Dealkenylative thiylation of C(sp^3)–C(sp^2) bonds

Andrew J. Smaligo and Ohyun Kwon*

Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095-1569, United States

Supporting Information Placeholder

ABSTRACT: Carbon–carbon bond fragmentations are useful methods for the functionalization of molecules. The value of such cleavage events is maximized when paired with a subsequent bond formation. Herein we report a protocol for the cleavage of a C(sp^3)–C(sp^2) bond, followed by the formation of a new C(sp^3)–S bond. This reaction is performed in non-anhydrous solvent and open to the air, employs common starting materials, and can be used to rapidly diversify natural products. We have also subjected the thiylated products to various synthetic transformations, demonstrating their utility as synthetic intermediates.

The formation of carbon–heteroatom bonds in organic compounds is an important step in the synthesis of many drug molecules. After oxygen and nitrogen, sulfur is the heteroatom found most frequently in FDA-approved drugs (Figure 1A).[1] Thioethers and their higher-oxidation-state derivatives are also versatile and widely used synthetic intermediates.[2] Some of the most prevalent means of alkyl aryl thioether synthesis are alkylation (e.g., S_N2, Mitsunobu reaction), addition to unsaturated bonds (e.g., Michael addition, hydrothiylation), and cross-coupling.[2] Less frequent are reports of trapping of a carbon radical with an aryl disulfide species (Figure 1B), a transformation that typically requires the use of specialized radical precursors (*e.g.*, organometallic species, Barton esters, trialkyl boranes), carboxylic acids, or simple alkanes.[3–10] This approach is limited in its applicability because of the syntheses of the requisite coupling partners, harsh reaction conditions (high temperatures, long reaction times), and low selectivity for C–H abstraction (in the case of alkane starting materials). Consequently, a more broadly applicable method for the generation of carbon radicals from readily available starting materials, including natural products, would be highly useful.

Recent methodological advancements in the area of C–C bond activation have enabled a number of powerful transformations. Specifically, C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) bond fragmentations have proven to be effective methods for functionalizing molecules, with regard to both total synthesis and the preparation of pharmaceutically relevant compounds.[11–15] The value of such transformations can be increased when paired with a subsequent bond-forming event. Nevertheless, reports of C(sp^3)–C(sp^2) bond cleavage followed by C(sp^3)–heteroatom bond formation remain scarce (e.g., Baeyer–Villiger oxidation[16,17]), despite the ubiquity of alkenes in organic molecules, especially within natural products.[18] In this paper, we report a simple method for the dealkenylative thiylation of alkenes (**1**) to give alkyl aryl sulfides (**3**) under mild conditions (Figure 1C). We have found that alkyl radicals generated through the single electron transfer (SET)-based reductive cleavage of α-alkoxy hydroperoxides[15,19–23] (generated during the ozonolysis of alkenes **1**) can be trapped with an aryl disulfide (**2**)

