

Unconventional Reactivity of Ethynylbenziodoxolone (EBX) Reagents and Thiols: Scope and Mechanism

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Abstract: 1,2-Dithio-1-alkenes are biologically active molecules widely implemented throughout organic synthesis, functional materials, coordination chemistry, and pharmaceuticals. Traditional methods for accessing 1,2-dithio-1-alkenes often demand transition metal catalysts, specialized or air-sensitive ligands, high temperatures, and disulfides (R_2S_2). Here, a general and efficient strategy utilizing ethynylbenziodoxolone (EBX) reagents and thiols is presented which results in the formation of 1,2-dithio-1-alkenes with excellent regioselectivity and stereoselectivity through unprecedented reactivity between the EBX and the thiol. This operationally simple procedure utilizes mild conditions, resulting in a broad substrate scope and high functional group tolerance. The observed and unexpected reactivity has been rationalized through both experimental results and density functional theory (DFT) calculations.

Introduction

Multisubstituted olefins are valuable building blocks and precursors in organic chemistry.^[1] 1,2-Dithio-1-alkenes are an example of these compounds that have found widespread application in organic synthesis,^[2] functional materials,^[3] coordination chemistry,^[4] and in pharmaceuticals (Figure 1d).^[5] Despite their synthetic utility, approaches for the synthesis of 1,2-dithio-1-alkenes leave room for improvement. Palladium,^[6] rhodium,^[7] and nickel^[8a] catalysts have been employed extensively to promote the additions of disulfides (R_2S_2) to terminal alkynes, forming (Z)-1,2-dithio-1-alkenes. Functional group tolerance is limited in these systems as these systems require relatively sensitive catalysts, disulfides (R_2S_2), or harsh conditions. As such, the development of a mild, general, and versatile strategy tolerant to a range of functional groups is therefore highly desirable.

Ethynylbenziodoxol(on)es (EBXs)^[9] have demonstrated their utility as electrophilic alkynylation reagents that readily engage a range of carbon,^[10] sulfur,^[11] nitrogen,^[12] and phosphorus^[13] nucleophiles. Other reactions involving EBX reagents have also been pursued, including the Pd(II)-catalyzed transformation of

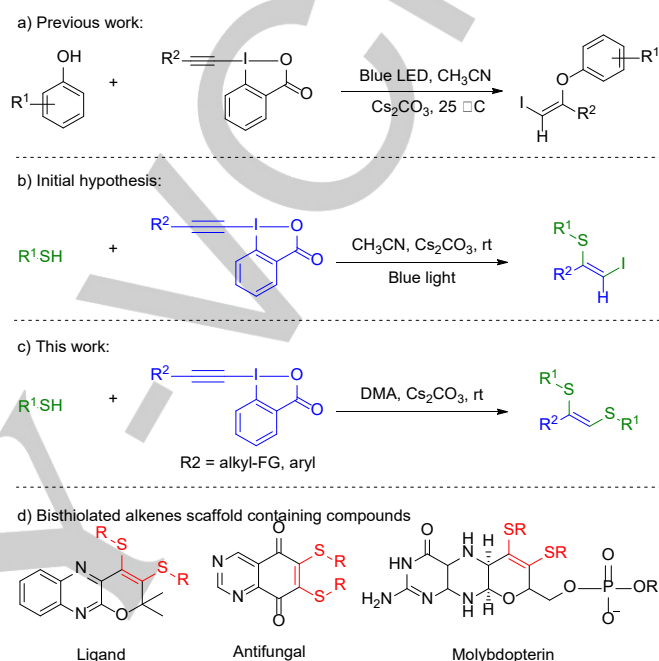


Figure 1. (a) Reaction of EBX reagents and phenols under visible light irradiation. (b) Initial hypothesis: Reactions of EBX reagents and thiols to form (Z)-2-iodovinyl phenyl thioethers. (c) This work: Reaction of EBX reagents and thiols to form (Z)-1,2-dithio-1-alkenes. (d) Examples of bis-thiolated alkene scaffold containing compounds.

alkynylbenziodoxoles with *N*-aryl imines and carboxylic acids^[14] and copper-catalyzed oxyalkynylation of diazo compounds.^[15] Although several effective methods have been reported for the transformation of EBX reagents, the vast majority of these focus on the use of the EBX as an alkynylation agent. In contrast, the addition of two equivalents of a (pro)-nucleophile to the electrophilic C–C triple bond of EBX is widely underdeveloped. Herein, we describe the discovery and development of this mode of reactivity between EBX reagents and thiols where two equivalents of thiol add to the C–C triple bond to produce (Z)-1,2-bis-thiolated alkene derivatives (Figure 1c). Experimental and computational mechanistic studies indicate that *cis* regioselectivity observed in the final products is through *cis*-selective nucleophilic RSH addition followed by a *cis*-specific radical RSH addition. This reaction constitutes a powerful alternative to traditional processes for producing multisubstituted olefins and can enable the rapid construction of molecular complexity.

Our interest in visible light-driven and transition metal free chemistry^[16] recently led to the development of a visible-light-promoted reaction of phenols and EBX reagents in the presence of Cs_2CO_3 to form (Z)-2-iodovinyl phenyl ethers (Figure 1a). This

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transformation occurs via the formation of an electron donor-acceptor (EDA) complex in which an electron is transferred from the phenoxide anion to the vinylbenziodoxolone.^[17] We also previously disclosed that thiophenoxide can act as an electron donor under visible light irradiation, forming an EDA complex with aryl halides en route to the construction of C–S bonds.^[18] Based on these previous electron donor-acceptor protocols, we questioned whether it would be possible to access (Z)-2-iodovinyl phenyl thioethers from EBX reagents by using thiophenols as the electron donor (**Figure 1b**).

