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A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols

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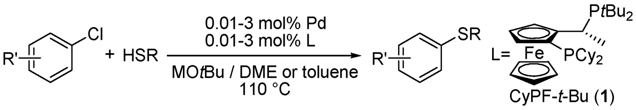
Palladium-catalyzed coupling has become a principal method of forming aromatic carbon−heteroatom bonds. Among this class of reactions, the synthesis of arylamines and aryl ethers from aryl halides has experienced significant development.[1−4] However, parallel studies to develop the synthesis of aryl sulfides have been less fruitful.[5,6] Migita first reported the coupling of iodo and bromoarenes with thiols using $Pd(PPh_3)_4$ as catalyst,[7,8] and many ligands have now been tested for this reaction.[9−15] However, the published reactions occur with low turnover numbers (TON ≤ 50), encompass chloroarenes containing only nitrile and ester functionality,[11] and do not include any reactions of aryl tosylates. These drawbacks have limited the use of this reaction to prepare sulfides with biological activity or sulfides that lead to biologically active compounds.[16]

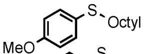
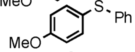
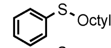
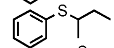
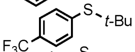
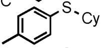
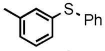
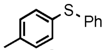
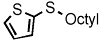
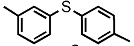
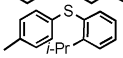
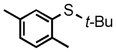
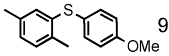
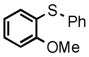
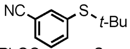
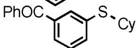
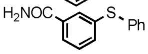
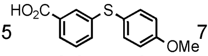
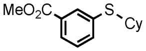
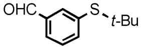
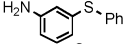
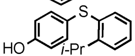
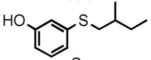
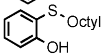
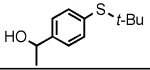
The limitations of these reactions could result from the notorious sensitivity of late metal catalysts to substrates containing reactive sulfur functionality. Although palladium thiolates form easily and undergo relatively fast reductive eliminations with aryl groups,[17−19] the lifetime and concentrations of the catalysts used for the coupling of aryl halides with thiols are likely to be limited by displacement of dative ligands by thiolates to form anionic thiolate complexes or by the formation of bridging thiolate complexes that undergo slow reductive elimination.[17] Thus, a more reactive catalyst for the coupling of thiolates might contain a bisphosphine that binds the metal strongly enough to prevent formation of anionic or bridging thiolate complexes, while simultaneously promoting oxidative addition and reductive elimination.

With these requirements in mind, we considered that the restricted backbone conformation, steric hindrance, and strong electron donation of the Josiphos ligand, CyPF-*t*-Bu (**1** in Table 1),[20] could create practical catalysts for the coupling of thiols with aryl chlorides and tosylates. We show here that complexes generated from this ligand couple a broad range of thiols with aryl halides and sulfonates, and that reactions conducted with the Josiphos ligand occur with turnover numbers and tolerance of functional groups that far surpass those of previous catalysts. This catalyst also allows diarylsulfides to be prepared from two different bromoarenes and a hydrogen sulfide surrogate.

We initially assessed catalyst activity by conducting the coupling of the electron-rich 4-chloroanisole with 1-octanethiol. These studies showed that 0.1 mol % of equimolar amounts of $Pd(OAc)_2$ and ligand in DME (1,2-dimethoxyethane) at 110 °C[21] with NaO*t*Bu (1.1 equiv) as base formed the aryl sulfide in high yield in less than 4 h (Table 1, entry 1). Reactions of alkylthiols with weaker carbonate or phosphate bases occurred to low conversions and formed large amounts of dialkyl disulfide. Reactions in other solvents or at lower temperatures also either occurred to lower conversions, required longer reaction times, or both. The coupling of aromatic thiols under the same conditions produced undesired symmetrical sulfides in a 5−10% combined yield,[11,22] but reactions of aromatic thiols with KO*t*Bu as base and $Pd(dba)_2$ as precursor in toluene formed the aryl sulfide in high yield with only traces of side products (Table 1, entry 2). Reactions under the standard conditions, but without catalyst, formed mostly disulfides and less than 5% of the desired aryl sulfides.