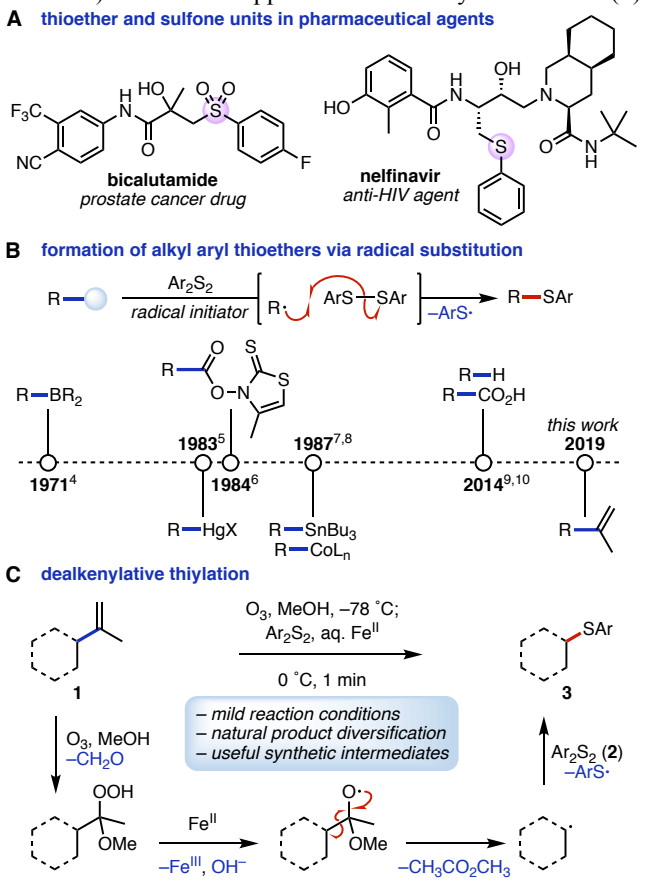


Figure 1. (A) Two examples of pharmaceuticals featuring aryl alkyl thioether and sulfone units. (B) Timeline of the formation of aryl alkyl thioethers through radical substitution. (C) Mechanism of dealkenylative thiylation.

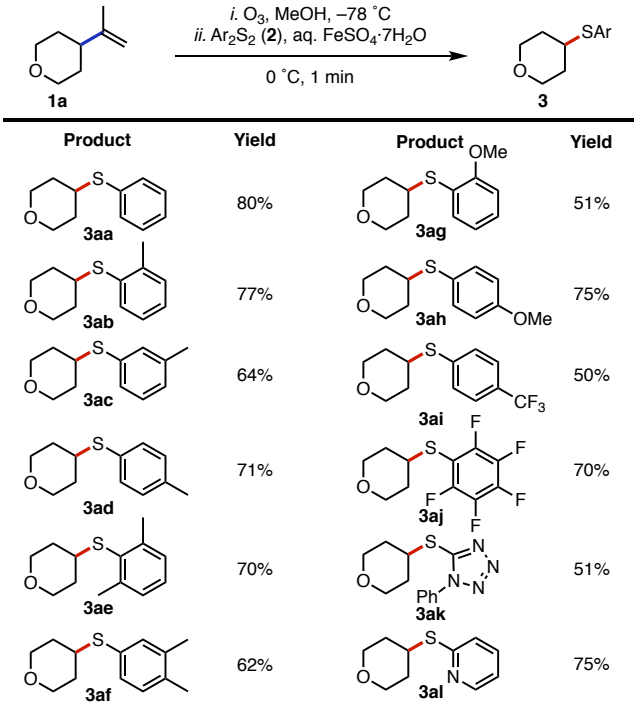


Figure 2. Substrate scope of the aryl disulfide coupling partner in the dealkenylative thiylation of **1a**. Experiments performed on 1.0 mmol scale. Isolated yields after SiO_2 chromatography. See the SI for experimental details.

to form a new C(sp^3)–S bond in **3**. In contrast to previously reported carbon radical-based methods for C(sp^3)–S bond formation, this transformation is performed under mild reaction conditions (below room temperature, within 1 min, open to air, non-anhydrous solvent), employs common olefins as starting materials, and is stereoselective when the starting materials contain stereocenters.

A survey of the reaction parameters revealed the optimal conditions for the dealkenylative thiylation to be ozonolysis of the alkene at –78 °C in methanol, followed by treatment with 3.0 equivalents of the aryl disulfide and 1.2 equivalents of ferrous sulfate heptahydrate (added as a 5 wt/vol% aqueous solution[24]) at 0 °C (see Table S1 in the Supporting Information for details). Under these optimized conditions and using 4-isopropenyltetrahydropyran (**1a**) as our alkene substrate, we examined the scope of the aryl disulfide reaction partner (Figure 2). Phenyl disulfide (**2a**) gave the product **3aa** in 80% yield, while various tolyl and xylyl disulfides also produced their thiylation products **3ab**–**3af** in yields of 62–77%. Electron-rich and -poor aryl disulfides were competent partners, generating the expected products **3ag**–**3aj** in yields of 50–75%. 1-Phenyltetrazol-5-yl and 2-pyridyl disulfides, notable for use of their thioether and sulfone derivatives in cross-coupling reactions,[25] were also compatible, providing the thioethers **3ak** and **3al** in yields

