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A General Palladium-Catalyzed Coupling of Aryl Bromides/Triflates and Thiols

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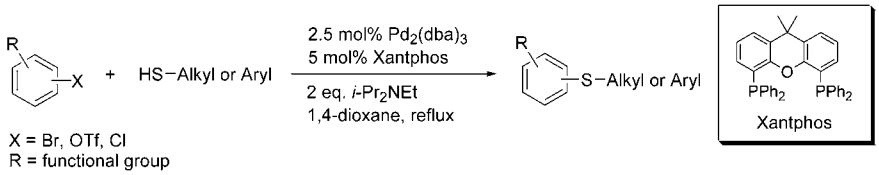
ABSTRACT



We have developed an efficient palladium-catalyzed carbon–sulfur bond formation reaction of aryl bromides, triflates, and activated aryl chloride. Using this protocol, we have shown tolerance to a wide variety of aryl thiols and alkyl thiols that can also be used as sulfide equivalents.

Aryl sulfides are a common functionality found in numerous pharmaceutically active compounds.[1] Indeed, a number of drugs in therapeutic areas such as diabetes and inflammatory, immune, Alzheimer's, and Parkinson's diseases contain the aryl sulfide functionality.[2] The traditional method[3] for forming an aryl−sulfur bond is a substitution reaction via an addition−elimination mechanism. However, these reactions often require high temperature and long reaction times for nonactivated haloarenes. Recently, Kang and co-workers reported the synthesis of alkyl aryl sulfides via lithium aryl thiolates that are prepared from aryl bromide and *n*-BuLi in the presence of sulfur.[4] In 1980, Migita and co-workers first reported the Pd-catalyzed cross-coupling reaction of aryl bromides with thiols.[5] Since then, many reports have appeared in the literature describing the formation of aryl sulfides using transition-metal catalysts (Pd, Ni, Cu).[6] The substantial contributions by Venkataraman,[7] Buchwald,[8] and Palomo[9] have demonstrated the combination of aryl iodides with thiols using copper catalyst. In contrast to the more widely investigated cross-coupling of thiol with aryl halides,

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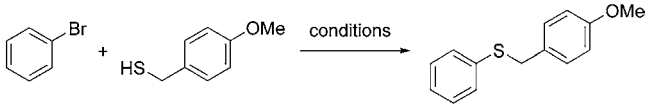
Cu- or Pd-catalyzed aryl sulfide formation from aryl triflates has received little attention. Aryl triflates are very attractive alternatives to aryl halides given that they can be prepared in a straightforward manner from readily available and cheap phenolic precursors. Recently, researchers at Merck reported the successful Pd-catalyzed cross-coupling of aryl triflates and alkane thiols;[6h] however, this methodology was problematic when using aryl thiols. In conjunction with development of our drug candidate, we required a synthesis of diaryl sulfide. Herein we wish report a general Pd-catalyzed cross-coupling of aryl bromides/triflates/chlorides with alkyl/aryl thiols.

We screened a number of phosphine ligands, bases, solvents, and reaction temperatures for preliminary optimization of the palladium-catalyzed reaction using bromobenzene and *p*-methoxybenzyl thiol as a test reaction (Table 1).

Table 1. Evaluation of Different Catalyst Systems for the Formation of Diaryl Sulfides