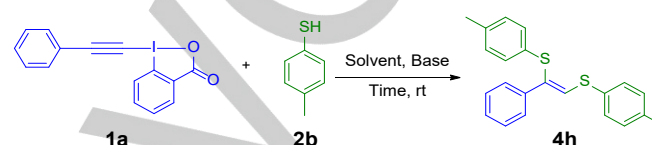
Results and Discussion

A principal concern in the development of the targeted process was the competitive reaction between thiols and EBX reagents to form thio-alkynes.^[11] To investigate the feasibility of our hypothesis, we examined similar conditions to our previously reported reaction between EBX and phenols (1.5 equiv **2b**, 1.5 equiv Cs₂CO₃ in 0.01 M CH₃CN under blue light irradiation at room temperature) (Table 1, entry 1).^[16] Contrary to our expectation, the unexpected dithioalkene product **4h** was obtained on the basis of crude ¹H NMR analysis. Compared to thio-alkynylation products obtained in previous EBX reactions,^[11] this product is indicative of a new and complementary mode of reactivity. Subsequently, we observed substantial improvement in the yield of **4h** by improving the loading of **2b** to 4.0 equiv. (entry 2). However, control experiments revealed that the desired product was also detected in good yield (entry 3) in the absence of blue light irradiation or in complete darkness (entries 3 and 8). Upon further investigation, we identified *N,N*-dimethylacetamide or *N,N*-dimethylformamide as optimal solvents (Table 1, entries 7, 9, 10, 14–17), and employed 4.0 equivalents of **2b** with Cs₂CO₃ as base to achieve good yields (entries 7, 11–13). In screening other bases, we observed reduced yields with triazabicyclodecene, Na₂CO₃, and K₂CO₃ (entry 6, 9–10, 18). Notably, 85% yield of product was achieved in the presence of water (Table S1, entry 14). We employed high purity bases, including Cs₂CO₃ (99.995%) and K₂CO₃ (99.995%), and observed similarly high yields, suggesting that trace impurities are not responsible for this transformation (Table S1, entry 20–21).

Encouraged by these initial results, we investigated the scope of reactivity with respect to the EBX reagent. As shown in **Scheme 1**, mercaptobenzothiazoles reacted with a variety of aromatic and functionalized alkyl-EBX reagents. *Para*-methyl substituted Ph-EBX is tolerated, affording the desired product in 71% yield, while presence of a methyl substituent at the *ortho* position of the aryl ring significantly reduced the yield (**3c**, **3d**). Substrates with either electron-withdrawing groups (cyano, ester, aldehyde, bromo and trifluoromethyl) or electron-donating groups (methyl and methoxy) underwent transformation efficiently to afford the corresponding (Z)-1,2-bis(arylthio)alkene derivatives (**3b**, **3e–3i**) in good yields (69–92%). Furthermore, the functional group tolerance of the alkyl-EBX reagents was highlighted by the successful synthesis of (Z)-1,2-bis(arylthio)alkenes bearing

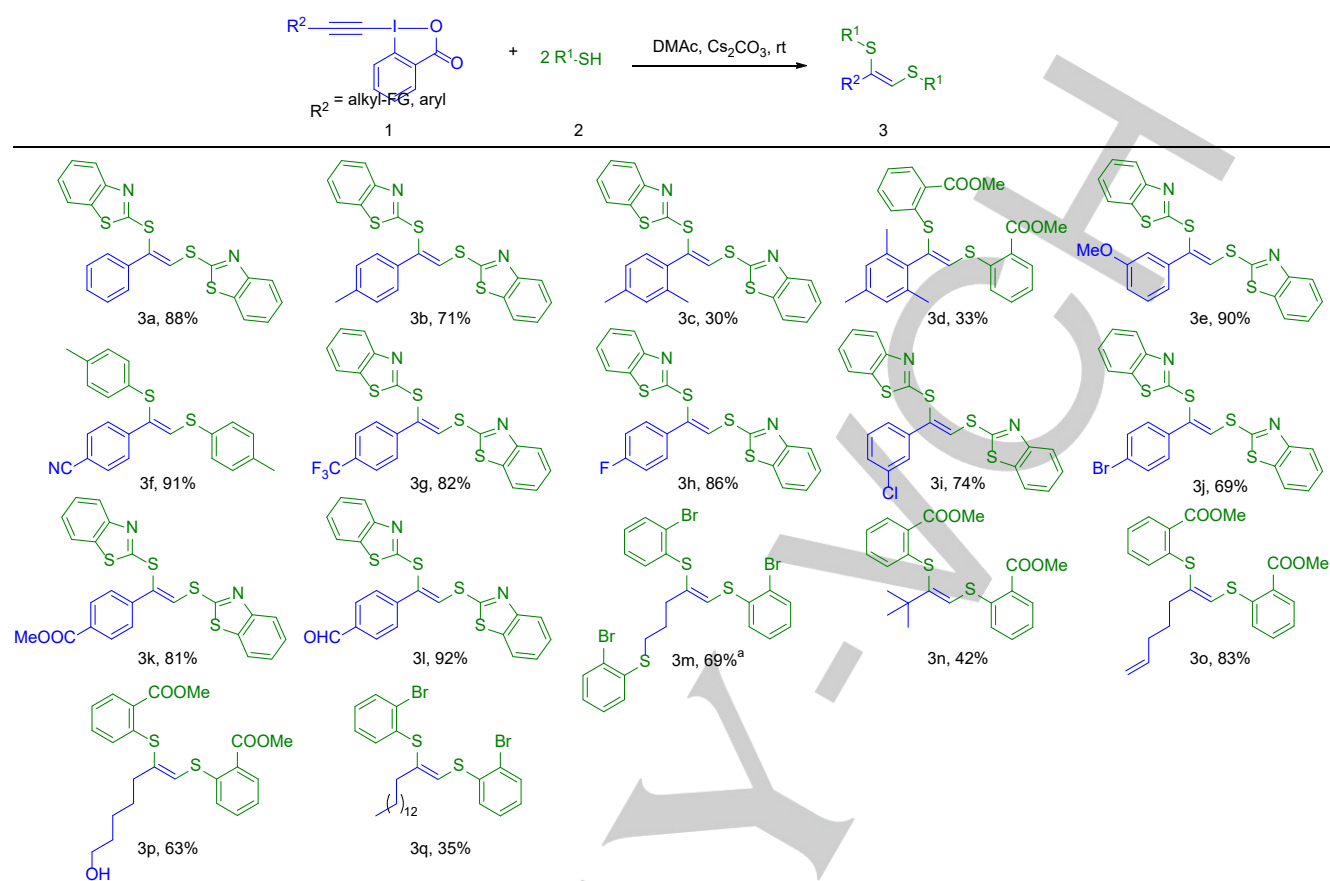
hydroxy and alkene groups in 63% and 83% yield, respectively (**3o**, **3p**). However, presence of a chlorine atom on the alkyl-EBX led to substitution by an aromatic thiol (**3m**). In addition, *t*-butyl and tetradecyl-EBX reacted with methyl thiosalicylate to form the corresponding product in 42% and 35% yield, respectively (**3n**, **3q**). Importantly, all EBX reagents give the desired bithiolated alkenes with Z-selectivity. Markedly, the thio-alkyne product could be isolated with triisopropylsilyl-EBXs under the standard reaction conditions (see SI pS14). The configuration of **3c–d**, **3m–p** was determined by using nuclear Overhauser effect spectroscopy (NOESY) analysis (see SI, pS4).

