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# Palladium-Catalyzed Direct Arylation of Methyl Sulfoxides with Aryl Halides

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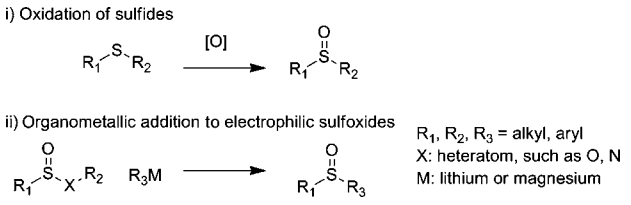
Supporting Information

**ABSTRACT:** The palladium-catalyzed $\alpha$-arylation of unactivated sulfoxides has been developed. The weakly acidic $\alpha$-protons of sulfoxides are reversibly deprotonated by LiO*t*Bu, and a palladium phosphine complex facilitates the arylation. A variety of aryl methyl sulfoxides were coupled with aryl bromides. More challenging coupling partners, such as alkyl methyl sulfoxides (including dimethyl sulfoxide) and aryl chlorides proved to be suitable under the optimized conditions. This method was utilized to synthesize bioactive benzyl sulfoxide intermediates.

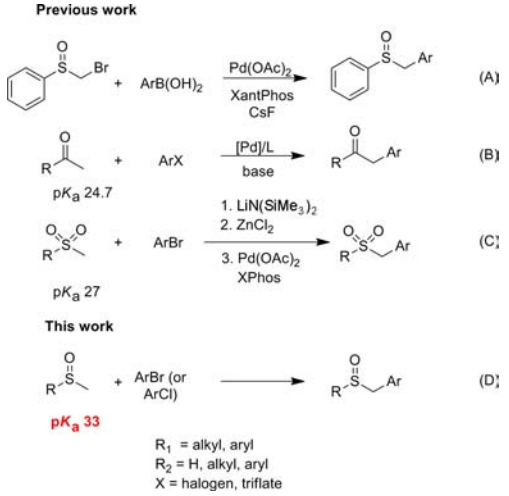
Sulfoxides exhibit a wide range of biological properties, including anticancer,[1a−d] antihepatitis,[1e] and antibacterial activity,[1f] and are useful bioisosteres.[2] They are also important intermediates in organic chemistry and have been widely used as ligands in catalysis.[3] The two most common approaches for generating sulfoxides are (i) oxidation of sulfides[4] and (ii) substitution reactions of electrophilic sulfoxide derivatives with organometallic nucleophiles[5] (Scheme 1). Despite the popularity of these methods, both suffer from limited functional group tolerance because either strong oxidizing agents or reactive organolithium or Grignard reagents are employed. Benzyl phenyl sulfoxides have also been accessed by a Pd-catalyzed Suzuki cross-coupling employing prefunctionalized coupling partners (Scheme 2A).[6] A more efficient and atom-economical route to benzyl sulfoxides would be the direct arylation of methyl sulfoxides. Despite the similarity of this approach to the well-known $\alpha$-arylation of carbonyl compounds,[7] $\alpha$-arylation of unactivated sulfoxides is unknown.

**Scheme 1. Two Synthetic Approaches to Sulfoxides**




Transition-metal-catalyzed cross-coupling reactions to form C−C bonds are one of the most powerful tools in modern organic synthesis.[8] Among these, the $\alpha$-arylation of carbonyl compounds has received significant attention (Scheme 2B).[7] As the p$K_a$ of the $\alpha$-hydrogens increases, however, such reactions become more challenging. For example, the $\alpha$-arylation of unactivated *sulfones* was recently reported by Zhou et al. from Merck (Scheme 2C).[9] The higher p$K_a$ of methyl phenyl sulfone (p$K_a$ = 29[10a]) relative to acetophenone (p$K_a$ = 24.7[10b]) allowed the Merck team to achieve deprotonation of the weakly acidic sulfone with LiN(SiMe$_3$)$_2$ and transmetalation with ZnCl$_2$ before the cross-coupling. In the case of methyl phenyl sulfoxide [p$K_a$ = 33 in dimethyl sulfoxide (DMSO)[10c]], a stronger base must be used for deprotonation, such as lithium diisopropylamide,[11a,b] Li(*i*-Pr)(*c*-Hex),[11b] or *n*-BuLi.[11c] These bases, however, are less practical for cross-coupling reactions because of their limited compatibility with catalysts and coupling partners. The challenge in developing the direct $\alpha$-arylation of unactivated sulfoxides was to identify a suitable combination of base and catalyst. Herein we report the first example of palladium-catalyzed direct arylation of methyl sulfoxides with aryl halides (Scheme 2D). Interestingly, a little-known indolyl phosphine outperformed the industry-standard phosphines in this challenging reaction.