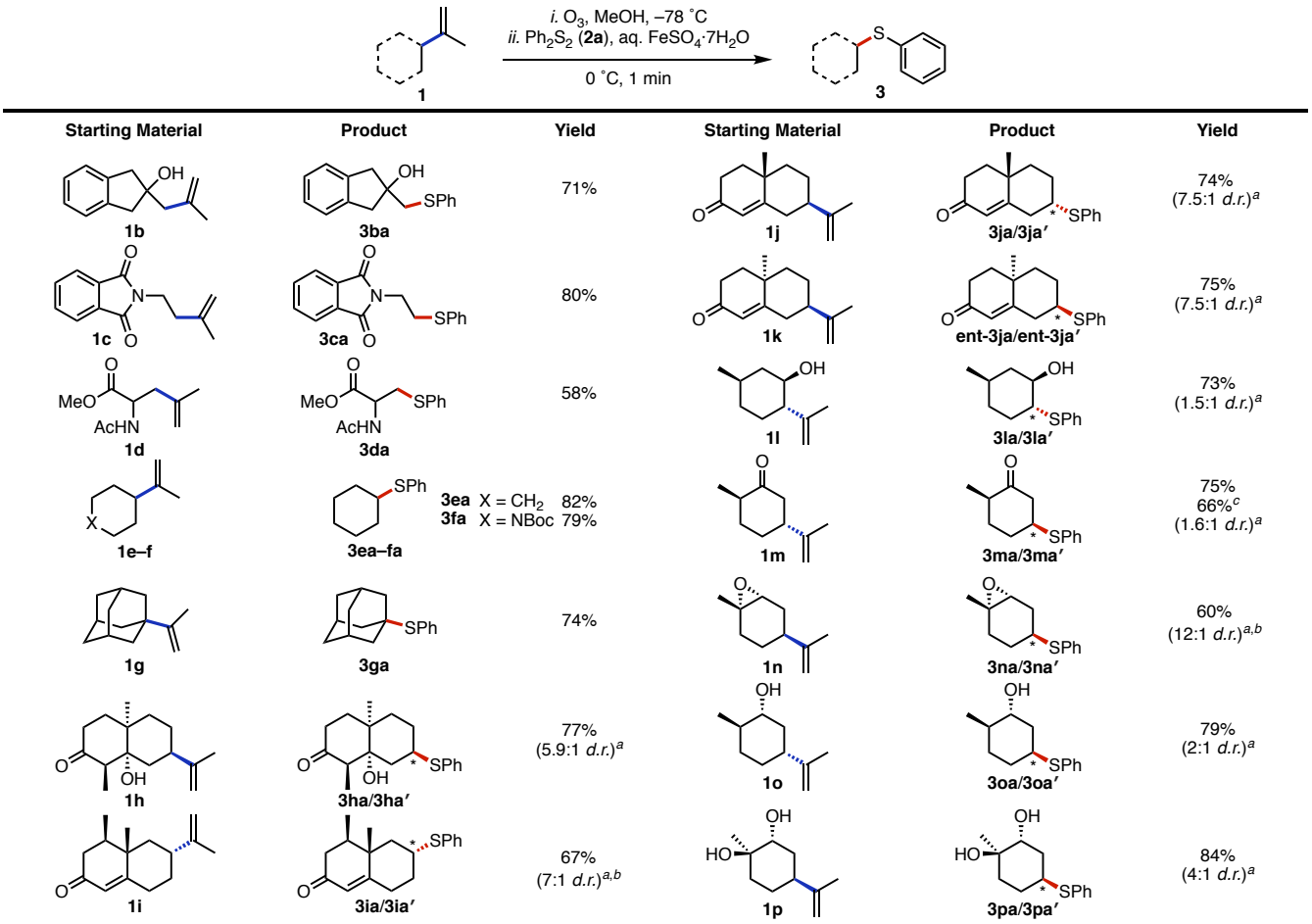


Figure 3. Substrate scope of alkene coupling partner. Experiments performed on 1.0 mmol scale. Isolated yields after SiO_2 chromatography. See the SI for experimental details. [a]Major diastereoisomer displayed. [b]Inseparable mixture of diastereoisomers. [c]10.0 mmol scale.

of 51 and 75%, respectively. Attempts to employ dialkyl disulfides as coupling partners were unfruitful, presumably because of side reactions resulting from the generation of reactive alkylthiyl radical intermediates.[3]

