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Dealkenylative Thiylation of C(sp³)–C(sp²) Bonds

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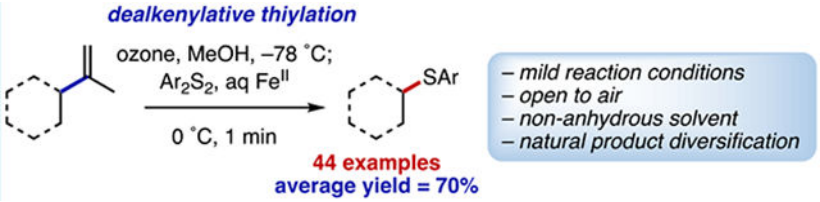
Abstract

Carbon–carbon bond fragmentations are useful methods for the functionalization of molecules. The value of such cleavage events is maximized when paired with subsequent bond formation. Herein we report a protocol for the cleavage of an alkene C(sp^3)–C(sp^2) bond, followed by the formation of a new C(sp^3)–S bond. This reaction is performed in nonanhydrous solvent and open to the air, employs common starting materials, and can be used to rapidly diversify natural products.

Graphical Abstract



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 radical precursors (e.g., organometallic species, Barton esters, trialkyl boranes), carboxylic acids, simple alkanes, or a peroxide species.[3–11] This approach is sometimes limited in its

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, detailed discussions, compound characterization, and NMR spectra (PDF)

Accession Codes

CCDC 1913869 and 1917888 contain 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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applicability because of the syntheses of the requisite coupling partners, the harsh reaction conditions (high temperatures, long reaction times), or the low selectivity for C–H abstraction (in the case of alkane starting materials). Consequently, a method for the generation of carbon radicals under mild reaction conditions 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.[12] 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 the total synthesis and the preparation of pharmaceutically relevant compounds.[12,13] The value of such transformations can be increased when paired with a subsequent bond-forming event. Nevertheless, reports of alkene C(sp^3)–C(sp^2) bond cleavage, followed by C(sp^3)–heteroatom bond formation remain uncommon[13a,e,14] despite the ubiquity of alkenes in organic molecules, especially within natural products.[15] In this Letter, we report a simple method for the dealkenylative thiylation of alkenes (**1**, **4**, and **6**) to give alkyl aryl sulfides (**3**, **5**, and **7**) 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[13,14,16] (generated during the ozonolysis of alkenes **1**)[17] can be trapped with an aryl disulfide (**2**) to form a new C(sp^3)–S bond in **3**. In contrast with 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, nonanhydrous 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 equiv of the aryl disulfide and 1.2 equiv of ferrous sulfate heptahydrate (added as a 5% w/v aqueous solution[16f]) at 0 °C. (See Table S1 in the Supporting Information for details.) Under these optimized conditions and using 4-isopropenylte-trahydropyran (**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, whereas various tolyl and xylyl disulfides also produced their thiylation products **3ab–af** in yields of 62–77%. Electron-rich and -poor aryl disulfides were competent partners, generating the expected products **3ag–aj** in yields of 50–75%. 1-Phenyl-tetrazol-5-yl and 2-pyridyl disulfides, notable for the use of their thioether and sulfone derivatives in cross-coupling reactions,[18] were also compatible, providing the thioethers **3ak** and **3al** in yields of 51 and 75%, respectively. Attempts to employ dialkyl disulfides as coupling partners were unfruitful, presumably because of the 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–d** supplied the thioethers **3ba–da** in yields of 58–80%. Secondary (**1e**, **1f**) and tertiary (**1g**) radical precursors were also compatible, furnishing the desired products **3ea–ga** 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–k** 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.[19] 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 **31a–pa**, 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 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–k**.

