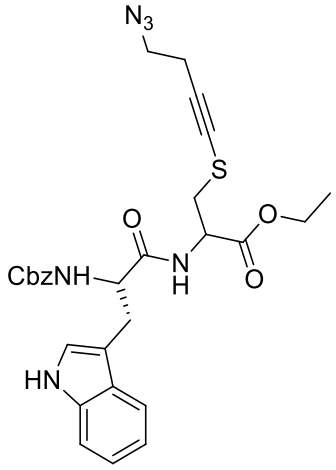
Following general procedure **GPE**, The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 1:2 to 1:1 as mobile phase affording **19b** (77.0 mg, 0.135 mmol, 68%) as a white solid. Rf (EtOAc:pentane 1:2, $KMnO_4$ staining) = 0.2. Melting point = 141.3-143.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1 H), 7.65 (d, 1 H, *J* = 7.9 Hz), 7.39-7.29 (m, 6 H), 7.18 (ddd, I H, *J* = 8.1, 6.9, 1.2 Hz), 7.13-7.02 (m, 2 H), 6.67 (d, 1 H, *J* = 7.5 Hz), 5.56 (d, 1 H, *J* = 7.8 Hz), 5.15-5.09 (m, 2 H), 4.76 (dt, 1 H, *J* = 7.5, 4.9 Hz), 4.57 (d, 1 H, *J* = 7.5 Hz), 4.27-4.02 (m, 2 H), 3.53 (t, 2 H, *J* = 6.3 Hz, $CH_2C\mathit{H}_2Cl$), 3.38 (dd, 1 H, *J* = 14.9, 5.2 Hz), 3.20 (dd, 1 H, *J* = 14.5, 7.3 Hz), 3.07-2-95 (m, 2 H), 2.28 (t, 2 H, *J* = 6.8 Hz, $CCC\mathit{H}_2CH_2$), 1.82 (p, 2 H, *J* = 6.6 Hz, $CCCH_2C\mathit{H}_2$), 1.26 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2C\mathit{H}_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 169.4, 156.0, 136.4, 136.3, 128.6, 128.3, 128.2, 127.5, 123.6, 122.4, 119.9, 118.8, 111.4, 110.2, 92.7, 68.6, 67.2, 62.1, 55.6, 52.3, 43.7, 37.2, 31.2, 28.6, 17.4, 14.1. IR ν 3061 (w), 2955 (w), 1716 (s), 1672 (s), 1513 (s), 1453 (m), 1343 (m), 1223 (s), 1031 (m), 748 (s). HRMS (ESI) $C_{29}H_{32}ClN_3NaO_5S^+$ $[M+Na]^+$ clac. = 592.1643; $[M+Na]^+$ obs.= 592.1637.

Ethyl 3-((3-(benzyloxy)-3-methylbut-1-yn-1-yl)thio)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)propanoate (19c)



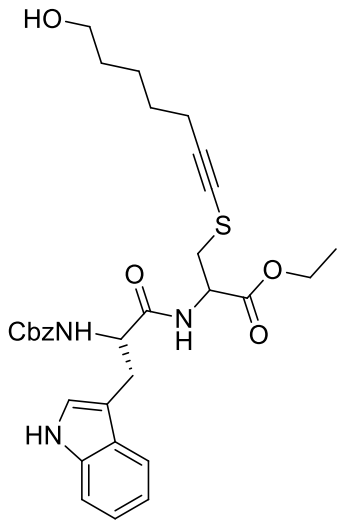
Following general procedure **GPE**, The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 1:3 as mobile phase affording **19c** (104 mg, 0.162 mmol, 81%) as a light yellow oil. Rf (EtOAc:pentane 2:5, $KMnO_4$ staining) = 0.24. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1 H), 7.66 (d, 1 H, *J* = 7.9 Hz), 7.43-7.25 (m, 11 H), 7.20 (t, 1 H, *J* = 7.4, 1.2 Hz), 7.12 (t, 1 H, *J* = 7.5 Hz), 7.05 (s, 1 H), 6.62 (d, 1 H, *J* = 7.6 Hz), 5.55 (d, 1 H, *J* = 7.0 Hz), 5.18-5.11 (m, 2 H), 4.75 (dt, 1 H, *J* = 7.3, 5.2 Hz), 4.62-4.51 (m, 3 H), 4.24-4.10 (m, 2 H), 3.45-3.30 (m, 1 H), 3.21 (dd, 1 H, *J* = 14.6, 7.3 Hz), 3.15-3.00 (m, 2 H), 1.53 (s, 6 H, 2 x C*H*$_3$), 1.25 (t, 3 H, *J* = 7.2 Hz, $CO_2CH_2CH_3$).^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 169.3, 156.0, 139.0, 136.3, 136.2, 128.6, 128.4, 128.3, 128.2, 127.8, 127.5, 123.5, 122.4, 119.9, 118.8, 111.4, 110.1, 96.4, 73.2, 71.4, 67.2, 66.5, 62.1, 55.6, 51.9, 37.6, 28.9, 28.8, 28.5, 14.1. IR ν 3322 (m), 3061 (w), 2984 (m), 2935 (w), 2167 (w), 1709 (s), 1668 (s), 1498 (s), 1457 (m), 1232 (s), 1149 (s), 1051 (s), 746 (s). HRMS (ESI) $C_{36}H_{40}N_3O_6S^+$ $[M+H]^+$ calc. = 642.2632; $[M+H]^+$ obs.= 642.2610.

