HHS Public Access

Author manuscript

ACS Catal. Author manuscript; available in PMC 2020 July 05.

Published in final edited form as:

ACS Catal. 2019 July 5; 9(7): 6461–6466. doi:10.1021/acscatal.9b01913.

Monophosphine Ligands Promote Pd-Catalyzed C–S Cross-Coupling Reactions at Room Temperature with Soluble Bases

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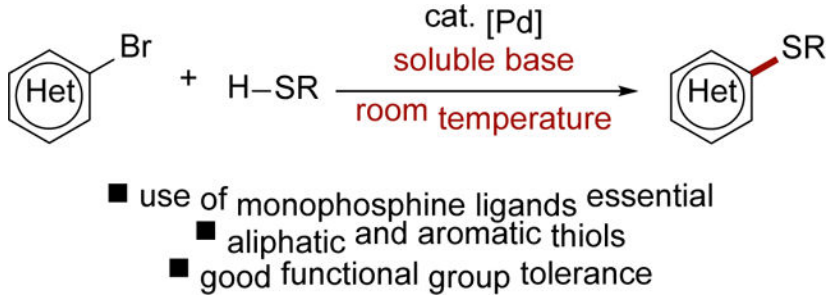
Abstract

The Pd-catalyzed cross-coupling of thiols with aromatic electrophiles is a reliable method for the synthesis of aryl thioethers, which are important compounds for pharmaceutical and agricultural applications. Since thiols and thiolates strongly bind late transition metals, previous research has focused on catalysts supported by chelating, bisphosphine ligands, which were considered less likely to be displaced during the course of the reaction. We show that by using monophosphine ligands instead, more effective catalysis can be achieved. Notably, compared to previous methods, this increased reactivity allows for the use of much lower reaction temperature, soluble bases, and base-sensitive substrates. In contrast to conventional wisdom, our mechanistic data suggest that the extent of displacement of phosphine ligands by thiols is, firstly, not correlated with the ligand bulk or thiol nucleophilicity, and secondly, not predictive of the effectiveness of a given ligand in combination with palladium.

Graphical Abstract



Aryl thioethers and derivatives such as sulfoxides and sulfones are increasingly important classes of molecules in the pharmaceutical industry[1] and for other applications.[2] For instance, *S*-aryl fragments are found in marketed drugs that treat schizophrenia (perphenazine),[3a] autoimmune disorders (nelfinavir mesylate),[3b] rheumatoid arthritis and

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MIT has filed patents on ligands and precatalysts that are described in this manuscript, from which S.L.B and former/current coworkers receive royalty payments.

organ rejection (azathioprine),[3c] cancer (axitinib,[3d] bicalutamide[3e]), and heart conditions (ticagrelor).[3f] Given the availability of thiols and aryl halides or pseudohalides, metal-catalyzed cross-coupling,[4,5] including Pd-catalyzed C–S coupling in particular,[6] has emerged as a popular synthetic route to these compounds.

It is well known that each of the elementary steps within the catalytic cycle (see below, Fig. 2A) is associated with a low activation barrier: definitive mechanistic investigations by Hartwig,[6k] as well as reports of relevant stoichiometric reactions involving palladium complexes,[7] indicate that each transformation can take place in seconds or minutes under ambient conditions. Nevertheless, the leading catalytic methods require elevated temperatures (refluxing toluene or dioxane) to obtain synthetically useful yields. This discrepancy is explained by the proclivity of palladium-based catalysts to form off-cycle resting state species in the presence of thiols. Two frequently cited pathways for catalyst deactivation are (1) the formation of unreactive LPd(H)SR or $[LPd(SR)_2]^-$ complexes[4a,5a,6a,d,h,k] and (2) the displacement of the phosphine ligand by the binding of multiple thiolate ligands.[4b,5a,6d,k,l,m]

