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# Palladium-Catalyzed Stereoselective Formation of Substituted Allylic Thioethers and Sulfones

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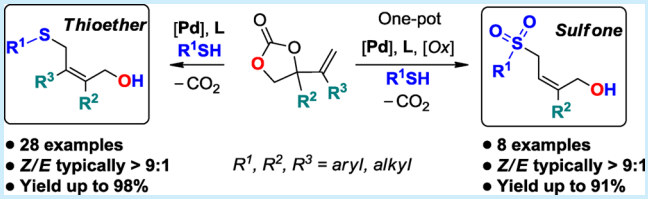
Supporting Information

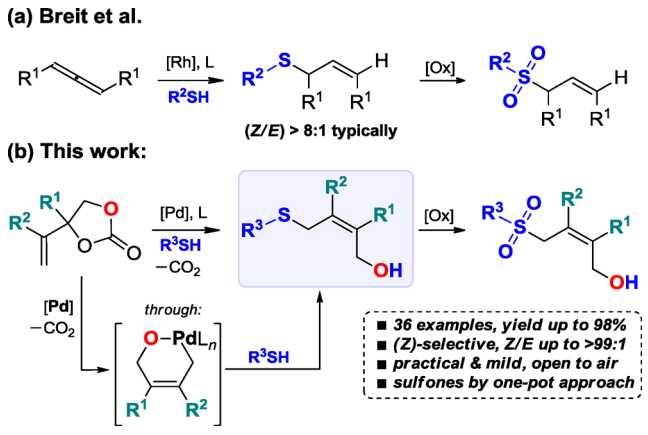
**ABSTRACT:** A general method is reported for the stereoselective preparation of highly functionalized allylic thioethers. This protocol is based on a Pd-catalyzed thiolation of modular vinyl cyclic carbonate substrates and features high (*Z*)-selectivity, good yields, minimal waste, ample product scope, and operational simplicity. A one-pot strategy was used for the stereoselective formation of pharma-relevant allylic sulfones derived from their in situ prepared thioether precursors.




Organosulfur compounds such as thioethers[1] and sulfones[2] are very important building blocks in synthetic and pharmaceutical chemistry, and their derivatives are representative in ∼20% of the best-selling US pharmaceuticals in 2012.[3] As a subclass of sulfur-containing compounds, a number of allylic thioethers have been found to be bioactive[4] and important reaction intermediates,[5] and they continue to attract interest from various synthetic communities.[6,7] Effective methodologies for the synthesis of allylic thioether/sulfones and related compounds include allylic substitution,[8] hydrothiolation of allenes[7,9] or alkynes,[10] and C−H bond functionalization.[11] Apart from these catalytic methodologies, stoichiometric approaches have also proven to be effective in this context.[12] Despite the impressive progress noted in this area, general catalytic methodology for the stereoselective synthesis of highly substituted allylic thioethers (see structure in the blue box of Scheme 1) remains underdeveloped.[13] A recent example of (*Z*)-selective allylic thioether and sulfone synthesis was reported by Breit et al. using hydrothiolation of allenes under Rh catalysis (Scheme 1, a),[7] but this approach is limited in substitution diversity around the allylic double bond. A stereoselective construction of multifunctionalized olefin scaffolds represents a rather challenging task in synthetic chemistry.[14]

Our group recently developed a Pd-catalyzed stereoselective methodology for the decarboxylative functionalization of vinyl carbonates toward synthetically useful, highly substituted (*Z*)-configured allylic amines and 1,4-but-2-enediols.[15] Key to the high (*Z*) selectivity found in these transformations was the in situ generation of a six-membered palladacycle revealed by DFT calculations (Scheme 1, b).[15b] We envisaged that, under suitable reaction conditions, the reaction of modular vinyl carbonates and thiol nucleophiles would give access to (*Z*)-allylic thioethers through nucleophilic attack onto the in situ formed Pd intermediate. Such a manifold would thus offer a practical route toward the challenging stereoselective synthesis of tri- and even tetrasubstituted allylic thioethers and sulfones (upon oxidation) from simple and accessible precursors (Scheme 1, b). (Allylic) sulfone scaffolds are frequently observed in relevant pharmaceutical compounds,[16] and thus, their synthesis is of significant importance.[17]

