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# Palladium-Catalyzed Synthesis of Aryl Vinyl Sulfides via 1,3-Oxathiolanes as Vinyl Sulfide Surrogates

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Supporting Information Placeholder
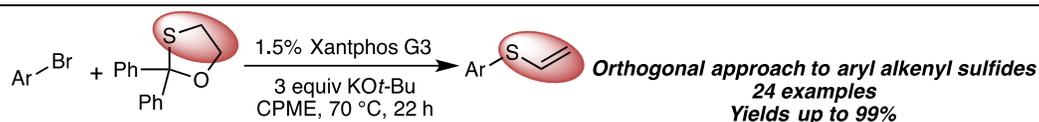
ABSTRACT: A non-traditional approach to synthesizing aryl vinyl sulfides is described. 2,2-diphenyl-1,3-oxathiolane slowly liberates vinyl sulfide anion under basic conditions. Using a Pd/Xantphos catalyst system to activate a wide range of aryl bromides, this transient sulfide species can be effectively trapped and fed into a traditional Pd^0/Pd^{II} catalytic cycle. Scope and limitations of the methodology are presented along with significant discussion of a competitive C–S bond activation by this catalyst system.

Recently, our group[1] and others[2] have reported on the palladium-catalyzed cross coupling of 2-aryl-1,3-dithianes as a polarity-reversed approach to access both diaryl ketones and diarylmethanes. After these first reports, our group has continued to probe the compatibility of 1,3-dithiane analogues under cross-coupling conditions and have unearthed some interesting reactivity (Figure 1, top panel) For example, when subjecting the one-carbon homolog, 2-benzyl-1,3-dithiane to palladium catalysis, none of the expected C–C bond is formed. Instead, a tandem benzylic deprotonation followed by ring opening of the dithiane leaves the pendant sulfur anion available for cross coupling.[3]

When we applied our standard conditions in an attempt to cross couple 4-bromoanisole with 2-phenyl-1,3-oxathiolane, none of the expected benzylic arylation product was observed. Instead, the crude reaction mixture contained (4-methoxyphenyl)vinyl sulfide **1** along with the symmetric diaryl sulfide (Figure 1, middle panel), hinting at a third reaction manifold for these Corey-Seebach reagents under cross-coupling conditions.

We were particularly intrigued by the vinyl sulfide component, as they are important motifs themselves as well as being used as building blocks in polymers[4] and in small molecule synthesis, e.g. as Michael acceptors,[5] 2+2 cycloaddition substrates,[6] and surrogates for enol ethers.[7] Though useful, there are but a handful of approaches to synthesize aryl alkenyl sulfides. Worse, nearly all of these approaches utilize an *identical disconnection strategy* that ultimately uses thiophenols as the nucleophilic sulfur-containing coupling partner.[8, 9, 10] Only a single example (of 85 found synthetic approaches to phenyl vinyl sulfide[11]) *inverts* the disconnection strategy by forming the aryl-sulfur bond with an external sulfur nucleophile (Figure 1, bottom panels). Interestingly, this approach utilizes a 1,3-oxathiolane as the masked vinyl sulfide anion, though

relying upon an *in situ* generated benzyne as the electrophilic partner, which greatly limits the scope and utility of the methodology.[12] Thus, developing a catalytic approach that takes advantage of the ubiquitous aryl bromide and provides a large pool of reagents to access a novel array of aryl alkenyl sulfides warranted further exploration.
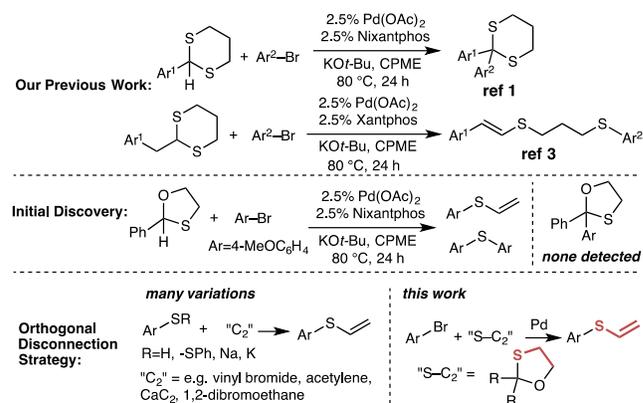

Figure 1. Previous work and initial discovery prompting this new methodology.