Ethyl 3-((4-azidobut-1-yn-1-yl)thio)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)propanoate (19d)



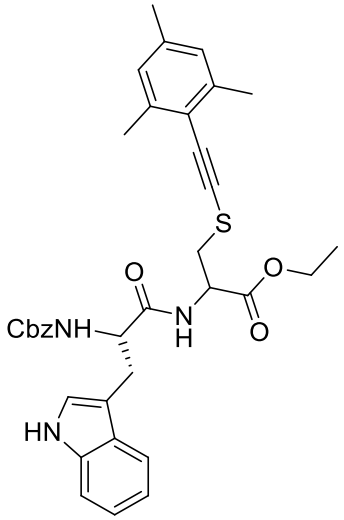
Following general procedure **GPE**, The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 2:3 as mobile phase affording **19d** (67 mg, 0.12 mmol, 60%) as a light yellow color solid. Rf (EtOAc:pentane 2:3, $KMnO_4$ staining) = 0.5. Melting point = 112.1-115.3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 1 H), 7.68 (d, 1 H, *J* = 7.2 Hz), 7.42-7.28 (m, 6 H), 7.19 (ddd, 1 H, *J* = 8.2, 7.1, 1.2 Hz), 7.15-7.05 (m, 2 H), 6.59 (d, 1 H, *J* = 7.5 Hz), 5.54 (d, 1 H, *J* = 7.9 Hz), 5.17-5.07 (m, 2 H), 4.78 (dt, 1 H, *J* = 7.5, 4.9 Hz), 4.57 (d, 1 H, *J* = 7.0 Hz), 4.25-4.03 (m, 2 H), 3.45-3.35 (m, 1 H), 3.26-3.16 (m, 3 H), 3.13-2.96 (m, 2 H), 2.33 (t, 2 H, *J* = 6.7 Hz, CCC*H*$_2$CH$_2$N$_3$), 1.26 (t, 3 H, *J* = 7.1 Hz, CO$_2$CH$_2$C*H*$_3$).^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 169.3, 156.0, 136.4, 136.3, 128.6, 128.3, 128.2, 127.6, 123.7, 122.4, 119.9, 118.8, 111.4, 110.2, 90.6, 70.4, 67.2, 62.1, 55.6, 52.5, 49.7, 36.9, 28.7, 20.9, 14.2. IR ν 3324 (w), 2929 (w), 2076 (w), 1718 (m), 1672 (m), 1512 (m), 1220 (m), 778 (s). HRMS (ESI) $C_{28}H_{30}N_6NaO_5S^+$ $[M+Na]^+$ calc. = 585.1891; $[M+Na]^+$ obs.= 585.1897.

Ethyl 2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)-3-((7-hydroxyhept-1-yn-1-yl)thio)propanoate (19e)



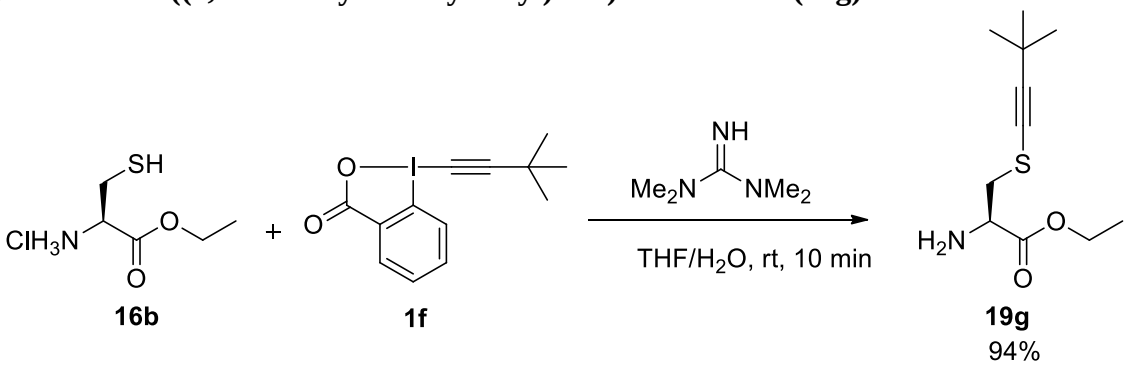
Following general procedure **GPE**, The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 2:1 as mobile phase affording **19e** (84.0 mg, 0.145 mmol, 73%) as a white solid. Rf (EtOAc:pentane 2:1, $KMnO_4$ staining) = 0.59. Melting point = 123.5-124.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1 H), 7.68 (d, 1 H, *J* = 7.9 Hz), 7.40-7.28 (m, 6 H), 7.18 (t, 1 H, *J* = 7.5 Hz), 7.15-7.05 (m, 2 H), 6.65 (d, 1 H, *J* = 7.1 Hz), 5.59 (d, 1 H, *J* = 7.9 Hz), 5.17-5.08 (m, 2 H), 4.76 (dt, 1 H, *J* = 7.5, 5.2 Hz), 4.56 (d, 1 H, *J* = 6.7 Hz), 4.23-4.08 (m, 2 H), 3.62 (t, 2 H, *J* = 6.2 Hz, C*H*$_2$OH), 3.44-3.28 (m, 1 H), 3.20 (dd, 1 H, *J* = 14.6, 7.5 Hz), 3.10-2.91 (m, 2 H), 2.22 – 2.05 (m, 2 H, CCC*H*$_2$), 1.77 (bs, 1 H, CH$_2$O*H*), 1.52 (p, 2 H, *J* = 6.6 Hz), 1.47-1.35 (m, 4 H), 1.25 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.3, 169.5, 156.1, 136.4, 136.3, 128.7, 128.3, 128.2, 127.6, 123.7, 122.4, 119.9, 118.9, 111.4, 110.3, 94.9, 67.4, 67.2, 62.7, 62.1, 55.6, 52.5, 37.1, 32.2, 28.7, 28.2, 25.0, 20.0, 14.2. IR ν 3340 (w), 2938 (w), 1731 (s), 1671 (s), 1512 (m), 1218 (m), 1032 (w), 752 (s). HRMS (ESI) $C_{31}H_{38}N_3O_6S^+$ $[M+H]^+$ calc. = 580.2476; $[M+H]^+$ obs.= 580.2472.