Subsequently, we investigated the substrate scope of the alkene coupling partner (Figure 3). The primary radical precursors **1b**–**1d** supplied the thioethers **3ba**–**3da** in yields of 58–80%. Secondary (**1e**, **1f**) and tertiary (**1g**) radical precursors were also compatible, furnishing the desired products **3ea**–**3ga** in yields of 74–82%. The reaction was tolerant to a range of functionalities, including alcohol, imide, amide, carboxylic ester, and carbamate groups. A powerful feature of the reaction is the ability to introduce heteroatom functionality in terpenoid [e.g., (+)-nootkatone, **1i**] and terpenoid-derived starting materials. The bicyclic ketones **1h**–**1k** gave their corresponding products in yields of 67–77% (5.9:1 to 7.5:1 *d.r.*). Notably, dealkenylative thiylation of the diastereoisomeric enones **1j** and **1k** resulted in the same distribution of product isomers. This observation is consistent with stereoselectivity trends commonly observed in reactions with cyclic radicals, in which the stereoselectivity of the addition is dictated by a combination of torsional and steric effects.[26] The commonly available terpenoids (–)-isopulegol (**1l**), *trans*-(+)-dihydrocarvone (**1m**), *cis*-(–)-limonene oxide (**1n**), (–)-dihydrocarveol (**1o**), and (–)-limonene-1,2-diol (**1p**) were also viable substrates, producing their products **3la**–**3pa**, respectively, in yields of 60–84%. When run using 10 mmol of *trans*-(+)-dihydrocarvone (**1m**), the reaction produced the thioethers **3ma**/**3ma′** in 66% yield. With the

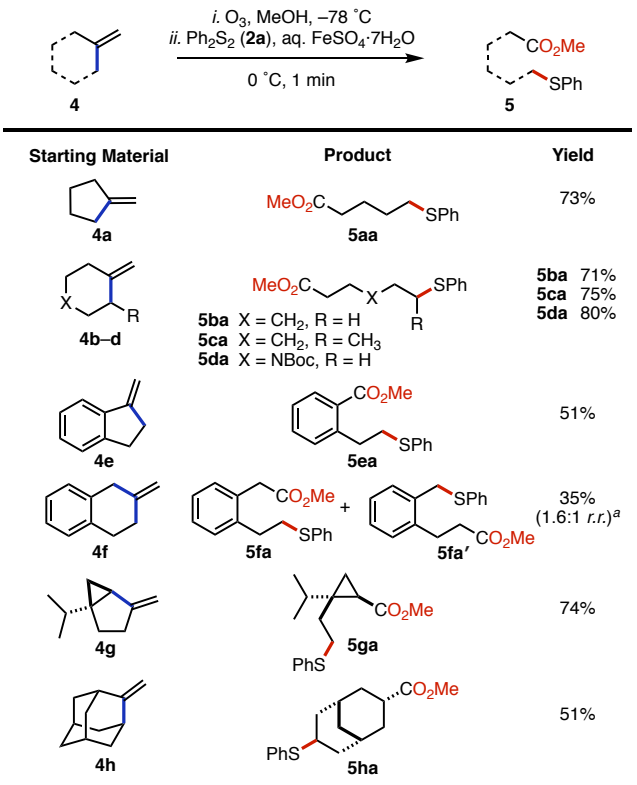


Figure 4. Dealkenylative thiylation of exo-methylene cycloalkanes. Experiments performed on 1.0 mmol scale. Isolated yields after SiO_2 chromatography. See the SI for experimental details. [a]Inseparable mixture of regioisomers.

exception of **3na** (12:1 *d.r.*), the diastereoisomeric ratios of the products from the monoterpenoids were lower (in the range from 1.5:1 to 4:1) than those of the decalinone substrates **1h**–**1k**.