After the initial discovery, we began our investigations by simplifying the system, utilizing 2,2-dimethyl-1,3-oxathiolane as the alkenyl sulfide equivalent. On paper, this system would have some obvious challenges, as the by-product acetone might be prone to alpha arylation.[13] However, the atom economy of acetone and the ease with which this by-product could be removed from the crude reaction mixture had enough appeal for us to begin our investigations here.

Initial optimization on bromobenzene, using the third generation Buchwald precatalyst scaffold[14] with Nixantphos lig-

and, the desired phenyl vinyl sulfide was generated, though with moderate conversion and undesired side product formation (Figure 2, panel A). A screen of ligands indicated that Nixantphos was indeed the most effective ligand. The closely related Xantphos did prove capable in this transformation, though with attenuated results[15] and significant by evidence of decomposition in the crude GC. For all other ligands attempted (**Figure 2,** Panel **B**, ligands **C–F**), none of the desired vinyl sulfide was detected by GC analysis of the reaction. Encouraged by the result with Nixantphos, we hypothesized that reaction turnover was being limited by the slow decomposition of the 2,2-dimethyl-1,3-oxathiolane. The use of 10 mol % 18-crown-6 increased the observed yield of phenyl vinyl sulfide (**Figure 2**, Panel **A**) presumably by increasing the basicity of the *tert*-butoxide anion and speeding the decomposition of the oxathiolane.[16]

Though conversion was still incomplete, the use of the crown ether improved the outcome significantly. In fact, for electron-rich and sterically bulky aryl bromides, these conditions proved synthetically useful, allowing us to isolate compounds **1–4** in 52-81% yields (**Figure 2**, Panel **C**). However, with aryl bromides that were electron-neutral or electron-poor, little if any of the desired aryl vinyl sulfide could be detected in the crude reaction mixture. The attempted cross coupling of 4-bromobenzotrifluoride, for example, provided none of the desired product (**5**). Interestingly, none of the anticipated α-arylation with the acetone by-product was ever detected in analysis of crude reaction mixtures, even when the desired vinyl sulfide formation was low.
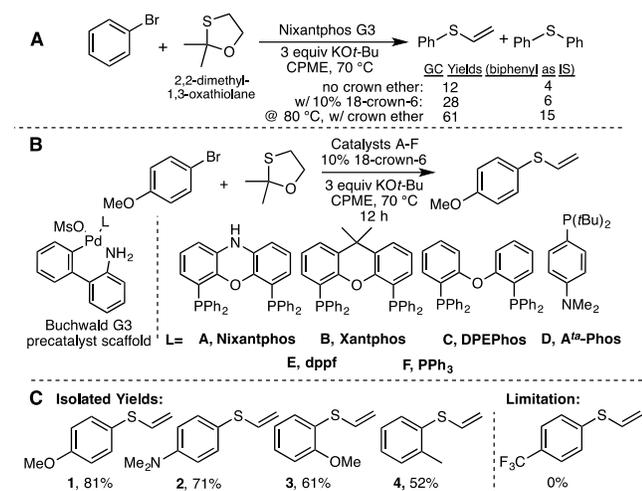

Figure 2. Initial results with reaction limitation.
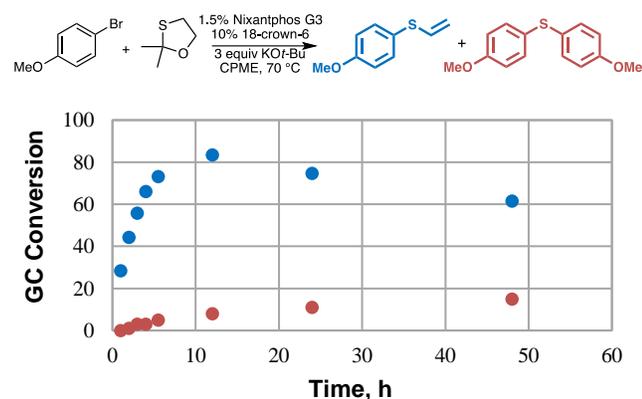

Figure 3. Multi-time point sampling of coupling reaction.

