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Copper-Catalyzed Oxyalkynylation of C−S Bonds in Thiiranes and Thiethanes with Hypervalent Iodine Reagents

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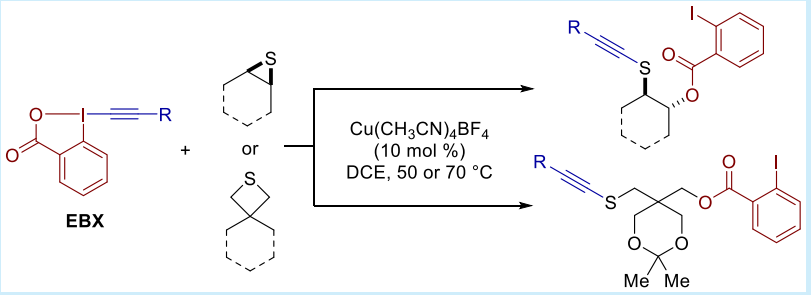
Supporting Information



ABSTRACT: We report the oxyalkynylation of thiiranes and thietanes using ethynylbenziodoxolone reagents (EBXs) to readily access functionalized building blocks bearing an alkynyl, a benzoate, and an iodide group. The reaction proceeds with high atom efficiency most likely through an alkynyl−episulfonium intermediate. The transformation is copper-catalyzed and compatible with a large array of thiiranes and thietanes.

Strain-promoted ring opening of small saturated heterocycles (three- and four-membered rings) is an attractive way to access 1,2- or 1,3-functionalized building blocks. This approach has been thoroughly investigated for oxygen and nitrogen heterocycles including epoxides,[1] aziridines,[2] and oxetanes.[3] In comparison, this strategy has been less explored for the sulfur analogues, thiiranes[1,4] and thietanes,[5] despite the importance of sulfur-containing molecules.[6] The more reactive thiiranium ion is a well-described intermediate and has been recently involved in the development of highly enantioselective transformations.[7] Its formation often relies on the reaction of alkenes with an electrophilic sulfur source or the nucleophilic substitution of a leaving group next to a thioether (Scheme 1a). Their generation by reaction of an electrophile with the sulfur atom is unusual.[7a,b] A few recent reports explored this method of activation either by alkylation for a subsequent ring expansion[8] or by arylation to induce a ring opening.[9]

In contrast, the generation of a noncyclic sulfonium ion by alkylation of thioethers is a well-known method.[7b,10] To the best of our knowledge, only one report published by Ochiai and co-workers presented their formation by alkynylation (Scheme 1b).[11] Ethynyliodonium salts were used to synthesize alkynyl(diphenyl)sulfonium salts. When thioanisole (**1**) was alkynylated with iodonium **2**, sulfonium intermediate **A** reacted with an excess of **1** to give thioalkyne **4**. Later, a mild and selective protocol for the formation of thioalkynes was proposed by our group using thiols and ethynylbenziodoxolones (EBX).[12] Iodonium salts were not suitable for this transformation, as they led to the formation of disulfides. Considering the high sulfur affinity of hypervalent iodine reagents, we anticipated that they could be used for the generation of an alkynylated episulfonium intermediate from the corresponding thiirane (Scheme 1c).

EBX reagents were expected to be superior in this reaction, as their activation using metal catalysis is well-established[13] and the released benzoate **5** can act directly as a nucleophile for the formed episulfonium, resulting in a highly atom-economical process.[14] The obtained β-hydroxy sulfide motif is found in a large array of bioactive molecules[15] and is mostly accessed by epoxide ring opening. The reverse approach exploiting thiirane chemistry has been less developed,[16] except for the acetolysis of carbohydrate bearing a thiirane at the C_5−C_6 position.[17]

Herein, we report the successful copper-catalyzed oxyalkynylation of thiiranes using EBX reagents. The reaction probably proceeds through the formation of an episulfonium intermediate and furnishes the desired β-hydroxy sulfides in moderate to good yields using operationally simple conditions. The methodology was also applied to the ring opening of thietanes to access 1,3-difunctionalized products.

We started our investigation by optimizing the reaction conditions using TIPS-EBX (**6a**) and the commercially available cyclohexene sulfide (**7a**) as a model substrate (Table 1; see Supporting Information for a full list of tested reaction conditions, Table S1). No product was observed in the absence of catalyst or in the presence of TMSCl as Lewis acid (entries 1 and 2). However, we were pleased to see that addition of a catalytic amount of $Cu(CH_3CN)_4BF_4$ afforded the desired

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Scheme 1. Strategies Exploiting Thiiranium and Sulfonium Ions for C−S Bond Activation