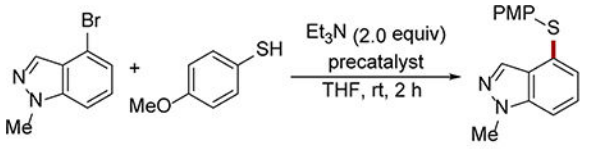
Although monophosphine-ligated palladium catalysts have shown exceptionally high reactivity in C–C,[8] C–N,[9] C–O,[10] C–F,[11] and C–CF_3 cross-coupling,[12] they have not yet been successfully applied in the development of C–S cross-coupling, which has instead relied primarily on catalysts derived from tightly binding chelating bisphosphine ligands. These ligands are thought to minimize deactivation by nucleophilic thiolate ligands (*vide supra*). After the pioneering studies of $Pd(PPh_3)_4$-catalyzed coupling of aryl halides with thiolate anions by Migita,[6n,6o] bidentate phosphines such as SL-J009[6k] (**L6**) and XantPhos[6m] (**L7**) have emerged as the ligands of choice for this transformation. Other strategies to circumvent phosphine displacement include the usage of an NHC ligand[6p] or employment of a Pd^I complex as a catalyst[6q]. Despite significant advances with regard to minimizing catalyst loading and maximizing turnover numbers, substantial limitations still remain. Foremost, the requirement to employ elevated temperatures renders the reaction conditions incompatible with many functional groups and medicinally important heterocycles. In particular, the combination of high temperature and strong base has been shown to cause significant problems for even mildly base-sensitive substrates, such as indazoles.[13] Furthermore, the requirement for such substantial energy input is wasteful considering the rapidity of the elementary steps under ambient conditions. Other methods require the pre-formation of sodium thiolate salts[6q] or the complete exclusion of disulfides from the reaction[6p]. Finally, the vast majority of C–S coupling protocols rely on insoluble, inorganic bases, which pose considerable challenges for miniaturization and for continuous flow applications. In view of the previous successes of biaryl monophosphine-based palladium catalysts in addressing similar issues in related cross-coupling reactions, we considered whether they might be effective for catalytic C–S coupling, in spite of concerns regarding thiolate-mediated deactivation.

We selected 4-bromo-1-methylindazole as a model substrate, since *N*-substituted indazoles and other base-sensitive heterocycles have proved challenging under state-of-the-art C–S cross-coupling conditions.[13] Although nitrogenous heterocycles such as indazole feature prominently in pharmaceuticals and bioactive natural products, base-mediated Kemp

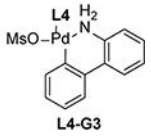
elimination is a major side-reaction when strong bases and prolonged heating are required.[14] In our study, the cross-coupling of this heteroaryl bromide was evaluated with 1-decanethiol in the presence of triethylamine, a soluble, organic base, and a number of oxidative-addition-complex precatalysts[15] (**P1**–**P5**) derived from monophosphine catalysts developed in our laboratory (for details, see the Supporting Information). Additionally, precatalysts bearing the two most frequently employed bisphosphine ligands, XantPhos (**L6**) and SL-J009–1 (**L7**), were also tested.

After two hours at room temperature, the reactions using precatalysts derived from tBuBrettPhos (**L2**) and tBuXPhos (**L4**) showed high yields of the desired product (97% and 100%, respectively). Reactions using complexes of ligands with smaller *P*-Cy groups in lieu of *P*-*t*Bu groups resulted in diminished activity. Notably, at the low temperatures employed, catalysts bearing bisphosphine ligands (**L6**, **L7**) failed to deliver useful amounts of the desired product. We also determined that when using a lower catalyst loading (0.2 mol%), *tert*-butanol is the best solvent for this transformation.

Table 2. Evaluation of catalysts and reaction conditions for Pd-catalyzed aryl thiol arylation.[a]



Entry	Precatalyst (mol%)	Yield (%)
1	**P2** (1%)	0
2	**P4** (1%)	15
3	**P5** (1%)	61
4	**L4-G3**[b] (1%)	100



[a] Conditions: aryl bromide (0.1 mmol, 1.0 equiv), thiol (1.2 equiv), triethylamine (2.0 equiv), precatalyst (indicated amount) in solvent (0.20 mL) for 2 h. The yield was determined by calibrated gas chromatography (GC) using dodecane as an internal standard. See the Supporting Information for more details. [b]Using LHMDS (2.4 equiv) instead of triethylamine. For extended screening data, see table S2 in the Supporting Information.