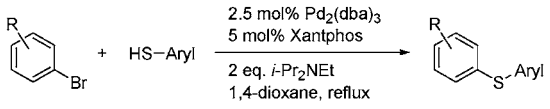


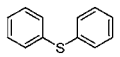
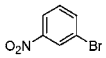
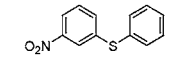
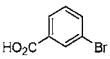
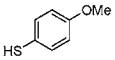
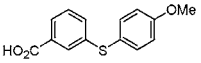
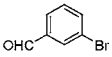
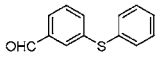
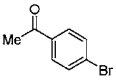
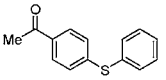
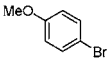
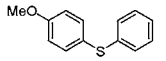
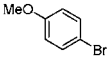
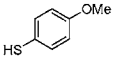
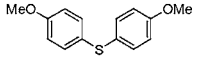
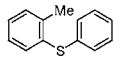
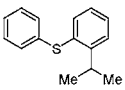
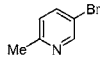
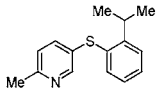
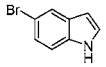
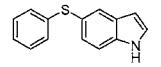
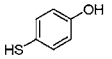
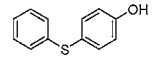
entry	conditions[a]	% yield
1	KO*t*-Bu, DMSO, 120°C	nd
2	$Pd(PPh_3)_4$, NaO*t*-Bu, *n*-BuOH, 120 °C	nd
3	$Pd(OAc)_2$, D-t-BPF, K_2CO_3, dioxane, reflux	10
4	POPd,[b] NaO*t*-Bu, toluene, reflux	15
5	$Pd(OAc)_2$, DPEphos, K_2CO_3, dioxane, reflux	21
6	$Pd(OAc)_2$, Xantphos, K_2CO_3, dioxane, reflux	32
7	$Pd_2(dba)_3$,[c] Xantphos, K_2CO_3, dioxane, reflux	40
8	$Pd_2(dba)_3$,[c] Xantphos, *i*-Pr_2NEt, dioxane, reflux	90
9	CuI, $HOCH_2CH_2OH$,[d] K_2CO_3, *i*-PrOH, 80 °C	nd

[a] Reactions were conduced with 5 mol % catalyst, 5 mol % ligand, 1.1 equiv of *p*-methoxybenzyl thiol, and 2.0 equiv of base for 15 h on a 2.0 mmol scale of bromobenzene. [b] POPd: $PdCl_2[(t\text{-Bu})_2P(OH)]_2$, purchased from Combiphos Catalysts, Inc. [c] 5 mol % Pd refers to 2.5 mol % $Pd_2(dba)_3$. [d] 2.0 equiv of $HO(CH_2)_2OH$.

As expected, in the absence of transition metal no aryl sulfide was detected (entry 1). Using $Pd(PPh_3)_4$ in *n*-BuOH gave no detectable amount of desired product (entry 2). Hartwig has had success in the Pd-catalyzed amination of aryl bromides based on the electronically rich and sterically hindered bidentate ferrocenyl ligand 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D-*t*-BPF).[10] Likewise, the DuPont group reported on the use of the attractive catalyst POPd for C−S bond formation.[6n−p] The Novartis group reported the synthesis of the diarylsulfides from aryl iodides and electron-rich aryl thiols using DPEphos.[6i] These ligands, however, were less active for our case (entries 3−5). After screening several palladium salts in combination with various phosphine ligands, we found that $Pd_2(dba)_3$ and Xantphos[11] led to complete conversion with *i*-Pr_2NEt as base in dioxane after 6 h at reflux temperature (entry 8).[12] The choice of the base is critical. Other bases such as Na_2CO_3, K_3PO_4, KF, and CsF and stronger bases such as NaO*t*-Bu or KO*t*-Bu decreased the yield. Solvent other than 1,4-dioxane, such as DMF, toluene, and CPME (cyclopentylmethyl ether), gave almost the same result, but THF gave only low yield. On the other hand, copper iodide (I) gave poor results (entry 9).

Table 2. Pd-Catalyzed Carbon−Sulfur Bond Formation of Aryl Thiols



entry	ArBr	ArSH	product	% yield[a]
1				85
2				90
3				83
4				86
5				90
6[b]				72
7				79
8				70
9				88
10				91
11				90
12				88

[a] Yields refer to the average isolated yield of two runs. [b] Using Cs_2CO_3 in place of *i*-Pr_2NEt.

In the first part of this study, these reaction conditions were applied to the coupling of various functionalized aryl

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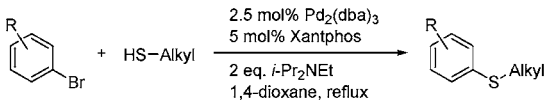
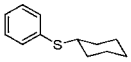
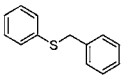
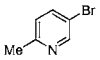
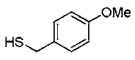
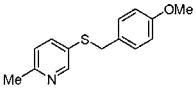
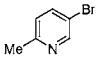
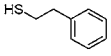
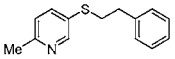
(12) Resulting *p*-methoxybenzyl phenyl sulfide was easily converted to the corresponding thiophenol by TFA. Akabori, S.; Sakakibara, S.; Shimonishi, Y.; Nobuhara, Y. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 433−434.

