Synthesis C. J. F. Cole et al. Special Topic

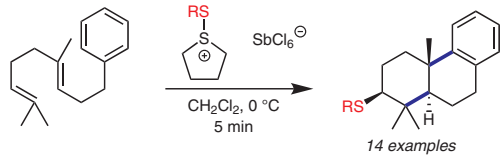
Synthesis of Enhanced, Isolable Disulfanium Salts and their Application to Thiiranium-Promoted Polyene Cyclizations

Charles J. F. Cole
Hyung Min Chi
Kenneth C. DeBacker
Scott A. Snyder*

The University of Chicago, Department of Chemistry,
5735 S. Ellis Avenue, Chicago, IL 60637, USA
sasnyder@uchicago.edu

Dedicated to Prof. Scott E. Denmark on the occasion of his 65th birthday.

Published as part of the *Special Section dedicated to Scott E. Denmark on the occasion of his 65th birthday*.



- Isolable and readily variable disulfanium salts where R = alkyl and aryl
- Generally higher yielding than other electrophilic sulfur transfer reagents for polyene cyclizations with yields up to 64%

Received: 15.03.2018
Accepted after revision: 09.04.2018
Published online: 14.06.2018
DOI: 10.1055/s-0037-1609754; Art ID: ss-2018-c0184-st

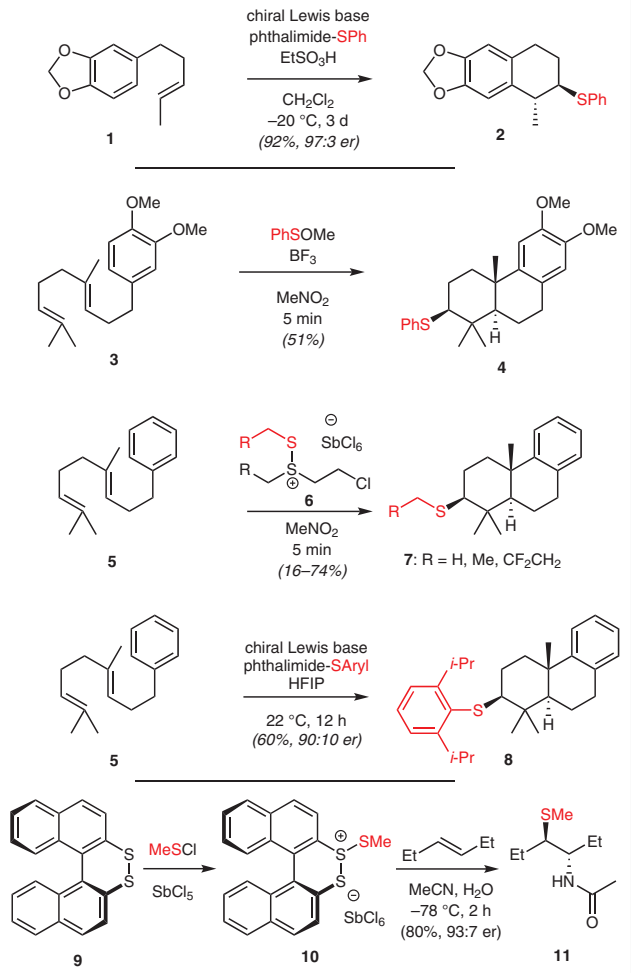
Abstract Although electrophile-promoted polyene cyclizations have long been a mainstay transformation for the rapid and stereocontrolled preparation of varied natural products and designed molecules, efforts to effect sulfur-promoted variants have arguably lagged behind other counterparts. This state of affairs is particularly true with alkyl sulfide-based electrophiles, even in racemic variants. Herein, building on previously reported discoveries, is described a distinct and modular method to prepare a range of isolable alkyl and aryl disulfanium salts that can affect thiiranium-based polyene cyclizations in moderate to good yields. In most of the substrates probed, these reagents provide superior yields to previously reported alternatives. In addition, initial efforts to develop an asymmetric variant of the process through the use of chiral versions of these reagents are discussed.

Key words alkyl sulfide, sulfuryl dichloride, disulfanium salts, geranyl acetate, tetrahydrothiophene, $SbCl_5$

Over the past decade, there has been a resurgence of interest in developing improved and more powerful reagents to affect both racemic and enantioselective electrophile-promoted polyene cyclizations.[1] One area where we have tried to contribute, in particular, has been in the development of better tools to promote halonium-based polyene cyclizations. A key finding was the discovery that the combination of a Lewis acid ($SbCl_5$), a Lewis base (Et_2S), and molecular halogens (X_2) could create a suite of reagents with broad applicability to effect racemic cyclizations incorporating chlorine, bromine, and iodine atoms, even with historically challenging substrates.[2] More recent explorations have questioned whether related designs, which reflect the Denmark paradigm of Lewis base activation of a Lewis acid,[3] could also generate potent sulfur-based electrophilic species.