Aromatic thiols differ significantly from aliphatic thiols in terms of acidity and nucleophilicity. Thus, unsurprisingly, the reaction conditions developed for aliphatic thiols proved to be suboptimal for the reactions of aryl thiols. For these substrates, we evaluated a subset of precatalysts in the coupling of the model aryl bromide with 4-methoxythiophenol. While catalysts based on **L2** and **L4** provided limited yields, the AlPhos(**L5**)-bound precatalyst provided a promising quantity of the C–S coupled product (61%, Table 2, entry 5). However, in view of the significant cost differences between tBuBrettPhos (**L4**) and AlPhos (**L5**), a similarly effective method using an **L4**-based precatalyst was desirable. Accordingly, with further optimization, we were able to achieve the same high yield using commercially available **L4-G3** by using LHMDS, another soluble base.[8a]

Having discovered efficient conditions for coupling reactions of both aliphatic and aromatic thiols, we examined their scope. First, a variety of aliphatic thiols were efficiently coupled with aryl or heteroaryl bromides, and many common functional groups on either partner were tolerated under the mild reaction conditions. In particular, both 5- and 6-membered heterocycle electrophiles, including an azaindole (**2f**), a thiophene (**2h**), a benzothiazole (**2i**), a pyrazole (**2j**), a thiazole (**2l**), and a quinoline (**2o**) were transformed in high yield, regardless of their electronic properties. Notably, many protic substituents are well tolerated, including a phenol (**2b**), primary aniline (**2c**), carboxylic acids (**2e**, **2l**), aliphatic alcohols (**2k**, **2m**), an amide (**2n**), and a sulfonamide (**2g**), without competing C–N or C–O coupling. For substrates with exceptionally low solubility in *tert*-butanol, THF can be used as a solvent or co-solvent, and excellent isolated yields are obtained (e.g., **2f**, **2k**).

The substrate scope of the aromatic thiol coupling was also good. Both electron-rich (**3b**, **3c**) and electron-deficient thiols (**3f**, **3g**) were arylated in high yields. Heterocyclic partners such as an unprotected indazole (**3a**), an isoquinoline (**3b**), and hindered pyridines (**3j**–**3l**) reacted well under these conditions. Importantly, no background reactions such as nucleophilic aromatic substitution were observed in the absence of palladium or ligand. Again, an aniline (**3d**) and a phenol (**3g**) underwent the desired C–S coupling transformation without competing C–N or C–O coupling. Finally, aryl bromides are chemoselectively converted in the presence of aryl chlorides, and thus chloroarene products such as **3f**, which are easily derivatized by further cross-coupling, can be produced in high isolated yield.

The effectiveness of these monophosphine catalyst systems raised important mechanistic questions. Historically, it has been assumed that chelating bisphosphine ligands should bind palladium more tightly, and thus, be less prone to thiol(ate)-mediated displacement and deactivation. However, under our conditions (room temperature, soluble base), monophosphine-based catalysts clearly outperformed the state-of-the-art bisphosphine systems. To resolve this discrepancy, we considered the following explanations. First, it was possible that the rate or extent of displacement of a given phosphine from palladium by thiolate ligands did not follow conventional predictions. For instance, perhaps biaryl monophosphine ligands are particularly difficult to displace. Second, the effectiveness of a given catalyst might not be well predicted by the distribution of ligand (Pd-bound or free) in the catalytic resting state.

To examine these hypotheses, we needed to establish the resting state of various catalysts during the steady-state portion of the catalytic reaction. Using NMR spectroscopy, we followed reactions using precatalysts derived from **L1**–**L7** under conditions similar to the optimal reaction conditions, except with slightly elevated catalyst loading for more accurate detection of intermediates. We measured the steady-state distribution of the ligand using ^{31}P NMR measurements made during the course of the coupling reaction.

In the coupling of aliphatic thiols, contrary to our expectations, free ligand was not observed in any case, except when a precatalyst based on **L1** was used. This indicated that, at least at room temperature and with only a weak base present, displacement of the phosphine ligand by alkyl thiolate(s) is not a significant problem for either mono- or bisphosphine ligands. Consistent with previous studies, the failure of bisphosphine ligands **L6** and **L7** to form

efficient catalysts under these reaction conditions is not due to phosphine displacement, but rather due to the formation of alternative, stable off-cycle species: a L_2Pd dimer in the case of **L6**, and a hydridopalladium thiolate in the case of **L7**.[6h]

The analogous experiments using aromatic thiols further underscore the difficulty of predicting the steady-state ligand distribution in these coupling reactions. In these cases, most ligands were observed to be in their unbound form during the course of the reaction. Surprisingly, XantPhos (**L6**), a bisphosphine ligand, was entirely unbound in its resting state, while **L5**, the most sterically hindered monophosphine ligand, remained partially Pd-bound. Finally, these data again caution against inferring the competency of catalysts from their resting state – for instance, in the case of the catalysts derived from **L2** and **L4**, although the phosphine appears to completely dissociate during the reaction, the desired arylation was still observed.