bromides and aryl thiols (Table 2). As demonstrated in Table 2, reactions conditions that affect the coupling of aryl bromides with aryl thiols can tolerate a variety of common functional groups such as ketones, nitro groups, carboxylic acids, and aldehydes (entries 2−5). In the case of coupling electron-rich aryl bromide with an electron-neutral aryl thiol, Cs_2CO_3 was found to be a superior base relative to *i*-Pr_2NEt (entry 6). On the other hand, the coupling of an electron-rich aryl bromide with an electron-rich aryl thiol gave the corresponding thioether in a good yield (entry 7). We were pleased to note that our protocol can also be used for the coupling of sterically hindered ortho-substituted aryl bromides (entry 8) and thiophenols (entries 9 and 10). As seen in entries 10 and 11, 5-bromo-2-methylpyridine and 5-bromoindole are also excellent substrates for this protocol. Also of interest is the result in entry 12 in which chemoselective C−S formation occurs in the presence of a phenolic OH group on the aryl thiol.

Alkylthiols were also found to be effective nucleophiles under these reaction conditions (Table 3). Cyclohexylmercaptan and benzylmercaptan were *S*-arylated in excellent yields (entries 1 and 2). We applied these optimized reaction conditions to heterocyclic substrates. 5-Bromo-2-picoline was efficiently converted to the corresponding thioethers products (entries 3 and 4[13]).

Table 3. Pd-Catalyzed Carbon−Sulfur Bond Formation of Alkyl Thiols

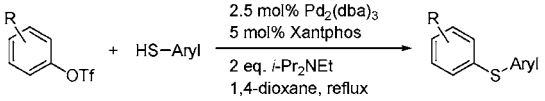


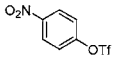
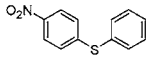
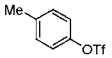
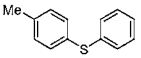
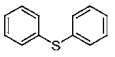
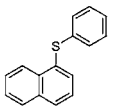
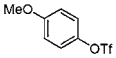
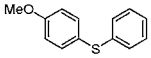
entry	ArBr	Alkyl–SH	product	% yield[a]
1				80
2				92
3				85
4				83

[a] Yields refer to the average isolated yield of two runs.

A wide range of aryl triflates was examined (Table 4). Good to excellent yields of coupled products were obtained with electronically deficient or neutral aryl triflates (entries 1−4). On the other hand, 4-methoxyphenyl triflate, an electron-rich aryl triflate, coupled with thiophenol in moderate yield (entry 5). To our knowledge, these results are the first examples of a coupling of aryl triflates with aryl thiols via transition-metal-catalyzed cross-coupling transformation.

Table 4. Pd-Catalyzed Carbon−Sulfur Bond Formation of Aryl Triflates

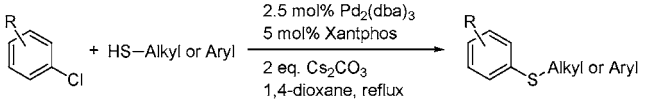


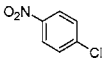
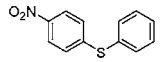
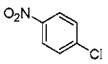
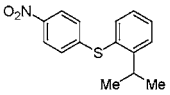
entry	ArOTf	ArSH	product	% yield[a]
1				92
2				79
3				90
4				92
5[b]				67[c]

[a] Yields refer to the average isolated yield of two runs. [b] Using Cs_2CO_3 in place of *i*-Pr_2NEt. [c] Reaction only proceeded to 72% conversion.

Our optimized catalyst system was effective for the coupling of activated aryl chlorides with aryl thiols (Table 5). In these cases, Cs_2CO_3 was a superior base relative to *i*-Pr_2NEt. Nonactivated aryl chlorides were found to be poor substrates for this reaction.

Table 5. Pd-Catalyzed Carbon−Sulfur Bond Formation of Activated Aryl Chlorides



entry	ArCl	Ar or Alkyl-SH	product	% yield[a]
1				85
2				75[b]

[a] Yields refer to the average isolated yield of two runs. [b] Reaction proceeded to only 80% conversion.