**Scheme 1. Different Strategies for Catalytic Stereoselective Synthesis of Allylic Thioethers and Sulfones**




We began our investigations using vinyl carbonate **A** (Table 1) and thiophenol as a benchmark reaction. Inspired by our previous research,[15] the combination of the White catalyst precursor (2.0 mol %) and bidentate phosphine **L1** (DPEPhos, 5.0 mol %) was first examined at rt (Table 1, entries 1−5). Unfortunately, in different solvents no reaction was observed (DMF, THF, MeOH, and $CH_3CN$). To our delight, when $Pd(dba)_2$ in $CH_3CN$ was used, a 16% yield of allylic thioether

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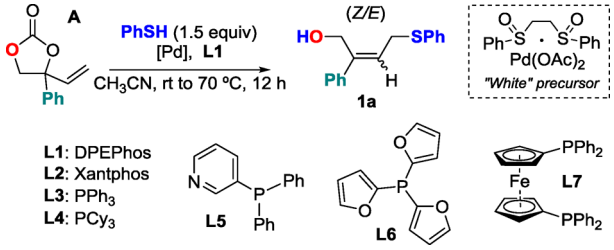
**Table 1. Screening Data for the Optimization of the Reaction Conditions toward Allylic Thioether 1a[a]**




| entry | [Pd] | L/solvent | $T$ (°C) | yield[b] (%) | $Z/E$[c] |
|---|---|---|---|---|---|
| 1 | white | **L1**, none | rt | 0 | |
| 2 | white | **L1**, DMF | rt | 0 | |
| 3 | white | **L1**, THF | rt | 0 | |
| 4 | white | **L1**, $CH_3CN$ | rt | 0 | |
| 5 | white | **L1**, MeOH | rt | 0 | |
| 6 | $Pd(dba)_2$ | **L1**, $CH_3CN$ | rt | 16 | 86:14 |
| 7 | $Pd(OAc)_2$ | **L1**, $CH_3CN$ | rt | 0 | |
| 8 | $Pd(dba)_2$ | **L1**, $CH_3CN$ | 50 | 77 | 91:9 |
| 9 | $Pd(dba)_2$ | **L1**, $CH_3CN$ | 70 | 84 | 92:8 |
| 10[d] | $Pd(dba)_2$ | **L1**, $CH_3CN$ | 70 | 91 | 94:6 |
| 11 | $Pd(dba)_2$ | **L2**, $CH_3CN$ | 70 | 83 | 94:6 |
| 12 | $Pd(dba)_2$ | **L3**, $CH_3CN$ | 70 | 0 | |
| 13 | $Pd(dba)_2$ | **L4**, $CH_3CN$ | 70 | 0 | |
| 14 | $Pd(dba)_2$ | **L5**, $CH_3CN$ | 70 | 0 | |
| 15 | $Pd(dba)_2$ | **L6**, $CH_3CN$ | 70 | 0 | |
| 16 | $Pd(dba)_2$ | **L7**, $CH_3CN$ | 70 | 0 | |
| 17[e] | $Pd(dba)_2$ | **L1**, $CH_3CN$ | 70 | 73 | 90:10 |
| 18[f] | $Pd(dba)_2$ | **L1**, $CH_3CN$ | 70 | 92 | 91:9 |

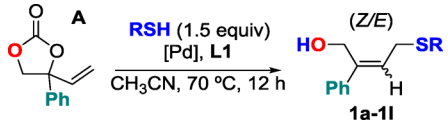
[a]Reaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiophenol (1.5 equiv), solvent (0.20 mL), catalyst (2.0 mol %), **L** (5.0 mol %), open to air, 12 h. [b]NMR yield using toluene as an internal standard. [c]Based on $^1$H NMR integration. [d][Pd] = 3.0 mol %. [e][Pd] = 3.0 mol %, thiophenol (1.2 equiv). [f][Pd] = 3.0 mol %, thiophenol (0.20 mmol) and carbonate substrate (0.22 mmol).

**1a** ($Z/E$ = 86:14) was noted (Table 1, entry 6). Increasing the temperature (Table 1, entries 8 and 9) gave a significantly improved yield of **1a** of up to 84% and higher selectivity ($Z/E$ = 92:8).