Table 1. Summary of Reaction discovery and optimization.



Entry	T (h)	Eq (2b)	Solvent	Base	Yield (%)
1	10	1.5	CH ₃ CN	Cs ₂ CO ₃	40 ^[a]
2	10	4.0	CH ₃ CN	Cs ₂ CO ₃	78 ^[a]
3	10	4.0	CH ₃ CN	Cs ₂ CO ₃	75 ^[b]
4	10	4.0	DMAc	Cs ₂ CO ₃	96
5	10	4.0	DMAc	Cs ₂ CO ₃	65 ^[c]
6	10	4.0	DMAc	TBD	86
7	1.0	4.0	DMAc	Cs ₂ CO ₃	95(93 ^[d])
8	1.0	4.0	DMAc	Cs ₂ CO ₃	81 ^[b]
9	1.0	4.0	DMAc	Na ₂ CO ₃	71
10	1.0	4.0	DMAc	K ₂ CO ₃	82
11	1.0	1.0	DMAc	Cs ₂ CO ₃	30
12	1.0	2.0	DMAc	Cs ₂ CO ₃	70
13	1.0	3.0	DMAc	Cs ₂ CO ₃	77
14	1.0	4.0	DMF	Cs ₂ CO ₃	98
15	1.0	4.0	DMSO	Cs ₂ CO ₃	86
16	1.0	4.0	CH ₃ CN	Cs ₂ CO ₃	64
17	1.0	4.0	THF	Cs ₂ CO ₃	60
18	1.0	4.0	THF	TBD	40

Reaction conditions: Room temperature, N₂. Yields are based on **2b**, determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. ^[a] Under blue light; ^[b] protected from light with foil; ^[c] under air; ^[d] Isolated yield; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DMAc, *N,N*-dimethylacetamide; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran.