In summary, we have found that certain biaryl monophosphine ligands form exceptionally effective catalysts that promote C–S coupling reactions under mild conditions, with soluble bases, and in the presence of many useful functional groups. These catalysts are sufficiently active that they promote thioether formation even when no phosphine-bound palladium species is observable by NMR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number R35GM122483. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank Dr. Tony Siu (Merck), Dr. Brett A. Hopkins (Merck), Dr. Scott McCann (MIT), Dr. Andy Thomas (MIT), and Dr. Christine Nguyen (MIT) for advice on the preparation of this manuscript. We thank Jacob M. Ganley (Merck) for assistance with preliminary experiments.

We are grateful to Sigma-Aldrich for gifts of ligands (XPhos, BrettPhos, tBuXPhos, tBuBrettPhos) and Solvias for a gift of the CyPF-tBu used in our research. We thank Rosina Ayore (Merck) and Wilfredo Pinto (Merck) for collecting HRMS data of aryl thioether products.

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(16). P4 and P*4 exist in equilibrium with a dearomatized isomer, as described in the Supporting Information. For a detailed investigation of this reversible rearrangement, see:Milner PJ; Maimone TJ; Su M; Chen J; Mu P; Buchwald SL Investigating the Dearomative Rearrangement of Biaryl Phosphine- Ligated Pd (II) Complexes. J. Am. Chem. Soc 2012, 134, 19922–19934. [PubMed: 23153301]

(17). The precatalyst L4.CH2Cl2 was purchased from Strem as the dichloromethane solvate and was used as purchased.See the Supporting Information for details.

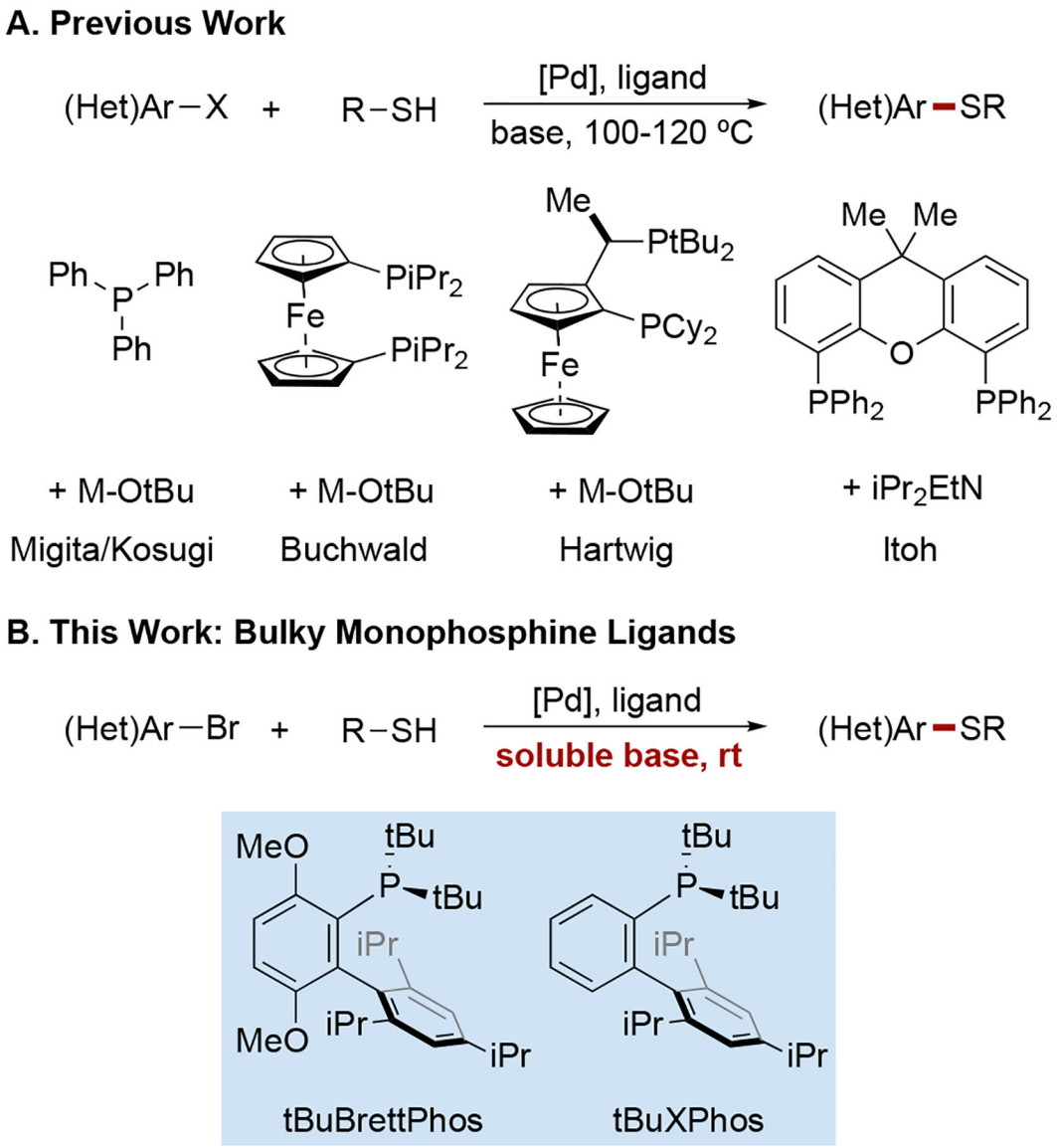
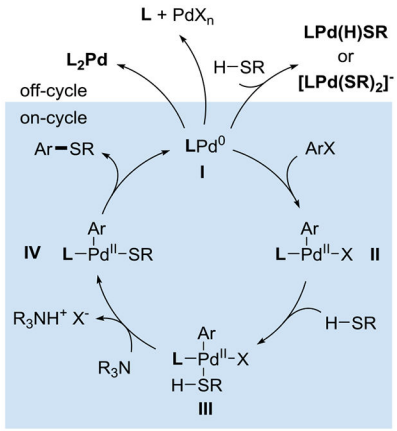
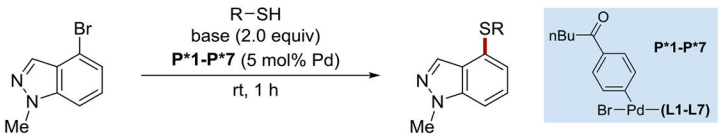