The catalysis was further enhanced with a higher Pd loading (3.0 mol %; 91% yield, $Z/E$ = 94:6; see Table 1, entry 10). Other phosphine ligands **L2**−**L7** were also tested but proved to be less productive (Table 1, entries 11−16), and a lower thiophenol amount also resulted in erosion of the yield of **1a** (1.2 equiv, Table 1, entry 17). Under the optimized conditions, the use of an excess of carbonate gave fairly similar results (Table 1, entry 18; 92% yield, $Z/E$ = 91:9). Thus, the best conditions toward the formation of allylic thioether ($Z$)-**1a** were the use of $Pd(dba)_2$ (3.0 mol %) and **L1** (5.0 mol %) in $CH_3CN$ at 70 °C (Table 1, entry 10). It is worth noting that no special precautions or base additives[18] were required, making the present protocol highly attractive from a practical point of view.

With the optimized conditions in hand, we then systematically varied the nature of both reaction partners, and first the scope in thiols was examined (Table 2). Generally, the decarboxylative thiolation approach proceeded with high stereoselectivity to provide the allylic thioethers **1a**−**l** in good yields and $Z/E$ ratios of typically >90:10. The presence of both electron-withdrawing (**1d**,**e**,**h**,**i**) and -donating groups (**1b**,**c**,**f**,**g**,**j**) in the aryl thiols is tolerated, and *para*- *meta*-, and

**Table 2. Investigated Scope in Thiol Partners To Produce Allylic Thioethers 1a−l[a]**




| entry | R | product | yield[b] (%) | $Z/E$ |
|---|---|---|---|---|
| 1 | $C_6H_5$ | **1a** | 90 | 94:6 |
| 2 | 4-Me-$C_6H_4$ | **1b** | 73 | 92:8 |
| 3 | 2-Me$C_6H_4$ | **1c** | 93 | 92:8 |
| 4[c] | 4-$CF_3C_6H_4$ | **1d** | 70 | 83:17 |
| 5[c] | 4-Br$C_6H_4$ | **1e** | 76 | 80:20 |
| 6 | 3-Me$C_6H_4$ | **1f** | 95 | 90:10 |
| 7 | 4-MeO$C_6H_4$ | **1g** | 83 | 93:7 |
| 8[c] | 4-COOH$C_6H_4$ | **1h** | 98 | 91:9 |
| 9 | 2-pyridyl | **1i** | 93 | >99:1 |
| 10[c] | 4-HO$C_6H_4$ | **1j** | 87 | 91:9 |
| 11[c] | adamantyl | **1k** | 98 | >99:1 |
| 12[c] | benzyl | **1l** | 50 | 92:8 |

[a]Reaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiol (1.5 equiv), $CH_3CN$ (0.20 mL), $Pd(dba)_2$ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h. [b]Isolated yield. [c]Thiol (0.20 mmol), carbonate substrate (0.22 mmol).

*ortho*-substitutions (Table 2, entries 2, 3, and 6) are endorsed. Deactivated thiophenols also showed sufficient reactivity (cf., synthesis of **1d** and **1h**). Variation of the thiol partners allows us to include synthetically useful aryl halides (**1e**), benzoic acid (**1h**), pyridyl (**1i**), and phenoxy (**1j**) groups. Apart from aryl thiols, alkyl thiols also proved to be feasible substrates leading to their respective allylic thioethers in high stereoselectivty (**1k** and **1l**, $Z/E$ > 92:8). In some cases, the catalytic procedure was optimized by using a slight excess of vinyl carbonate substrate. The ($Z$) configuration of the major isomer in all cases was supported by $^1$H NOESY (Supporting Information, SI) and for **1a** also by X-ray analysis (see the SI).

