General Synthesis of Alkenyl Sulfides by Palladium-Catalyzed Thioetherification of Alkenyl Halides and Tosylates

Noelia Velasco, Cintia Virumbrales, Roberto Sanz, Samuel Suárez-Pantiga* and Manuel A. Fernández-Rodríguez*†

Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain

Supporting Information Placeholder

Alkenyl sulfides are valuable building blocks widely used as enolate surrogates, Michael acceptors or as intermediates to 4- and 5-membered cyclic compounds. They have found applications in total synthesis and material science and are also frequently found in natural products, pharmaceuticals and biologically active compounds. Consequently, great effort has been made in the last decade for the development of general synthetic methodologies to access alkenyl sulfides. Among all the established strategies, the addition of thiols to alkynes is the most straightforward approach. Nevertheless, the regio- and stereoselectivity of the process is difficult to control in an efficient way, even under metal-catalyzed conditions, and the scope displays restrictions that include the addition of branched aliphatic thiols and the formation of fully substituted alkenyl sulfides. Alternatively, access to alkenyl sulfides from the corresponding alkenyl halides is also feasible by halogen-lithium exchange reactions followed by treatment with disulfides, although this protocol presents important drawbacks associated with the low functional group tolerance of organolithiums.

To overcome these limitations, the metal-catalyzed C–S cross-coupling reactions of haloalkenes appear as the best alternative for the preparation of alkenyl thioethers. In this sense, several copper-catalyzed protocols have been reported. However, these processes require high temperatures and/or high catalyst loadings and are typically restricted to iodoalkenes or β-bromostyrenes, whose reactions could be attributable to a non-catalyzed thiolate addition followed by bromide elimination. In contrast to related reactions with aryl halides, palladium-catalyzed couplings of haloalkenes with thiols have been poorly explored and the reported studies are limited to particular examples or to intramolecular reactions to produce benzol[β]thiophenes. These drawbacks have restrained the use of this methodology for the synthesis of relevant alkenyl thioethers. Therefore, the development of a general and scalable cross-coupling procedure for the C–S alkylation is highly desirable.

To this aim, the coupling of α-bromostyrene 1a with a slight excess of 1-decanethiol 2a (1.1 equiv) was selected as model reaction, and the most significant results are summarized in Table 1. Using Pd[η4-cyclooctene] (L2) or [allylPdCl] (L3) as ligand (L2) 3a was obtained in 93% yield that corresponds to a remarkable turnover number of 9300 (entry 4). Not surprisingly, reduced reaction time of less than 2 h was achieved by just using 0.1 mol % of the latter catalyst system (entry 5), whereas by using dppe as ligand (L2) 3a was obtained in 93% yield that corresponds to a remarkable turnover number of 9300 (entry 4). The cross-coupling of bulky thiols and trisubstituted bromoolefins, and functional group tolerance. In addition, the thioetherification of less reactive chloroalkenes and, for the first time, alkenyl tosylates was accomplished using a catalyst generated from CyPFtBu alkylbisphosphine ligand.
the reaction temperature was studied. When the transformation was performed at 90 ºC (entries 7–9), 70 ºC (entry 13) or even at 25 ºC (entry 14) full conversion was achieved just by increasing the catalyst loading up to 2.5 mol %. Furthermore, the use of 1,2-DME as solvent (entry 9) or bases different from LiHMDS such as NaOrBu, Cs₂CO₃ or K₂PO₄ was unproductive under the reported conditions (entries 10–12).