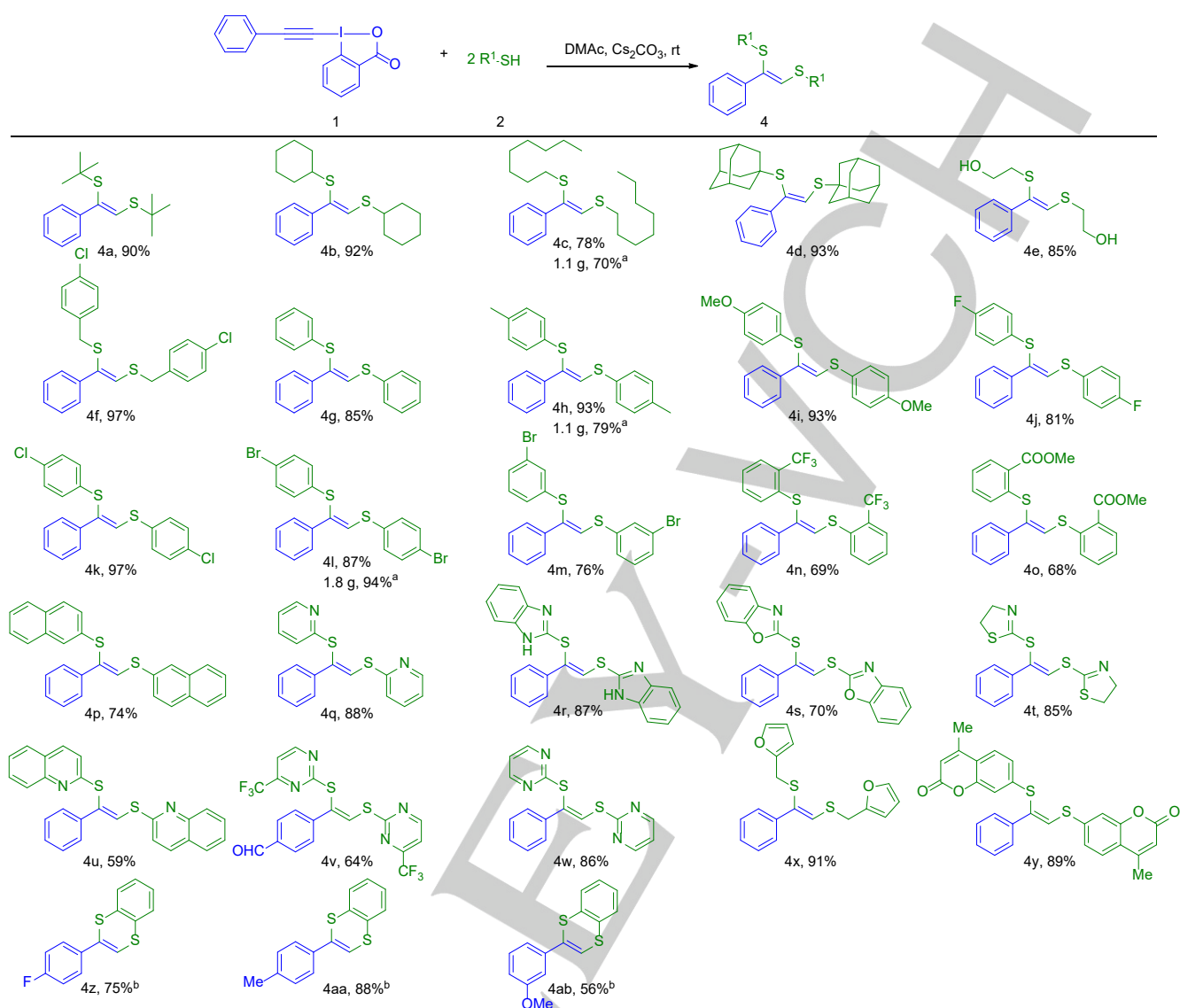


Scheme 1. Scope of Ethynylbenziodoxolones. ^a(5-Chloropent-1-ynyl)-1,2-benziodoxol-3(1*H*)-one.

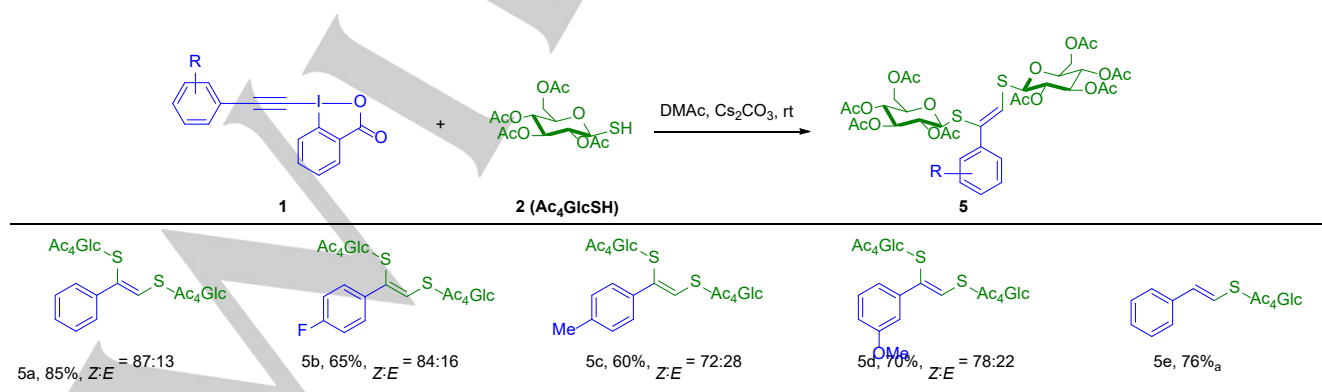
We next evaluated the thiol scope and found that a number of aliphatic and aromatic thiols were compatible under the standard reaction conditions (**Scheme 2**). Additionally, primary (**4c**, **4e**, **f**), secondary (**4b**), and tertiary alkyl thiols (**4a**, **4d**) were suitable. Aromatic thiols were broadly applicable, regardless of the steric and electronic properties of the aryl ring. As shown in **Scheme 2**, aromatic building blocks bearing common functional groups (methyl, methoxy, bromo, trifluoromethyl, and ester) are well tolerated under the reaction conditions, and the corresponding products were isolated in moderate to good yields (**4h–o**). Transformations with benzenethiol and 2-naphthalenethiol proceeded with 85% (**4g**) and 74% (**4p**) yield, respectively. To further support the functional group tolerance of the reaction, we turned our attention to the scope of heterocyclic thiols, which provide access to ubiquitous motifs found in pharmaceuticals, biologically active molecules, and agrochemicals. Alkenes containing heterocyclic rings, such as benzo[*d*]thiazole, pyridine, 1*H*-benzo[*d*]imidazole, 1-methyl-1*H*-imidazole, benzo[*d*]oxazole, 4,5-dihydrothiazole, quinoline, pyrimidine, furan, and coumarin could be converted effectively to the corresponding products (**4q–y**) in moderate to good yields. In addition, motivated by their unique electronic and biological properties,^[20] we established a synthetic route to benzo-1,4-dithiins through the use of (**4z–ab**)

benzene-1,2-dithiol. To demonstrate the potential synthetic value of this transformation, 4.0 mmol of the Ph-EBX reagent was subjected to the standard conditions to form the corresponding products in good yield (**4c**, **4h**, **4l**). The configurations of **4c**, **4v** and **4w** were determined by NOESY (see SI, pS7).

Alkenylthioglycosides are important structural motifs that exist in many biologically active compounds, as exemplified by leaf-closure glycosidase inhibitors.^[21] They can also be transformed to alkylthioglycosides,^[22] a reaction which can increase the diversity of thioglycoside family. The transition metal catalyzed alkenylation of thioglycosides has been reported recently,^[23] in which there is only one example of a bis-β-thioglycoside alkene. Herein, we disclose a conceptually different approach to bis-β-thioglycoside alkene derivatives based on EBX reagents, highlighting reactivity complementary to that of transition metal catalysts. In this process, stereoselectivity was observed and the *Z*:*E* ratio is shown in **Scheme 3**. Overall, the transformation tolerates both electron withdrawing and donating groups (**5b–d**), making this an attractive method for preparing alkenylthioglycosides. The configuration of **5b** was determined by NOESY (see SI, pS8). To our delight, good yield and excellent stereoselective were obtained with vinylbenziodoxolones, providing the alkenylthioglycoside **5e** as a single *E*-isomer.



Scheme 2. Thiol scope. ^aReaction conditions: **1** (4.0 mmol), **2** (16.0 mmol), Cs₂CO₃ (16.0 mmol), dimethylacetamide (20 mL), 20 hours, room temperature, N₂. Isolated yield reported. ^b0.4 mmol benzene-1,2-dithiol.