To probe further, we monitored the coupling of 4-bromoanisole with 2,2-dimethyl-1,3-oxathiolane using our best conditions (**Figure 3**), allowing the reaction to age for 48 h. Aliquots taken over the course of the reaction indicate that the desired aryl vinyl sulfide—once formed—is slowly consumed as a new product peak corresponding to bis-(4-methoxyphenyl)sulfide grows in. This experiment led us to believe that even under highly-optimized and substrate specific reaction conditions, we would never be able to fully suppress diaryl sulfide formation, resulting in moderate-to-low isolated yields of vinyl sulfides, and making this methodology less attractive to the synthetic community. Thus, we sought to investigate further this unwanted transformation in order to learn how to suppress it.

Recently, Walsh reported the use of *benzyl* sulfides as thiophenol surrogates in cross-coupling reactions[17] and so we wondered if the vinyl sulfide might be engaging with the palladium catalyst in a similar fashion. A control reaction was run between phenyl vinyl sulfide and two equivalents of 4-bromoanisole. After 24 h (**Scheme 1**, Panel **A**) at 90 °C, crude GC analysis showed 80% conversion of the starting materials and two new peaks: one corresponding to (4-methoxyphenyl)(phenyl)sulfane **25** and a second corresponding to anisole **26**. After 48 hours under the same conditions (Scheme 1, Panel **B**), starting materials were now consumed completely, though a range of biaryl and biarylthioether products were detected via GC analysis (**Scheme 1**, Panel **B**, bottom). It appears that the Pd-Xantphos catalyst is able to activate C(sp^2)–S bonds of both aryl and vinyl sulfides, here resulting in the scrambling of C–S bonds as well as to the apparent extrusion of a sulfur atom altogether leading to new C–C bond formation. Indeed, recent work by Jones and coworkers clearly demonstrates the ability for palladium to activate C(sp^2)–S bonds using the bidentate bisphosphine ligand, bis-(di*iso*propylphosphino)ethane.[18] It is not unreasonable to postulate that the bidentate Xantphos ligand might be engaging in a similar fashion.

Taken together with Walsh's work utilizing Nixantphos to activate C(sp^3)–S bonds in benzylic systems, we suspect this or a related ligand class might be useful in the development of new methodologies that utilize derivatives of aryl sulfides as pseudoelectrophiles in cross-coupling reactions. Work in this area has already begun in our labs and will be disclosed in due course.

Scheme 1. Phenyl Vinyl Sulfide as Coupling Partner.
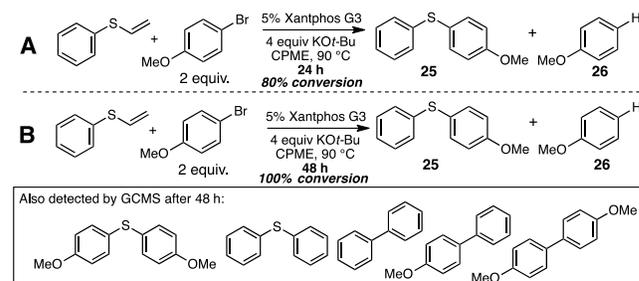
Still eager to develop a synthetically useful methodology *en route* to aryl vinyl sulfides, we turned our attention to the oxathiolane component of the coupling reaction. Our qualitative understanding of the reaction conditions to this point led our lab to believe that the base-catalyzed decomposition of the

oxathiolane was independent of palladium's catalytic role. We also developed an appreciation that the lifetime of the vinyl sulfide anion was rather short under the reaction conditions. We posited that more closely matching the rates of the two discrete reactions would lead to improved reaction profiles and yields of the desired aryl vinyl sulfides.

We reasoned that a move to 2,2-di*phenyl*-1,3-oxathiolane would increase the rate of base-promoted decomposition due to the inductive effects of the phenyl groups. We were excited to see significantly cleaner reaction profiles and higher isolated yields in this case (**Table 1**, Entries 1–4). Further, we were able to substitute the less expensive Buchwald G3 *Xantphos* precatalyst for the Nixantphos variant with no observed loss in reactivity, and catalyst loading could be lowered to a reasonable 1.5 mol % for most examples. Most excitingly, these optimized conditions now worked for very electron-poor aryl bromides (e.g. Table 1, Entries 5 and 14), a significant limitation of the initial work using 2,2-dimethyl-1,3-oxathiolane. A range of electronically- and sterically-diverse aryl bromides participated in the reaction, resulting in moderate-to-excellent isolated yields ranging from 58-99% after column chromatography.