Table 1. Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>cat. (mol %)</th>
<th>temp (ºC)</th>
<th>conv. (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L1</td>
<td>1 (1.0)</td>
<td>110</td>
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<td>2</td>
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<td>Pd₃(dba)/L2</td>
<td>1 (1.0)</td>
<td>110</td>
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<tr>
<td>3</td>
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<td>Pd₃(dba)/L3</td>
<td>1 (1.0)</td>
<td>110</td>
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<tr>
<td>4</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₂ (0.01)</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₃ (0.01)</td>
<td>110</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₂ (0.1)</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₂ (0.01)</td>
<td>90</td>
<td>46</td>
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<tr>
<td>8</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₂ (0.05)</td>
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<td>100</td>
</tr>
<tr>
<td>9</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₂ (0.05)</td>
<td>90</td>
<td>&lt; 5</td>
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<tr>
<td>10</td>
<td>NaOrBu</td>
<td>Pd₃(dba)/L₂ (0.05)</td>
<td>90</td>
<td>5</td>
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<tr>
<td>11</td>
<td>Cs₂CO₃</td>
<td>Pd₃(dba)/L₂ (0.05)</td>
<td>90</td>
<td>&lt; 5</td>
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<tr>
<td>12</td>
<td>K₂PO₄</td>
<td>Pd₃(dba)/L₂ (0.05)</td>
<td>90</td>
<td>5</td>
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<tr>
<td>13</td>
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<td>Pd₃(dba)/L₂ (0.1)</td>
<td>70</td>
<td>100</td>
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<tr>
<td>14</td>
<td>LiHMDS</td>
<td>Pd₃(dba)/L₂ (2.5)</td>
<td>25</td>
<td>100</td>
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</table>

*a Conversion and yield (in brackets) estimated by 1H NMR (300 Hz) employing CH₂Br₂ as internal standard. b Reaction completed in less than 2 h. c Reaction conducted in DME.

Having identified the combination Pd₃(dba)/dpff as the optimal catalytic system for the alkynyl thioetherification under low catalyst loading, the scope of this reaction was explored varying first the thiol counterpart (Scheme 1). Reaction conditions employing 0.1 mol % of catalyst were selected to ensure complete conversions in short reaction times (< 4 h). Thus, primary (2a), secondary (2b), tertiary alkyl thiols (2c) and even the bulky HSTIPS (2d) were successfully coupled under these conditions with α-bromostyrene in high to excellent yields. The efficiency of the formation of alkynyl thioethers 3b–d derived from branched secondary and tertiary aliphatic thiols 2b–d is highly remarkable because, as mentioned in the introduction, their access via the addition of the branched thiol to an alkynne is challenging. Moreover, this methodology could be efficiently applied to synthesize alkynyl sulfides from aryl thiols bearing neutral (3e) and both electron-donating (3f–i,m) and electron-withdrawing groups (3j–l). Furthermore, ortho substitution on the parent aryl thiol is well-tolerated providing access to the desired compounds also in high yields. Even the reaction with a di-ortho-substituted thiol occurred in excellent yield without the need of increasing the catalyst loading (3m). Not surprisingly, considering the established faster oxidative addition of alkynyl over aryl halides, ⁵ thirteen thioetherification of α-bromobenzonitrile (2l) took place selectively on the alkynyl position of 1a over the bromide on 2l. This result enhances the synthetic utility of the developed methodology allowing the preparation of alkynyl sulfides bearing bromine atoms in their structure amenable for further derivatizations. Finally, the developed catalytic system is also capable of coupling π-deficient (2n) or π-excessive (2o) heteroaromatic thiols.

Although the scope of the thiol coupling was surveyed employing 0.1 mol % of catalyst, overnight reactions of selected substrates in the presence of just 100 ppm of Pd/ligand occurred to completion and with comparable or slightly decreased yields (see compounds 3a,e,f,h,l). A limitation was found with sterically hindered tertiary alkyl thiol that produced the corresponding sulfides (3c,d) in lesser extent with 100 ppm of catalyst and, therefore, the catalyst loading could not be lowered from 0.1 mol %.

On the other hand, the demonstrated high efficiency of Pd₃(dba)/dpff as catalytic system makes this methodology amenable for scale up. Gratifyingly, reaction of α-bromostyrene 1a with decanal or α-bromobenzonitrile at 7 mmol scale provided 1.86 g (95% yield) and 1.78 g (87% yield) of the alkynyl thioethers 3a and 3l, respectively (Scheme 2).

Scheme 1. Pd-catalyzed coupling of α-bromostyrene 1a with alkyl and aryl thiols 2.

Isolated yields of reactions performed using 0.4 mmol of 1a. a Reaction conducted overnight with 0.01 mol % of catalyst. b Reaction performed at 7 mmol scale.