Subsequently, the vinyl carbonate reaction partner was varied (Table 3) to give access to a wider range of highly functionalized allylic thioethers **2a**−**l** in moderate to excellent yields (up to 97%) with high stereocontrol in most cases ($Z/E$ ratios of at least >80:20). Both aryl and alkyl substituents in the carbonate reagent (Table 3, "R") were tolerated. Different functionalities such as benzoic esters, aryl nitrile, and furyl groups (**2e**,**f**,**i**) can be readily introduced to further amplify the product diversity. Upon use of more sterically demanding vinyl carbonates that incorporate naphthyl or cyclohexyl substituents, the catalytic procedure was less productive (**2g** and **2j**; 51% and 48% yield, respectively). In the case of product **2l**, we observed the formation of a branched allylic thioether which affected the yield of the linear derivative (see the SI for details). The lower $Z/E$ ratios observed for **2f** and **2k** (Table 3) may be the result of the oxa-palladacycle (see Scheme 1b) being in equilibrium with a noncyclic intermediate at 70 °C. The carbonate R substituent in the acyclic species can affect the olefin geometry prior to attack of the thiol nucleophile through possible $\pi-\sigma-\pi$ alkene isomerization.[19] A higher tendency to form such an acyclic Pd intermediate causes loss in stereocontrol.

In order to further challenge the newly developed catalytic protocol for stereoselective allylic thioether formation, the synthesis of elusive tetrasubstituted derivatives was attempted, and the results are listed in Table 4. To our delight, the installation of both alkyl and aryl substituents ($R^2$ = Ph, Me) at


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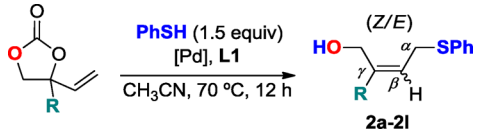
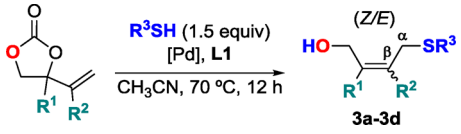
**Table 3. Investigated Scope in Vinyl Carbonate Partners To Produce Allylic Thioethers 2a–l[a]**




| entry | R | product | yield[b] (%) | Z/E |
|---|---|---|---|---|
| 1 | 4-Me-$C_6H_4$ | **2a** | 70 | 94:6 |
| 2 | 4-F-$C_6H_4$ | **2b** | 84 | 83:17 |
| 3 | 4-Br-$C_6H_4$ | **2c** | 88 | 87:13 |
| 4 | 4-Ph-$C_6H_4$ | **2d** | 97 | 94:6 |
| 5 | 4-$CO_2$Me-$C_6H_4$ | **2e** | 80 | 84:16 |
| 6 | 4-CN-$C_6H_4$ | **2f** | 91 | 67:33 |
| 7 | 2-naphthyl | **2g** | 51 | 89:11 |
| 8 | 3-Cl-$C_6H_4$ | **2h** | 71 | 80:20 |
| 9 | 2-furyl | **2i** | 99 | >99:1 |
| 10[c] | Cy | **2j** | 48 | 84:16 |
| 11[c] | $C_{10}H_{21}$ | **2k** | 87 | 70:30 |
| 12 | Me | **2l** | 40[d] | 80:20 |

[a]Reaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiophenol (1.5 equiv), $CH_3CN$ (0.20 mL), $Pd(dba)_2$ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h. [b]Isolated yield. [c]Thiophenol (0.20 mmol), carbonate substrate (0.22 mmol). [d]Branched product (30%) also formed.

**Table 4. Preparation of Elusive Tetrasubstituted Thioethers 3a–d[a]**



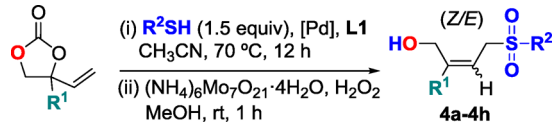

| entry | $R^1$ | $R^2$ | $R^3$ | product | yield[b] (%) | Z/E |
|---|---|---|---|---|---|---|
| 1 | *p*-Me$C_6H_4$ | Ph | Ph | **3a** | 48 | >99:1 |
| 2 | Ph | Me | Ph | **3b** | 62 | 94:6 |
| 3 | Ph | Me | 4-MeO$C_6H_4$ | **3c** | 65 | 98:2 |
| 4 | Ph | Me | 2-Me$C_6H_4$ | **3d** | 37 | 90:10 |

[a]Reaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiophenol (1.5 equiv), $CH_3CN$ (0.20 mL), $Pd(dba)_2$ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h. [b]Isolated yield.

the *β*-position of the allylic scaffold is feasible while maintaining excellent stereoselectiviy (Table 4, entries 1 and 2: **3a** and **3b**, *Z*/*E* > 94:6). However, the preparation of *α*-functionalized allylic thioethers, derived from internal olefin substrates, failed under these conditions probably for steric reasons (see the SI for details). Other combinations of $R^1$ and $R^2$ were then also probed (cf. the synthesis of **3c** and **3d**) and gave the targeted allylic thioethers in high to excellent stereoselectivity.