**Scheme 2. Suzuki Coupling of Bromosulfoxides and $\alpha$-Arylation of Carbonyls, Sulfones, and Sulfoxides**




We recently introduced approaches for direct arylation and allylation of weakly acidic benzylic hydrogens of $\eta^6$-arene

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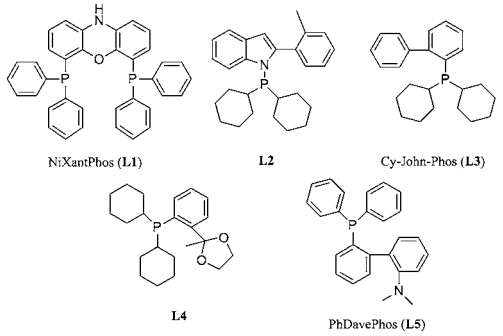
complexes of toluene, benzylic amines, benzylic ethers, and diphenylmethane derivatives.[12] Diphenylmethane derivatives were arylated via a deprotonative cross-coupling procedure (DCCP), even in the absence of arene-activating metals.[13] The DCCP entailed a reversible room-temperature deprotonation of the weakly acidic benzylic protons of diphenylmethane ($pK_a$ = 32) with concurrent palladium-catalyzed cross-coupling. On the basis of the success of this method, we initiated efforts to cross-couple methyl phenyl sulfoxide (**1a**) with bromobenzene (**2a**) under reaction conditions similar to those for the DCCP with diarylmethanes in the absence of arene-activating metals[13] [$KN(SiMe_3)_2$, cyclopenyl methyl ether (CPME), 10 mol % $Pd(OAc)_2$, and 15 mol % NiXantPhos (**L1** in Table 1)]. The coupled benzyl sulfoxide product (**3a**) was formed in 27% isolated yield at 80 °C (Table 1, entry 1). To build on this promising result, we screened six bases [LiO*t*Bu, NaO*t*Bu, KO*t*Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] and four solvents using microscale high-throughput experimentation (HTE) techniques. The leading base from this screening was LiO*t*Bu in CPME, which generated the desired product **3a** in moderate yield (42%; entry 2). The search for more active catalysts was continued with LiO*t*Bu and CPME by testing a series of sterically and electronically diverse mono- and bidentate ligands. Of the 112 ligands examined, **L2**–**L5**[14] were promising (see the Supporting Information for details), with *N*-(dicyclohexylphosphino)-2-(2′-tolyl)indole (**L2**) outperforming the others (entry 3 vs 4–6). To the best of our knowledge, this monodentate, bulky, electron-rich phosphine ligand, which was introduced by Kwong and co-workers,[14b] has been successfully employed only in one study of the Suzuki–Miyaura cross-coupling reaction. The microscale result using **L2** was successfully translated to laboratory scale, rendering product **3a** in 75% isolated yield. A decrease in temperature (entry 7) or catalyst/ligand loading (entry 8) was detrimental to the yield under these conditions. We next focused on the identification of more suitable palladium sources, substrate ratios, and temperatures. Of the conditions and ratios examined, better results for the direct $\alpha$-arylation were obtained on the microscale employing $Pd(OAc)_2$ (10 mol %), ligand **L2** (15 mol %), and a **1a**:**2a** ratio of 1:2 at 110 °C. Scaling the reaction to 0.1 mmol and increasing the concentration from 0.1 to 0.2 M resulted in isolation of **3a** in 93% yield (entry 9). Further increasing the concentration to 0.3 M resulted in a slightly lower yield (87%; entry 10), probably because of reduced solubility of the sulfoxide and base at this concentration. Therefore, 0.2 M was chosen for the substrate scope study.

