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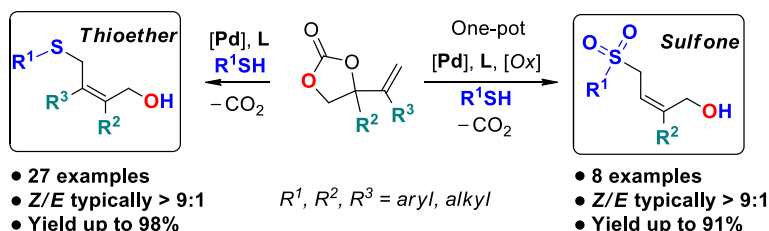
Palladium-Catalyzed Stereoselective Formation of Substituted Allylic Thioethers and Sulfones

José Enrique Gómez,[†] Wusheng Guo,^{*,†} and Arjan W. Kleij^{*,†,§}

[†]Institute of Chemical Research of Catalonia (ICIQ), the Barcelona Institute of Science and Technology, Av. Paisos Catalans 16, 43007 – Tarragona, Spain

[§]Catalan Institute of Research and Advanced Studies (ICREA), Pg. Lluís Companys 23, 08010 – Barcelona, Spain

Supporting Information Placeholder



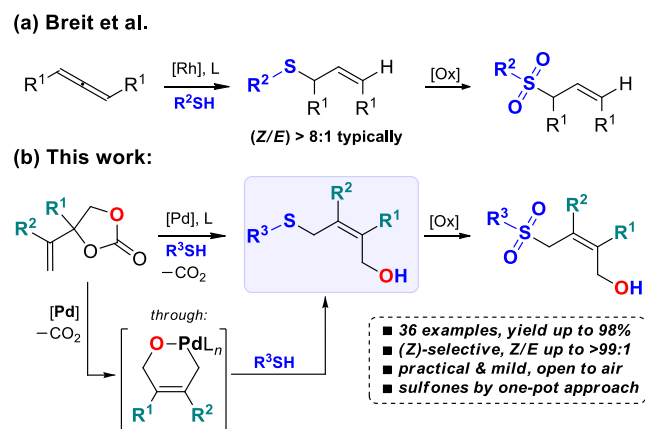
ABSTRACT: A general method is reported for the stereoselective preparation of highly functionalized allylic thioethers. This protocol is based on a Pd-catalyzed thiolation of modular vinyl cyclic carbonate substrates and features high (*Z*)-selectivity, good yields, minimal waste, ample product scope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

Organosulfur compounds such as thioethers¹ and sulfones² are very important building blocks in synthetic and pharmaceutical chemistry, and their derivatives were representative in around 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 bioactive⁴ and important reaction intermediates,⁵ and continue to attract the 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 alkenes^{7,9} or alkynes,¹⁰ and C–H bond functionalization.¹¹ Apart from these catalytic methodologies, also stoichiometric approaches have 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 multi-functionalized 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 towards synthetically useful, highly substituted (*Z*)-configured allylic amines and 1,4-but-2-ene-diols.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

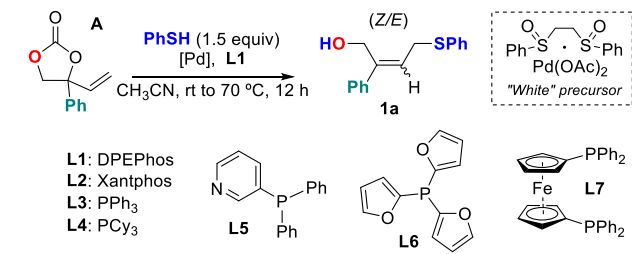
route towards the challenging stereoselective synthesis of tri- and even tetra-substituted allylic thioethers and sulfones (upon oxidation) from simple and accessible precursors (Scheme 1, b). (Allylic) sulfone scaffolds are frequently observed in relevant pharmaceutical compounds¹⁶ and thus their synthesis is of significant importance.¹⁷

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



We started 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 CH₃CN). To our delight, when Pd(dba)₂ in CH₃CN was used, a 16% yield of allylic thioether **1a** (*Z/E* = 86:14) was noted (Table 1, entry 6). Increasing the temperature (Table 1, entries 8-9) gave significantly improved yield of **1a** of up to 84% and higher selectivity (*Z/E* = 92:8).