We are also interested in developing protocols that would allow for the preparation of aryl thiols from the aryl halide/triflate substrates with thiol surrogates.[14] Pyridineethane thiol hydrochloride salt[15] and iso-octyl-3-mercaptopropionate[16] were excellent reagents for this purpose. These thiol sur-

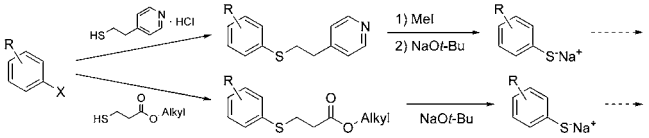
(13) The resulting picoline benzeneethane sulfide is converted into the corresponding picoline thiol by reductive metalation using Li metal with catalytic naphthalene. Screttas, C. G.; Heropoulos, G. A.; Micha-Screttas, M.; Steele, B. R.; Catsoulacos, D. P. *Tetrahedron Lett.* **2003**, *44*, 5633−5635.

(14) Thiourea: (a) Takagi, K. *Chem. Lett.* **1985**, 1307−1308. (b) Takagi, K. *Chem. Lett.* **1986**, 265−266. (c) Takagi, K. *Chem. Lett.* **1986**, 1379−1380. Trityl: Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739−2742. Ethyltrimethylsilyl: Flatt, A. K.; Tour, J. M. *Tetrahedron Lett.* **2003**, *44*, 6699−6702.

(15) Katritzky, A. R.; Khan, G. R.; Schwarz, O. A. *Tetrahedron Lett.* **1984**, *25*, 1223−1226.

(16) Becht, J.-M.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2003**, *68*, 5758−5761.

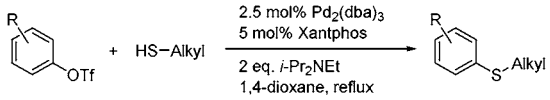
Scheme 1. Preparation of Thiophenols using Thiol Surrogates

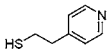
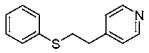
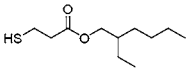
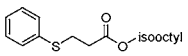
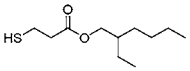
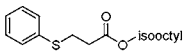
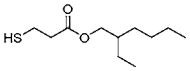
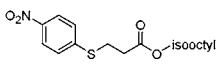


rogates are odorless and inexpensive and would be easily deprotected to the corresponding thiols under the mild basic conditions via a β-elimination reaction mechanism (Scheme 1). Without isolation of the resulting thiophenol sodium salts, the addition−elimination reaction could proceed successively.

Our reaction protocol does not require the use of a strong base such as NaO*t*-Bu, thus allowing the use of thiol nucleophiles. In Table 6 are shown the Pd-catalyzed cross-couplings of aryl halides/triflates with these thiol surrogates.

Table 6. Pd-Catalyzed Carbon−Sulfur Bond Formation of Thiol Surrogates

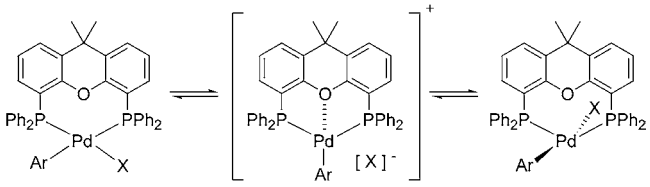


entry	ArX	Alkyl-SH	product	% yield[a]
1				92
2				88
3				90
4[b]				70

[a] Yields refer to the average isolated yield of two runs. [b] Using Cs_2CO_3 in place of *i*-Pr_2NEt.

Coupling of bromobenzene and 4-pyridineethanethiol gave the corresponding aryl alkyl sulfide in high yield (entry 1). The coupling of bromobenzene, triflate, and activated chloride with iso-octyl-3-sulfanylpropanoate proceeded in high to moderate yields (entries 2−4).

Scheme 2. Possible Pathway for *cis*−*trans* Isomerization



van Leeuwen reported that the possible effect of the oxygen atom on Xantphos might be the stabilization of an ionic intermediate that can be formed during the interchange from the *cis*- to *trans*-complexes (Scheme 2).[17] Buchwald suggested that the bite angle of this *trans*-complex is much larger than usual.[18] This unusually large bite angle might be a result of interaction of the oxygen atom on Xantphos with the palladium. We propose that these effects have an impact on the reductive elimination rate.

In summary, we have developed a general and efficient Pd-catalyzed C−S bond formation for both aryl and alkane thiols with aryl bromides using $Pd_2(dba)_3$ and Xantphos without formation of their disulfide compounds. This method was also applied successfully to aryl triflates and activated chlorides for the cross-coupling reaction. The use of new thiol surrogates for the Pd-catalyzed sulfide formation of aryl halides and triflates was realized. Further study of this and related Pd-catalyzed C−S bond formation are in progress.

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Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047996T

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