Scheme 3. Reactions of thioglycoside with Ph-EBX. ^a(*E*)-1-styryl-1,2-benziodoxol-3-(1H)-one was used.

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To understand the unconventional reactivity patterns between ethynylbenziodoxolone (EBX) reagents and thiols described above a combined experimental and computational mechanistic study was undertaken. Calculations were performed with dispersion-corrected density functional theory (DFT)^[24] with ω B97X-D/def2-QZVPP single point energies computed at stationary points optimized at the ω B97X-D/6-311+G(d,p)^[25-27] level of theory (6-311G(d,p) for I atoms). The involvement of anionic species (described below) necessitated the inclusion of diffuse basis functions for non-hydrogenic atoms during all stages of the investigation. Solvation by DMAc was described by the SMD continuum solvation model in the optimizations and single-point corrections.^[28] In benchmark studies performed on geometric and thermodynamic properties of hypervalent iodine species, the ω B97X-D functional with valence triple- ζ polarized basis set ranked highly.^[29] In our studies, the use of alternate basis sets (e.g., def2-TZVPPD) to describe the I atom during

geometry optimization gave unchanged geometries (**Figure S6a**) and had minimal impact upon computed energy profiles computed at 1 M concentration and 298.15 K (**Figure S6b**).

Firstly, we analyzed the effect of the salt used in the reaction. In the absence of Cs_2CO_3 , the desired product could also be detected in 30% yield by crude ^1H NMR (**Figure 2a**). However, the addition of different salts accelerates the reaction dramatically, in accordance with the anion's basicity ($\text{Cs}_2\text{CO}_3 > \text{Na}_2\text{CO}_3 > \text{CsF} > \text{CsI} > \text{KPF}_6$). The type of metal employed as the cation does not affect the reaction yield to a great extent and most likely it only modulates the basicity of the counteranion (i.e. Cs_2CO_3 and Na_2CO_3 lead to 83% and 80% yield, respectively). Taking into account the fact that thiophenols are much more acidic than phenols in non-aqueous solvent (e.g., in DMSO thiophenol $\text{pK}_a = 10.3$, vs. 18.0 for phenol),^[30] the above data suggest that the formation of a deprotonated thiol to form a thiolate is required for an efficient reaction.^[11b]

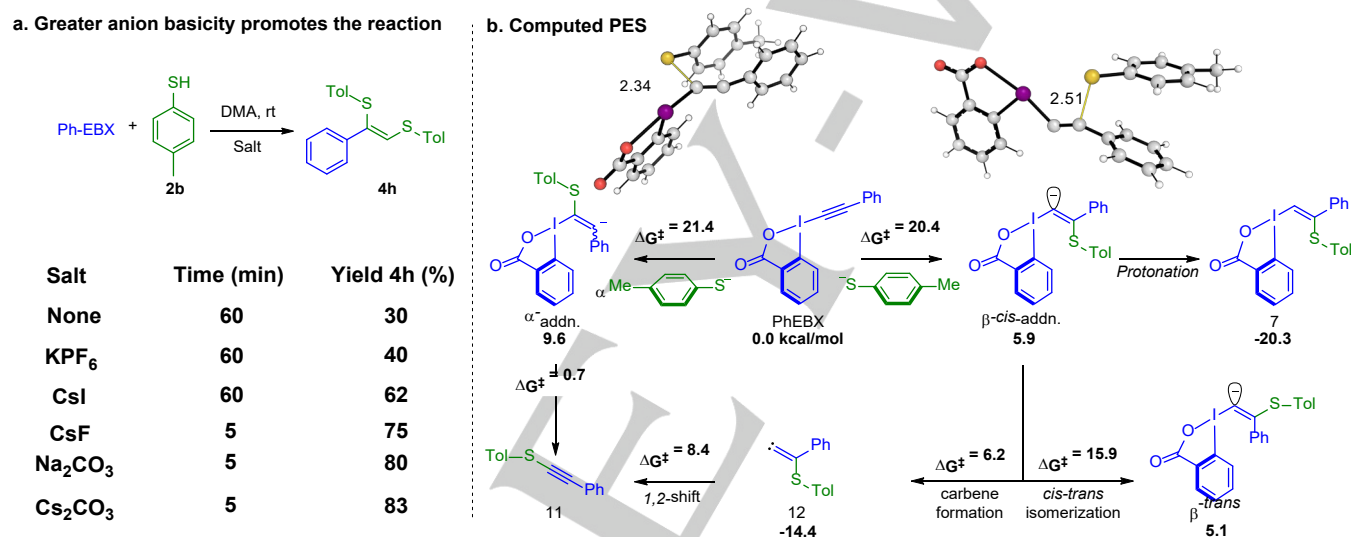


Figure 2. (a) Reaction yields obtained using different salts as additives. (b) Computed pathways for the addition of RS^- nucleophile to PhEBX (Gibbs energies in kcal/mol, distances in Å).

Prompted by these experimental findings, we computationally evaluated reaction pathways for the addition of a thiophenolate (pTolS^-) to PhEBX (**Figure 2b**). Additionally, we considered the possibility of RS^\bullet radicals reacting with EBX. We located transition structures (TSs) for the initial C-S bond formation at both α - and β -positions of the alkyne, occurring either *cis*- or *trans*-to the in-plane benziodoxolone group. The anionic thiolate shows a kinetic preference for addition to the β -position, with a high degree of *cis*-selectivity: this TS is 3.4 kcal/mol more favorable than the *trans*-TS (**Figure S2**). The origins of this regio- and stereo-selectivity, which is consistent with experimental observations, are discussed in greater detail below. In contrast to anionic pathways, thiyl radical additions favor the α -position of the alkyne by 4.8 kcal/mol over β -addition (**Figure S3**). Our calculations predict the resulting carbanionic intermediate to be configurationally stable, since the barrier towards *cis*-*trans*

isomerization via $\text{C}=\text{C}$ -I angle-bending is 15.9 kcal/mol, whereas lower energy pathways exist toward different fates for this species (**Figure 2b**). Loss of an iodophenylacetate anion is one such pathway to form carbene **12**, itself able to undergo a 1,2-shift to form the thioalkyne consistent with previously reported experimental and computational studies. The absence of such product in our experimental studies suggests an alternative fate, namely protonation of the β -*cis*-carbanion to form *cis*-vinylbenziodoxolone thioether **7**, is instead operative. Indeed, using sub-stoichiometric quantities of base, Waser and coworkers have previously reported products analogous to **7**, presumably as the result of protonation of carbanionic intermediates.^[31] Experimentally, we were able to observe the formation of **7** under standard reaction conditions after 5 mins (**Figure 3a**). The conversion of **7** to 1,2-dithio-1-alkene **8** was also successful, in addition to the conversion of **9** to provide vinyl sulfide **10** (**Figure**