Next, we found that alkenes containing *exo*-methylene groups (**4**) were converted into the corresponding phenyl-thiyl-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, whereas the Boc-protected piperidine **4d** also cleanly supplied the thioether **5da** in 80% yield. 1-Methyleneindane (**4e**) furnished its product **5ea** in 51% yield, whereas 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. The 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–c**) supplied the expected products **7aa–ca**, respectively, in yields from 63 to 75%. (+)-2-Carene (**6d**) furnished a 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 the 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.[20]

Figure 6 presents several examples of synthetic applications in which we have employed this transformation. With regard to medicinal agents, this process can be a tool for the functionalization of biologically active compounds. We examined the reaction of betulin (**1q**), which has wide biological activities (in particular, anticancer and anti-HIV properties)[21] yet few functional group handles on the skeleton. Notably, the cleavage of the C-19 C(sp^3)–C(sp^2) bond, followed by the introduction of a heteroatom at this position is rare,[22] with most modifications occurring at the C-3 or C-28 positions.[23] Dealkenylative

thiylation of betulin readily furnished the thioethers **3ql** and **3ql′** in 78% yield (1.2:1 d.r.). The 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 widely used in organic synthesis. When dealkenylative thiylation is combined with terpenoid precursors, enantiopure synthetic intermediates are readily generated. 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.[24] 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[18a] to provide the arylated products **11/11′** in 47% overall yield (4.3:1 d.r.). Finally, the 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,[25] and this approach establishes a route toward biorenewable terpenoid-based caprolactones that are both diastereomerically and enantiomerically pure.

In summary, we have demonstrated that alkene $C(sp^3)$–$C(sp^2)$ bond fragmentation and $C(sp^3)$–S bond formation can be combined under mild operating conditions when employing abundantly available starting materials.[26] This transformation, which occurs upon ozonolysis and the 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 toward the application of this technology in the preparation of pharmaceutically and synthetically useful adducts are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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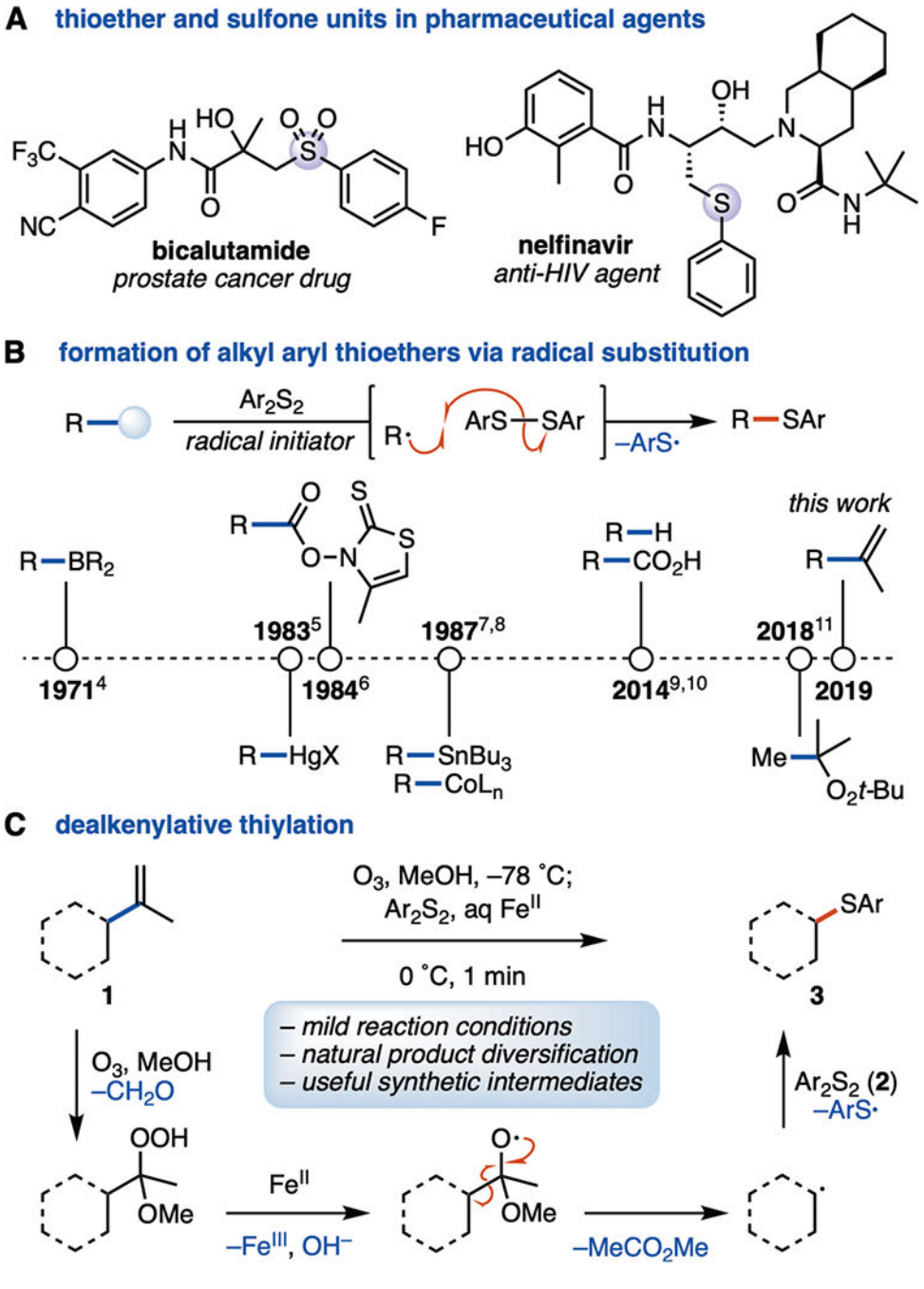

