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Carbon–Sulfur Bond Formation of Challenging Substrates at Low Temperature by Using Pd-PEPPSI-IPent**

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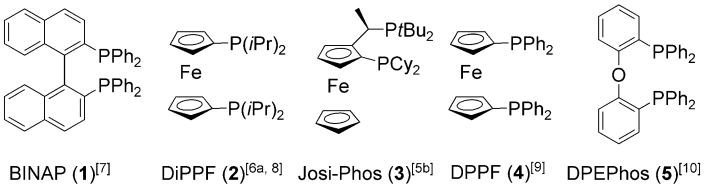
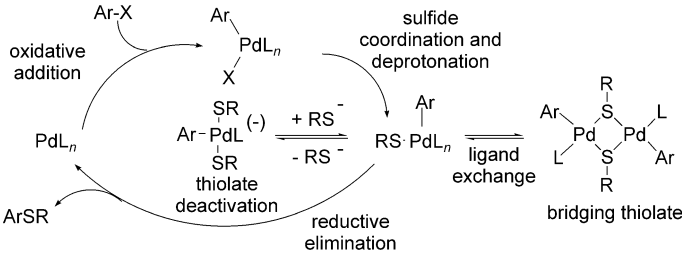
Aryl ethers and thioethers[1] are moieties encountered in the structure of a number of natural products and pharmaceutically relevant compounds. Classical methods to prepare aryl thioethers, including the reaction of an aromatic compound with sulfur and nucleophilic aromatic substitution (NAS) of haloarenes with substituted thiophenols, often require forcing conditions and that can lead to disappointing yields.[2] The discovery in 1978 by Migita and co-workers[3] that these NAS reactions could be catalyzed by Pd has been followed up in the last decade by the development of improved catalysts using a variety of metals to perform these sulfination reactions with better selectivity and under milder conditions.[4] While a couple of reports have disclosed a few select examples that proceed at 70 °C or lower,[5] the bulk of these catalyzed sulfinations have been done above this temperature, typically at, or in excess of 100 °C. Attempts to couple challenging substrates, which are hindered, electronically disfavored, or both, all require temperatures in excess of 100 °C to proceed.[6] Here we report on the use of the diisopentylphenylimidazolium (IPent) N-heterocyclic carbene (NHC) ligand on Pd (i.e., **9**) for the sulfination of haloarenes and heteroarenes with a variety of different types of sulfur nucleophiles under the most generally mild conditions yet reported.

Ligands that have demonstrated the most general application in Pd-catalyzed sulfination reactions are shown in Scheme 1. Within this collection, Josi-Phos is perhaps the ligand that has been demonstrated to be the most active. With this in mind we set out to compare the reactivity of precatalyst **9** with Josi-Phos. Hartwig and co-workers have proposed that a major impediment to Pd-catalyzed sulfination is movement of intermediates off the catalytic cycle into thiolate-derived resting states (see Scheme 2).[5b] We reasoned that the IPent ligand with its profound steric bulk could accelerate reductive elimination sufficiently to mitigate such exchange reactions.



Scheme 1. Ligands that have been demonstrated to be effective in Pd-catalyzed sulfination reactions.



Scheme 2. Catalytic cycle for Pd-catalyzed sulfination.

Optimal conditions for sulfination with Josi-Phos have been reported by Hartwig and co-workers (Table 1, entries 1–4).[5a] Coupling of relatively active bromobenzene with unhindered thiophenol proceeded well at 50 °C (Table 1, entry 1), while chlorobenzene required higher temperature (70 °C, Table 1, entry 3). When the oxidative addition partner became more hindered the bromide now required 110 °C to complete (Table 1, entry 2) and the corresponding chloride now failed to couple at all (0 %), even under the most forcing conditions (Table 1, entry 4). Pd-PEPPSI-IPent has been demonstrated to be highly active in low-temperature Suzuki–Miyaura,[11,12] Negishi,[13] and Stille–Migita[14] couplings, thus we opted to examine its reactivity focusing only on hindered 2,6-dimethyl substrates. Initially, no reactivity at all was observed at 40 °C (Table 1, entry 5). We have observed that while organometallics reduce **9** rapidly, aminations with alkylamines show induction periods that we have attributed to catalyst activation.[15] With this in mind we examined activation using, first, morpholine and indeed this led to excellent conversion at just 40 °C (Table 1, entry 6). With dibutylmagnesium (Table 1, entry 7), a more effective reductant, everything could now be nicely carried out at room temperature illustrating the unprecedented reactivity of Pd-PEPPSI-IPent in sulfination.

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[**] PEPPSI = pyridine, enhanced precatalyst, preparation, stabilization, and initiation. IPent = diisopentylphenylimidazolium derivative.