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3b). These observations are consistent with the intermediacy of vinylbenziodoxolones en route to the final 2-dithio-1-alkene products. Additionally, the reactions of thiols with vinylbenziodoxolones provide a convenient entry to vinyl sulfides usually prepared by transition metal catalyzed cross-couplings.^[19]

Conversion of vinylbenziodoxolone **7** into the 1,2-dithio-1-alkene product was probed experimentally and computationally. Several experimental observations support the hypothesis that this second C-S bond forming event involves a thiyl radical, rather than a thiolate. Sub-stoichiometric amounts of the free-radical initiator 2,2'-Azobis(2-methylpropionitrile) (AIBN) were found to promote product formation (**Figure 4a**). TEMPO trapping experiments were also consistent with the formation of thiyl radicals from the thiol pro-nucleophile, whereas no evidence for radical formation was found for disulfide and sodium thiolate, both of which fail to produce any 1,2-dithio-1-alkene product (**Figure 4a** and Control Experiments section in the ESI). The use of sodium thiolate **2b'** gives rise to **7** without subsequent conversion

(**Figure 4b**). Collectively, these observations suggest that while alkyne addition can be accomplished in the anionic manifold, the second addition operates via a thiyl radical pathway. Accordingly, the computed TS for C-S bond formation between **7** and a thiyl radical was located for the α - and β -positions, with the α -TS being more favorable by 11.6 kcal/mol (**Figure S5**). In a concerted, but highly asynchronous fashion, the C-I bond is cleaved during this step to produce a *cis*-configured 1,2-dithio-1-alkene. The low barrier found for **TS-II** (10.9 kcal/mol, **Figure 3b**) suggests that the rate-limiting step is not **TS-II**, but the RS^\bullet radical formation from RSH that takes place before the second RSH addition. This point is also supported by the catalytic effect of AIBN in conditions where the rate-limiting step is the second radical addition (when using Cs_2CO_3), which is probably caused by an acceleration of RS^\bullet radical formation (see Control Experiments section in the ESI). The involvement of RSH was also investigated computationally but, in all the cases, the energy barriers of these processes were considerably higher than the barrier of the radical pathway (**Figure S4**).

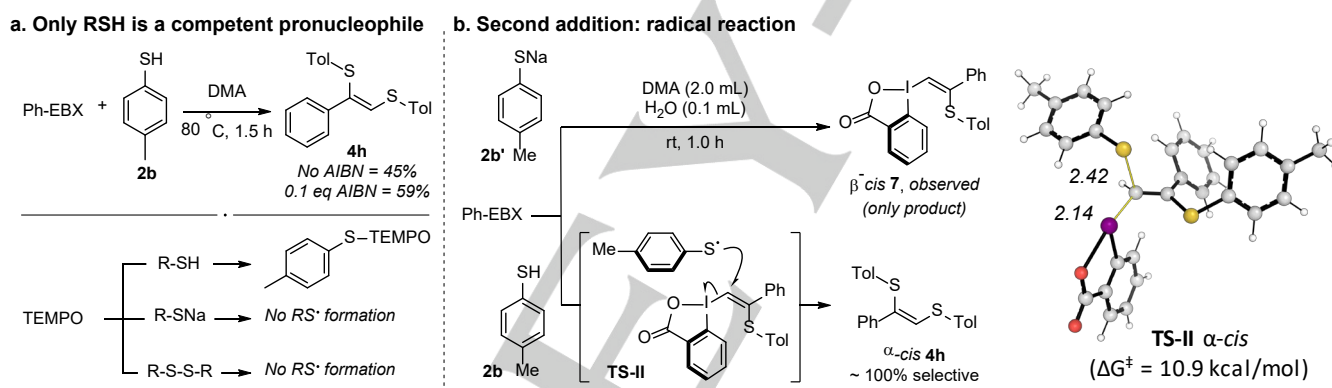


Figure 4. (a) AIBN promotes the reaction, while TEMPO trapping experiments implicate the formation of thiyl radicals. (b) Experimentally, TolSNa only leads to vinylbenziodoxolone formation, while TolSH is required for 1,2-dithio-1-alkene formation. Yields were determined by ^1H NMR.

The results suggest that the first RSH addition takes place through a general base-promoted nucleophilic addition, since radical additions lead completely to the α addition, which is opposite to the experimentally observed results. This outcome is not surprising since previous studies regarding EBX derivatives showed that nucleophilic attacks occur favorably at β positions^[11b,17,32] while radical attacks take place preferentially at α positions.^[33] The nucleophilic preference toward the β addition is consistent with the calculations of the condensed Fukui index, $f_+(r)$, which is a good quantitative predictor for the position of attack (**Table S2**).^[34] Higher values of $f_+(r)$ in C atoms are associated with greater susceptibility toward nucleophilic attack. It is worth mentioning that, contrary to previous studies where other EBX derivatives were used,^[11b,c] intermediate **7** is stable and only leads to **4h** and not to **11** or other isomers of **7** under the experimental reaction conditions employed.