Next, we found that alkenes containing exo-methylene groups (**4**) were converted into the corresponding phenylthiyl-containing methyl carboxylates (**5**) (Figure 4). The simple cycloalkenes **4a** and **4b** generated their products **5aa** and **5ba** cleanly in yields of 73 and 71%, respectively. 1-Methylene-2-methylcyclohexane (**4c**) provided its product **5ca** in 75% yield, while the Boc-protected piperidine **4d** also cleanly supplied the thioether **5da** in 80% yield. 1-Methyleneindane (**4e**) furnished its product **5ea** in 51% yield, while 2-methylenetetralin (**4f**) displayed the poorest efficiency, providing **5fa**/**5fa′** (1.6:1 *r.r.*) in only 35% yield. The naturally occurring terpene (±)-sabinene (**4g**) produced a single diastereoisomer of the trisubstituted cyclopropane **5ga** in 74% yield. Fragmentative coupling of methyleneadamantane (**4h**) also generated the *exo*-phenylthio ester **5ha** exclusively in 51% yield.

Cycloalkenes bearing endocyclic olefins (**6**) were also competent substrates, providing phenylthio-aldehydes (**7**) as products (Figure 5). Simple hydrocarbon substrates (**6a**–**6c**) supplied the expected products **7aa**–**7ca**, respectively, in yields from 63 to 75%. (+)-2-Carene (**6d**) furnished a

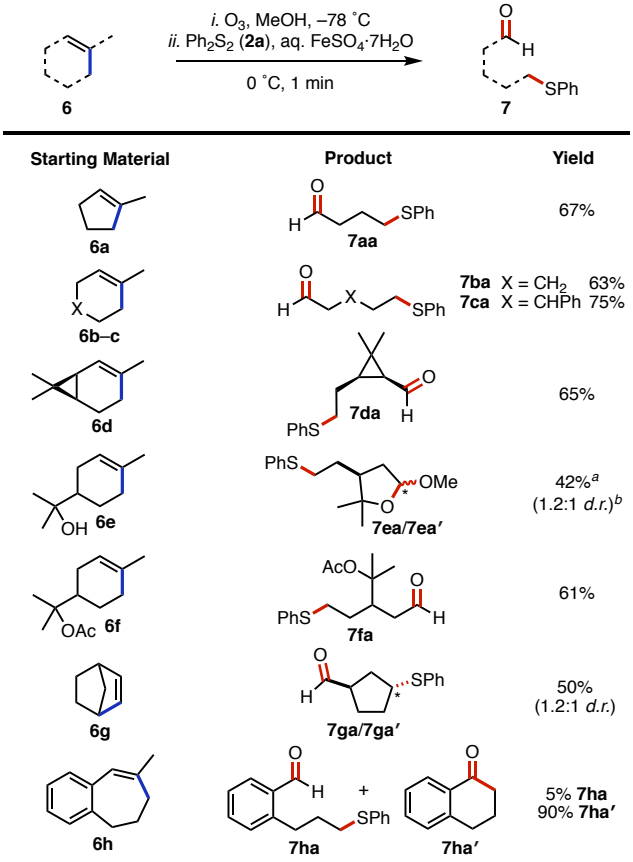


Figure 5. Dealkenylative thiylation of cyclic alkenes. Experiments performed on 1.0 mmol scale. Isolated yields after SiO_2 chromatography. See the SI for experimental details. [a]Solid $FeSO_4 \cdot 7H_2O$ was added at room temperature. [b]Inseparable mixture of diastereoisomers.

single diastereoisomer of the tetrasubstituted cyclopropane **7da** in 65% yield. α-Terpineol (**6e**) gave the cyclic ketals **7ea**/**7ea′** in 42% yield (1.2:1 *d.r.*), the result of intramolecular trapping of the aldehyde; in contrast, the corresponding acetate **6f** produced the uncyclized product **7fa** in 61% yield. Upon fragmentation, norbornylene (**6g**) generated the products **7ga** and **7ga′** (1.2:1 *d.r.*) in 50% yield. Intriguingly, attempts to extend this transformation to generate benzaldehydes resulted in cyclization of the intermediate radical, rather than trapping with the disulfide species. 6-Methyl-5,6-didehydrobenzocycloheptane (**6h**) provided the desired product **7ha** in only 5% yield, while generating α-tetralone (**7ha′**) in 90% yield.[27]