Figure 1.

(A) Pharmaceuticals featuring thioether and sulfone units. (B) Timeline of aryl alkyl thiother formation via radical substitution. (C) Mechanism of dealkenylative thiylation.

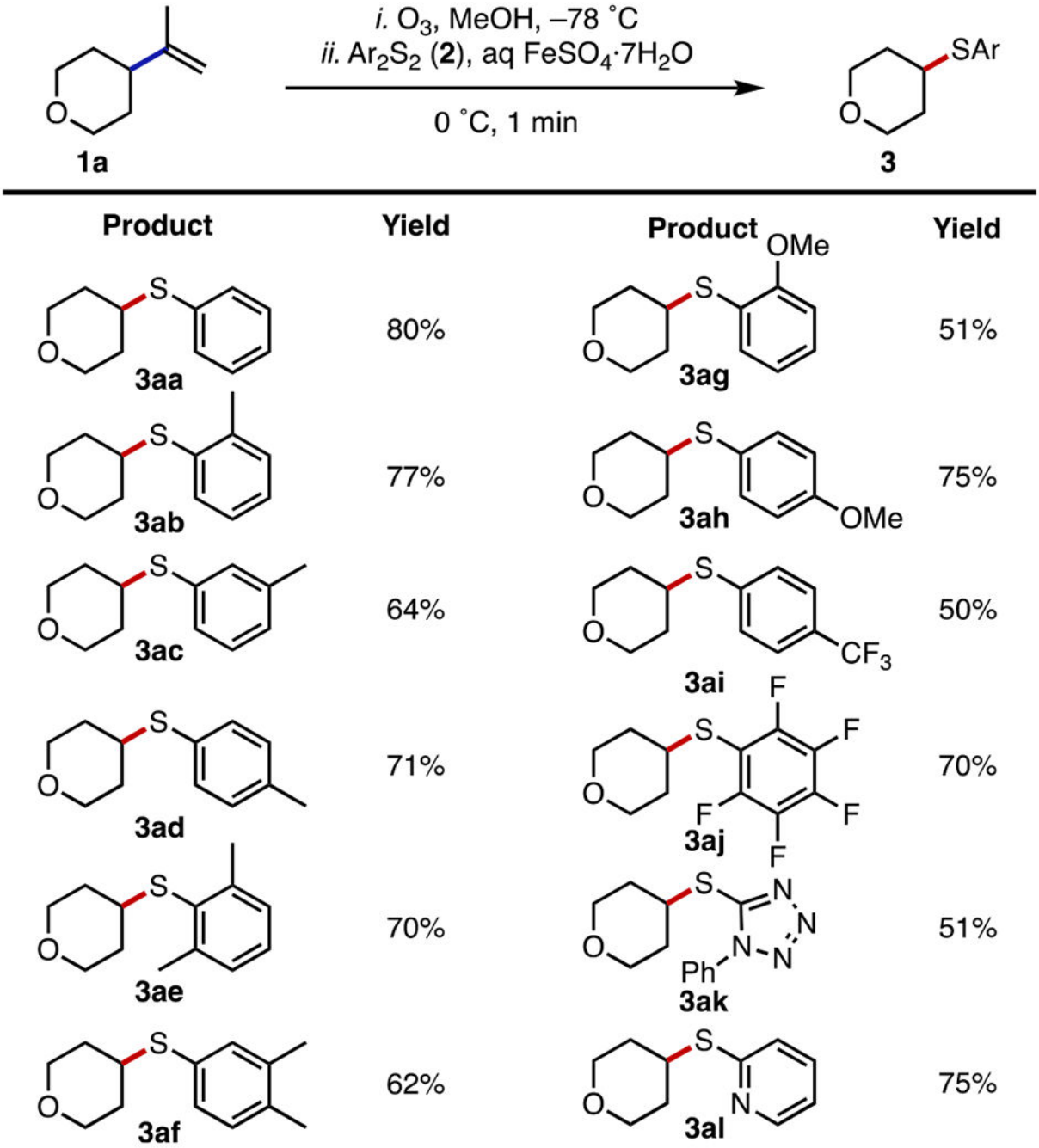

Figure 2.