Table 1. Palladium-Catalyzed Coupling of Aryl Chlorides with Thiols Using CyPF-*t*-Bu Ligand[a]



Entry	Cat. [mol%]	Product	Yield [%][b]
1	0.1		98
2	0.1		98
3	0.05		91
4	0.01		85
5	0.05		91
6[c]	2		89
7	0.1		82
8	0.05		98
9[c]	2		91
10	0.1		98
11	0.05		86
12	0.1		95
13[c]	3		83[d]
14	0.05		96
15[e]	0.1		93
16	0.25		97
17	0.5		89
18	1		92
19	1		97
20[f]	0.05		90
21	0.05		86
22[f]	0.25		70
23[f]	0.25		74
24[g]	0.5		72
25[g]	0.25		91
26[f]	0.25		91
27[f]	2		91
28[f]	0.5		85
29[f]	2		97
30[h]	0.5		93

[a] Reactions were conducted using a 1:1 ratio of $Pd(OAc)_2$ to ligand, 1 mmol of ArCl and thiol, and NaO*t*Bu (1.1 equiv) at 110 °C in DME (1.5 mL), except for reactions of ArSH in entries 2, 10−13, 16, and 18−19, which were carried out using $Pd(dba)_2$ and KO*t*Bu in toluene (1.5 mL). [b] Isolated yield. [c] Performed at 70 °C. [d] 93% conversion. [e] LiHMDS used as base. [f] 2.4 equiv of NaO*t*Bu. [g] Cs_2CO_3 used as base. [h] 1.02 equiv of NaO*t*Bu.

Reactions of a series of aryl chlorides and thiols were evaluated under these conditions, and the results are summarized in Table 1. Primary, secondary, and tertiary aliphatic thiols and aromatic thiols were successfully coupled with activated and nonactivated aryl chlorides. Excellent yields in short reaction times were obtained using 1 or 2 orders of magnitude less catalyst than had been used in previous couplings to form aryl sulfides (8500 turnovers, entry 4). Even the more sterically demanding substrates coupled in high yield using catalyst loadings in the range of 0.25−1 mol % (entries 16−19). Reactions at lower temperatures (70 °C) simply required increasing the amount of catalyst to 2−3 mol % and increasing reaction times to 24 h (entries 6, 9, and 13).

This coupling of chloroarenes with thiols is tolerant of a wide range of common functional groups (Table 1, entries 20−30).

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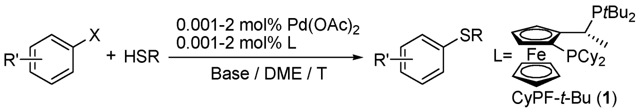
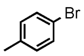
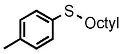
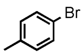
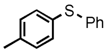
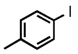
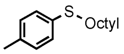
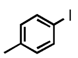
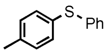
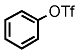
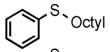
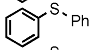
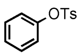
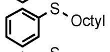
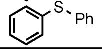
Table 2. Coupling of Aryl Bromides, Iodides, and Sulfonates with Thiols Catalyzed by Pd(OAc)$_2$ and CyPF-*t*-Bu Ligands[a]



CyPF-*t*-Bu (**1**)

Entry	ArX	Cat. [mol%]	Base	T [°C]	Product	Yield [%][b]
1		0.001	NaO*t*Bu	110		99
2		0.05	NaO*t*Bu	90		96
3		1	NaO*t*Bu	50		97
4		0.01	NaO*t*Bu	110		98
5		0.1	NaO*t*Bu	90		99
6		1	NaO*t*Bu	50		91
7		0.001	NaO*t*Bu	110		84[c]
8		0.01	NaO*t*Bu	90		97
9		0.5	NaO*t*Bu	25		96
10		0.001	NaO*t*Bu	110		82[c]
11		0.01	NaO*t*Bu	90		95
12		0.5	NaO*t*Bu	25		97
13		0.25	K_2CO_3	110		95
14		2	Na_2CO_3	110		79[c]
15		2	Na_2CO_3	110		86
16		4	Na_2CO_3	110		-

