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

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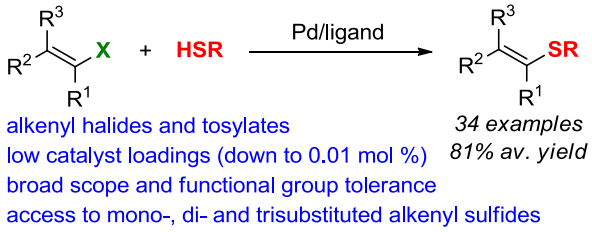
Supporting Information Placeholder



ABSTRACT: The cross-coupling reaction of alkenyl bromides with thiols catalyzed by palladium complexes derived from inexpensive dppf ligand is reported. These reactions occur under low catalyst loading, in high yields and display wide scope, including the 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 CyPF*t*Bu alkylbisphosphine ligand.

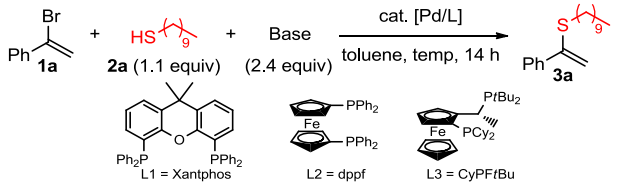
Alkenyl sulfides are valuable building blocks widely used as enolate surrogates, Michael acceptors or as intermediates to 4- and 5-membered cyclic compounds.[1] They have found applications in total synthesis[2] and material science[3] and are also frequently found in natural products, pharmaceuticals and biologically active compounds.[4] Consequently, great effort has been made in the last decade for the development of general synthetic methodologies to access alkenyl sulfides.[5] Among all the established strategies, the addition of thiols to alkynes is the most straightforward approach. Nevertheless, the regio- and steroselectivity of the process is difficult to control in an efficient way, even under metal-catalyzed conditions,[5,6] and the scope displays restrictions that include the addition of branched aliphatic thiols[5d] 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.[7] 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.[7a,8] In contrast to related reactions with aryl halides,[5b,c] palladium-catalyzed couplings of haloalkenes[9] with thiols have been poorly explored and the reported studies are limited to particular examples[10] or to intramolecular reactions to produce benzo[*b*]thiophenes.[11] 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 alkenylation 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 $Pd_2(dba)_3$ as palladium source, several ligands were tested. Initial results with 1.0 mol % of catalyst indicated that ferrocenyl phosphines L2 and L3 were the most efficient ligands, achieving total conversion to the desired alkenyl sulfide **3a** after 14 h (entries 1–3). Reactions in the absence of palladium or with catalysts derived from biaryl phosphine ligands, such as Sphos, RuPhos, BrettPhos or XPhos, led to < 5% conversion to the coupled product accompanied with thiol oxidation to disulfide.[12] Encouraged by the results with bisphosphine ligands L2 and L3, the catalyst loading was considerably decreased (entries 4–6). At very low catalyst amounts (0.01 mol %) CyPF*t*Bu ligand (L3) failed to promote the reaction to full conversion (entry 5), whereas by using dppf 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 6). Reactions employing other palladium sources such as $Pd(OAc)_2$, $Pd[P(o\text{-}tol)_3]_2$ or $[allylPdCl]_2$ were not or less efficient under the same conditions.[12] Next, the dependence on

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 NaO*t*Bu, Cs_2CO_3 or K_3PO_4 was unproductive under the reported conditions (entries 10–12).

Table 1. Optimization of reaction conditions.



entry	base	cat. (mol %)	temp (ºC)	conv. (%)[a]
1	LiHMDS	$Pd_2(dba)_3$/L1 (1.0)	110	< 50
2	LiHMDS	$Pd_2(dba)_3$/L2 (1.0)	110	100
3	LiHMDS	$Pd_2(dba)_3$/L3 (1.0)	110	100
4	LiHMDS	$Pd_2(dba)_3$/L2 (0.01)	110	100 (93)
5	LiHMDS	$Pd_2(dba)_3$/L3 (0.01)	110	52
6[b]	LiHMDS	$Pd_2(dba)_3$/L2 (0.1)	110	100 (94)
7	LiHMDS	$Pd_2(dba)_3$/L2 (0.01)	90	46
8	LiHMDS	$Pd_2(dba)_3$/L2 (0.05)	90	100 (90)
9[c]	LiHMDS	$Pd_2(dba)_3$/L2 (0.05)	90	< 5
10	NaO*t*Bu	$Pd_2(dba)_3$/L2 (0.05)	90	< 5
11	Cs_2CO_3	$Pd_2(dba)_3$/L2 (0.05)	90	< 5
12	K_3PO_4	$Pd_2(dba)_3$/L2 (0.05)	90	< 5
13	LiHMDS	$Pd_2(dba)_3$/L2 (0.1)	70	100 (94)
14	LiHMDS	$Pd_2(dba)_3$/L2 (2.5)	25	100 (93)