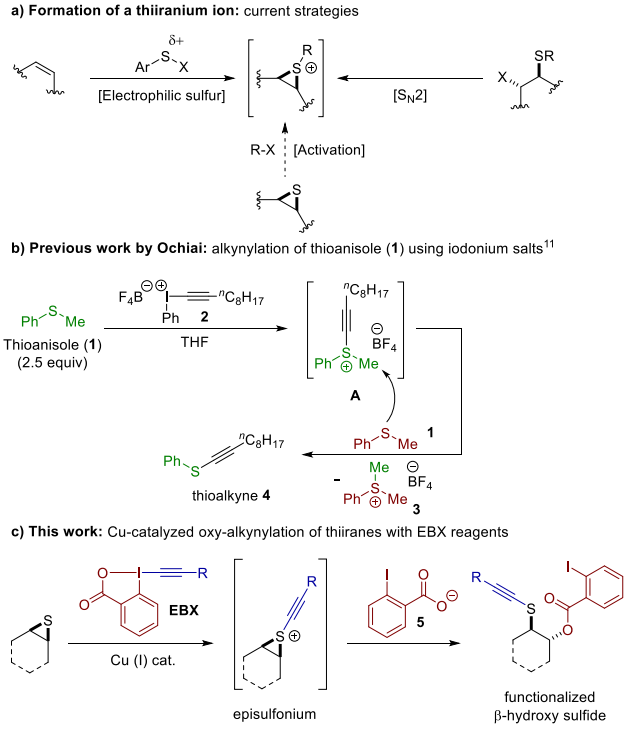
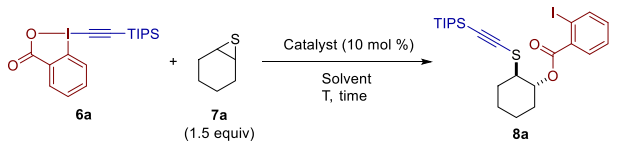


Table 1. Optimization of the Oxyalkynylation[a]



entry	catalyst	solvent	T (°C)	time (h)	yield (%)[b]
1	none	THF	70	24	traces
2[c]	TMSCl	THF	30	4	not observed
3	$Cu(CH_3CN)_4BF_4$	THF	rt	24	53
4	$Cu(CH_3CN)_4BF_4$	DCE	rt	24	66
5	**$Cu(CH_3CN)_4BF_4$**	**DCE**	**50**	**1.5**	**65**
6[d]	$Cu(CH_3CN)_4BF_4$	DCE	100	0.5	67
7	$Cu(OTf)_2$	DCE	50	1.5	66

[a]Reaction conditions: TIPS-EBX (**6a**) (0.1 mmol), cyclohexene sulfide (**7a**) (0.15 mmol), catalyst (10 mol %), solvent (0.07 M), reactions were carried out under N_2 atmosphere. [b]Isolated yield. [c]1 equiv of TMSCl was used. [d]Reaction was performed under microwave irradiation.

product **8a** in 53% yield as a single diastereoisomer (entry 3). The relative *trans* configuration was confirmed by X-ray crystallography. Different solvents were screened: replacing THF with DCE increased the yield to 66% (entry 4). Working at higher temperatures resulted in a significant lower reaction time with no influence on the yield (entries 4−6). Next, we examined a range of copper catalysts (see Supporting Information). A similar yield was obtained only when $Cu(OTf)_2$ was used (entry 7). Oligomers containing multiple cyclohexyl sulfide motifs were identified as byproducts of the reaction. To reduce this side reactivity different concentrations, stoichiometries of **6a**/**7a** and copper loadings were examined (see Table S2 for details), but the reaction yield was constantly between 45 and 65%.[18]

With the optimized conditions in hand (entry 5), we first investigated a range of structurally diverse thiiranes (Scheme 2). Using cyclopentene sulfide allowed the synthesis of **8b** in a slightly improved yield. Incorporation of an oxygen or a protected nitrogen atom in the ring afforded **8c** and **8d** in good and moderate yield, respectively. Simple ethylene sulfide **6e** provided a lower yield of **8e** (46%). However, this result has to be put in perspective with the known tendency of **7e** to polymerize, as well as its low boiling point (55 °C).[19] When the reaction was performed with unsymmetrical propylene sulfide, **8f** was obtained as a mixture of regioisomers (2.1:1 rr), the major one resulting from the attack of the carboxylate at the most substituted position. A similar outcome was observed with a longer alkyl chain (product **8g**). Using the disubstituted analogue **7h** led to a significant improvement of the regioselectivity (15.5:1 rr), although with a diminished yield of **8h**. When the reaction was run with the enantioenriched substrate **7i**, it afforded **8i** with full conservation of the ee for both regioisomers. In this case, we were surprised to observe an inversion of regioselectivity. We hypothesize that it could be due to the inductive effect of the nearby oxygen. The synthesis of **8j** incorporating two protected alcohols was achieved in a lower yield.