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

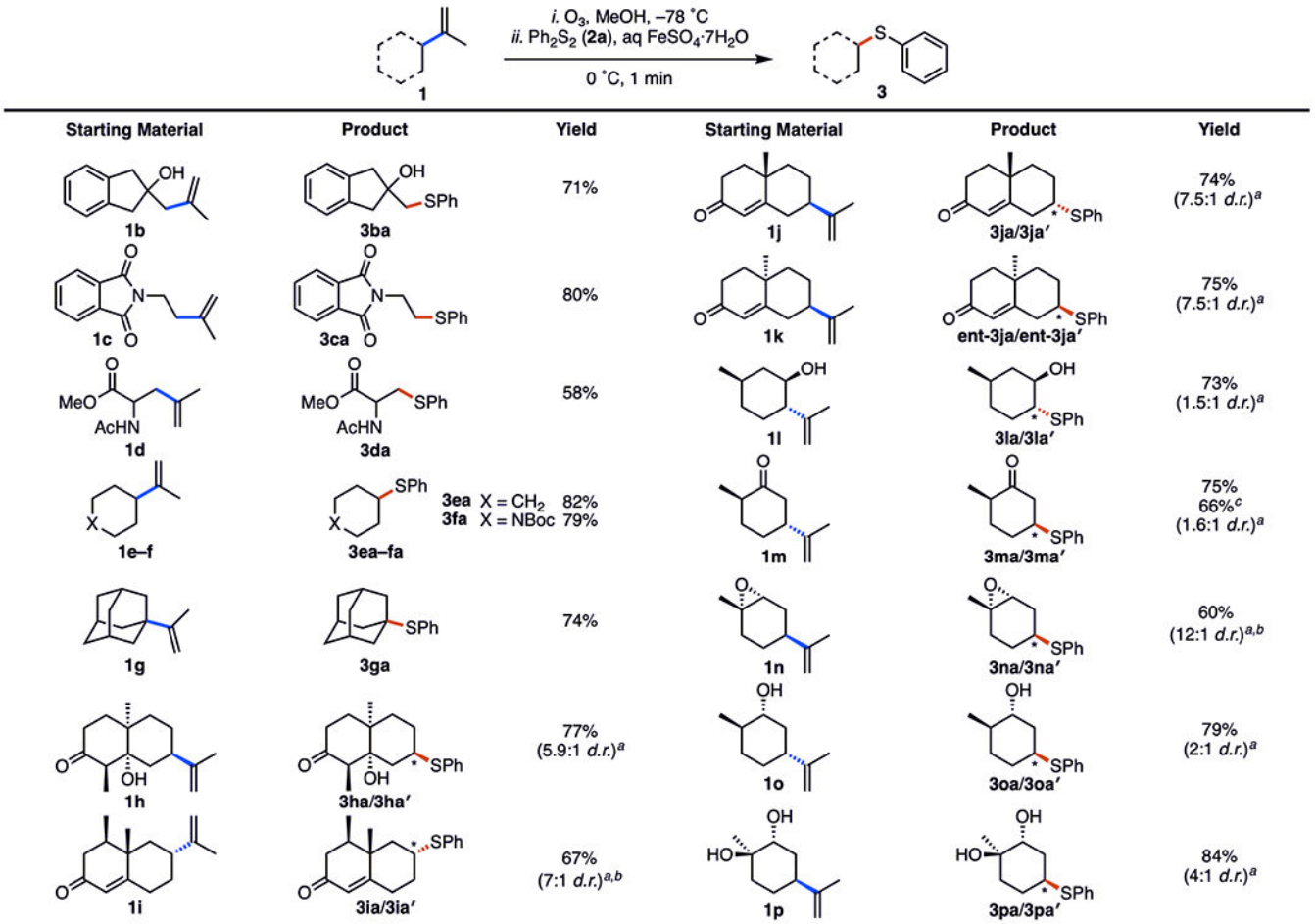

Figure 3.