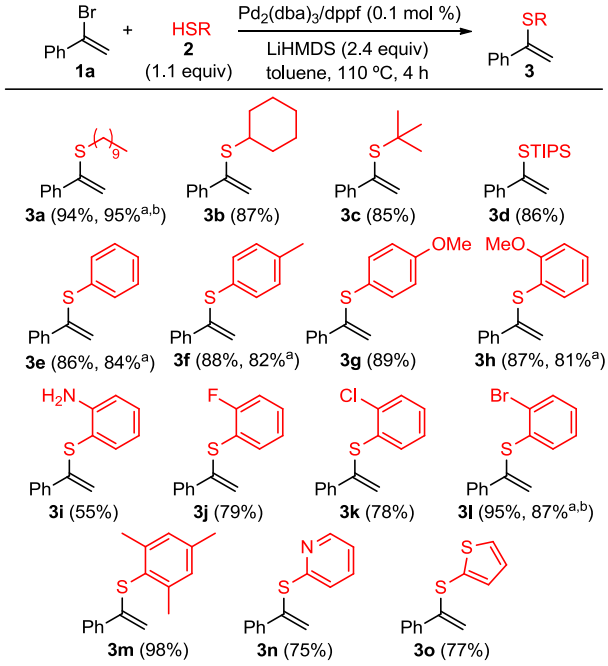
[a] Conversion and yield (in brackets) estimated by ^{1}H NMR (300 Hz) employing CH_2Br_2 as internal standard. [b] Reaction completed in less than 2 h. [c] Reaction conducted in DME.

Having identified the combination $Pd_2(dba)_3$/dppf as the optimal catalytic system for the alkenyl 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 alkenyl 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 alkyne is challenging. Moreover, this methodology could be efficiently applied to synthesize alkenyl 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 alkenyl over aryl halides,[13] thioetherification of *o*-bromobenzenethiol (**2l**) took place selectively on the alkenyl position of **1a** over the bromide on **2l**. This result enhances the synthetic utility of the developed methodology allowing the preparation of alkenyl 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 thiols 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 $Pd_2(dba)_3$/dppf as catalytic system makes this methodology amenable for scale up. Gratifyingly, reaction of α-bromostyrene **1a** with decanethiol or *o*-bromobenzenethiol at 7 mmol scale provided 1.86 g (95% yield) and 1.78 g (87% yield) of the alkenyl thioethers **3a** and **3l**, respectively (Scheme 2).

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

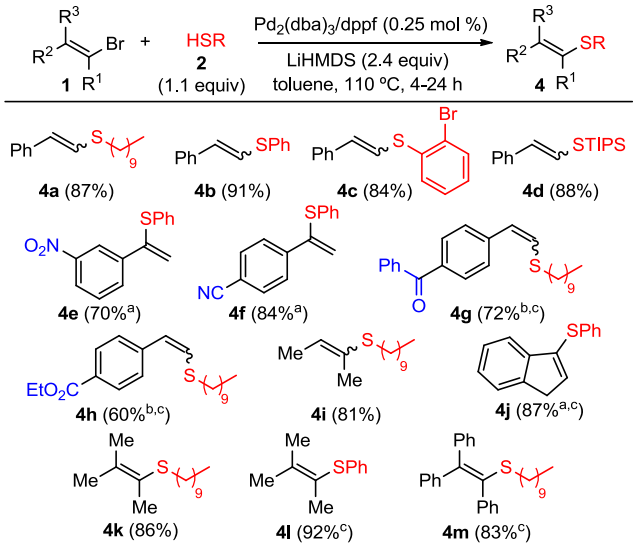


Isolated yields of reactions performed using 0.4 mmol of **1a**. [a] Reaction conducted overnight with 0.01 mol % of catalyst. [b] Reaction performed at 7 mmol scale.