Ethyl 2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(1H-indol-3-yl)propanamido)-3-((mesitylethynyl)thio)propanoate (19f)



Following general procedure **GPE**, The crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 1:2 as mobile phase affording **19f** (98 mg, 0.16 mmol, 80%) as a white solid. Rf (EtOAc:pentane 1:2, $KMnO_4$ staining) = 0.32. Melting point = 147.0-149.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (s, 1 H), 7.61 (d, 1 H, *J* = 7.9 Hz), 7.39-7.29 (m, 6 H), 7.18 (ddd, 1 H, *J* = 8.1, 7.0, 1.2 Hz), 7.09 (t, 1 H, *J* = 7.5 Hz), 7.01 (s, 1 H), 6.83 (s, 2 H), 6.76 (d, 1 H, *J* = 7.3 Hz), 5.46 (d, 1 H, *J* = 7.7 Hz), 5.14-5.04 (m, 2 H), 4.81 (dt, 1 H, *J* = 7.3, 5.0 Hz), 4.57 (d, 1 H, *J* = 6.8 Hz), 4.18-3.85 (m, 2 H), 3.38-3.27 (m, 1 H), 3.27-3.06 (m, 3 H), 2.34 (s, 6 H, 2 x ArC*H*$_3$), 2.26 (s, 3 H, ArC*H*$_3$), 1.17 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): 171.3, 169.4, 156.0, 140.8, 138.1, 136.3, 136.3, 128.6, 128.3, 128.2, 127.8, 127.5, 123.4, 122.4, 119.9, 119.8, 118.8, 111.4, 110.2, 91.1, 84.4, 67.2, 62.1, 55.7, 52.2, 38.2, 28.4, 21.4, 21.1, 14.0. IR ν 3301 (m), 2161 (w), 1729 (m), 1692 (m), 1646 (s), 1536 (s), 1250 (s), 1041 (m), 904 (s), 853 (w). HRMS (ESI) $C_{35}H_{38}N_3O_5S^+$ $[M+H]^+$ calc. = 612.2527; $[M+H]^+$ obs.= 612.2538.

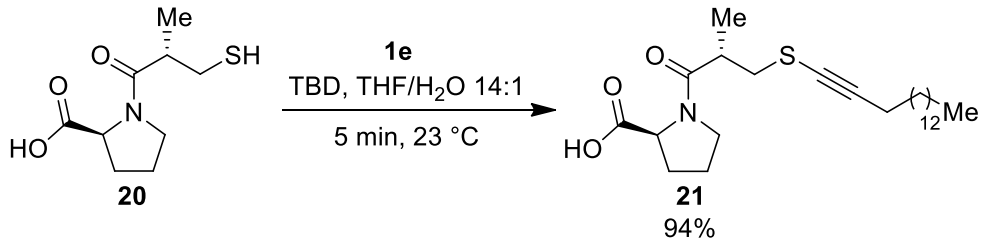
(R)-2-Amino-1-((3,3-dimethylbut-1-yn-1-yl)thio)hexan-3-one (19g)



A 25 mL round bottom flask was charged with a magnetic stirring bar, L-cysteine ethyl ester hydrochloride (**16b**) (74.3 mg, 0.400 mmol, 1.00 eq.), TMG (110 µL, 0.880 mmol, 2.20 eq.),