Figure 1.
Overview of phosphine ligand development for Pd-catalyzed C–S cross-coupling.

A. Mechanism of Pd-Catalyzed Thiol Arylation **B. On-/Off-Cycle Ligand Distribution vs. Performance**





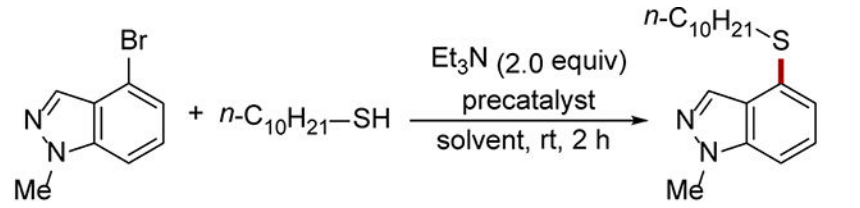
Ligand	(R = 1-decyl)[a] Ligand Resting State	(R = 1-decyl)[a] Yield[c] (catalytic reaction)	(R = 4-methoxyphenyl)[b] Ligand Resting State	(R = 4-methoxyphenyl)[b] Yield[c] (catalytic reaction)
XPhos (**L1**)	free **L**[d]	0	free **L**	18
tBuXPhos (**L2**)	**II**	97	free **L**	95
BrettPhos (**L3**)	**II**	38	free **L**	35
tBuBrettPhos (**L4**)	**II**	100	free **L**	100
AlPhos (**L5**)	**II**	67	**II** + free **L**	99
XantPhos (**L6**)	**L_2Pd**	7	free **L**	14
CyPF-tBu (**L7**)	**LPd(H)SR**	4	**$[LPd(SR)_2]^-$**	61

Figure 2.

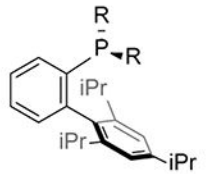
Mechanistic studies. See the Supporting Information for details. [a]Using triethylamine as the base, experiments conducted in benzene-d_6. [b]Using LHMDS as the base, experiments conducted in THF. [c]Yield of the catalytic reaction as determined by GC after 2 h. [d]Measured in $CDCl_3$ rather than benzene.

Table 1.