At the time of our initial investigations, the Denmark group had already developed a powerful chiral Lewis base promoted cyclization to afford monocyclic sulfides such as **2** (Scheme 1).[4] High enantiocontrol was achieved through the generation of configurationally stable phenylthiiranium ions in the presence of a chiral selenophosphoramide catalyst. Extensions of that system to polyene cyclizations were not yet reported (vide infra), with the only examples in the literature for those processes being racemic events using aryl sulfide based electrophiles with electron-rich terminating groups, such as the conversion of **3** into **4** as achieved by Livinghouse.[5] We recently found that linear dialkyl sulfanium salts of type **6**, generated by combining $SbCl_5$ with 1,2-dithioethers and Cl_2, could cyclize an array of electron-rich as well as electron-neutral and -deficient substrates in acceptable to good yields, ultimately incorporating three different alkyl sulfide groups onto the respective frameworks.[6] We also discovered that these reagents often performed better than other commercially available electrophilic alkyl sulfide reagents such as dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF).[7]

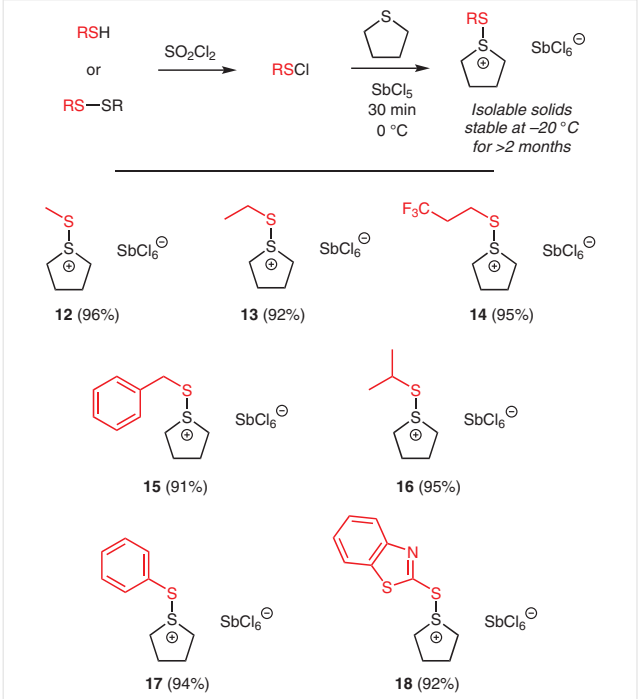
Just a short while ago, the Denmark group, in a landmark discovery contemporaneous with these efforts, reported the first cases of effective asymmetric polyene cyclizations initiated by thiiranium ions.[8] Their process used an appropriate chiral Lewis base with a distinct aryl sulfide electrophile in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) to convert electron-rich substrates such as **5** into **8** in good yield and with high levels of enantioselectivity. Despite this important advance, effecting the same reactions, even in racemic form, remains particularly challenging for alkyl sulfide-based systems, with additional tools beyond those of type **6** likely needed. Herein, we report a different approach for the preparation of a variety of isolable and reactive alkylsulfanium species, one that enhances significantly the



Scheme 1 Leading examples of C–C bond-forming cyclizations initiated by electrophilic sulfur reagents and inspiration for the design of new electrophilic tools

overall array of alkyl sulfides that can be directly incorporated into polyene cyclization products. Importantly, increased yields are observed for many substrates, particularly variants that performed poorly with reagents of type **6**. We also show that chiral versions of these reagents can afford modest levels of enantioselection.

Our design for new alkyl- and aryl sulfide electrophiles was inspired by the work of Pasquato and co-workers, wherein a potent alkyl sulfide electrophile was generated by the reaction of a chiral cyclic disulfide with MeSCl in the presence of $SbCl_5$.[9] This species could generate products such as **11** following asymmetric thiiranium opening with acetonitrile. We wondered if the use of a cyclic monosulfide could achieve appropriate activation of a variety of sulfides, hoping that with the right cyclic sulfide perhaps a more strained sulfonium species could be generated that could lead to even more effective sulfur transfer. As shown in Scheme 2, our optimized variant of that synthetic process combined tetrahydrothiophene with $SbCl_5$ and an array of sulfenyl chlorides generated either from commercial disulfide or thiol precursors using known procedures.[10] Following stirring of those three components at 0 °C for 30 minutes, subsequent filtration provided an array of semi-crystalline thiolane-based disulfanium salts **12–18** in yields greater than 90% on 1 mmol scale. Just like our previously prepared salts of type **6** (cf. Scheme 1),[6] these materials were challenging to characterize based on their seeming instability when dissolved in organic solvents. As such, their structures are assumed based on stoichiometry and the Pasquato precedent.[9] Despite that solvolytic instability, however, these materials were stable when stored at –20 °C for several months with disulfanium salt **12** retaining complete reactivity even when stored at 10 °C for one week.

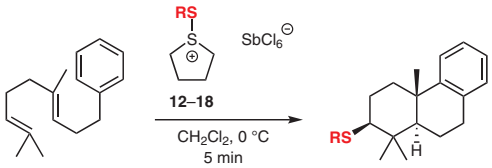


Scheme 2 Preparation of cycloalkyl disulfanium salts

To evaluate the power of this diverse array of new tools, each was reacted with substrate **5** to afford products **19–25** as shown in Table 1. In all cases, yields for the cyclization were good, ranging from 43–64%. Of note, relative to the yields we previously obtained for **19** and **20** using reagents of type **6** (cf. Scheme 1),[6] higher throughputs were obtained with salts **12** and **13**, while **14** was effectively commensurate in efficiency in producing **21** (Table 1, entries 1–3). Significantly, however, more hindered alkyl sulfides that we found challenging to prepare and utilize in reagent form **6**, such as those leading to the benzyl and isopropyl congeners **22** and **23**,[6] worked quite well here. For reasons that are presently unclear to us, compound **22** was initially obtained as a 4:1 mixture of diastereomers, though the major diaste-

reomer could be isolated in pure form; all other substrates effectively afforded single products. Finally, the aryl-based reagents performed equally well, with the success of reagent **18** providing a reactive handle within product **25** to potentially affect a Julia–Kocienski coupling if desired.[11] Worth noting is that strain within the reagents might be partially responsible for the efficiency of these transformations, as use of the 6-membered counterpart of **13** afforded **20** in slightly inferior yield (58%, compared to 64% in entry 2); the more highly strained 4-membered sulfide was not probed.