Experimentally, the addition of the first RSH molecule to form **7** is highly *cis* selective and this regioselectivity is pre-served along the formation of final product **4h**. A plausible explanation behind the favored *cis* selectivity relies on the network of noncovalent interactions formed in **TS-I**, the selectivity-determining step of the first addition. More specifically, the main difference between the β -*cis* and β -*trans* additions is the formation of a stabilizing S-I halogen bond^[35] in the transition state that leads to the *cis* position (**Figure 4**), which might be the most relevant factor favoring this regioselectivity (2.5 kcal/mol based on NBO analysis). This halogen interaction mainly comprises the orbital overlap of one of the S lone electron pairs and the σ^* of the C-I bond ($n_S \rightarrow \sigma_{CI}^*$) and is potentially the driving force that led to *cis* selectivity when using ROH in previous analogous additions (**Figure S8**).^[17]

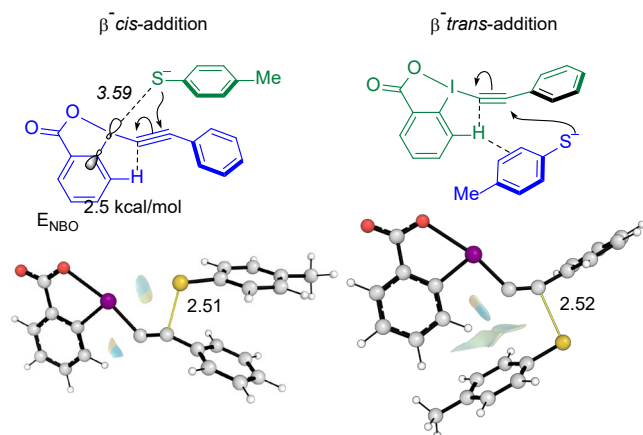


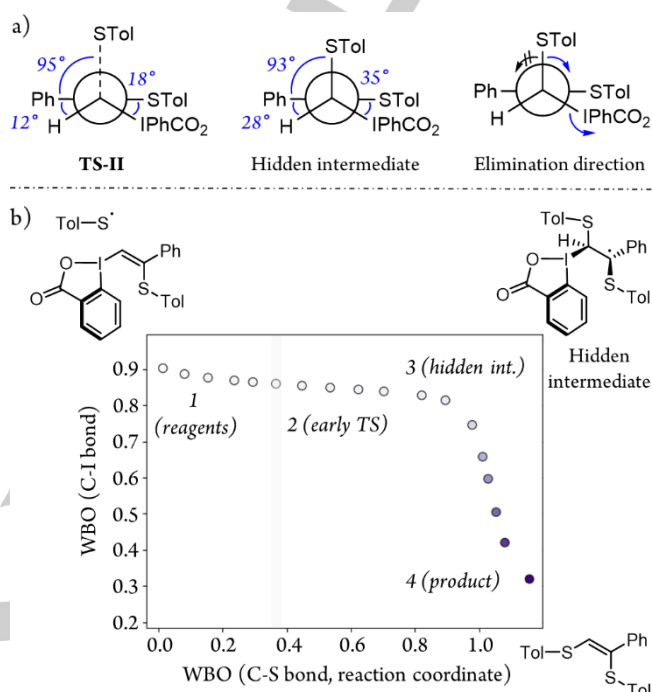
Figure 5. Structure of the most favorable **TS-I** found with β -*cis* and β -*trans* selectivity, including the energy of the S–I halogen bond in β -*cis* **TS-I** calculated with NBO. Coloured surfaces in the NCIPLOT^[36] analysis (bottom) represent non-covalent interactions (NCI): As the surfaces become bluer, the NCI are stronger, and as the surfaces become yellow, the NCI are weaker.

Interestingly, the RS^\bullet addition to **7** (**TS-II**) is *cis*-specific, since the RS group always follows the same direction (elimination direction) to replace the IPhCO_2 group (**Figure 5a**).^[37] In order to gain more insight into this step, we analyzed the spin densities, Wiberg bond orders (WBO),^[38] and geometries along its intrinsic reaction coordinate (IRC) (**Figure 5b**). The results suggest that this addition is a concerted process in which the second C–S bond is formed and the C–I bond cleaves with no stable intermediate generated before **4h**. In this concerted transformation, first the C–S bond is formed while the C=C double bond becomes a single bond, forming a hidden intermediate.^[39] Then, the C–I bond breaks at the same time as the double bond is recovered.

Even though the first RXH addition shows similar activation barrier and common features for RSH and ROH, the products obtained from **13** differ in a great extent (**Figure 6a**). One major difference is that when using ROH nucleophiles,^[17] the process requires light to proceed while no light is needed when using RSH nucleophiles. Also, reactions with RSH nucleophiles do not change their outcomes when using light irradiation.

It was suggested that the formation of product **14** is triggered by the HOMO / LUMO electron transfer depicted in **Figure 6b**.^[17] In fact, when this electron transfer process is emulated through optimizing the geometries of anion radical versions of **13**, the products observed are analogous to **14** with ROH and RSH (**Figure S7**). Interestingly, the orbital lobes involved in the electron transfer are identical for RSH and ROH, and this process shows practically the same characteristics when using both types of RXH, indicating that this competitive pathway could potentially take place when using RS^\bullet nucleophiles. However, the reaction times needed for the electron transfer were much higher than the times required for this new double RSH addition that leads to **4** (14 h and less than 5 min for the electron transfer using ROH and the double RSH addition, respectively). This observation indicates that even though an electron transfer process is suitable when using RS^\bullet nucleophiles after formation of **13**, the radical RS^\bullet

addition that generates **4** takes place before any possible electron transfer. When using ROH derivatives, no radicals seem to be formed in the reaction media (**Figure 7c**) and, therefore, there not any viable and fast pathways competing against the electron transfer.



Three regions	Spin density in part:			
	Region	1	2	3
	Tol-S•	0.99	0.66	0.12
	IPhCO ₂	0.00	0.01	0.04
	HC=CR ₂	0.01	0.32	0.84

Figure 6. (a) Dihedral angles of **TS-II** and the hidden intermediate formed during the second RS addition along with the elimination direction of the IPhCO_2 group. (b) WBO of the breaking C–I bond as the forming C–S bond creates throughout the IRC of the most stable **TS-II**, along with the spin density of different regions of the molecule as the TS progresses. The color intensity of the points is related to the degree of cleavage of the C–I bond.