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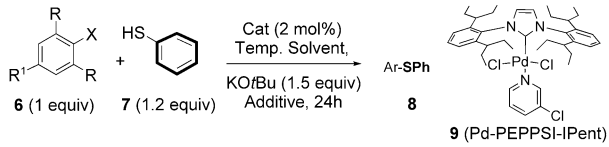
Table 1. Comparison of Josi-Phos and Pd-PEPPSI-IPent in the sulfination of hindered aryl halides with thiophenol.



6 (1 equiv) 7 (1.2 equiv) 8 9 (Pd-PEPPSI-IPent)

Entry	R	R^1	X	Cat	Solvent, Temp [°C]	Additive	Yield [%][a]
1	H	Me	Br	**3**[b]	DME, 50	–	91
2	Me	Me	Br	**3**[b]	DME, 110	–	93
3	H	Me	Cl	**3**[b]	DME, 70	–	83
4	Me	Me	Cl	**3**[b]	DME, 110	–	0
5	Me	H	Cl	**9**	toluene, 40	–	0
6	Me	H	Br	**9**	toluene, 40	morpholine (2.5 mol%)	99
7	Me	H	Br	**9**	toluene, 23	Bu_2Mg (8 mol%)	98
8	Me	H	Br	**9**	toluene,[c] 70	LiO*i*Pr (20 mol%)	98
9	Me	H	Cl	**9**	toluene,[d] 23	LiO*i*Pr (20 mol%)	98[e]
10	Me	H	Br	**9**	toluene,[d] 23	LiO*i*Pr (20 mol%)	99[f]

[a] Yields are reported on isolated products following silica gel chromatography; reactions were performed in duplicate. [b] Josi-Phos ligand (**3**) was mixed with $Pd(OAc)_2$ to form the active catalyst (catalyst loading 1–3 mol%).[5a] [c] A mixture containing **6**, **9**, and LiO*i*Pr was heated to 80°C for 30 min, cooled to 23°C, **7** and KO*t*Bu added, and the reaction mixture heated to 70°C for 24 h. [d] A mixture containing **6**, **9**, and LiO*i*Pr was heated to 80°C for 30 min, cooled to 23°C, **7** and KO*t*Bu added, and the reaction mixture stirred at 23°C for 24 h. [e] Reaction was halted after 6 h.

Alkyl thiols are known to be much more difficult to couple than thiols at sp^2-carbon centers.[17] Nonetheless, coupling proceeded very well over a range of alkyl centers including 1° (e.g., **25**, **26**, and **31**), 2° (**27** and **28**), and 3° thiols (**29**, **30**, and **32**). We also investigated hindered triisopropylsilyl(TIPS)-protected thiols as nucleophiles, a clever concept developed by Hartwig and co-workers to introduce sulfur, after deprotection of the TIPS moiety, as a single atom to generate aryl thiols that are not otherwise readily available.[2] All of the examples attempted (e.g., **33** to **37**) worked very well at 40°C including heterocyclic oxidative addition examples (e.g., **24**, Table 2). So, in all cases, relative to examples published in the literature, Pd-PEPPSI-IPent shows no apparent sensitivity to bulk imposed by substituents placed *ortho* to the halide in sulfination reactions.

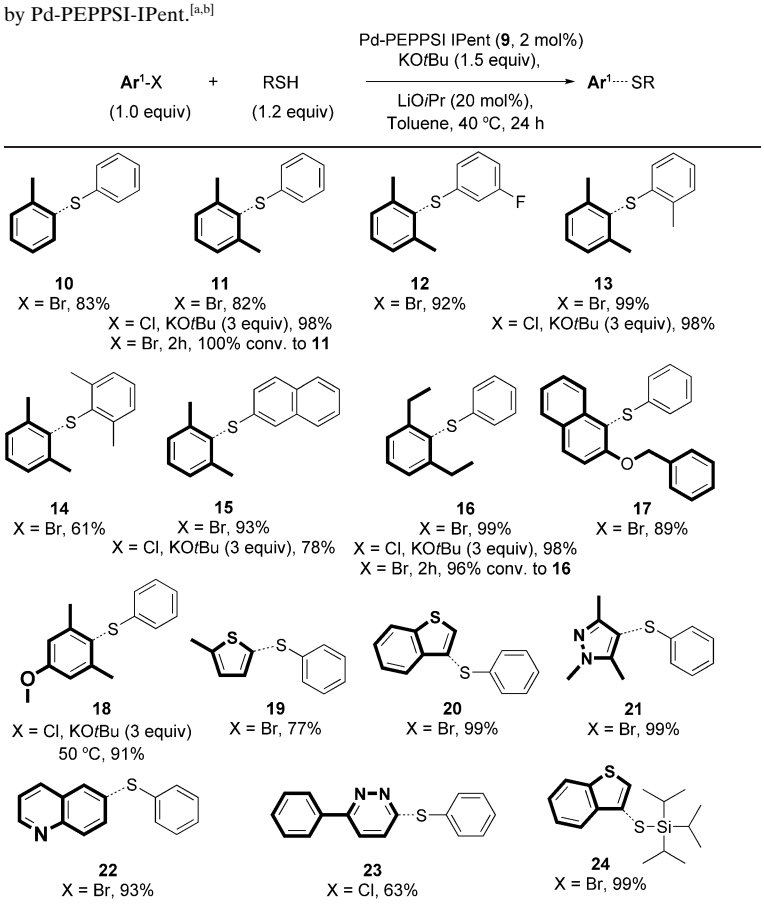
Having demonstrated wide, general application of this standard sulfination protocol using **9** at 40°C, we decided to investigate the rates of these reactions. From the representative examples that we picked (e.g., **11** and **16**, Table 2), it is clear that