Figure 6 presents several examples of synthetic applications in which we have employed this transformation. With regard to medicinal agents, this process should be a powerful tool for the generation of new leads in drug discovery. For example, we examined the reaction of betulin (**1q**), which has wide biological activities (in particular, anti-cancer properties)[28] and features a structure more complex than those presented in Figure 3. Notably, the introduction of a heteroatom at the C-19 position of betulin is practically unknown, despite the numerous reported synthetic modifications to this scaffold.[28,29]

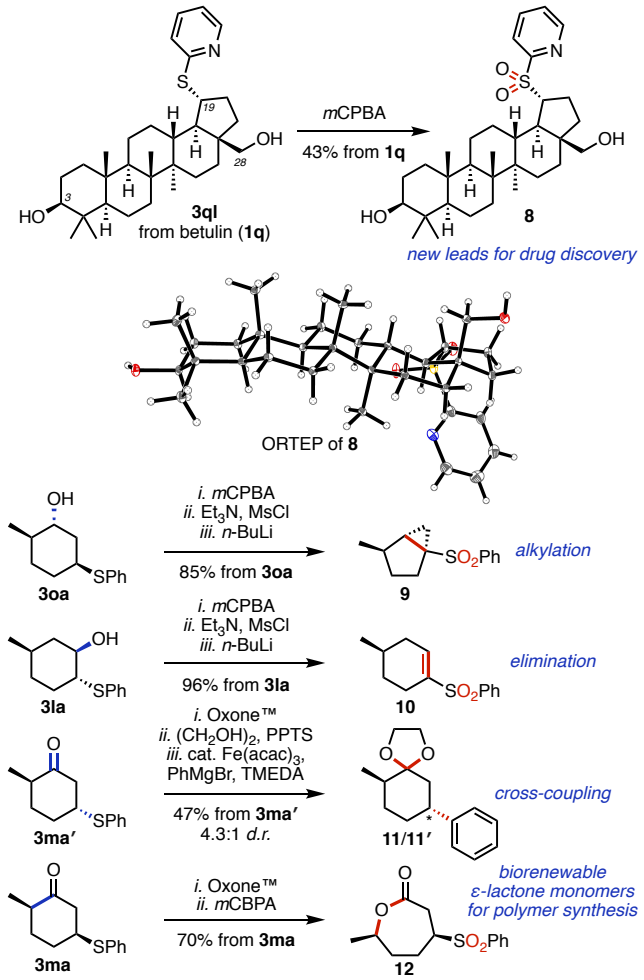


Figure 6. Synthetic transformations of the thioether products. Experiments performed on ≥0.5 mmol scale. Isolated yields after SiO_2 chromatography. See the SI for experimental details.

Dealkenylative thiylation of betulin readily furnished the thioethers **3ql** and **3ql′** in 78% yield (1.2:1 *d.r.*). Subsequent oxidation of the major diastereoisomer (**3ql**) gave the sulfone **8** (see ORTEP of the solid state structure in Figure 6) in 43% overall yield from betulin, providing facile access to previously inaccessible derivatives of this natural product. Sulfones and sulfides are also useful functional group handles that are used widely in organic synthesis. When dealkenylative thiylation is combined with terpenoid precursors, enantiopure synthetic intermediates are generated readily. Oxidation, mesylation, and intramolecular alkylation of the dihydrocarveol-derived thioether **3oa** produced the enantiomerically pure bicyclo[3.1.0]hexane **9** in 85% overall yield. Vinyl sulfides and sulfones are also useful synthetic precursors.[30] A sequence of oxidation, mesylation, and elimination generated a single enantiomer of the vinyl sulfone **10** in 96% yield from the thioether **3la**. When employing the dihydrocarvone-derived thioether **3ma′**, we found that the protected sulfone underwent iron-catalyzed cross-coupling[25a] to provide the arylated products **11**/**11′** in 47% overall yield (4.3:1 *d.r.*). Finally, oxidation of the thioether **3ma** to the sulfone, followed by Baeyer–Villiger oxidation, gave the lactone **12** in 70% yield. Caprolactones are employed widely as monomers for polymer synthesis,[31] and this approach establishes a route toward bio-renewable terpenoid-based caprolactones that are both diastereomerically and enantiomerically pure.