Table 1 Electrophilic Sulfur-Promoted Polyene Cyclization of Homogeranyl Benzene **5** Employing Disulfanium Salts **12–18**

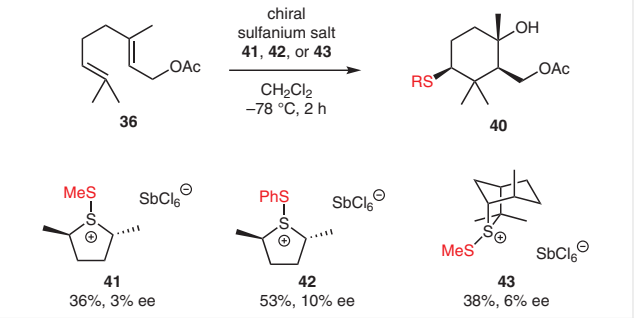


Entry	Sulfur reagent	Product	Yield (%)	Previous yield (%) from ref. 6
1	**12** (R = Me)	**19**	55	42
2	**13** (R = Et)	**20**	64	52
3	**14** (R = $CF_3CH_2CH_2$)	**21**	54	55
4	**15** (R = Bn)	**22**	43[a]	trace
5	**16** (R = *i*-Pr)	**23**	50	trace
6	**17** (R = Ph)	**24**	45	–
7	**18** (R = heteroaryl)	**25**	64	–

[a] Initially obtained as a 4:1 mixture of diastereomers; major diastereomer isolated in 35% yield.

To assess substrate scope in a broader sense, we elected to use reagent **13** for those purposes, viewing an ethyl-based electrophile as being arguably less reactive than some of the other alkyl-based alternatives (such as **12** and **14**) on both steric and electronic grounds. It was also an effective counterpoint to evaluate the reagent previously generated of type **6**[6] that could also transfer an ethyl sulfide unit. Table 2 provides the seven substrates that we have probed to date, including both electron-rich (Table 2, entries 1–5) as well as electron-deficient (entries 6 and 7) materials. With the exception of substrate **30**, reagent **13** outperformed the reagents of type **6** we previously prepared,[6] in some cases providing product where none had been observed before (entries 1 and 2), and in another more than doubling the throughput (entry 7).

Finally, to assess whether chiral, cyclic monosulfides could afford appropriate reagents for chiral transfer, we prepared three variants possessing two different scaffolds and two different electrophilic sulfur species for transfer.[12] In all cases, cyclization of **36** to **40** was achieved, though the chiral selection observed was generally low (55:45 er at best) (Scheme 3). Of note, some differences in both yield and enantioselection were observed based on the electrophile used (reagent **41** vs **42**), though it is hard to say at this point whether there is a great difference based on scaffold geometry (reagent **41** vs **43**).

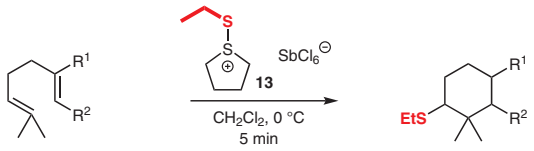


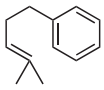
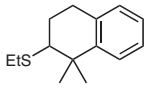
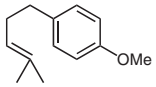
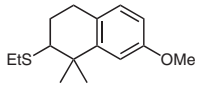
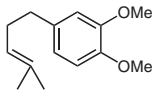
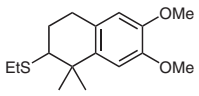
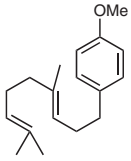
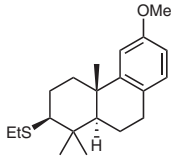
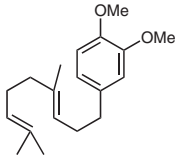
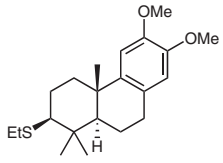
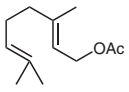
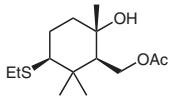
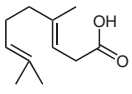
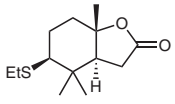
Scheme 3 Preliminary reaction of chiral disulfanium salts **41**, **42**, and **43** with geranyl acetate (**36**)

In conclusion, a more modular and variable approach has been developed to readily prepare an array of electrophilic sulfur transfer reagents that possess stability appropriate to storage, and also seem to have enhanced reactivity relative to previously explored thiiranium sources, particularly those that are alkyl-based. Future work seeks to build on these results, both in terms of generating additional electrophilic reagents of broad types based on this design as well as rendering these processes efficient with regards to enantioselection.[13]

All reactions were carried out under an argon atmosphere with anhydrous solvents under anhydrous conditions, unless otherwise noted. Anhydrous THF, toluene, Et_2O, CH_2Cl_2, and MeCN were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by TLC carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as visualizing agent, and an aqueous solution of cerium ammonium molybdate or a solution of $KMnO_4$ in aqueous $NaHCO_3$ and heat as developing agents. (2*R*,5*R*)-2,5-Dimethylthiolane,[2f] 2-benzothiazole disulfide,[14] and all monoalkene and polyene cyclization substrates[6] were prepared according to the procedures described in the literature. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative TLC separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. Standard abbreviations were used to explain the multiplicities. IR spectra were recorded on a PerkinElmer 1000 series FT-IR spectrophotometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (electro-

Table 2 Scope of Diverse Monoalkenes and Polyenes Cyclizations as Effected with Ethyldisulfanium Salt **12**



Entry	Substrate	Product	Yield (%)	Previous yield (%) from ref. 6
1	 **26**	 **27**	55	0
2	 **28**	 **29**	28	0
3	 **30**	 **31**	10[a]	52
4	 **32**	 **33**	50	50
5	 **34**	 **35**	37	29
6	 **36**	 **37**	42	35
7	 **38**	 **39**	47	20

[a] Protocyclization observed: 10%.

spray ionization) at the University of Chicago Mass Spectroscopy Core Facility. All er values were determined by HPLC on a Daicel CHIRALCEL OD-H column.