Next, the thioetherification of a collection of diverse bromoalkanes was accomplished in short reaction times (typically < 4 h) using just 0.25 mol % of catalyst system (Scheme 2). Under these conditions, β-bromostyrene, used as a mixture of geometrical isomers, successfully reacted with a variety of alkyl and aryl thiols, including challenging sterically hindered ones, affording the corresponding alkynyl sulfides (4a–d) in high to excellent yields. It should be noted that reactions of β-bromostyrene without catalyst, gave mostly rise to disulfides and less than 5% of the desired alkynyl sulfides, thus ruling out the addition-elimination mechanism described in copper-catalyzed related couplings. ⁷² Notably, the functional group tolerance of the methodology is not restricted to halogens, alcoxy or free amino groups, showed in scheme 1, and has been extended to more demanding functionalities. Thus, alkynyl bromides bearing a nitro or a nitrile coupled with thiophenol to form the corresponding sulfides (4e–f) in good
yields. Moreover, reactions of substrates having ketone or ester groups, unsuccessful under the standard conditions, occurred in the presence of CyPFBu ligand (1.0 mol %) and the weaker Cs₂CO₃ base (4g–h). Regarding the substitution degree of the resultant sulfide, the method is also competent in the preparation of disubstituted (acyclic 4h and cyclic 4i) and trisubstituted alkenyl sulfides (4j–l) using catalyst loadings up to 1.0 mol % and reaction times between 4 and 24 h. Remarkably, the latter fully substituted alkenyl thiocarbamates (4j–l) are inherently not accessible by the thiol addition to alkynes strategy.

**Scheme 2. Pd-catalyzed coupling of diverse alkenyl bromides 1 with representative thiols 2.**

Isolated yields of reactions performed at 0.4 mmol scale. a Reaction conducted with 1.1 equiv of base. b Reaction performed with CyPFBu as ligand and Cs₂CO₃ as base. c Reaction conducted with 1.0 mol % of catalyst system.

Once the generalization of the alkenyl thioetherification process with a wide range of alkenyl bromides was demonstrated, we decided to evaluate other halogenated as potential coupling partners with 1-decanethiol (1a) and thiophenol (1e) (Table 2). Whereas more reactive iodoalkanes performed similarly to their parent bromoalkanes (entries 1–2), less reactive chloroalkanes failed to react with the catalyst derived from dppf ligand, even at higher loadings (1.0 mol %). Nevertheless, as it was demonstrated for related thioetherifications of aryl chlorides,¹⁴ bis-phosphine CyPFBu was revealed as the ligand of choice for the coupling of chloroalkanes enabling the synthesis of alkenyl sulfides 3a and 3e by simply using 0.5–1.0 mol % of this catalytic system (entries 3–4). Reactions of 1-chlorocyclopentene also occurred with the model thiol under the same reaction conditions (entries 5–6).

**Table 2. Pd-catalyzed coupling of alkenyl iodides and chlorides with decanethiol and thiophenol.**

In conclusion, a general, selective and scalable methodology for the synthesis of alkenyl sulfides through palladium-catalyzed C–S bond cross-coupling has been developed based on the use of inexpensive bisphosphine dppf ligand. This synthetic approach is capable of coupling a wide variety of aliphatic and (hetero)aromatic thiols to alkenyl bromides with diverse substitution patterns and functionalities under very low catalyst loading (generally 0.01–0.25 mol %) in high yields. The scope of the process is broad and includes the employment of sterically hindered alkyl and aryl thiols and the access to fully substituted alkene derivatives, overcoming the main synthetic limitations of the metal-catalyzed direct reaction of thiols with alkynes. In addition, catalytic species generated from Pd₃(dba)₃ and CyPFBu ligand allowed less reactive chloroalkanes and, for the first time, readily available tosylalkenenes to be also active coupling counterparts for the alkenyl thioetherification with both alkyl and aryl thiols.
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, characterization data and NMR spectra for all new compounds (PDF).

AUTHOR INFORMATION

Corresponding Authors

*E-mail: mangel.fernandezt@uah.es

*E-mail: svsuarez@ubu.es

Present Addresses

departmento de Química Orgánica y Química Inorgánica, Universidad de Alcalá, 28805, Alcalá de Henares, Madrid, Spain.

Notes

The authors declare no competing financial interest.

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REFERENCES


(13) For an additional competition experiment that further demonstrates the greater reactivity of alkenyl bromides over aryl bromides with thiols under the developed catalytic conditions, see SI.