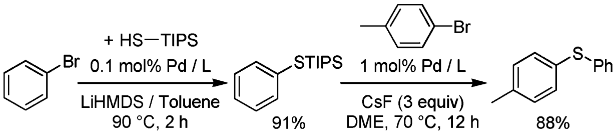
[a] Reactions conducted using a 1:1 ratio of Pd(OAc)$_2$ to ligand, 1 mmol of both ArCl and thiol, and 1.1 equiv of NaO*t*Bu at 110 °C in DME (1.5 mL). [b] Isolated yield. [c] ~90% conversion.

Chloroarenes bearing a nitrile, ketone, amide, and carboxylic acid, as well as unprotected amino and aromatic or aliphatic hydroxyl groups, coupled under the standard conditions to form the corresponding aryl sulfide in good to excellent yields. Moreover, reactions of aryl chlorides with ester or aldehyde groups that are incompatible with nucleophilic alkoxide bases occurred in high yield in the presence of the weaker Cs_2CO_3 base (entries 24 and 25).

Having obtained results on the coupling of chloroarenes, we probed the scope of the reactions of other aryl halides and sulfonates (Table 2). As expected, the coupling of aryl bromides and iodides is even more efficient than the analogous coupling of chlorides. For example, reactions of *p*-bromotoluene with octane- and benzenethiol in the presence of only 10−100 ppm of catalyst afforded excellent yields of sulfide product, corresponding to 99 000 and 9800 turnovers (entries 1 and 4). Reactions of the related iodoarenes occurred with 84 000 and 82 000 turnovers (entries 7 and 10). These values are 2 or 3 orders of magnitude greater than those produced by previous catalysts. In addition, reactions of bromoarenes can be performed at 90 or 50 °C using 1 mol % catalyst (entries 2, 3, and 5, 6). Furthermore, coupling of iodoarenes occurred at room temperature with only 0.5 mol % catalyst (entries 8−9, and 11−12). No appreciable amounts of byproducts were detected from reactions of aromatic thiols.

Aryl sulfonates are attractive alternatives to aryl halides because they can be easily synthesized from phenols. In the presence of potassium or sodium carbonate base, the coupling of phenyl triflate with aliphatic and aromatic thiols occurred with 0.25 and 2.0 mol % catalyst (entries 13 and 14). A 2 mol % combination of metal and ligand catalyzed the first coupling of an aryl tosylate with a thiol (entry 15).[23−25] In contrast to the reaction of octanethiol, the reaction of benzenethiol with the aryl tosylate did not occur (entry 16).

Because of the greater availability of aryl halides than of aromatic thiols, the coupling of two aryl halides with a hydrogen sulfide surrogate would be an attractive alternative to the coupling of an aryl halide with an aromatic thiol. As shown in eq 1, the coupling of phenyl bromide occurred with triisopropylsilanethiol (TIPS−SH)[26] as a hydrogen sulfide surrogate in high yield, and the resulting protected thiol coupled with *p*-bromotoluene in the presence of the same catalyst and CsF. Using this protocol, a representative unsymmetrical diaryl sulfide was isolated in 80% overall yield, *starting from two different aryl bromides.*



(1)

In summary, we have described a general, highly efficient and functional-group-tolerant catalyst system for the coupling of aryl halides and triflates with thiols that typically occur with TONs that are 2 or 3 orders of magnitude higher than those of related couplings by previous catalysts. The results of these studies are consistent with the hypothesis that ligand **1** overcomes the tendency of thiolates to inactivate previous catalysts by displacement of the dative ligand. Studies of the mechanism of this coupling process will be the subject of future work.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and complete ref 16. This material is available free of charge via the Internet at http://pubs.acs.org.

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