In summary, we have demonstrated that $C(sp^3)$–$C(sp^2)$ bond fragmentation and $C(sp^3)$–S bond formation can be combined under mild operating conditions when employing abundantly available starting materials. This transformation, which occurs upon ozonolysis and subsequent Fe^{II}-mediated SET-based reduction, is a facile means for the diversification of natural products. We have also demonstrated that the thiylated adducts could be elaborated for use in organic synthesis and in the preparation of biologically relevant materials. On a fundamental level, we have established a deconstructive strategy of using olefins for the introduction of heteroatoms in organic compounds. Further efforts directed towards the application of this technology in the preparation of pharmaceutically and synthetically useful adducts are underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, detailed discussions, compound characterization, and NMR spectra (PDF). Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC 1913869 (**3la′**) and CCDC 1917888 (**8**).

AUTHOR INFORMATION

Corresponding Author

ohyun@chem.ucla.edu

Funding Sources

Financial support for this study was provided by the NIH (R01GM071779). A.J.S. thanks the Majeti–Alapati fellowship for funding.

ACKNOWLEDGMENT

We thank the UCLA Molecular Instrumentation Center for the NMR spectroscopy and mass spectrometry instrumentation and for the X-ray diffraction studies (S. I. Khan).

REFERENCES

(1) (a) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem.* **2016**, *16*, 1200–1216. (b) Scott, K. A.; Njardarson, J. T. *Top. Curr. Chem.* **2018**, *376*, 1–34.

(2) (a) Block, E. *J. Chem. Ed.* **1971**, *48*, 814–824. (b) Patai, S. *The Chemistry of Functional Groups—The Chemistry of the Thiol Group*; Wiley: London, UK, 1974. (c) Block, E. *Reactions of Organosulfur Compounds*; Blomquist, A. T., Wasserman, H. H., Eds.; Academic Press: New York, 1978. (d) Jones, D. N. *Comprehensive Organic Chemistry*; Barton, D. J., Ollis, D. W., Eds.; Pergamon: New York, 1979; Vol. 3. (e) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: San Diego, 1994. (f) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: New York, 1996. (g) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem*. **2011**, *7*, 582–595. (h) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590–608.

(3) (a) Deńeś, F.; Schiesser, C. H.; Renaud, P. *Chem. Soc. Rev*. **2013**, *42*, 7900–7942. (b) Deńeś, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587–2693.

(4) Brown, H. C.; Midland, M. M. *J. Am. Chem. Soc.* **1971**, *93*, 3291–3293.

(5) (a) Russell, G. A.; Tashtoush, H. *J. Am. Chem. Soc.* **1983**, *105*, 1398–1399. (b) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 3530–3538.

(6) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron Lett.* **1984**, *25*, 5777–5780.

(7) (a) Patel, V. F.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1451–1454. (b) Branchaud, B. P.; Meier, M. S.; Malekzadeh, M. N. *J. Org. Chem.* **1987**, *52*, 212–217.

(8) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H.; Hershberger, J. *Organometallics* **1987**, *6*, 1414–1419.

(9) Wang, P.-F.; Wang, X.-Q.; Dai, J.-J.; Feng, Y.-S.; Xu, H.-J. *Org. Lett.* **2014**, *16*, 4586–4589.

(10) (a) Zhao, J.; Fang, H.; Han, J.; Pan, Y.; Li, G. *Adv. Synth. Catal.* **2014**, *356*, 2719–2724. (b) Du, B.; Jin, B.; Sun, P. *Org. Lett.* **2014**, *16*, 3032–3035. (c) Sahoo, S. K. *J. Chem. Sci.* **2015**, *127*, 2151–2157.

(11) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 414–429.

(12) Nairoukh, Z.; Cormier, M.; Marek, I. *Nat. Rev. Chem.* **2017**, *1*, 1–16.

(13) Fumagali, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404–9432.

(14) Roque, J. B.; Kuroda, Y.; Göttemann, L. T.; Sarpong, R. *Nature* **2018**, *564*, 244–248.

(15) Smaligo, A. J.; Swain, M.; Quintana, J. C.; Tan, M. F.; Kim, D. A.; Kwon, O. *Science* **2019**, *364*, 681–685.

(16) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625–3633.

(17) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363–2366.

(18) Ertl, P.; Schuhmann, T. *J. Nat. Prod.* **2019**, *82*, 1258–1263.