Next, we examined different hypervalent iodine reagents. Substitution of the TIPS group by aryl substituents was well-tolerated and showed little impact on the reaction (**8k−m**). Alkyl-EBX gave also good results (**8n−o**). A lower yield was observed for **8p**, and decreasing the temperature furnished a slightly better result. Modification of the iodobenzoic acid core with a methoxy, a nitro, or a fused benzene ring allowed the synthesis of products **8q−s** in good yields. Importantly, vinylbenziodoxolone reagents (VBX) could be used successfully in the transformation, providing the oxyvinylated products **8t−u** in promising yields without further optimization.

We next examined the transformation of the less strained thietane heterocycles (Scheme 3). We were pleased to see that simple thiacyclobutane (**9a**) reacted under similar reaction conditions to deliver 1,3-functionalized thioalcohol **10a** in moderate yield. Introduction of a phenyl group at the 3-position of the thiacyclobutane did not affect the transformation (product **10b**). Spirocyclic substrates **9c** and **9d** gave improved yields of products **10c** and **10d** and demonstrated the selectivity of the reaction for sulfur heterocycles. Considering the good results obtained with four-membered rings, the reaction of tetrahydrothiophene (**9e**) was examined next. At higher temperature (100 °C), we could obtain the 1,4-functionalized thioalcohol **10e** in moderate yield.

To highlight the synthetic utility of our method, further functionalizations of **8a** were performed (Scheme 4a). We first focused on the reactivity of the iodobenzoate ester: Sonogashira cross-coupling with the iodine afforded **11** in good yield, and the saponification of the iodobenzoic ester allowed the synthesis of the free alcohol **12**. Next, we turned our attention toward the thioalkyne function. A sequence of TIPS deprotection followed by copper-catalyzed alkyne−azide cycloaddition afforded triazole **14** in excellent yield. A scale-up reaction (2 mmol) was then carried out using Ph-EBX (**6k**) and cyclohexene sulfide (**7a**) (Scheme 4b). The reaction gave a similar yield at this scale. The synthesized phenyl thioalkyne **8k** was hydrated to afford thioester **15** in good yield.

A series of experiments were carried out to gain more insight into the reaction mechanism (Scheme 5). We first attempted the ring opening of cyclohexene sulfide (**7a**) in the presence of a

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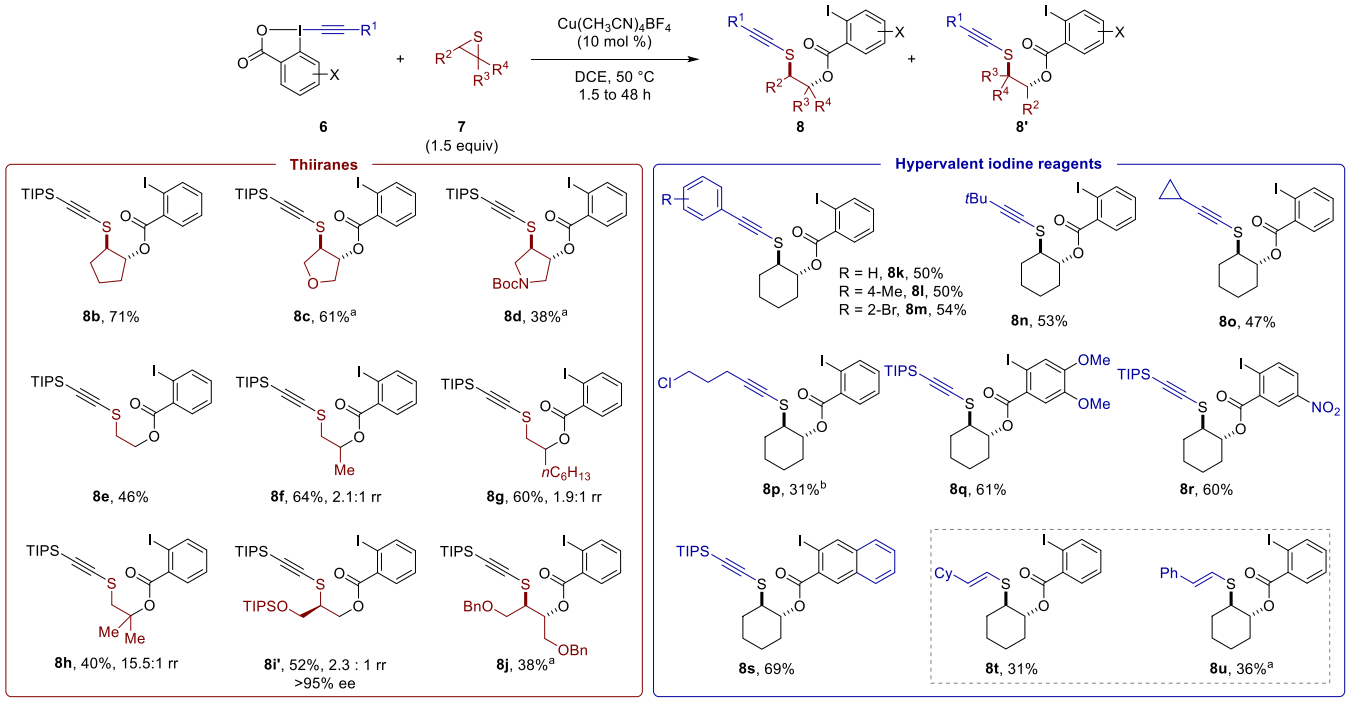
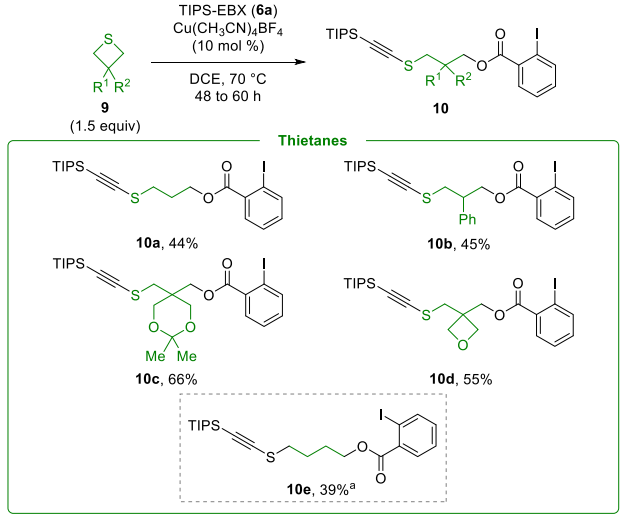
Scheme 2. Scope of the Oxyakynylation with Thiiranes and HIRs*