Disulfanium Salts; General Procedure

To a solution of the thiol or alkyl disulfide (1.0 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C was added SO_2Cl_2 (0.090 mL, 1.1 mmol, 1.1 equiv) dropwise. This mixture was stirred at 0 °C for 30 min, unless otherwise specified, and subsequently transferred to a flask containing tetrahydrothiophene (0.089 mL, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C followed by the dropwise addition of $SbCl_5$ (1.0 M solution in CH_2Cl_2, 1.0 mL, 1.0 mmol, 1.0 equiv). Upon completion, pentane (5 mL) was added and the mixture filtered to give the desired disulfanium salt as a semi-crystalline solid. The salt was dried under

vacuum for 10–20 min and then immediately stored at –20 °C. Due to their instability in typical organic solvents at 23 °C, all salts were characterized by ATR-FTIR spectroscopy and melting point analysis.

Methyl Disulfanium Salt (12)

Prepared from Me_2S_2 following the procedure above at –20 °C to afford **12** as a deep purple solid (0.450 g, 96%); mp 101–102 °C.

IR (film): 3337, 3005, 2942, 1444, 1306, 1271, 965, 872, 687 cm^{-1}.

Ethyl Disulfanium Salt (13)

Prepared from Et_2S_2 following the procedure above to afford **13** as an off-white solid (0.444 g, 92%); mp 88–89 °C.

IR (film): 3006, 2954, 2870, 1445, 1302, 1269, 1249, 893, 669 cm^{-1}.

3,3,3-Trifluoropropyl Disulfanium Salt (14)

Prepared from 3,3,3-trifluoropropane thiol following the procedure above to afford **14** as a grey solid (0.523 g, 95%); mp 75–78 °C.

IR (film): 2996, 2947, 1309, 1240, 1139, 1094, 870, 634 cm^{-1}.

Benzyl Disulfanium Salt (15)

Prepared from benzyl mercaptan following the procedure above to afford **15** as an orange-yellow solid (0.496 g, 91%); mp 64–65 °C.

IR (film): 2943, 1453, 1410, 1306, 1246, 872, 696 cm^{-1}.

Isopropyl Disulfanium Salt (16)

Prepared from isopropyl mercaptan following the procedure above to afford **16** as an off-white solid (0.472 g, 95%); mp 107–109 °C.

IR (film): 2949, 1443, 1411, 1306, 1249, 1048, 874 cm^{-1}.

Phenyl Disulfanium Salt (17)

Prepared from Ph_2S_2 following the procedure above, starting at 0 °C and slowly warming to 23 °C to afford **17** as a pale orange solid (0.500 g, 91%); mp 108–110 °C.

IR (film): 2994, 2945, 1442, 1400, 1305, 1270, 1247, 862, 764, 703, 690 cm^{-1}.

2-Benzothiazole Disulfanium Salt (18)

Prepared from benzothiazole disulfide following the procedure above starting at 0 °C and heating to reflux to afford **18** as a bright yellow solid (0.541 g, 92%); mp 118–119 °C.

IR (film): 3064, 1427, 1312, 1237, 1005, 756, 705, 669 cm^{-1}.

Chiral Phenyl Disulfanium Salt (42)

Prepared from Ph_2S_2 and (2*R*,5*R*)-2,5-dimethylthiolane following the procedure above, starting at 0 °C and slowly warming to 23 °C to afford **42** as a black solid (0.453 g, 94%); mp 92–93 °C.

IR (film): 2976, 2912, 1442, 1307, 1251, 999, 751, 684 cm^{-1}.

Thiiranium-Promoted Polyene Cyclizations Using Reagents 12–18; General Procedure

To a solution of the alkene substrate (0.1 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C was quickly added a solution of the disulfanium salt (0.11 mmol, 1.1 equiv) in CH_2Cl_2 (0.25 mL) in a single portion (see Tables 1 and 2). After stirring the resultant mixture for 5 min, the reaction contents were quenched by the addition of a sat. aq. $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to give a crude residue, which was further purified by flash column chromatography or preparative TLC as indicated.

Methyl(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (19)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 4:1), followed by preparative TLC (hexanes/CH_2Cl_2, 3:1) to afford **19** as a colorless oil (15.0 mg, 55%); R_f = 0.25 (hexanes/CH_2Cl_2, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.13 (tdt, *J* = 7.7, 1.6, 0.8 Hz, 1 H), 7.08 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.06–7.03 (m, 1 H), 3.00–2.83 (m, 2 H), 2.38 (dt, *J* = 13.1, 3.4 Hz, 1 H), 2.29 (dd, *J* = 12.7, 4.0 Hz, 1 H), 2.15 (s, 3 H), 2.12–2.06 (m, 1 H), 1.97–1.89 (m, 2 H), 1.82–1.70 (m, 1 H), 1.54–1.46 (m, 1 H), 1.39 (dd, *J* = 12.2, 2.2 Hz, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 0.94 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