Table 1. Substrate Scope, Limitations

entry	aryl bromide	yield (%)[a]
1	4-bromoanisole	95, 85[b]
2	4-bromo-*N,N*-dimethylaniline	90
3	2-bromoanisole	92[c]
4	2-bromotoluene	93[c]
5	4-bromobenzotrifluoride	83
6	3-bromoanisole	75
7	3-bromotoluene	80
8	4-bromo-*tert*-butylbenzene	91
9	4-chlorobromobenzene	94
10	4-fluorobromobenzene	66[d]
11	4-bromobiphenyl	91
12	2-bromo-6-methoxynaphthalene	90
13	bromobenzene	84[d]
14	3-bromobenzotrifluoride	89
15	5-bromobenzofuran	82
16	1-bromonaphthalene	76[c]
17	2-bromonaphthalene	92
18	4-trifluoromethoxybromobenzene	75[d]
19	1,4-dibromobenzene	70[e]
20	6-bromoquinoline	66[c]
21	2-bromo-4-*tert*-butyltoluene	97[c]
22	3-bromo-4-methylbiphenyl	99
23	2-fluoro-4-bromoanisole	59[c]
24	2-(*tert*-Butyldimethylsilyloxy)-6-bromonaphthalene	58

[a] Isolated yield after column chromatography; average of two runs agreeing to within 5%. [b] From 4-iodoanisole. [c] 6 mol % of the Pd catalyst. [d] Products are volatile. [e] 2.2 equivalents of the oxathiolane, 6 equivalents base. Some limitations include:
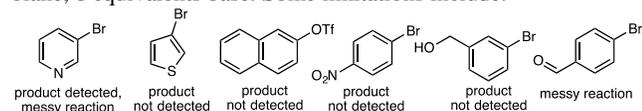
In the case of some of the sterically challenging substrates (e.g. Entries 3, 4, 16, 21, and 23), the use of 6% of the palladium catalyst provided cleaner reaction profiles and higher iso-

lated yields. The developed conditions engaged some heteroaryl bromides (Table 1, Entries 15, 20), though other heteroaryl bromides proved a limitation to the method (Table 1, Inset); while 3-bromopyridine did engage in the desired coupling, the messy reaction and low conversion led to our inability to cleanly isolate the desired product. The catalyst could selectively activate aryl bromides in the presence of the chloride, allowing for the possibility of iterative aryl functionalization (Table 1, Entry 9). Phenyl triflate did not engage in the cross coupling which is in line with our previous studies using Xantphos or Nixantphos-based catalyst systems.[1,3]

Figure 4 presents a plausible catalytic cycle for both the desired synthesis of aryl vinyl sulfides and speculates upon the palladium-catalyzed C–S bond activation of the catalyst.
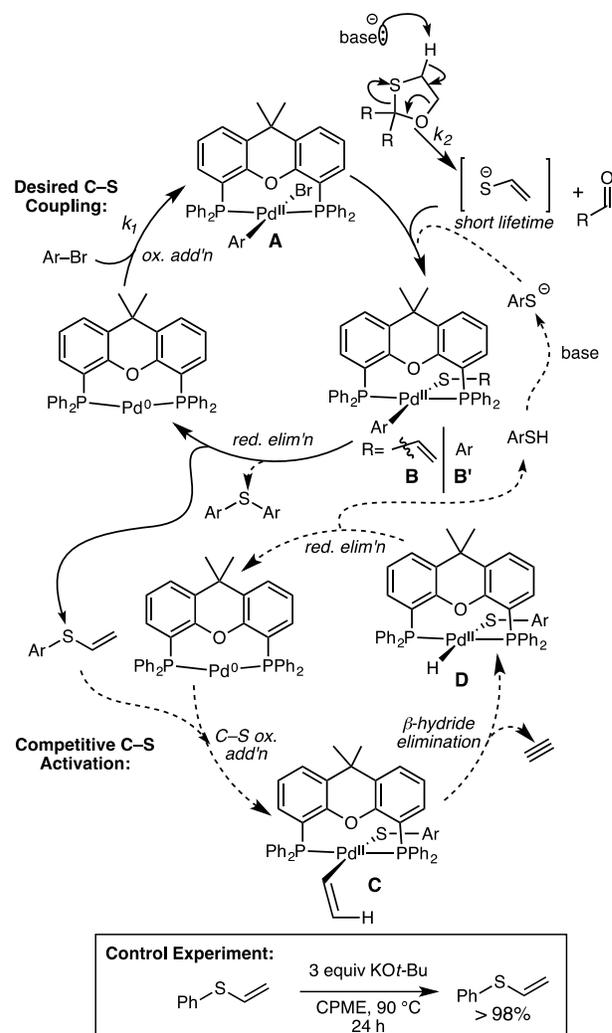