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

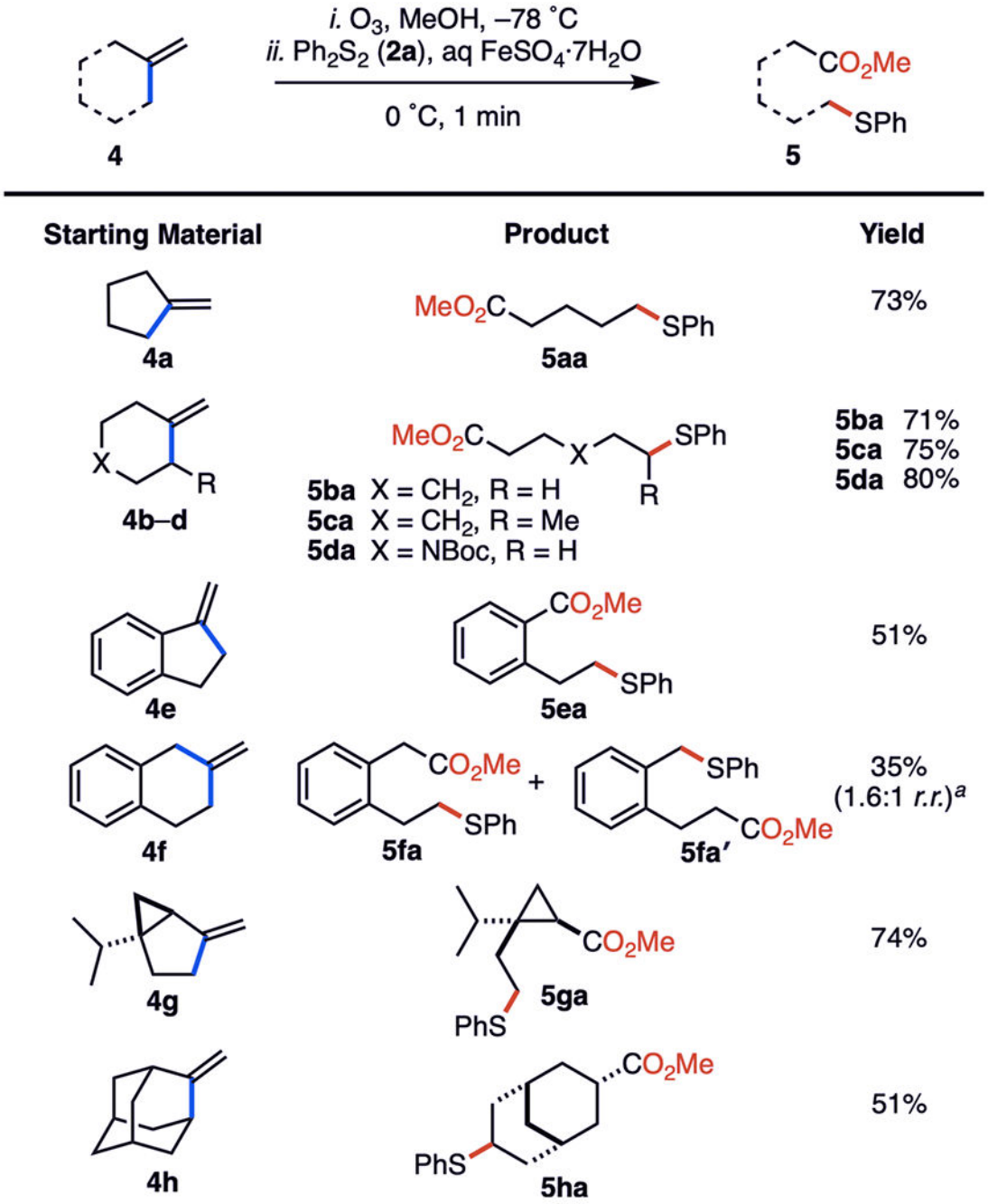

Figure 4.