Ethyl(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (20)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 4:1), followed by preparative TLC (hexanes/CH_2Cl_2, 3:1) to afford **20** as a colorless oil (18.0 mg, 64%); R_f = 0.25 (hexanes/CH_2Cl_2, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.16–7.11 (m, 1 H), 7.08 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.06–7.03 (m, 1 H), 2.96 (ddd, *J* = 17.2, 6.6, 1.9 Hz, 1 H), 2.87 (ddd, *J* = 17.4, 11.6, 7.2 Hz, 1 H), 2.58 (qq, *J* = 12.4, 7.4 Hz, 2 H), 2.39–2.33 (m, 2 H), 2.06 (dq, *J* = 14.0, 3.8 Hz, 1 H), 2.02–1.90 (m, 2 H), 1.82–1.70 (m, 1 H), 1.61–1.47 (m, 2 H), 1.39 (dd, *J* = 12.2, 2.2 Hz, 1 H), 1.27 (t, *J* = 7.4 Hz, 3 H), 1.22 (s, 6 H), 0.93 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

(3,3,3-Trifluoropropyl)(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (21)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 4:1), followed by preparative TLC (hexanes/CH_2Cl_2, 3:1) to afford **21** as a colorless oil (19.0 mg, 54%); R_f = 0.35 (hexanes/CH_2Cl_2, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.13 (td, *J* = 7.5, 1.7 Hz, 1 H), 7.09 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.05 (dd, *J* = 7.5, 1.6 Hz, 1 H), 2.96 (ddd, *J* = 17.3, 6.7, 1.9 Hz, 1 H), 2.91–2.84 (m, 1 H), 2.72 (qdd, *J* = 12.8, 9.7, 6.5 Hz, 2 H), 2.43–2.37 (m, 2 H), 2.36–2.33 (m, 2 H), 2.07–1.90 (m, 3 H), 1.82–1.70 (m, 1 H), 1.51 (ddd, *J* = 13.0, 10.9, 4.4 Hz, 1 H), 1.40 (dd, *J* = 12.1, 2.2 Hz, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 0.93 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

Benzyl(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (22)

The crude material was obtained as a mixture of diastereomers (4:1), which was purified by flash column chromatography (hexanes/CH_2Cl_2, 20:1), followed by preparative TLC (hexanes/CH_2Cl_2, 3:1) to afford the major diastereomer **22** as a pale yellow oil (11.4 mg, 35%); R_f = 0.30 (hexanes/CH_2Cl_2, 4:1).

IR (film): 3060, 3026, 2965, 2927, 1489, 1453, 1389, 756, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 4 H), 7.21 (dd, *J* = 7.7, 1.7 Hz, 2 H), 7.11 (t, *J* = 6.2 Hz, 1 H), 7.06 (dt, *J* = 7.1, 1.4 Hz, 1 H), 7.02 (dd, *J* = 7.2, 1.6 Hz, 1 H), 3.78 (d, *J* = 13.3 Hz, 1 H), 3.72 (d, *J* = 13.3 Hz, 1 H), 2.96 (dd, *J* = 16.8, 6.8 Hz, 1 H), 2.82 (ddd, *J* = 17.5, 11.6, 7.3 Hz, 1 H),

2.31 (dt, *J* = 13.1, 3.4 Hz, 1 H), 2.27–2.20 (m, 1 H), 2.00–1.91 (m, 2 H), 1.87 (ddt, *J* = 13.4, 7.3, 2.1 Hz, 1 H), 1.72 (dtd, *J* = 13.4, 11.9, 6.7 Hz, 1 H), 1.45–1.35 (m, 1 H), 1.30–1.25 (m, 2 H), 1.20 (s, 3 H), 1.05 (s, 3 H), 0.91 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.5, 139.0, 135.1, 129.1, 129.1, 56.4, 52.1, 39.2, 38.5, 37.9, 36.6, 30.8, 29.6, 28.0, 24.9, 19.9, 17.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{31}S^+$: 351.2141; found: 351.2142.

Isopropyl(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (23)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 5:1), followed by preparative TLC (hexanes/CH_2Cl_2, 3:1) to afford **23** as a colorless oil (15.0 mg, 50%); R_f = 0.26 (hexanes/CH_2Cl_2, 4:1).

IR (film): 3060, 2966, 2928, 2361, 1489, 1450, 1042, 758, 722 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.12 (t, *J* = 7.7 Hz, 1 H), 7.08 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.04 (dd, *J* = 7.6, 1.7 Hz, 1 H), 3.00–2.83 (m, 3 H), 2.39–2.32 (m, 2 H), 2.07–1.90 (m, 3 H), 1.81–1.72 (m, 1 H), 1.51 (dt, *J* = 11.1, 6.6 Hz, 1 H), 1.40 (dd, *J* = 12.2, 2.2 Hz, 1 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 1.27 (d, *J* = 7.1 Hz, 3 H), 1.21 (d, *J* = 3.3 Hz, 6 H), 0.92 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.6, 135.2, 129.1, 125.9, 125.5, 124.6, 56.1, 52.3, 39.5, 38.5, 37.9, 35.3, 30.9, 29.8, 29.4, 25.0, 24.13, 24.07, 20.0, 17.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{31}S^+$: 303.2141; found: 303.2147.

Phenyl(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (24)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 4:1) to afford **24** as a colorless oil (15.1 mg, 45%); R_f = 0.33 (hexanes/CH_2Cl_2, 4:1).