(19) Kumamoto, J.; De La Mare, H. E.; Rust, F. F. *J. Am. Chem. Soc.* **1960**, *82*, 1935–1939.

(20) De La Mare, H. E.; Kochi, J. K.; Rust, F. F. *J. Am. Chem. Soc.* **1961**, *83*, 2013.

(21) Murai, S.; Sonoda, N.; Tsutsumi, S. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1187–1190.

(22) Schreiber, S. *J. Am. Chem. Soc.* **1980**, *102*, 6163–6165.

(23) Fisher, T. J.; Dussault, P. H. *Tetrahedron* **2017**, *73*, 4233–4258.

(24) Huang, D.; Schuppe, A. W.; Liang, M. Z.; Newhouse, T. R. *Org. Biomol. Chem.* **2016**, *14*, 6197–6200.

(25) (a) Denmark, S. E.; Cresswell, A. J. *J. Org. Chem.* **2013**, *78*, 12593–12628. (b) Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D.-H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Nuhant, P.; Baran, P. S. *Science* **2018**, *360*, 75–80. (c) Hughes, J.; Fier, P. *ChemRxiv. Preprint* **2019**, DOI: 10.26434/chemrxiv.8141993.

(26) (a) Giese, B. *Angew. Chem. Int. Ed.* **1989**, *8*, 969–1146. (b) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251–263.

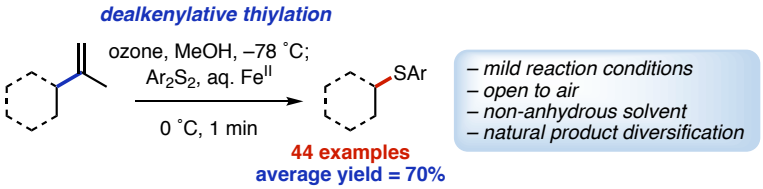
(27) See the Supporting Information for a proposed mechanism for the formation of **7ha´** from **6h**.

(28) (a) Alakurtti, S.; Mäkelä, T.; Koskimies, S.; Yli-Kauhaluoma, J. *Eur. J. Pharm. Sci.* **2006**, *29*, 1–13. (b) Genet, C.; Strehle, A.; Schmidt, C.; Boudjelal, G.; Lobstein, A.; Schoonjans, K.; Souchet, M.; Auwerx, J.; Saladin, R.; Wagner, A. *J. Med. Chem.* **2010**, *53*, 178–190. (c) Grymel, M.; Zawojak, M.; Adamek, J. *J. Nat. Prod.* **2019**, *82*, 1719–1730.

(29) (a) Aplin, R. T.; Chan, R. P. K.; Halsall, T. G. *J. Chem. Soc. C* **1969**, 2322–2327. (b) Dutta, G.; Bose, S. N. *Tetrahedron Lett.* **1988**, *29*, 5807–5810. (c) Heller, L.; Kahnt, M.; Loesche, A.; Grabandt, P.; Schwarz, S.; Brandt, W.; Csuk, R. *Eur. J. Med. Chem.* **2017**, *126*, 652–668. (d) Kahnt, M.; Heller, L.; Grabandt, P.; Al-Harrasi, A.; Csuk, R. *Eur. J. Med. Chem.* **2018**, *143*, 259–265.

(30) (a) Creech, G. S.; Kwon, O. *Chem. Sci.* **2013**, *4*, 2670–2674. (b) Fang, Y.; Luo, Z.; Xu, X. *RSC Adv.* **2016**, *6*, 59661–59676.

(31) (a) Lowe, J. R.; Martello, M. T.; Tolman, W. B.; Hillmyer, M. A. *Polym. Chem.* **2011**, *2*, 702–708. (b) Tschan, M. J.-L.; Brulé, E.; Haquette, P.; Thomas, C. M. *Polym. Chem.* **2012**, *3*, 836–851.


dealkenylative thiylation
ozone, MeOH, –78 ˚C;
Ar_2S_2, aq. Fe^{II}
0 ˚C, 1 min
SAr
44 examples
average yield = 70%
– mild reaction conditions
– open to air
– non-anhydrous solvent
– natural product diversification