So as not to contaminate the sulfination products by amination with catalytic morphline, and to improve the practical aspects of handling a highly-active organometallic like dibutylmagnesium, we developed an activation protocol using LiO*i*Pr.[16] Catalyst activation occurred most reliably at 80°C and sulfination occurred smoothly, either at 70°C (Table 1, entry 8) or at room temperature (Table 1, entries 9 and 10). Finally we examined the corresponding hindered chloride (Table 1, entry 9) and smooth conversion to product was again observed.

With the reaction optimization studies complete, we examined the sulfination scope of aryl and heteroaryl halides and aryl sulfides at 40°C (Table 2). The reactions performed well under these mild conditions, regardless of how sterically or electronically deactivated the oxidative addition partner (see examples in Table 2). Similarly, hindrance on the sulfide (e.g., **14** and **24**) was also nicely tolerated. Of very special note is the coupling leading to aryl thioether **18**, which is derived from an oxidative addition partner that is both strongly sterically and electronically deactivated. There are no successful reports of the coupling of this type of product in the literature under any conditions; attempts to couple using Josi-Phos under the conditions given in Table 1 failed to provide any sulfinated product. Heterocyclic halides couple with no issues, which is ideal for the production of drug-like structures (e.g., structures **19** through **24**).

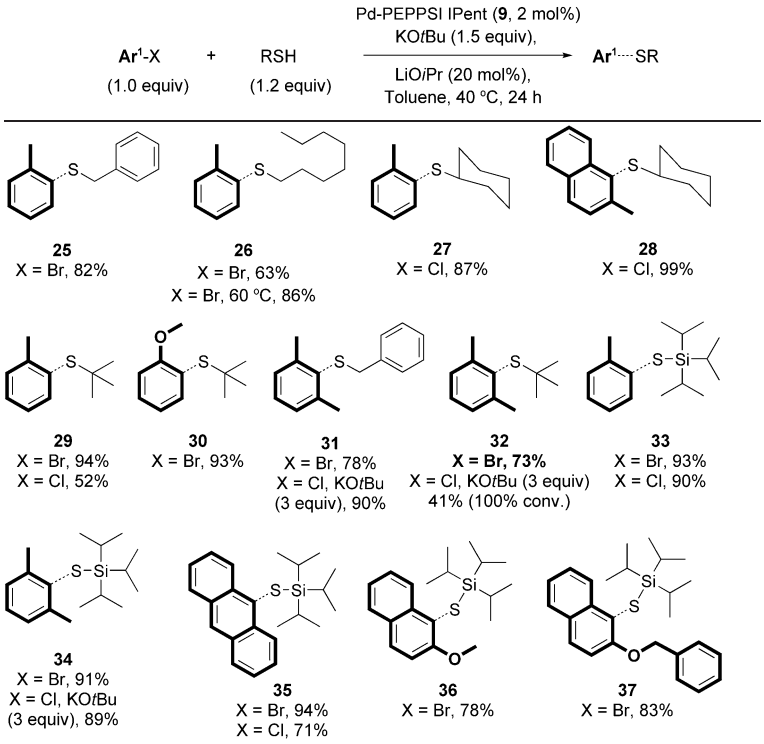
With the thiophenol derivatives showing good reactivity, attention was then focused on non-aromatic thiols (Table 3).

Table 2. Sulfination of aryl halides and heteroaryl halides with aryl sulfides catalyzed by Pd-PEPPSI-IPent.[a,b]



[a] Yields are reported on isolated products following silica gel chromatography. [b] Changes to reaction conditions are listed under the product.