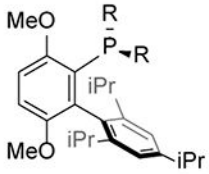
Evaluation of catalysts and reaction conditions for Pd-catalyzed alkyl thiol arylation.[a]



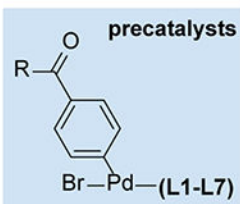
Entry	Precatalyst (mol%)	Solvent	Yield (%)
1	**P1** (1%)	THF	6
2	**P2** (1%)	THF	96
3	**P3** (1%)	THF	34
4	**P4** (1%)	THF	100
5	**P5** (1%)	THF	34
6	**P*6** (1%)	THF	9
7	**P*7** (1%)	THF	8
8	**P2** (0.2%)	THF	13
9	**P2** (0.2%)	PhMe	13
10	**P2** (0.2%)	MeCN	49
11	**P2** (0.2%)	CyH	16
12	**P2** (0.2%)	tBuOH	73



L1, R = Cy, XPhos
L2, R = tBu, tBuXPhos

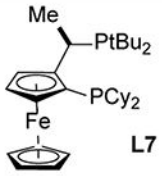


L3, R = Cy, BrettPhos
L4, R = tBu, tBuBrettPhos

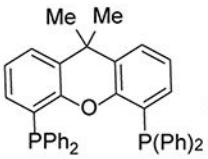


P1-P7
(R = OCH_2CH_2TMS)

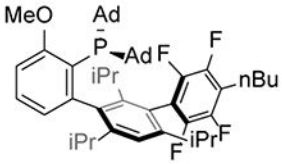
P*1-P*7
(R = nBu)



L7



L6, XantPhos

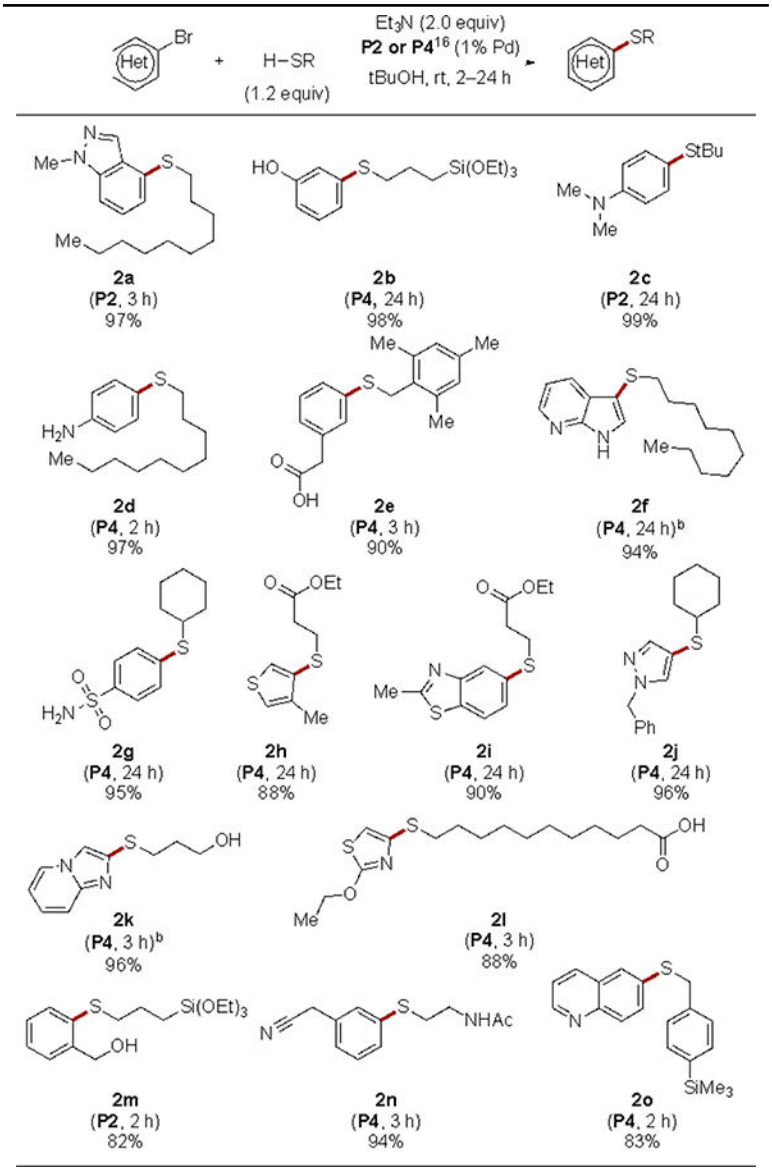


L5, AlPhos

[a]Conditions: aryl bromide (0.1 mmol, 1.0 equiv), thiol (1.2 equiv), triethylamine (2.0 equiv), precatalyst (indicated amount) in solvent (0.20 mL) for 2 h. The yield was determined by calibrated gas chromatography (GC) using dodecane as an internal standard. See the Supporting Information for more details.