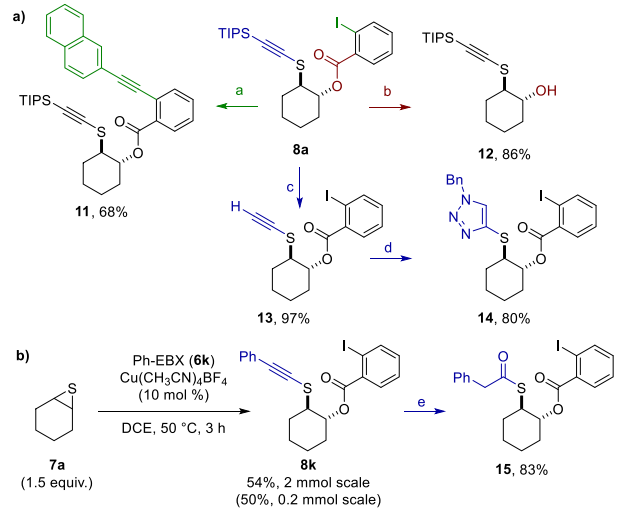
*The major regioisomer is drawn; rr = regioselectivity ratio. Reaction was carried out on 0.2 mmol scale. [a]Reaction was heated to 70 °C. [b]Reaction was stirred at rt.

Scheme 3. Scope Extension to Thietanes and Tetrahydrothiophene*



*Reactions were carried out on 0.2 mmol scale. [a]The reaction mixture was heated to 100 °C under microwave irradiation.

Scheme 4. Product Modifications



[a]Conditions: (a) **8a** (1.0 equiv), 2-ethynylnaphthalene (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (20 mol %), Et_3N (30 mM), 40 °C, 2.5 h; (b) **8a** (1.0 equiv), K_2CO_3 (2.5 equiv), EtOH (0.1 M), 45 °C, 30 h; (c) **8a** (1.0 equiv), TBAF (1.2 equiv), THF (80 mM), 0 °C, 1 h; (d) **13** (1.0 equiv), BnN_3 (1.2 equiv), $Cu(H_2O)_5SO_4$ (10 mol %), sodium ascorbate (20 mol %), $CHCl_3/H_2O$ 15:1 (60 mM), rt, 24 h; (e) **8k** (1.0 equiv), PTSA (1.0 equiv), SiO_2 (15.0 equiv), CH_2Cl_2 (0.2 M), 40 °C, 24 h.

copper catalyst and sodium benzoate or benzoic acid (Scheme 5, eq 1). No product formation was observed after 3 days, highlighting the importance of the hypervalent iodine reagents for thiirane activation. We applied our standard conditions to cyclohexene oxide (**17**) (eq 2). Even if epoxides are more prone to a ring-opening reaction due to their higher ring strain,[4b] no trace of product **18** was observed. This result confirmed the selectivity of the transformation for sulfur heterocycles. The reaction was attempted using iodonium salt **6v** instead of EBX (eq 3). When cesium benzoate or benzoic acid was added to replace the missing nucleophile, the desired product was formed only in trace amounts. The addition of a radical scavenger led to the formation of the desired product **8a** with a decreased yield (eq 4). No TEMPO adducts were detected. Nevertheless, a radical pathway cannot be excluded at this stage, as such intermediates may be too unstable to be isolated.