Table 3. Sulfination of aryl halides with alkyl- and TIPS-protected sulfides catalyzed by Pd-PEPPSI-IPent.[a,b]

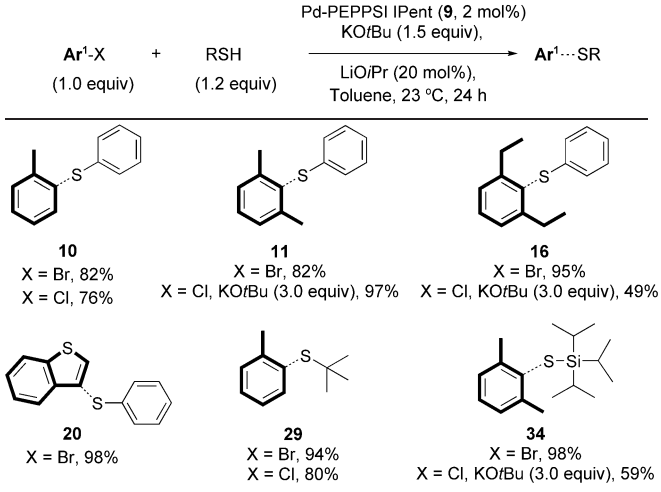


[a] Yields are reported on isolated products following silica gel chromatography. [b] Changes to reaction conditions are listed under the product.

the reactions complete far sooner than the 24 h used as part of our standard protocol; both reactions were fully converted when samples were taken at 2 h. This encouraged us to reinvestigate the temperature. Again we randomly chose examples of aryl bromides and chlorides from Tables 2 and 3 and found that even the most sterically hindered examples couple well at room temperature (Table 4). The rate curve for even the hindered and electronically deactivated 1-chloro-2,6-dimethylbenzene substrate demonstrates that sulfination is complete after just 4–5 h at room temperature with no induction period.[19] To our knowledge, despite several reported attempts,[5] no other catalyst has been able to perform this conversion.

In summary, Pd-PEPPSI-IPent has been demonstrated to be extremely reactive in metal-catalyzed sulfination. The catalyst shows very broad substrate scope including aryl and heteroaryl halides with aryl, alkyl, and silyl sulfides under the most mild set of generally applicable reaction conditions reported to date. The reactions work well at 40 °C, but appears to work similarly well at room tempertature (23 °C) with very good reaction rates.

Table 4. Room-temperature sulfinations with Pd-PEPPSI-IPent.[,18a,b]



[a] Yields are reported on isolated products following silica gel chromatography. [b] Changes to reaction conditions are listed under the product.

Experimental Section

General sulfination conditions using Pd-PEPPSI-IPent: In a glovebox, an oven-dried vial (4 mL screw-cap threaded) equipped with magnetic stir bar was charged with Pd-PEPPSI-IPent (4 mg, 2 mol %) and LiO*i*Pr (3.7 mg, 20 mol %). The vial was sealed with a Teflon-lined screw cap, removed from the glove box, and the aryl/heteroaryl halide (1 equiv, 0.25 mmol) was added by using a syringe followed by toluene (1 mL); alternatively if the aryl/heteroaryl halide was a solid at room temperature, it was dissolved in toluene and then transferred to the vial. The resulting mixture was then stirred at 80 °C for 30 min to ensure precatalyst activation and then was cooled to 23 °C over approximately 5 min. A solution of KO*t*Bu (1.5 equiv, 0.375 mmol) in toluene (1 mL) was then added at 23 °C by using a syringe, before adjusting the temperature to the indicated value to conduct the reaction. The aryl, alkyl, or TIPS thiol (1.2 equiv, 0.3 mmol) was then added dropwise and the reaction mixture stirred at the indicated temperature and time. At this point the reaction mixture was cooled (if necessary) to room temperature and the pH adjusted to 5 with 1 M HCl (ca. 1 mL). The aqueous layer was extracted with diethyl ether (3×1 mL) and the organic phases pooled, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Alternatively, in the case of TIPS-protected thiols, the reaction mixture was directly filtered through a small plug of celite, then eluted with diethyl ether (3 mL). After drying over anhydrous Na_2SO_4, the solvent was removed in vacuo. The residue from both workup procedures was purified subsequently by flash chromatography on silica gel.

Acknowledgements

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Keywords: cross-coupling · palladium · PEPPSI · sulfination

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[19] For the rate curve for the sulfination of 1-chloro-2,6-dimethylbenzene with thiophenol using Pd-PEPPSI-IPent at room temperature, see Figure S1 in the Supporting Information.

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