Figure 4. Plausible catalytic cycle for desired C–S coupling (solid lines) and for the undesired competitive C–S activation (dashed). Inset: A control reaction supports the role for palladium on phenyl vinyl sulfide decomposition.

Mechanistically, the desired cross coupling likely proceeds through a very traditional Pd[0]/Pd[II] catalytic cycle. After oxidative addition, intermediate **A** is intercepted by vinyl sulfide and undergoes ligand exchange providing intermediate **B**. Reductive elimination furnishes the aryl vinyl sulfide and regenerates Pd[0].

For the competitive C–S activation, we provide merely a *plausible* catalytic cycle, as significant further work remains to more accurately elucidate the mechanism. Qualitatively, we know that in the synthesis of the diaryl sulfides, pressure builds in the reaction vial as the reaction progresses. Additionally, we know that two equivalents of aryl bromide are needed to fully consume the phenyl vinyl sulfide, and the des-halogenated aryl bromide is observed via GC of the crude reaction mixture. We are unsure at this juncture whether the reduction of the aryl bromide is essential to the turnover of the catalyst or if it is simply a second unproductive path for the system, and though the extent to which the des-halogenated anisole was formed was not determined, a full 2.0 equivalents of the aryl bromide was needed to completely consume the vinyl sulfide in this reaction. Work continues in this area.

Thus, for the competitive C–S activation pathway, oxidative addition to the aryl vinyl sulfide to furnish putative intermediate **C**, could quickly undergo beta-hydride elimination. Loss of acetylene gas leads to intermediate **D** before reductive elimination regenerates the Pd[0] catalyst, and forms the thiophenol. Thiophenols are excellent substrates for palladium-catalyzed cross coupling[19] and would almost certainly out-compete the ligand exchange onto the Pd[II] Intermediate **A** and form intermediate **B'** (R=aryl) before furnishing the diaryl sulfide upon reductive elimination. A preliminary control reaction has been run, subjecting phenyl vinyl sulfide to *tert*-butoxide in CPME at 90 °C. After 24 h, we were able to re-isolate the phenyl vinyl sulfide in >98%, indicating that the palladium catalyst seems to be essential for the decomposition/initial activation of the aryl vinyl sulfides.

In conclusion, we have reported a new catalytic approach to synthesize aryl vinyl sulfides. Importantly, this approach takes advantage of widely available aryl bromides instead of relying upon less common thiophenols. Current reaction scope indicates that this reaction is amenable to a wide range of electronically diverse aryl bromides, and future plans for in-depth mechanistic studies to more fully understand the mechanism are underway. Finally, application of this methodology to include oxathiolanes with C4 and/or C5 substitution will furnish more highly substituted alkenyl sulfides and is currently underway.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all compounds (PDF). ^{1}H and ^{13}C NMR spectra for all compounds (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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Ar—Br + Ph—⧨(S)(O)Ph →[1.5% Xantphos G3][3 equiv KO*t*-Bu][CPME, 70 °C, 22 h] Ar—S—CH=CH₂

$$\text{Ar}-\text{Br} \; + \; \text{Ph}\overset{\text{Ph}}{\underset{}{\diagdown}}\!\!\underset{O}{\overset{S}{\triangle}} \xrightarrow[\substack{\text{3 equiv KO}t\text{-Bu}\\ \text{CPME, 70 °C, 22 h}}]{\text{1.5\% Xantphos G3}} \text{Ar}-S-\!\!\diagup\!\!\diagdown$$

Orthogonal approach to aryl alkenyl sulfides
24 examples
Yields up to 99%