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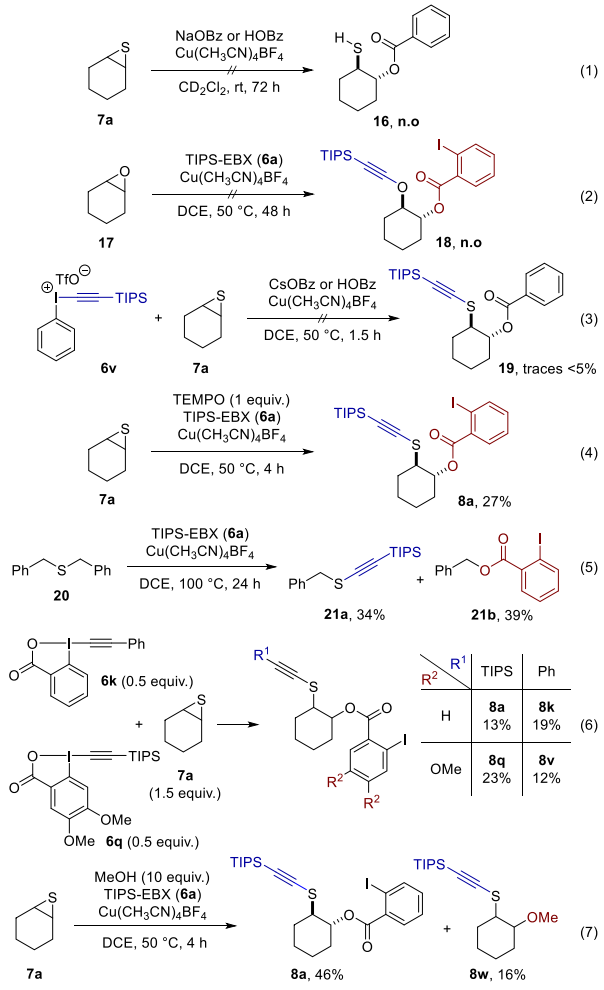
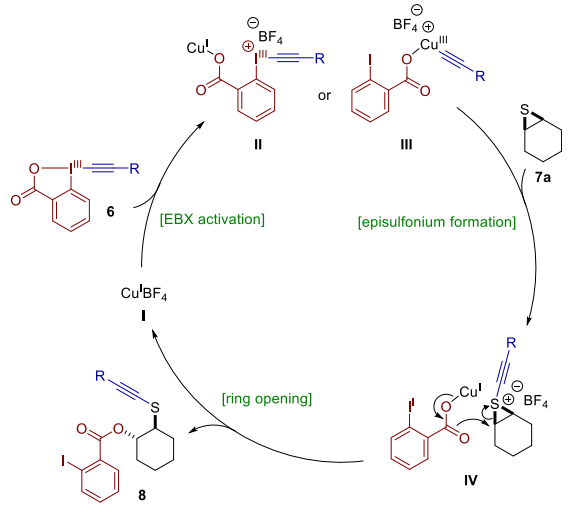
Scheme 5. Additional Experiments for Mechanism Elucidation



Considering the successful ring opening of nonstrained tetrahydrothiophene (Scheme 3, **10e**), we wondered if noncyclic thioethers could be cleaved using our method. We were pleased to see that dibenzyl sulfide **20** reacted to afford the corresponding thioalkyne **21a** and benzyl ester **21b** in moderate yields at 100 °C (eq 5). A competitive experiment was carried out with **6k** and **6q** possessing different alkynes and iodobenzoic cores (eq 6). In total, four different products were isolated: the expected products **8k** and **8q** and the crossover products **8a** and **8v** bearing one functional group from each reagent. This showed that external addition can occur but is less favored (~1:2 ratio). Indeed, when the reaction was performed in the presence of an excess of methanol, ether product **8w** could be obtained in 16% yield together with 46% of **8a** (eq 7).[20]

Based on these results, we propose a possible reaction mechanism in Scheme 6. First, the copper(I) catalyst activates EBX reagent **6**. Two different modes of activation could be envisaged: formation of the iodonium salt **II** or oxidative transfer to generate the copper(III) complex **III**.[21] In the former case, activated iodonium salt **II** would react directly with cyclohexene sulfide (**7a**) to give sulfonium **IV**. Both a concerted α-addition–elimination or a β-addition/α-elimination/1,2-shift pathway could be considered.[22] In the latter case, coordination of the copper(III) center followed by reductive elimination would lead to sulfonium **IV**.[23] At this stage, exchange of carboxylates could happen. Sulfonium **IV** then undergoes a ring opening by

Scheme 6. Proposed Speculative Mechanism



nucleophilic attack of the copper carboxylate, affording the desired product **8** and regenerating the initial copper catalyst **I**. The product formed has a relative *trans* configuration resulting from a SN_2 attack of the carboxylate.