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

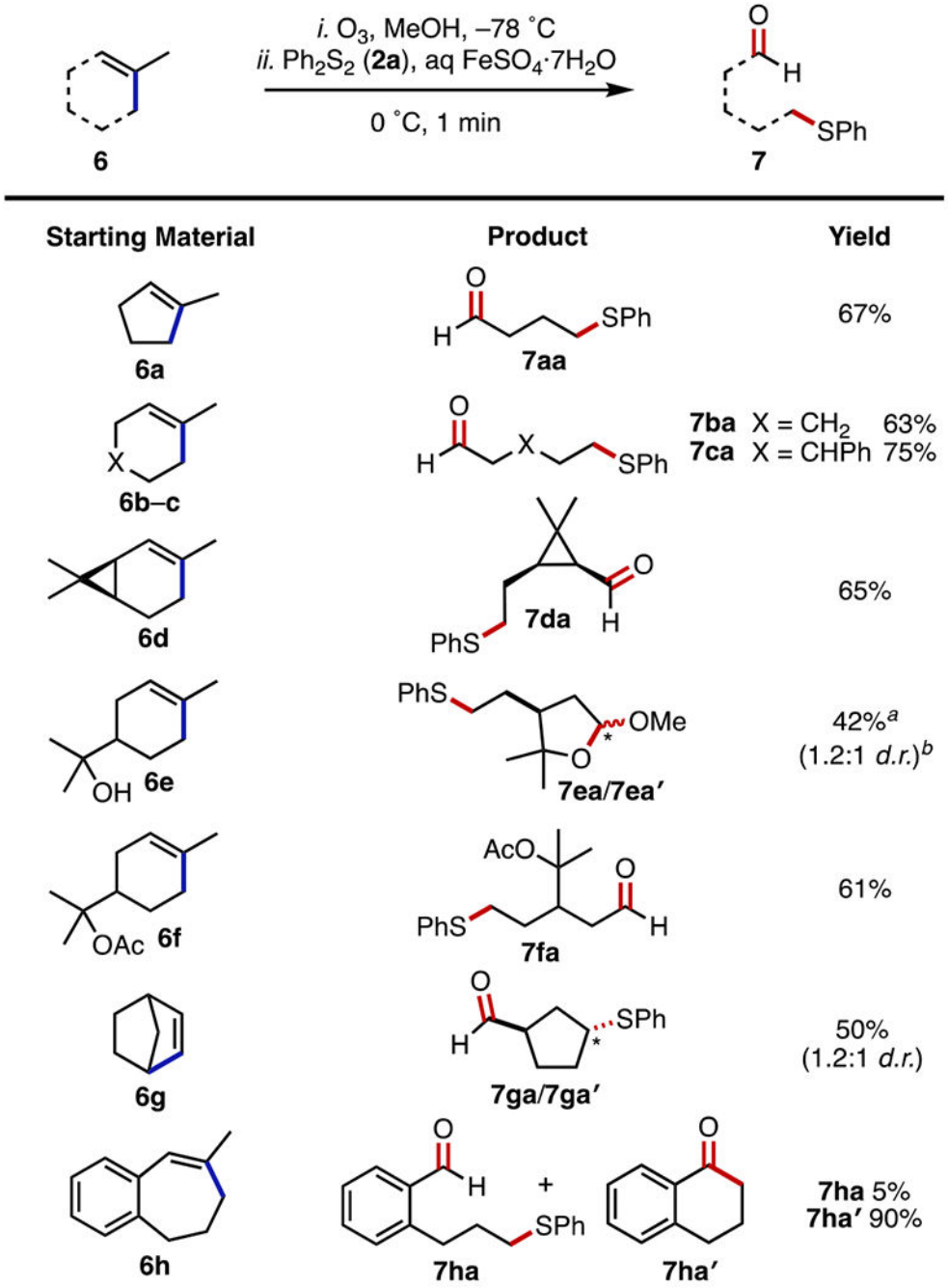

Figure 5.