THF (5.0 mL) and water (0.5 mL). After stirring the resulting solution for 5 minutes at room temperature, ^{t}Bu-EBX (**1f**) (131 mg, 0.400 mmol, 1.00 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 10 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography using EtOAc:pentane 1:1 as mobile phase affording **19g** (86.0 mg, 0.375 mmol, 94%) as a colorless oil. Rf (EtOAc:pentane 1:1, $KMnO_4$ staining) = 0.48. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.20 (q, 2 H, *J* = 7.1 Hz, COC*H*$_2$CH$_3$), 3.79 (dd, 1 H, *J* = 8.2, 4.2 Hz, C*H*CH$_2$S), 3.12 (dd, 1 H, *J* = 13.2, 4.2 Hz, CHC*H*$_2$S), 2.75 (dd, 1 H, *J* = 13.2, 8.2 Hz, CHC*H*$_2$S), 1.88 (s, 2 H, N*H*$_2$), 1.28 (t, 3 H, J = 7.1 Hz, CH$_2$C*H*$_3$), 1.20 (s, 9 H, C(C*H*$_3$)$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 102.9, 66.0, 61.5, 54.2, 40.6, 31.0, 28.8, 14.3. IR 3386 (w), 2972 (m), 2869 (w), 2362 (w), 1738 (s), 1598 (w), 1459 (w), 1368 (w), 1251 (s), 1191 (s), 1107 (w), 1030 (m), 859 (w). HRMS (ESI) $C_{11}H_{20}NO_2S^+$ $[M+H]^+$ calc. = 230.1209; $[M+H]^+$ obs.= 230.1212.

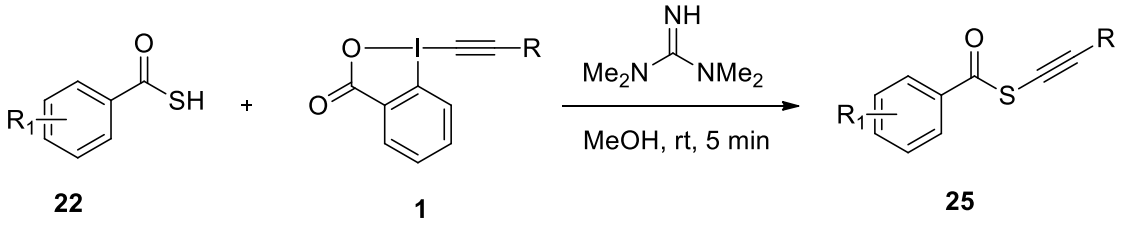
(S)-1-((S)-3-(Hexadec-1-yn-1-ylthio)-2-methylpropanoyl)pyrrolidine-2-carboxylic acid (21)



A 25 mL round bottom flask was charged with a magnetic stirring bar, captopril (**20**) (130 mg, 0.600 mmol, 1.00 eq.) and triazabicyclodecene (TBD, 167 mg, 0.600 mmol, 1.00 eq.). The mixture was dissolved in THF (7.0 mL) and water (0.5 mL) to achieve a thiol concentration of 80 mM. Upon dissolution, the corresponding R-EBX reagent (**1e**, 309 mg, 0.660 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred in an open flask for 5 minutes at room temperature and then quenched by adding 1.0 M aq. HCl (15 mL). The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (pentane:EtOAc 20:1 to 7:3) affording **21** (247 mg, 0.563 mmol, 94%) as a white solid. R_f (pentane:EtOAc 1:1 and 1% acetic acid) = 0.37. Melting point = 60.4-63.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.0 (bs, 1 H, COO*H*), 4.58 (dd, 1 H, *J* = 7.9, 3.5 Hz, NC*H*), 3.78-3.69 (m, 1 H, CH$_2$N), 3.68-3.59 (m, 1 H, CH$_2$N), 3.14-

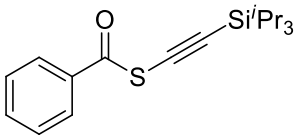
3.03 (m, 1 H), 2.91 (dd, 1 H, *J* = 13.0, 8.8 Hz, CHC*H*$_2$S), 2.67 (dd, 1 H, *J* = 13.0, 5.4 Hz, CHC*H*$_2$S), 2.26 (t, 2 H, *J* = 7.0 Hz, CCC*H*$_2$CH$_2$), 2.23-1.96 (m, 4 H), 1.47 (p, 2 H, *J* = 7.0 Hz, CCCH$_2$C*H*$_2$), 1.40-1.14 (m, 25 H), 0.85 (t, 3 H, *J* = 6.7 Hz, CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz):[9] δ 175.4, 174.5, 95.0, 68.0, 59.4, 47.6, 38.5, 38.2, 32.0, 29.8, 29.7, 29.4, 29.2, 29.0, 28.9, 28.3, 24.9, 22.8, 20.2, 16.9, 14.2. IR ν 2927 (w), 2855 (w), 1722 (w), 1633 (w), 1465 (w), 1442 (w), 1195 (w), 908 (s), 732 (s). HRMS (ESI) $C_{25}H_{44}NO_3S^+$ $[M+H]^+$ calc. = 438.3036; $[M+H]^+$ obs. = 438.3032.