In summary, we have described an atom-efficient copper-catalyzed ring opening of thiiranes and thietanes through the use of hypervalent iodine reagents. The transformation works with different cheap copper sources at a broad range of concentrations and temperatures. In the case of unsymmetrical episulfides, the product resulting from the addition on the carbon-bearing substituents stabilizing better a partial positive charge was observed. Based on the relevant literature and our control experiments, we propose a speculative reaction mechanism involving formation of an episulfonium intermediate for C–S bond activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04157.

Experimental procedures and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1962904 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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†J.B. and G.P. contributed equality to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Murphree, S. S. Three-Membered Heterocycles. Structure and Reactivity. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 11−162.

(2) (a) Hu, X. E. Nucleophilic Ring Opening of Aziridines. *Tetrahedron* **2004**, *60*, 2701−2743. (b) Lu, P. Recent Developments in Regioselective Ring Opening of Aziridines. *Tetrahedron* **2010**, *66*, 2549−2560. (c) Akhtar, R.; Naqvi, S. A. R.; Zahoor, A. F.; Saleem, S. Nucleophilic Ring Opening Reactions of Aziridines. *Mol. Diversity* **2018**, *22*, 447−501.

(3) (a) Malapit, C. A.; Howell, A. R. Recent Applications of Oxetanes in the Synthesis of Heterocyclic Compounds. *J. Org. Chem.* **2015**, *80*, 8489−8495. (b) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 12150−12233. (c) Ahmad, S.; Yousaf, M.; Mansha, A.; Rasool, N.; Zahoor, A. F.; Hafeez, F.; Rizvi, S. M. A. Ring-Opening Reactions of Oxetanes: A Review of Methodology Development and Synthetic Applications. *Synth. Commun.* **2016**, *46*, 1397−1416.

(4) (a) Sander, M. Thiiranes. *Chem. Rev.* **1966**, *66*, 297−339. (b) Chew, W.; Harpp, D. N. Recent Aspects of Thiirane Chemistry. *Sulfur Rep.* **1993**, *15*, 1−39.

(5) (a) Rousseau, G.; Robin, S. Four-Membered Heterocycles: Structure and Reactivity. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 163−268. (b) Kurgane, B. V.; Giller, S. A. Ring Opening of Thietane. *Chem. Heterocycl. Compd.* **1971**, *7*, 557−558. (c) Palmer, D. C.; Taylor, E. C. Thietane Alkylations. A General Synthesis of 3-Halopropyl Benzyl Sulfides. *J. Org. Chem.* **1986**, *51*, 846−850. (d) Zheng, T.; Tan, J.; Fan, R.; Su, S.; Liu, B.; Tan, C.; Xu, K. Diverse Ring Opening of Thietanes and Other Cyclic Sulfides: An Electrophilic Aryne Activation Approach. *Chem. Commun.* **2018**, *54*, 1303−1306.

(6) Cremlyn, R. J. W. *An Introduction to Organosulfur Chemistry*; Wiley: Chichester, 1996.

(7) (a) Rayner, C. M. Synthetic Transformations Involving Thiiranium Ion Intermediates. In *Organosulfur Chemistry*; Elsevier, 1995; Chapter 3, Vol. *1*, pp 89−131. (b) *The Chemistry of the Sulphonium Group*; Stirling, C. J. M., Ed. *The Chemistry of Functional Groups*; Wiley: Chichester, 1981. (c) Lin, S.; Jacobsen, E. N. Thiourea-Catalysed Ring Opening of Episulfonium Ions with Indole Derivatives by Means of Stabilizing Non-Covalent Interactions. *Nat. Chem.* **2012**, *4*, 817−824. (d) Denmark, S. E.; Jaunet, A. Catalytic, Enantioselective, Intramolecular Carbosulfenylation of Olefins. *J. Am. Chem. Soc.* **2013**, *135*, 6419−6422. (e) Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. Mechanistic, Crystallographic, and Computational Studies on the Catalytic, Enantioselective Sulfenofunctionalization of Alkenes. *Nat. Chem.* **2014**, *6*, 1056−1064. (f) Hartmann, E.; Denmark, S. E. Structural, Mechanistic, Spectroscopic, and Preparative Studies on the Lewis Base Catalyzed, Enantioselective Sulfenofunctionalization of Alkenes. *Helv. Chim. Acta* **2017**, *100*, No. e1700158.

(8) Dong, J.; Du, H.; Xu, J. Synthesis of Functionalized Thietanes via Electrophilic Carbenoid-Induced Ring Expansion of Thiiranes with Sulfonium Acylmethylides as Carbene Precursors. *J. Org. Chem.* **2019**, *84*, 10724−10739.