Table 1. Screening Data for the Optimization of the Reaction Conditions towards Allylic Thioether **1a.**^a



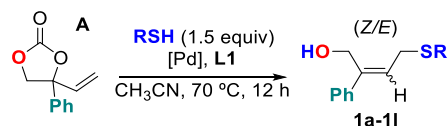
entry	[Pd]	L/solv	<i>t</i> (°C)	yield (%) ^b	<i>Z/E</i> ^c
1	"White"	L1 , none	rt	0	-
2	"White"	L1 , DMF	rt	0	-
3	"White"	L1 , THF	rt	0	-
4	"White"	L1 , CH ₃ CN	rt	0	-
5	"White"	L1 , MeOH	rt	0	-
6	Pd(dba) ₂	L1 , CH ₃ CN	rt	16	86:14
7	Pd(OAc) ₂	L1 , CH ₃ CN	rt	0	-
8	Pd(dba) ₂	L1 , CH ₃ CN	50	77	91:9
9	Pd(dba) ₂	L1 , CH ₃ CN	70	84	92:8
10 ^d	Pd(dba) ₂	L1 , CH ₃ CN	70	91	94:6
11	Pd(dba) ₂	L2 , CH ₃ CN	70	83	94:6
12	Pd(dba) ₂	L3 , CH ₃ CN	70	0	-
13	Pd(dba) ₂	L4 , CH ₃ CN	70	0	-
14	Pd(dba) ₂	L5 , CH ₃ CN	70	0	-
15	Pd(dba) ₂	L6 , CH ₃ CN	70	0	-
16	Pd(dba) ₂	L7 , CH ₃ CN	70	0	-
17 ^e	Pd(dba) ₂	L1 , CH ₃ CN	70	73	90:10
18 ^f	Pd(dba) ₂	L1 , CH ₃ CN	70	92	91:9

^aReaction 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. ^bNMR yield using toluene as an internal standard. ^cBased on ¹H 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).

The catalysis was further enhanced with a higher Pd loading (3.0 mol %; 91% yield, *Z/E* = 94:6; 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 excess of carbonate gave fairly similar results (Table 1, entry 18; 92% yield, *Z/E* = 91:9). Thus, the best conditions towards the formation of allylic thioether (*Z*)-**1a** were the use of Pd(dba)₂ (3.0 mol %), **L1** (5.0 mol %) in CH₃CN at 70 °C (Table

1, entry 10). It is worth noting that no special precautions or base additives¹⁸ were required making the present protocol highly attractive from a practical point of view.

Table 2. Investigated Scope in Thiol Partners to Produce Allylic Thioethers **1a–1l.**^a



entry	R	product	yield (%) ^b	<i>Z/E</i>
1	C ₆ H ₅	1a	90	94:6
2	4-Me-C ₆ H ₄	1b	73	92:8
3	2-Me-C ₆ H ₄	1c	93	92:8
4 ^c	4-CF ₃ -C ₆ H ₄	1d	70	83:17
5 ^c	4-Br-C ₆ H ₄	1e	76	80:20
6	3-Me-C ₆ H ₄	1f	95	90:10
7	4-MeO-C ₆ H ₄	1g	83	93:7
8 ^c	4-COOH-C ₆ H ₄	1h	98	91:9
9	2-pyridyl	1i	93	>99:1
10 ^c	4-HO-C ₆ H ₄	1j	87	91:9
11 ^c	Adamantyl	1k	98	>99:1
12 ^c	Benzyl	1l	50	92:8

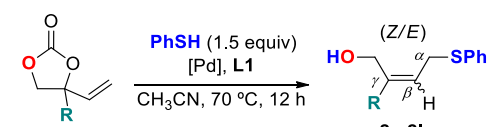
^aReaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiol (1.5 equiv), CH₃CN (0.20 mL), Pd(dba)₂ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h; ^bIsolated yield. ^cThiol (0.20 mmol), carbonate substrate (0.22 mmol).

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 providing the allylic thioethers **1a–1l** in good yields and *Z/E* ratios typically being >90:10. Both the presence of electron-withdrawing (**1d**, **1e**, **1h** and **1i**) and -donating groups (**1b**, **1c**, **1f**, **1g**, **1j**) in the aryl thiols is tolerated, and *para*-*meta*- and *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 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 stereoselectivity (**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 ¹H NOESY (Supporting Information, SI), and for **1a** also by X-ray analysis (see SI).

Subsequently, the vinyl carbonate reaction partner was varied (Table 3) giving access to a wider range of highly functionalized allylic thioethers **2a–2l** 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**, **2f** and **2i**) can be readily introduced further amplifying the product diversity. Upon using 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 SI for details). The observed 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 non-cyclic 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 π - σ - π alkene isomerization.¹⁹ A higher tendency to form such an acyclic Pd-intermediate causes loss in stereocontrol.