Alkynylation of Thioacids



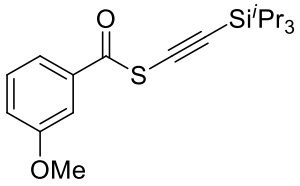
22 **1** **25**

S-((Triisopropylsilyl)ethynyl) benzothioate (24a)



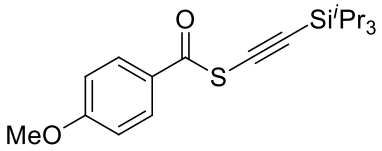
Benzothioic acid (**22a**) (100 mg, 0.707 mmol, 1.00 eq.) was dissolved in dry THF (9 mL) and TIPS-EBX (**1c**) (300 mg, 0.707 mmol, 1.00 eq.) was added to the solution. The resulting mixture was stirred for 20 minutes at room temperature. Next, the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (pentane) to afford **24a** (213 mg, 0.668 mmol, 94%) as a yellow oil. Rf (pentane/EtOAc 10:1, $KMnO_4$) = 0.76. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96-7.79 (m, 1 H, Ar*H*), 7.67-7.55 (m, 2 H, Ar*H*), 7.52-7.38 (m, 2 H, Ar*H*), 1.15 (m, 21 H, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.5, 135.4, 134.3, 129.0, 127.4, 109.4, 85.8, 18.6, 11.3. IR ν 2943 (w), 2866 (w), 2105 (w), 1704 (m), 1462 (w), 1203 (m), 1178 (w), 884 (s), 859 (s), 735 (m), 675 (s). HRMS (ESI) $C_{18}H_{27}OSSi^+$ $[M+H]^+$ calc. =319.1546; $[M+H]^+$ obs. = 319.1532.

S-((Triisopropylsilyl)ethynyl) 3-methoxybenzothioate (24b)



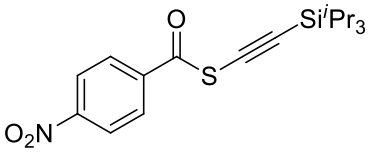
3-Methoxybenzothioic acid (**22b**) (100 mg, 0.594 mmol, 1.00 eq.) was dissolved in dry THF (8 mL) and TIPS-EBX (**1a**) (255 mg, 0.594 mmol, 1.00 eq.) was added to the solution. The resulting mixture was stirred for 4 h at room temperature. Next, the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (pentane/EtOAc 99:1 to 5:1) to afford **24b** (167 mg, 0.479 mmol, 80%) as a colorless oil. Rf (pentane/EtOAc 5:1, $KMnO_4$) = 0.81. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49-7.41 (m, 1 H, Ar*H*), 7.37 (t, *J* = 1.3 Hz, 1 H, Ar*H*), 7.37-7.33 (m, 1 H, Ar*H*), 7.13 (ddd, *J* = 8.3, 2.7, 1.1 Hz, 1 H, Ar*H*), 3.82 (s, 3 H, OC*H*$_3$), 1.16 (m, 21 H, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.2, 156.0, 136.6, 130.0, 120.8, 119.9, 111.5, 109.3, 86.0, 55.4, 18.6, 11.3. IR ν 2945(w), 2867 (w), 2255 (w), 2106 (w), 1702 (w), 1464 (w), 1264 (w), 906 (s), 728 (s). HRMS (ESI) $C_{19}H_{29}O_2SSi^+$ $[M+H]^+$ calc. =349.1652; $[M+H]^+$ obs. = 349.1655.

S-((Triisopropylsilyl)ethynyl) 4-methoxybenzothioate (24c)



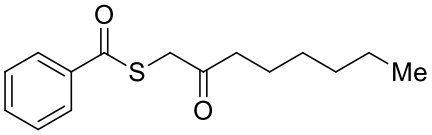
4-Methoxybenzothioic acid (**22c**) (93.0 mg, 0.400 mmol, 1.00 eq.) was dissolved in dry THF (5.0 mL) and TIPS-EBX (**1a**) (171 mg, 0.400 mmol, 1.00 eq.) was added to the solution. The resulting mixture was stirred for 1 h at room temperature. Next, the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (pentane/EtOAc 99:1 to 5:1) to afford **24c** (123 mg, 0.353 mmol, 88%) as a colorless oil. Rf (pentane/EtOAc 19:1, $KMnO_4$) = 0.8. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.79 (m, 2 H, Ar*H*), 6.97-6.88 (m, 2 H, Ar*H*), 3.85 (s, 3 H, OC*H*$_3$), 1.21-1.09 (m, 21 H, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.6, 164.6, 129.8, 128.1, 114.3, 108.8, 86.4, 55.7, 18.7, 11.4. IR ν 2944 (w), 2866 (w), 2105 (w), 1703 (m), 1600 (m), 1508 (w), 1463 (w), 1265 (m), 1214 (m), 1168 (s), 1030 (w), 886 (s), 859 (s). HRMS (ESI) $C_{19}H_{28}NaO_2SSi^+$ $[M+Na]^+$ calc. = 371.1471; $[M+Na]^+$ obs. = 371.1479.