Next, the thioetherification of a collection of diverse bromoalkenes 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 alkenyl 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 alkenyl sulfides, thus ruling out the addition-elimination mechanism described in copper-catalyzed related couplings.[7a] 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, alkenyl 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 CyPF*t*Bu ligand (1.0 mol %) and the weaker Cs_2CO_3 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 thioethers (**4j-l**) are inherently not accessible by the thiol addition to alkynes strategy.

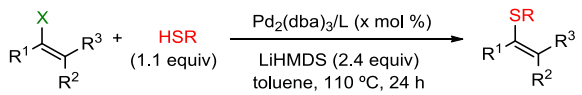
Scheme 2. Pd-catalyzed coupling of diverse alkenyl bromides 1 with representative thiols 2.

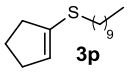
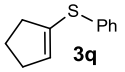


Isolated yields of reactions performed at 0.4 mmol scale. [a] Reaction conducted with 1.1 equiv of base. [b] Reaction performed with CyPF*t*Bu as ligand and Cs_2CO_3 as base. [c] Reaction conducted with 1.0 mol % of catalyst system.

Once the generalization of the alkenyl thioetherification process with a wide range of alkenyl bromides was demonstrated, we decided to evaluate other haloalkenes as potential coupling partners with 1-decanethiol (**1a**) and thiophenol (**1e**) (Table 2). Whereas more reactive iodoalkenes performed similarly to their parent bromoalkenes (entries 1–2), less reactive chloroalkenes 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 CyPF*t*Bu was revealed as the ligand of choice for the coupling of chloroalkenes 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 thiols under the same reaction conditions (entries 5–6).

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

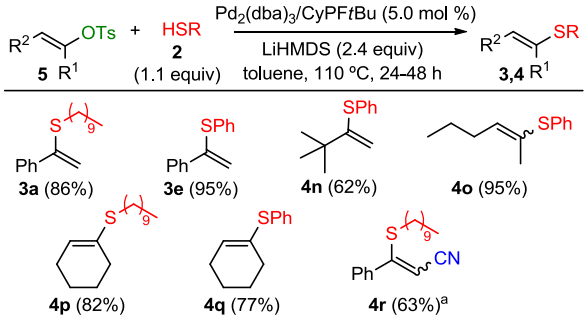


entry	halide	thiol	L (x mol %)	product	Yield (%)[a]
1			dppf (0.05)	**3a**	91
2		HSPh	dppf (0.01)	**3e**	72
3			CyPF*t*Bu (1.0)	**3a**	75
4		HSPh	CyPF*t*Bu (0.5)	**3e**	80
5			CyPF*t*Bu (0.5)	 **3p**	75
6		HSPh	CyPF*t*Bu (0.5)	 **3q**	55

[a] Isolated yields of reactions performed at 0.4 mmol scale.

Alkenyl sulfonates are attractive alternatives to halides, as they are easily synthesized from abundantly available ketones increasing the range of available substitution patterns. Among sulfonates, alkenyl tosylates are more convenient counterparts than the corresponding triflates because of the lower cost of the sulfonating reagents used for their preparation, as well as their greater crystallinity and stability to water, which allows their storage.[15] However, this stability makes the oxidative addition to Pd(0) more challenging and, therefore, alkenyl tosylates are less reactive in palladium-catalyzed processes.[16] Consequently, couplings of alkenyl tosylates with thiols are unknown. Interestingly, a 5 mol % of the combination $Pd_2(dba)_3$/CyPF*t*Bu ligand, catalyzed the coupling of α-(*p*-toluenesulfonyl)styrene with both decanothiol and thiophenol in high yields (Scheme 3, **3a**,**e**). The usefulness of this reaction was further demonstrated with the efficient couplings of alkenyl tosylates derived from branched aliphatic, alkyl disubstituted, cyclic or functionalized ketones (Scheme 3, **4n-r**), for which corresponding bromoalkenes are not easily available.

Scheme 3. Pd-catalyzed coupling of alkenyl tosylates 5 with representative thiols 2.



Isolated yields of reactions performed at 0.4 mmol scale. [a] Cs_2CO_3 (2.0 equiv.) used as base.

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 $Pd_2(dba)_3$ and CyPF*t*Bu ligand allowed less reactive chloroalkenes and, for the first time, readily available tosyloxyalkenes 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).

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Notes

The authors declare no competing financial interest.

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(12) See Supporting Information for details.

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