IR (film): 3070, 3057, 2965, 2935, 2360, 1456, 1437, 757, 734, 722, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.39 (m, 2 H), 7.32–7.25 (m, 2 H), 7.23–7.18 (m, 2 H), 7.11 (td, *J* = 8.0, 7.5, 1.9 Hz, 1 H), 7.08 (td, *J* = 7.2, 1.5 Hz, 1 H), 7.04 (dd, *J* = 7.6, 1.8 Hz, 1 H), 3.00–2.84 (m, 6.0 Hz, 3 H), 2.31 (dt, *J* = 13.1, 3.4 Hz, 1 H), 2.08–1.99 (m, 2 H), 1.99–1.92 (m, 1 H), 1.85–1.74 (m, 1 H), 1.51–1.47 (m, 1 H), 1.45 (dd, *J* = 12.2, 2.2 Hz, 1 H), 1.32 (s, 3 H), 1.23 (s, 3 H), 1.04 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.4, 137.0, 135.1, 131.5, 129.1, 129.0, 126.5, 125.9, 125.5, 124.6, 61.1, 52.4, 39.2, 38.8, 38.0, 30.9, 30.2, 28.1, 25.0, 19.9, 17.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{29}S^+$: 337.1984; found: 337.1983.

(2-Benzothiazole)(1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (25)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 1:1), followed by preparative TLC (hexanes/EtOAc, 10:1) to afford **25** as a colorless oil (25.0 mg, 64%); R_f = 0.76 (hexanes/EtOAc, 4:1).

IR (film): 3060, 2964, 2942, 2360, 1456, 1426, 989, 755, 724 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.1 Hz, 1 H), 7.74 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.14 (td, *J* = 7.4, 1.7 Hz, 1 H), 7.10 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.06 (dd, *J* = 7.5, 1.7 Hz, 1 H), 3.95 (dd, *J* = 12.8, 4.1 Hz, 1 H), 3.03–2.86 (m, 2 H), 2.40 (dt, *J* = 13.1, 3.5 Hz, 1 H), 2.32 (dq, *J* = 13.9, 3.8 Hz, 1 H), 2.15 (qd, *J* = 13.5, 3.4 Hz, 1 H), 1.97 (ddt, *J* = 13.3, 7.1, 2.1 Hz, 1 H), 1.87–1.69 (m, 3 H), 1.61 (dd, *J* = 12.2, 2.2 Hz, 1 H), 1.28 (s, 3 H), 1.27 (s, 3 H), 1.06 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.6, 153.5, 149.2, 135.5, 135.0, 129.1, 126.1, 126.0, 125.7, 124.6, 124.2, 121.7, 121.0, 60.6, 52.2, 39.2, 38.8, 37.9, 30.8, 30.0, 28.4, 25.0, 20.0, 18.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{28}NS_2^+$: 394.1658; found: 394.1650.

(1,1-Dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)(ethyl)sulfane (27)

The crude material was purified by preparative TLC (hexanes/CH_2Cl_2, 4:1) to afford **27** as a colorless oil (12.0 mg, 55%); R_f = 0.31 (hexanes/CH_2Cl_2, 4:1).

IR (film): 3026, 2964, 2927, 2868, 1489, 1457, 1263, 1042, 758, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.6 Hz, 2 H), 7.24–7.17 (m, 2 H), 3.13 (ddd, *J* = 14.2, 10.1, 4.6 Hz, 1 H), 2.84 (s, 1 H), 2.73–2.58 (m, 2 H), 2.46 (dd, *J* = 11.7, 2.3 Hz, 1 H), 2.08–1.99 (m, 1 H), 1.66–1.59 (m, 1 H), 1.29 (t, *J* = 7.5 Hz, 3 H), 1.27 (s, 3 H), 1.15 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.0, 128.60, 128.59, 128.57, 128.56, 126.1, 72.8, 61.2, 34.7, 34.5, 29.0, 27.1, 25.7, 15.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}S^+$: 221.1358; found: 221.1356.

(7-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)(ethyl)sulfane (29)

The crude material was purified by flash column chromatography (hexanes/CH_2Cl_2, 2:1), followed by preparative TLC (hexanes/EtOAc, 20:1) to afford **29** as a pale yellow oil (6.8 mg, 28%); R_f = 0.74 (hexanes/EtOAc, 4:1).

IR (film): 2965, 2931, 2870, 2833, 1610, 1504, 1251, 1186, 1076, 1046, 804 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 8.4 Hz, 1 H), 6.87 (s, 1 H), 6.68 (d, *J* = 8.3 Hz, 1 H), 3.79 (s, 3 H), 2.88 (d, *J* = 16.8 Hz, 1 H), 2.82–2.72 (m, 2 H), 2.67–2.56 (m, 2 H), 2.24–2.16 (m, 1 H), 2.06–1.95 (m, 1 H), 1.51 (s, 3 H), 1.33–1.25 (m, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.0, 146.8, 129.8, 127.2, 112.5, 111.6, 55.4, 54.4, 39.1, 30.0, 29.2, 27.5, 27.3, 26.3, 15.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}OS^+$: 251.1464; found: 251.1471.

(6,7-Dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)(ethyl)sulfane (31)

The crude material was purified by flash column chromatography (hexanes/EtOAc, 2:1) to afford **31** as a colorless oil (3.0 mg, 10%); R_f = 0.47 (hexanes/EtOAc, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 (s, 1 H), 6.51 (s, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 2.88–2.73 (m, 3 H), 2.68–2.56 (m, 2 H), 2.23–2.17 (m, 1 H), 2.05–1.97 (m, 1 H), 1.50 (s, 3 H), 1.30 (t, *J* = 7.3 Hz, 3 H), 1.28 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

Ethyl(6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)sulfane (33)