S-((Triisopropylsilyl)ethynyl) 4-nitrobenzothioate (24d)



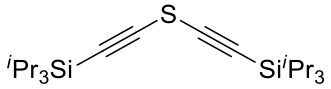
4-Nitrobenzothioic acid (**22d**) (81.0 mg, 0.400 mmol, 1.00 eq.) was dissolved in dry THF (5.0 mL) and TIPS-EBX (**1a**) (171 mg, 0.400 mmol, 1.00 eq.) was added to the solution. The resulting mixture was stirred for 1 h at room temperature. Next, the mixture was concentrated under reduced pressure. The crude oil was purified by flash chromatography (pentane/EtOAc 99:1 to 5:1) to afford **24d** (135 mg, 0.371 mmol, 93%) as colorless oil. Rf (pentane/EtOAc 19:1, $KMnO_4$) = 0.81. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36-8.30 (m, 2 H, Ar*H*), 8.07-8.00 (m, 2 H, Ar*H*), 1.20-1.05 (m, 21 H, TIPS). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.8, 151.0, 139.9, 128.5, 124.4, 111.4, 84.0, 18.7, 11.3. IR ν 2945 (w), 2866 (w), 2108 (w), 1705 (m), 1531 (m), 1351 (m), 1194 (m), 900 (m), 860 (s), 844 (s). HRMS (ESI) $C_{18}H_{25}AgNO_3SSi^+$ $[M+Ag]^+$ calc. = 470.0370; $[M+Ag]^+$ obs. = 470.0385.

S-(2-oxooctyl) benzothioate (26)



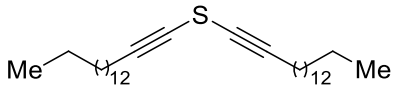
Benzothioic acid (**22a**) (100 mg, 0.740 mmol, 1.00 eq.) was dissolved in dry THF (9.5 mL) and Hex-EBX **(1d**) (260 mg, 0.740 mmol, 1.00 eq.) was added. The resulting mixture was stirred for 20 minutes at room temperature. Next, the mixture was concentrated under reduced pressure and purified by column chromatography (pentane/EtOAc 99:1) to afford the **26** (90.0 mg, 0.330 mmol, 45%) as a yellow light oil. R_f = (pentane/EtOAc 9:1) = 0.4. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-7.88 (m, 2 H, Ar*H*), 7.64-7.49 (m, 1 H, Ar*H*), 7.50-7.37 (m, 2 H, Ar*H*), 3.91 (s, 2 H, SC*H*$_2$CO), 2.60 (t, *J* = 7.4 Hz, 2 H, COC*H*$_2$), 1.76-1.43 (m, 2 H), 1.39-1.15 (m, 6 H), 0.86 (t, 3 H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.2, 190.5, 136.2, 133.8, 128.7, 127.4, 41.8, 38.9, 31.5, 28.8, 23.8, 22.5, 14.0. IR ν 2929 (w), 2857 (w), 1719 (w), 1664 (s), 1450 (w), 1208 (s), 1177 (w), 914 (s), 774 (m), 688 (s), 649 (m). HRMS (ESI) $C_{15}H_{21}O_2S^+$ $[M+H]^+$ calc. = 265.1257; $[M+H]^+$ obs. = 265.1256.

Bis((triisopropylsilyl)ethynyl)sulfane (25a)



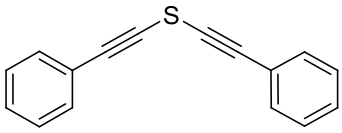
Following general procedure **GPF**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using pentane affording **25a** (60.0 mg, 0.152 mmol, 76%) as a colorless oil. Rf (pentane, $KMnO_4$ staining) = 0.85. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.07 (s, 42 H, TIPS).^{13}C NMR ($CDCl_3$, 100 MHz): δ 100.6, 87.9, 18.7, 11.4. IR ν 2944 (m), 2862 (m), 2099 (w), 1464 (w), 989 (w), 883 (m), 844 (s). HRMS (ESI) $C_{22}H_{43}SSi_2^+$ $[M+H]^+$ calc. = 395.2619; $[M+H]^+$ obs. = 395.2601.

Di(hexadec-1-yn-1-yl)sulfane (25b)



Following general procedure **GPF**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using pentane affording **25b** (62.0 mg, 0.131 mmol, 66%) as a white solid. Rf (pentane, $KMnO_4$ staining) = 0.8. Melting point = 35.2-37.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.30 (t, 4 H, *J* = 7.1 Hz, CCC*H*$_2$CH$_2$), 1.52 (p, 4 H, *J* = 7.3 Hz, CCCH$_2$C*H*$_2$), 1.43-1.31 (m, 4 H), 1.29-1.22 (m, 40 H), 0.88 (t, 6 H, *J* = 6.8 Hz, CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz):[9] δ 96.4, 62.6, 32.1, 29.9, 29.8, 29.8, 29.8, 29.7, 29.5, 29.3, 29.0, 28.5, 22.9, 20.2, 14.3. IR ν 2931 (s), 2853 (s), 2200 (w), 1466 (m), 722 (w). HRMS (ESI) $C_{32}H_{58}S$ [M+] calc. = 474.4259; [M+] obs. = 474.4250.