(9) Frei, P.; Jones, D. H.; Kay, S. T.; McLellan, J. A.; Johnston, B. F.; Kennedy, A. R.; Tomkinson, N. C. O. Regioselective Reaction of Heterocyclic *N* -Oxides, an Acyl Chloride, and Cyclic Thioethers. *J. Org. Chem.* **2018**, *83*, 1510−1517.

(10) Kaiser, D.; Klose, I.; Oost, R.; Neuhaus, J.; Maulide, N. Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts. *Chem. Rev.* **2019**, *119*, 8701−8780.

(11) Ochiai, M.; Nagaoka, T.; Sueda, T.; Yan, J.; Chen, D. W.; Miyamoto, K. Synthesis of 1-Alkynyl(diphenyl)onium Salts of Group 16 Elements via Heteroatom Transfer Reaction of 1-Alkynyl(Phenyl)-λ3-Iodanes. *Org. Biomol. Chem.* **2003**, *1*, 1517−1521.

(12) (a) Frei, R.; Waser, J. A Highly Chemoselective and Practical Alkynylation of Thiols. *J. Am. Chem. Soc.* **2013**, *135*, 9620−9623. (b) Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P. A.; Chauvier, C.; Waser, J. Fast and Highly Chemoselective Alkynylation of Thiols with Hypervalent Iodine Reagents Enabled through a Low Energy Barrier Concerted Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 16563−16573.

(13) (a) Hari, D. P.; Caramenti, P.; Waser, J. Cyclic Hypervalent Iodine Reagents: Enabling Tools for Bond Disconnection via Reactivity Umpolung. *Acc. Chem. Res.* **2018**, *51*, 3212−3225. (b) Hari, D. P.; Nicolai, S.; Waser, J. Alkynylations and Vinylations. *PATAI'S Chemistry of Functional Groups*; Wiley, 2018.

(14) Recent examples of atom-economical reactions with hypervalent iodine reagents: (a) Modha, S. G.; Greaney, M. F. Atom-Economical Transformation of Diaryliodonium Salts: Tandem C-H and N-H Arylation of Indoles. *J. Am. Chem. Soc.* **2015**, *137*, 1416−1419. (b) Buendia, J.; Darses, B.; Dauban, P. Tandem Catalytic C(sp3)-H Amination/Sila-Sonogashira−Hagihara Coupling Reactions with Iodine Reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 5697−5701. (c) Hari, D. P.; Waser, J. Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds with Hypervalent Iodine Reagents. *J. Am. Chem. Soc.* **2016**, *138*, 2190−2193. (d) Wang, M.; Wei, J.; Fan, Q.; Jiang, X. Cu(II)-Catalyzed Sulfide Construction: Both Aryl Groups Utilization of Intermolecular and Intramolecular Diaryliodonium Salt. *Chem. Commun.* **2017**, *53*, 2918−2921. (e) Pisella, G.; Gagnebin, A.; Waser, J. Copper-Catalyzed Insertion of Diazo Compounds into Vinyl Hypervalent Iodine Reagents to Generate Allylic Esters. *ChemRxiv* **2019**, DOI: 10.26434/chemrxiv.7892513.v1. Review: (f) Boelke, A.; Finkbeiner, P.; Nachtsheim, B. J. Atom-Economical Group-Transfer Reactions with Hypervalent Iodine Compounds. *Beilstein J. Org. Chem.* **2018**, *14*, 1263−1280. (g) Wang, M.; Chen, S.; Jiang, X. Atom-Economical Applications of Diaryliodonium Salts. *Chem. - Asian J.* **2018**, *13*, 2195−2207.

(15) (a) Takada, N.; Umemura, N.; Suenaga, K.; Uemura, D. Structural Determination of Pteriatoxins A, B and C, Extremely Potent Toxins from the Bivalve Pteria Penguin. *Tetrahedron Lett.* **2001**, *42*, 3495−3497. (b) Wu, H.; Zhang, Y.; Huang, J.; Zhang, Y.; Liu, G.; Sun, N.; Yu, Z.; Zhou, Y. Clinical Trial of Arotinolol in the Treatment of Hypertension: Dippers vs. Non-Dippers. *Hypertens. Res.* **2001**, *24*, 605−610. (c) Capra, V.; Thompson, M. D.; Sala, A.; Cole, D. E.; Folco, G.; Rovati, G. E. Cysteinyl-Leukotrienes and Their Receptors in Asthma and Other Inflammatory Diseases: Critical Update and Emerging Trends. *Med. Res. Rev.* **2007**, *27*, 469−527. (d) de Castro, M. V.; Ióca, L. P.; Williams, D. E.; Costa, B. Z.; Mizuno, C. M.; Santos, M. F. C.; de Jesus, K.; Ferreira, É. L. F.; Seleghim, M. H. R.; Sette, L. D.; Pereira Filho, E. R.; Ferreira, A. G.; Gonçalves, N. S.; Santos, R. A.; Patrick, B. O.; Andersen, R. J.; Berlinck, R. G. S. Condensation of Macrocyclic Polyketides Produced by *Penicillium* Sp. DRF2 with Mercaptopyruvate Represents a New Fungal Detoxification Pathway. *J. Nat. Prod.* **2016**, *79*, 1668−1678.