We then set out to develop a one-pot strategy toward the stereoselective synthesis of highly substituted allylic sulfones by combining the Pd-catalyzed allylic thioether formation and in situ oxidation. Various conditions were tested using vinyl carbonate **A** and thiophenol as model reaction (see the SI for more details). We were pleased to find that a combination of $(NH_4)_6Mo_7O_{21}{\cdot}4H_2O$ and $H_2O_2$ (after initial and in situ formation of allylic thioether **1a**) gave 90% isolated yield of sulfone product **4a** (Table 5, entry 1) with excellent stereocontrol (*Z*/*E* = 94:6).[20] This one-pot strategy was then utilized to prepare different, highly functionalized sulfones

**Table 5. One-Pot Synthesis of Highly Substituted Sulfones[a]**




| entry | $R^1$ | $R^2$ | product | yield[b] (%) | Z/E |
|---|---|---|---|---|---|
| 1 | Ph | Ph | **4a** | 90 | 94:6 |
| 2 | Ph | 4-MeO$C_6H_4$ | **4b** | 83 | 93:7 |
| 3 | Ph | 3-Me$C_6H_4$ | **4c** | 89 | 90:10 |
| 4 | Ph | benzyl | **4d** | 48 | 91:9 |
| 5[c] | Ph | 2-pyridyl | **4e** | 91 | 87:13 |
| 6 | 4-$CO_2$Me$C_6H_4$ | Ph | **4f** | 76 | 84:16 |
| 7 | 4-F$C_6H_4$ | Ph | **4g** | 77 | 93:7 |
| 8 | 4-Me$C_6H_4$ | Ph | **4h** | 72 | 93:7 |

[a]Reaction conditions: (i) carbonate substrate (0.20 mmol), thiol (1.5 equiv), $CH_3CN$ (0.20 mL), $Pd(dba)_2$ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h; (ii) $(NH_4)_6Mo_7O_{21}{\cdot}4H_2O$, $H_2O_2$ (4 equiv, 30 wt % in $H_2O$), MeOH (0.20 mL), rt, 1 h. X-ray structure measured for sulfone (*Z*)-**4a**; see the SI. [b]Isolated yield. [c]Thiol (0.20 mmol), carbonate substrate (0.22 mmol).

(Table 5, entries 2–8). Gratifyingly, the oxidation step did not interfere with the presence of other (functional) groups under these conditions including benzyl (**4d**), pyridyl (**4e**), methyl ester (**4f**), halide (**4g**), and in all cases primary alcohol and internal alkene groups. The same level of stereoselectivity was found in the sulfone synthesis, and generally good to excellent yields for **4a–h** were obtained. X-ray analysis of **4a** unambiguously confirmed the (*Z*)-configuration of this trisubstituted allylic sulfone (see the SI).

In summary, we herein report a general catalytic method for the (*Z*)-selective preparation of a diverse series of highly functionalized and substituted allylic thioethers and sulfones. This methodology is based on a Pd-catalyzed decarboxylative functionalization of readily available and modular vinyl cyclic carbonates and features minimal waste release, wide scope, and operationally simplicity. Based on our previous mechanistic investigations,[1Sb] the (*Z*)-selectivity in the present catalytic protocol is ascribed to a nucleophilic attack of the thiol reagent onto an in situ generated (*Z*)-configured six-membered palladacycle that guides the stereoselective course of the developed process for the (*Z*) allylic thioethers.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02981.

Experimental details and copies of relevant NMR and IR spectra for all new products (PDF)
X-ray data for compound **1a** (CIF)
X-ray data for compound **4a** (CIF)

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## Notes

The authors declare no competing financial interest.

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