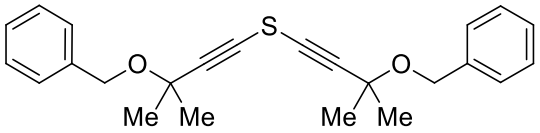
Bis(phenylethynyl)sulfane (25c)



Following general procedure **GPF**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using pentane affording **25c** (14 mg, 0.060 mmol, 30%) as a colorless oil. Rf (pentane, $KMnO_4$ staining) = 0.77. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.43 (m, 4 H, Ar*H*), 7.38-7.29 (m, 6 H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 132.1, 129.2, 128.5, 122.3, 94.8, 72.1. IR ν 3060 (w), 2925 (s), 2854 (m), 2176 (w), 1597 (w), 1489 (s), 1444 (m).The characterization data is in accordance with reported literature values.[21]

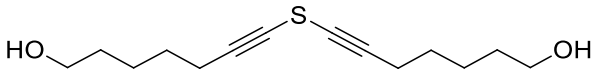
Bis(3-(benzyloxy)-3-methylbut-1-yn-1-yl)sulfane (25d)

[21] Voets, M.; Smet, M.; Dehaen, W. *J. Chem. Soc., Perkins Trans. 1* **1999**, 1473.



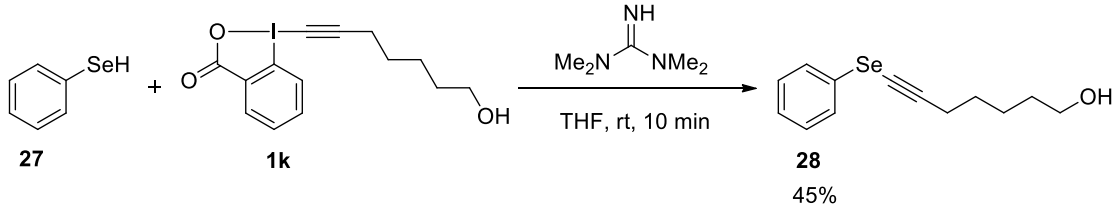
Following general procedure **GPF**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 1:50 as mobile phase affording **25d** (56.0 mg, 0.148 mmol, 74%) as a colorless oil. Rf (EtOAc:pentane 1:60 $KMnO_4$ staining) = 0.5. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.23 (m, 8 H, Ar*H*), 7.22-7.16 (m, 2 H, Ar*H*), 4.54 (s, 4 H, 2 x ArCH_2), 1.59 (s, 12 H, 4 x CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.8, 128.5, 127.9, 127.6, 97.9, 71.5, 68.0, 66.9, 28.6. IR ν 2986 (m), 2170 (w), 1735 (w), 1470 (w), 1462 (w), 1382 (m), 1234 (m), 1156 (s), 1055 (s), 900 (m), 738 (s). HRMS (ESI) $C_{24}H_{26}O_2S$ [M+] calc. = 378.1654; [M+] obs. = 378.1653.

7,7'-thiobis(hept-6-yn-1-ol) (25e)



Following general procedure **GPF**, the crude reaction mixture was concentrated in vacuo and purified by flash chromatography using EtOAc:pentane 1:1 as mobile phase affording **25e** (41.0 mg, 0.162 mmol, 81%) as a light yellow solid. Rf (EtOAc:pentane 1:1, $KMnO_4$ staining) = 0.16. Melting point = 37.2-39.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.64 (t, 4 H, *J* = 6.4 Hz, CH_2OH), 2.33 (t, 4 H, *J* = 6.8 Hz, CCC$H_2$$CH_2$), 1.64 (bs, 2 H, CH_2O*H*), 1.61-1.51 (m, 8 H), 1.51-1.42 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 96.1, 62.9, 62.9, 32.3, 28.1, 25.1, 20.2. IR ν 3350 (m), 2937 (s), 2862 (s), 2195 (w), 1731 (w), 1459 (m), 1329 (m), 1058 (s), 757 (m). HRMS (ESI) $C_{14}H_{22}NaO_2S^+$ $[M+Na]^+$ calc. = 277.1233; $[M+Na]^+$ obs. = 277.1237.

7-(Phenylselanyl)hept-6-yn-1-ol(28)