The crude material was purified by preparative TLC (hexanes/EtOAc, 6:1) to afford **33** as a colorless oil (16.0 mg, 50%); R_f = 0.73 (hexanes/EtOAc, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.97 (dd, *J* = 8.4, 1.1 Hz, 1 H), 6.78 (d, *J* = 2.7 Hz, 1 H), 6.67 (dd, *J* = 8.4, 2.6 Hz, 1 H), 3.77 (s, 3 H), 2.90 (ddd, *J* = 16.7, 6.5, 1.8 Hz, 1 H), 2.84–2.75 (m, 1 H), 2.58 (qq, *J* = 12.4, 7.4 Hz, 2 H), 2.39–2.28 (m, 2 H), 2.05 (dq, *J* = 14.0, 3.8 Hz, 1 H), 2.00–1.88 (m, 2 H), 1.80–1.68 (m, 1 H), 1.50 (td, *J* = 13.2, 3.8 Hz, 1 H), 1.37 (dd, *J* = 12.1, 2.2 Hz, 1 H), 1.26 (t, *J* = 7.4 Hz, 3 H), 1.23–1.19 (m, 6 H), 0.92 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

(6,7-Dimethoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)(ethyl) sulfane (35)

The crude material was purified by flash column chromatography (hexanes/EtOAc, 7:1), followed by preparative TLC (hexanes/EtOAc, 4:1) to afford **35** as a colorless oil (12.8 mg, 37%); R_f = 0.48 (hexanes/EtOAc, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 2.8 Hz, 1 H), 6.52 (s, 1 H), 3.84 (s, 3 H), 2.82 (qd, *J* = 16.8, 6.8 Hz, 2 H), 2.66–2.50 (m, 2 H), 2.33 (ddd, *J* = 28.6, 10.1, 3.5 Hz, 2 H), 2.09–2.01 (m, 1 H), 1.93 (dt, *J* = 17.5, 9.6 Hz, 2 H), 1.73 (dt, *J* = 18.6, 11.9 Hz, 1 H), 1.49 (t, *J* = 13.2 Hz, 1 H), 1.36 (d, *J* = 12.1 Hz, 1 H), 1.26 (t, *J* = 7.4 Hz, 3 H), 1.21 (d, *J* = 2.8 Hz, 6 H), 0.91 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

{6-Hydroxy-2,2,6-trimethyl-3-[(ethyl)thio]cyclohexyl}methyl Acetate (37)

The crude material was purified by flash column chromatography (hexanes/EtOAc, 10:1 → 1:1) to afford **37** as a colorless oil (11.5 mg, 42%); R_f = 0.5 (hexanes/EtOAc, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.38 (dd, *J* = 11.8, 5.4 Hz, 1 H), 4.31 (dd, *J* = 11.9, 4.9 Hz, 1 H), 2.62–2.48 (m, 3 H), 2.34 (dd, *J* = 12.5, 3.8 Hz, 1 H), 2.06 (s, 3 H), 1.98 (dq, *J* = 13.9, 3.6 Hz, 1 H), 1.84 (dt, *J* = 12.9, 3.3 Hz, 1 H), 1.69–1.57 (m, 2 H), 1.50 (td, *J* = 13.4, 3.7 Hz, 1 H), 1.25 (t, *J* = 7.4 Hz, 3 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 0.85 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

5-(Ethylthio)-4,4,7a-trimethylhexahydrobenzofuran-2(3*H*)-one (39)

The crude material was purified by flash column chromatography (hexanes/EtOAc, 10:1 → 1:1) to afford **39** as a colorless oil (11.4 mg, 47%); R_f = 0.38 (hexanes/EtOAc, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.57 (ttd, *J* = 12.4, 7.4, 5.0 Hz, 2 H), 2.48 (dd, *J* = 16.4, 14.7 Hz, 1 H), 2.43–2.37 (m, 1 H), 2.34 (dd, *J* = 16.3, 6.6 Hz, 1 H), 2.24–2.15 (m, 1 H), 2.07–1.98 (m, 2 H), 1.74 (ddt, *J* = 9.0, 7.3, 2.0 Hz, 2 H), 1.35 (s, 3 H), 1.26 (t, *J* = 7.4 Hz, 3 H), 1.13 (s, 3 H), 0.89 (s, 3 H).

Note that all NMR data matched that previously reported.[6]

5-(Phenylthio)-4,4,7a-trimethylhexahydrobenzofuran-2(3*H*)-one (40)

To a solution of geranyl acetate (**36**; 0.021 mL, 0.1 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) at –78 °C was quickly added a solution of the chiral phenyl disulfanium salt **42** (0.062 g, 0.11 mmol, 1.1 equiv, prepared by same method described above) in CH_2Cl_2 (0.25 mL) all at once. After stirring for 2 h at –78 °C, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (5 mL), warmed to 23 °C, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to give a crude residue, which was further purified by flash column chromatography (hexanes/EtOAc, 3:1) to afford **40** as a colorless oil (17.0 mg, 53%, 45:55 er); R_f = 0.49 (hexanes/EtOAc, 1:1).

Note that similar reaction scales were used in the investigations with the other chiral disulfanium salts.

HPLC: OD-H column, 1.0 mL/min, hexanes/*i*-PrOH (9:1), 36 °C, 254 nm; t_R (major) = 6.37 min, t_R (minor) = 9.48 min (55:45 er).

IR (film): 3461, 3057, 2970, 2938, 2873, 1736, 1479, 1368, 1245, 1026, 740, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 2 H), 7.29 (t, *J* = 8.4 Hz, 2 H), 7.25–7.20 (m, 1 H), 4.42 (dd, *J* = 11.8, 5.2 Hz, 1 H), 4.33 (dd, *J* = 11.8, 5.0 Hz, 1 H), 2.88 (dd, *J* = 12.5, 3.8 Hz, 1 H), 2.07 (s, 3 H), 1.95 (dq, *J* = 14.2, 3.7 Hz, 1 H), 1.80 (dt, *J* = 13.1, 3.4 Hz, 1 H), 1.75–1.65 (m, 2 H), 1.46 (td, *J* = 13.5, 4.0 Hz, 1 H), 1.33 (s, 3 H), 1.23 (s, 3 H), 0.96 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.2, 136.4, 132.0, 129.1, 126.9, 72.1, 63.2, 60.7, 56.9, 42.6, 39.2, 29.9, 29.0, 23.8, 21.4, 17.6.