Conclusion

In conclusion, we have discovered unprecedented reactivity between ethynylbenziodoxolones and thiols for the regioselective synthesis of 1,2-dithio-1-alkenes that complements previously reported protocols. This operationally simple methodology with versatile functional group tolerance is demonstrated in 50 examples. Furthermore, thioglycosides are also well tolerated (5 examples, 50–85% yield). It is noteworthy that benzo-1,4-dithiins have been realized in good yield (3 examples, 56–88% yield). This newly developed protocol has also been applied to the gram-scale synthesis of 1,2-dithio-1-alkenes, which are not readily accessible

by other means. Mechanistic experimental and computational studies suggest that this reaction follows a novel reaction mechanism between ethynylbenziodoxolones and thiols. The *cis* regioselectivity observed in the final products is created through a combination of two steps: *cis*-selective nucleophilic RSH addition (**TS-I**) followed by a *cis*-specific radical RSH addition (**TS-II**). Interestingly, different inorganic salts accelerate the reaction acting as basic additives in the first RSH addition. Under the standard reaction conditions using Cs_2CO_3 , the results suggest that the rate-limiting step is the formation of RS^\bullet radicals from RSH that takes place before the second RSH addition.

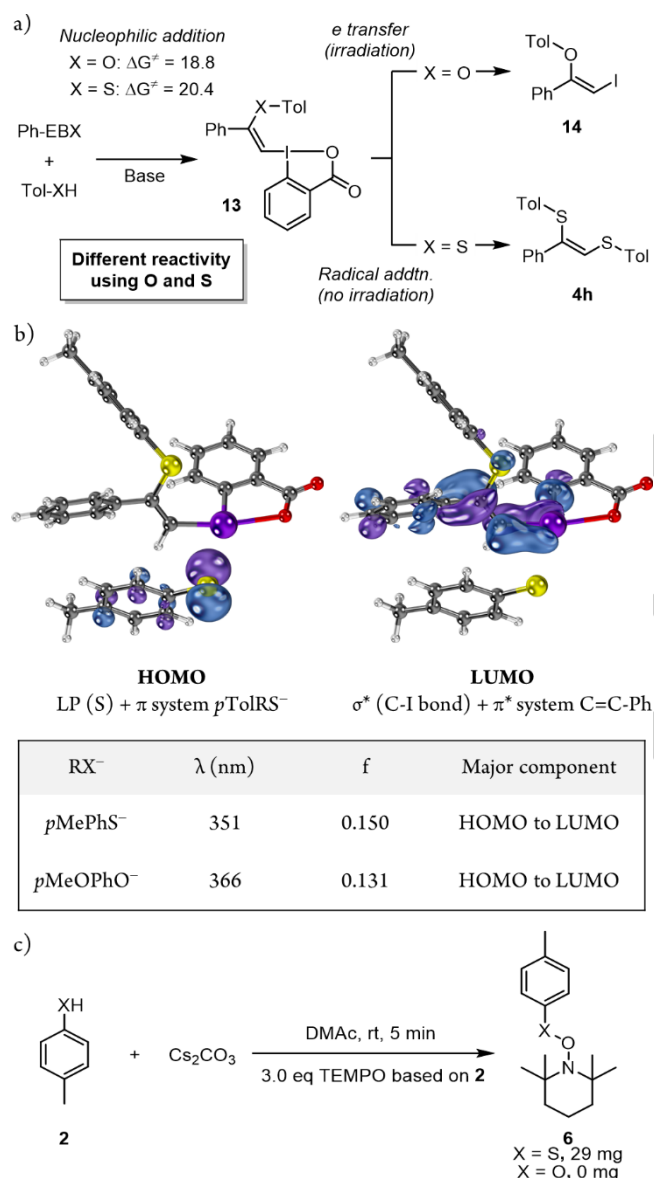


Figure 7. (a) Reactivity observed when using RSH and ROH with Ph-EBX. (b) Representation of the HOMO and LUMO, along with the excitation wavelengths (λ), oscillator strength (f) and major component of the first electronic transition of complex [13–XTol] when using pTolS⁻ and pMeOPhO⁻. These parameters were calculated using TD-DFT. In both cases, the first electronic transition corresponds to the electron transfer taking place from RX⁻ to intermediate 13. (c) Radical trapping experiments using pTolSH and pTolOH.

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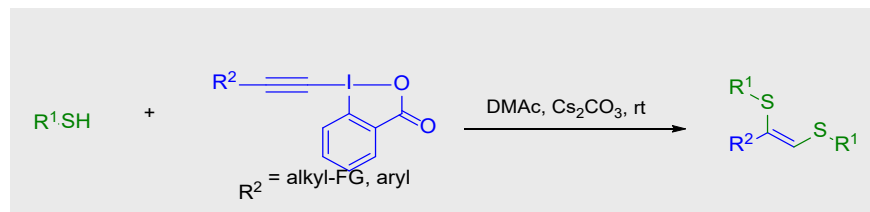
Keywords: 1,2-dithio-1-alkenes • ethynylbenziodoxolone • thiols • *cis* regioselectivity • density functional theory

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Entry for the Table of Contents

RESEARCH ARTICLE



Ethynylbenziodoxolone (EBX) reagents react with thiols form 1,2-dithio-1-alkenes with *cis* regiocontrol. Experimental results and density functional theory (DFT) calculations support that *cis* regioselectivity observed in the final products is through *cis*-selective nucleophilic RSH addition followed by a *cis*-specific radical RSH addition. The process is unique to EBX reagents.

Dr. Bin Liu, Dr. Juan V. Alegre-Requena,
Prof. Robert S. Paton, Prof. Garret M.
Miyake*

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Unconventional Reactivity of
Ethynylbenziodoxolone (EBX)
Reagents and Thiols: Scope and
Mechanism