Table 3. Investigated Scope in Vinyl Carbonate Partners to Produce Allylic Thioethers 2a-2l^a



entry	R	product	yield (%) ^b	<i>Z/E</i>
1	4-Me-C ₆ H ₄	2a	70	94:6
2	4-F-C ₆ H ₄	2b	84	83:17
3	4-Br-C ₆ H ₄	2c	88	87:13
4	4-Ph-C ₆ H ₄	2d	97	94:6
5	4-CO ₂ Me-C ₆ H ₄	2e	80	84:16
6	4-CN-C ₆ H ₄	2f	91	67:33
7	2-naphthyl	2g	51	89:11
8	3-Cl-C ₆ H 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

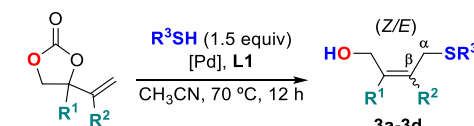
^aReaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiophenol (1.5 equiv), CH₃CN (0.20 mL), Pd(dba)₂ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h. ^bIsolated yield. ^cThiophenol (0.20 mmol), carbonate substrate (0.22 mmol). ^dBranched product (30%) also formed.

In order to further challenge the newly developed catalytic protocol for stereoselective allylic thioether formation, the synthesis of elusive tetra-substituted derivatives was attempted and the results are listed in Table 4. To our delight, the installation of both alkyl- and aryl-substituents (R² = Ph, Me) at the β -position of the allylic scaffold is feasible while maintaining excellent stereoselectivity (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 because of steric reasons (see SI for details). Other combinations of R¹ and R² were then also probed (*cf.*, 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 towards 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 a model reaction (see SI for more details). We were pleased to find that a combination of (NH₄)₆Mo₇O₂₁·4H₂O and H₂O₂ (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, 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**), methylester (**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-4h** were obtained. X-ray analysis of **4a** unambiguously confirmed the (*Z*)-configuration of this tri-substituted allylic sulfone (see SI).

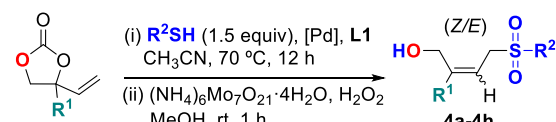
Table 4. Preparation of Elusive Tetra-Substituted Thioethers 3a-3d^a



entry	R ¹	R ²	R ³	product	yield (%) ^b	<i>Z/E</i>
1	<i>p</i> -Me-C ₆ H ₄	Ph	Ph	3a	48	>99:1
2	Ph	Me	Ph	3b	62	94:6
3	Ph	Me	4-MeO-C ₆ H ₄	3c	65	98:2
4	Ph	Me	2-Me-C ₆ H ₄	3d	37	90:10

^aReaction conditions unless otherwise stated: carbonate substrate (0.20 mmol), thiophenol (1.5 equiv), CH₃CN (0.20 mL), Pd(dba)₂ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h. ^bIsolated yield.

Table 5. One-Pot Synthesis of Highly Substituted Sulfones^a



entry	R ¹	R ²	product	yield (%) ^b	<i>Z/E</i>
1	Ph	Ph	4a	90	94:6
2	Ph	4-MeO-C ₆ H ₄	4b	83	93:7
3	Ph	3-Me-C ₆ H 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 ₆ H ₄	Ph	4f	76	84:16
7	4-F-C ₆ H ₄	Ph	4g	77	93:7
8	4-Me-C ₆ H ₄	Ph	4h	72	93:7

^aReaction conditions: (i) carbonate substrate (0.20 mmol), thiol (1.5 equiv), CH₃CN (0.20 mL), Pd(dba)₂ (3.0 mol %), **L1** (5.0 mol %), 70 °C, 12 h; (ii) (NH₄)₆Mo₇O₂₁·4H₂O, H₂O₂ (4 equiv, 30 wt % in H₂O), MeOH (0.20 mL), rt, 1 h; X-ray structure measured for sulfone (*Z*)-**4a**, see SI. ^bIsolated yield. ^cThiol (0.20 mmol), carbonate substrate (0.22 mmol).

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 operational simplicity. Based on our previous mechanistic investigations,^{15b} 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

Experimental details and copies of relevant NMR and IR spectra for all new products, X-ray data in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

* wguo@icq.es

* akleij@icq.es

Notes

The authors declare no competing financial interest.

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