HRMS (ESI): *m*/*z* [M + H^+ – H_2O] calcd for $C_{18}H_{25}O_2S^+$: 305.1570; found: 305.1574.

Acknowledgment

We thank Dr. Florian Schevenels for the preparation of substrates **30**, **32**, and **34**, Dr. Jennifer Pitzen for the preparation of substrate **38**, Mr. Jonathan Keim and Mr. Minxing Shen for helpful discussions, and Dr. Antoni Jurkiewicz and Dr. C. Jin Qin for assistance with NMR and mass spectrometry, respectively. Financial support for this work came from the University of Chicago and includes a Metcalf Fellowship that supported the work and training of K.C.D. during the summer of 2017.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609754.

References

(1) For a recent review on cation-π cyclization chemistry see: Snyder, S. A.; Levinson, A. M. In *Comprehensive Organic Synthesis*, 2nd ed., Vol. 3, Part 5; Knochel, P.; Molander, G. A., Eds.; Elsevier: Amsterdam, **2014**, 268–291; and references cited therein.

(2) (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. (b) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898. (d) Snyder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I. *J. Am. Chem. Soc.* **2012**, *134*, 17714. (e) Brucks, A. P.; Treitler, D. S.; Liu, S.-A.; Snyder, S. A. *Synthesis* **2013**, *45*, 1886. (f) Shen, M.; Kretschmer, M.; Brill, Z. G.; Snyder, S. A. *Org. Lett.* **2016**, *18*, 5018.

(3) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (b) Hartmann, E.; Denmark, S. E. *Helv. Chim. Acta* **2017**, *100*, e1700158; doi: 10.1002/hlca.201700158.

(4) (a) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308. (b) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419. (c) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915.

(5) (a) Edstrom, E.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1986**, 279. (b) Edstrom, E.; Livinghouse, T. *J. Am. Chem. Soc.* **1986**, *108*, 1334. (c) Edstrom, E.; Livinghouse, T. *J. Org. Chem.* **1987**, *52*, 949. (d) Harring, S. R.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 6388. For a more recent example, see: (e) Moore, J. T.; Soldi, C.; Fettinger, J. C.; Shaw, J. T. *Chem. Sci.* **2013**, *4*, 292.

(6) Schevenels, F. T.; Shen, M.; Snyder, S. A. *Org. Lett.* **2017**, *19*, 2.

(7) For a review, see: (a) Adams, E. J.; Oscarson, S. *Dimethyl(methylthio)sulfonium Tetrafluoroborate (DMTSF), In e-Encyclopedia of Reagents for Organic Synthesis* **2005**, doi: 10.1002/047084289X.rd349.pub2. For the original reagent disclosure, see: (b) Meerwein, H.; Zenner, K.-F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, *688*, 67. For an early reagent of related design, see: (c) Helmkamp, G. K.; Cassey, H. N.; Olsen, B. A.; Pettitt, D. J. *J. Org. Chem.* **1965**, *30*, 933. For representative uses in synthesis, see: (d) Trost, B. M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, *104*, 3225. (e) Trost, B. M.; Shibata, T.; Martin, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 3228. (f) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231. (g) Trost, B. M.; Martin, S. F. *J. Am. Chem. Soc.* **1984**, *106*, 4263. (h) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6159.

(8) Tao, Z.; Robb, K.; Zhao, K.; Denmark, S. E. *J. Am. Chem. Soc.* **2018**, *140*, 3569.

(9) Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.* **1994**, *13*, 1565.

(10) For general preparative methods of alkyl and aryl sulfenyl chlorides, see: (a) Organ, H. M. *Methanesulfenyl Chloride*, In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, **2001**. (b) Zelčans, G.; Hutton, T. K.; Rios, R.; Shibata, N. *Benzenesulfenyl Chloride*, In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, **2001**.

(11) The recent polyene cyclization paper by Denmark[8] illustrates just such an example, indicating that the neighboring dimethyl substituents do not prevent effective reaction.

(12) For selected examples using chiral sulfonium species see: (a) Breau, L.; Ogilvie, W. W.; Durst, T. *Tetrahedron Lett.* **1990**, *31*, 35. (b) Julienne, K.; Metzner, P.; Henryon, V.; Greiner, A. *J. Org. Chem.* **1998**, *63*, 4532. (c) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731. (d) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620. (e) Zanardi, J.; Lamazure, D.; Minière, S.; Reboul, V.; Metzner, P. *J. Org Chem.* **2002**, *67*, 9083. (f) Davoust, M.; Cantagrel, F.; Metzner, P.; Brière, J.-F. *Org. Biomol. Chem.* **2008**, *6*, 1981. (g) Illa, O.; Namutebi, M.; Saha, C.; Ostovar, M.; Chen, C. C.; Haddow, M. F.; Nocquet-Thibault, S.; Lusi, M.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 11951.

(13) For example, switching sulfides for certain diphosphines in this same design has led to effective generation of HCl, HBr, DCl, and DBr on laboratory scale: (a) Schevenels, F. T.; Shen, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2017**, *139*, 6329. For a general and excellent set of reviews on the presence of sulfur in pharmaceutical molecules, see: (b) Ilardi, R. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (c) Smith, B. R.; Eastman, C. M.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 9764.

(14) Párkányi, C.; Abdelhamid, A. O. *Heterocycles* **1985**, *23*, 2917.