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

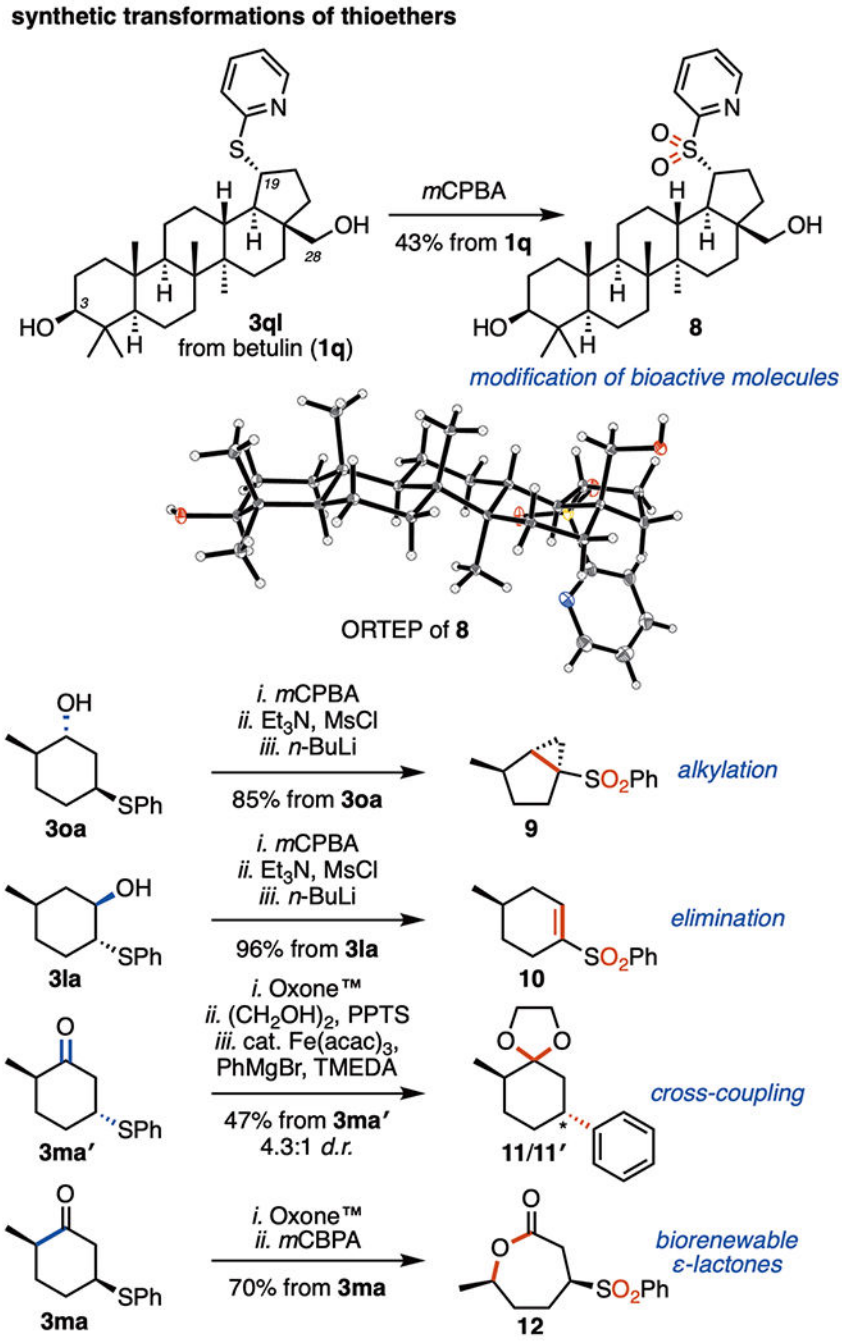

Figure 6.

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