Table 2.

Scope of the aliphatic thiol coupling reaction.[a]

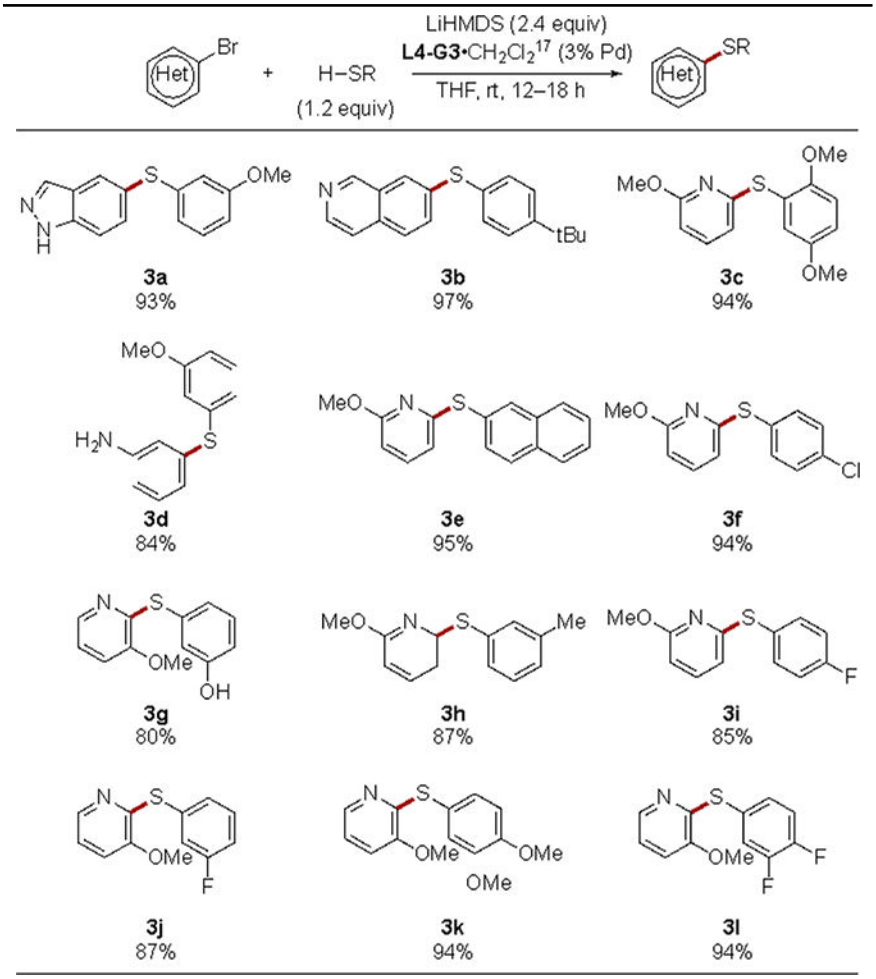


[a]Conditions: aryl bromide (1.0 mmol, 1.0 equiv), thiol (1.2 equiv), triethylamine (2.0 equiv), precatalyst[16] (1 mol%) in *tert*-butanol (2.0 mL). The precatalyst used and reaction time are indicated in parentheses. Yields represent average isolated yields from two independent replicates. For examples of reactant combinations that fail to provide useful yields of coupling product under our conditions, see table S1. See the Supporting Information for details.

[b]THF was used as the solvent instead of *tert*-butanol.

Table 3.

Scope of the aromatic thiol coupling reaction.[a]



[a]Conditions: aryl bromide (1.0 mmol, 1.0 equiv), thiol (1.2 equiv), LHMDS (2.4 equiv), precatalyst[17] (3 mol%) in THF (2.0 mL). Yields represent average isolated yields from two independent replicates. See the Supporting Information for details.