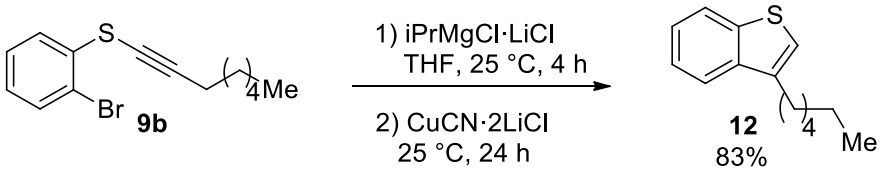


27 **1k** **28**
45%

A 25 mL round bottom flask was charged with a magnetic stirring bar, benzeneselenol (**27**) (42.0 μL, 0.400 mmol, 1.00 eq.), TMG (60.0 μL, 0.480 mmol, 1.20 eq.) and THF (5.0 mL). After stirring the resulting solution for 5 minutes at room temperature, C_5-OH-EBX (**1k**) (158 mg, 0.440 mmol, 1.10 eq.) was added as a solid in one portion. The resulting reaction mixture was stirred for 10 minutes at room temperature. Next, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude oil was purified by flash chromatography using EtOAc:pentane 1:2 as mobile phase affording **28** (45.0 mg, 0.178 mmol, 45%) as a colorless oil. Rf (EtOAc:pentane 1:2, $KMnO_4$ staining) = 0.58. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48-7.40 (m, 2 H, Ar*H*), 7.26-7.20 (m, 2 H, Ar*H*), 7.20-7.13 (m, 1 H, Ar*H*), 3.58 (t, 2 H, *J* = 6.4 Hz, CH_2CH_2OH), 2.40 (t, 2 H, *J* = 6.9 Hz, $CCCH_2CH_2$), 1.60-1.48 (m, 4 H), 1.48-1.39 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 129.5, 129.4, 128.7, 126.9, 104.4, 62.9, 57.9, 32.3, 28.6, 25.1, 20.7. IR ν 3356 (m), 3066 (w), 2944 (m), 2861 (m), 2180 (w), 1583 (w), 1477 (m), 1438 (m), 1328 (w), 1068 (m), 1024 (m), 736 (s). HRMS (ESI) $C_{13}H_{17}OSe^+$ $[M+H]^+$ calc. = 269.0439; $[M+H]^+$ obs.= 269.0445.

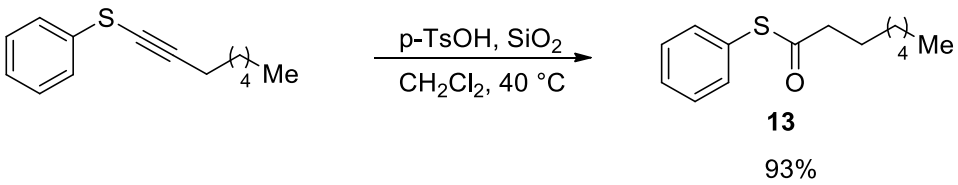
6. Transformation of Thioalkynes

3-Hexyl-benzothiophene (12)



Following a slightly modified procedure,[22] the bromide **9b** (230 mg, 0.774 mmol, 1.00 eq.) was added to a flame-dried 25 mL round bottom flask and dissolved in dry THF (1.55 mL). To the clear colorless solution was added 2.0 M ^{i}PrMgCl·LiCl in THF (426 µL) at room temperature under nitrogen and the light yellow reaction mixture was stirred at room temperature for 4 h. Next, a solution of the copper catalyst (1.0 M, 232 µL, 0.232 mmol, 0.300 eq. prepared from 66.6 mg of CuCN, 63.0 mg of LiCl in 0.74 mL of dry THF) was added dropwise *via* a syringe. The light yellow reaction mixture was further stirred for 24 h at room temperature under nitrogen. The reaction mixture was cooled to 0 °C using an ice/water bath and quenched with half sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography using pentane affording **12** (140 mg, 0.642 mmol, 83%) as a colorless oil. Rf (pentane) = 0.75. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91-7.86 (m, 1 H, Ar*H*), 7.80-7.75 (m, 1 H, Ar*H*), 7.44-7.33 (m, 2 H, Ar*H*), 7.09 (s, 1 H, Ar*H*), 2.89-2.82 (m, 2 H, ArCH_2), 1.82-1.72 (m, 2 H), 1.50-1.29 (m, 6 H), 0.97-0.89 (m, 3 H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.6, 139.3, 137.4, 124.2, 123.8, 123.0, 121.9, 120.9, 31.9, 29.4, 29.3, 28.7, 22.8, 14.3. IR ν 2926 (s), 2856 (m), 1460 (m), 1429 (m), 843 (w). HRMS (ESI) $C_{14}H_{19}S^+$ $[M+H]^+$ calc. = 219.1202; $[M+H]^+$ obs. = 219.1204.

S-phenyl octanethioate (13)



Following a reported procedure,[23] octynyl(phenyl)sulfane (87.0 mg, 0.400 mmol, 1.00 eq.) and *p*-TsOH (84.0 mg, 0.440 mmol, 1.00 eq.) were dissolved in dry DCM (2 mL) to which

[22] Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 1958.
[23] Braga, A. L.; Martins, T. L. C.; Silveira, C. C.; Rodrigues, O. E. D. *Tetrahedron* **2001**, *57*, 3297.

0.4 g of silica gel was added. The resulting suspension was heated at 40 °C and stirred for 10 h (after 1 h the color of the mixture became orange). Then, DCM (5 mL) was added and the silica gel was removed by filtration and the mixture was concentrated under reduced pressure. The crude oil was purified by column chromatography (pentane/EtOAc 15:1) to afford **13** (97.0 mg, 0.411 mmol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63-7.42 (m, 5 H, Ar*H*), 2.66 (t, 2 H, C*H*$_2$CO), 1.80-1.66 (m, 2 H), 1.49-1.15 (m, 8 H), 0.91 (t, 3 H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz,): δ 197.5, 134.5, 129.3, 129.1, 128.0, 43.7, 31.6, 29.5, 28.5, 25.6, 22.6, 14.1. The characterization data is in accordance with reported literature values.[24]

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