(16) (a) Marakalala, M. B.; Mmutlane, E. M.; Kinfe, H. H. β-Hydroxy Sulfides and Their Syntheses. *Beilstein J. Org. Chem.* **2018**, *14*, 1668−1692. (b) Iranpoor, N.; Owji, J. Efficient, Mild, and Regioselective Conversion of Thiiranes to Alkoxy and Acetoxy Disulphides and Dithianes with Ce(IV) Based Oxidants. *Tetrahedron* **1991**, *47*, 149−154. (c) Iranpoor, N.; Shekarriz, M.; Shiriny, F. Highly Efficient, Regio- and Stereoselective Ring Opening of Epoxides and Thiiranes with $Ce(OTf)_4$. *Synth. Commun.* **1998**, *28*, 347−366. (d) Iranpoor, N.; Firouzabadi, H.; Chitsazi, M.; Ali Jafari, A. Reactions of Epoxides and Episulfides with Electrophilic Halogens. *Tetrahedron* **2002**, *58*, 7037−7042. (e) Movsumzade, M. M.; Shatirova, M. I.; Dzhafarova, U. Sh.; Niyazova, N. K. Investigation of Chemical Properties and Antimicrobial

DOI: 10.1021/acs.orglett.9b04157
Org. Lett. XXXX, XXX, XXX−XXX

Activity of Acetylene Glycidyl Ethers. *Russ. J. Gen. Chem.* **2018**, *88*, 389−392.
(17) (a) Rowell, R. M.; Whistler, R. L. Derivatives of A-D-Glucothiopyranose. *J. Org. Chem.* **1966**, *31*, 1514−1516. (b) Calvo-Flores, F. G.; García-Mendoza, P.; Hernández-Mateo, F.; Isac-García, J.; Santoyo-González, F. Applications of Cyclic Sulfates of *Vic* -Diols: Synthesis of Episulfides, Olefins, and Thio Sugars. *J. Org. Chem.* **1997**, *62*, 3944−3961. (c) Liao, X.; Větvička, V.; Crich, D. Synthesis and Evaluation of 1,5-Dithia- d -Laminaribiose, Triose, and Tetraose as Truncated β-(1→3)-Glucan Mimetics. *J. Org. Chem.* **2018**, *83*, 14894−14904.
(18) We also attempted the use of in situ-generated unstable cyclohexene selenide. See: Chan, T. H.; Finkenbine, J. R. Reaction of Epoxides with Phosphine Selenides and Trifluoroacetic Acid. Evidence for the Formation of Episelenides. *Tetrahedron Lett.* **1974**, *15*, 2091−2094. However, no product was obtained.
(19) Zelčans, G.; Gervay-Hague, J.; Maulie, I. Ethylene Sulfide. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, 2010.
(20) The use of an EBX reagent bearing a less nucleophilic 2-iodo-5-nitrobenzoate did not increase the product ratio in favor of ether **8w**. No reaction was observed when using an ethynylbenziodoxole reagent derived from hexafluoro-2-(2-iodophenyl)propan-2-ol.
(21) (a) Holt, D.; Gaunt, M. J. Copper-Catalyzed Oxy-Alkenylation of Homoallylic Alcohols to Generate Functional *Syn*-1,3-Diol Derivatives. *Angew. Chem., Int. Ed.* **2015**, *54*, 7857−7861. (b) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. Copper-Catalyzed Electrophilic Carbofunctionalization of Alkynes to Highly Functionalized Tetrasubstituted Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 5332−5335. (c) Hickman, A. J.; Sanford, M. S. High-Valent Organometallic Copper and Palladium in Catalysis. *Nature* **2012**, *484*, 177−185.
(22) Wodrich, M. D.; Caramenti, P.; Waser, J. Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents: α- or β- π-Addition? *Org. Lett.* **2016**, *18*, 60−63.
(23) Another plausible mechanism not depicted here would involve non-oxidative alkyne transfer from iodine to copper, resulting in an iodine(III)-activated Cu(I) acetylide, similarly to the computed mechanism for the gold-catalyzed alkynylation of indoles: Ariafard, A. A Density Functional Theory (DFT) Mechanistic Study of Gold(I)-Catalyzed Alkynylation of the Indole and Pyrrole Substrates, Using a Hypervalent Iodine Reagent. *ACS Catal.* **2014**, *4*, 2896−2907.

DOI: 10.1021/acs.orglett.9b04157
Org. Lett. XXXX, XXX, XXX−XXX