Under the optimized conditions in Table 1, entry 9, the scope of the direct arylation of **1a** with various aryl bromides was investigated (Table 2). A wide range of substrates exhibited excellent reactivity, including those with electron-donating (**3b**, **3c**), electron-withdrawing (**3d**, **3e**, **3h**), and ortho or meta substituents (**3f**, **3g**). In the case of 4-bromochlorobenzene, a concentration of 0.1 M was found to be optimal for chemoselective activation of the bromide, providing **3e** in 81% isolated yield. When the DCCP with **1a** was scaled to 8 mmol (1.12 g) with 3-bromotrifluoromethylbenzene (**2h**), the

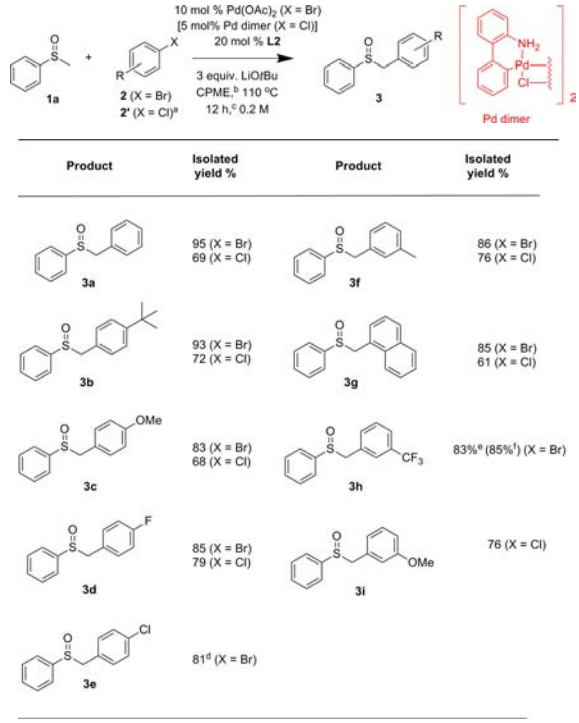
**Table 1. Optimization of the $\alpha$-Arylation of Methyl Phenyl Sulfoxide (1a)**




| entry | ligand | base | [Pd]/ligand mol % | conc. (M) | *T* (°C) | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **L1** | $KN(SiMe_3)_2$ | 10/15 | 0.1 | 80 | 27 |
| 2 | **L1** | LiO*t*Bu | 10/15 | 0.1 | 80 | 42 |
| 3 | **L2** | LiO*t*Bu | 10/20 | 0.1 | 110 | 75 |
| 4 | **L3** | LiO*t*Bu | 10/20 | 0.1 | 110 | 16 |
| 5 | **L4** | LiO*t*Bu | 10/20 | 0.1 | 110 | 23 |
| 6 | **L5** | LiO*t*Bu | 10/20 | 0.1 | 110 | 44 |
| 7 | **L2** | LiO*t*Bu | 10/20 | 0.1 | 80 | 40 |
| 8 | **L2** | LiO*t*Bu | 5/10 | 0.1 | 110 | 40 |
| 9 | **L2** | LiO*t*Bu | 10/20 | 0.2 | 110 | 93[b] |
| 10 | **L2** | LiO*t*Bu | 10/20 | 0.3 | 110 | 87 |

[a]Determined by $^1$H NMR analysis of the crude reaction mixtures. [b]Isolated yield after chromatographic purification.

**Table 2. Substrate Scope of Aryl Bromides and Chlorides in Pd-Catalyzed $\alpha$-Arylation of Unactivated Sulfoxides**




[a]For aryl chlorides, the palladium source was changed to 5 mol % Pd dimer and 0.33 mmol of $H_2O$ was added. [b]For aryl chlorides, the solvent was toluene. [c]For aryl chlorides, the reaction time was 24 h. [d]0.1 M, 36 h. [e]48 h. [f]**1a** (8 mmol), **2j** (16 mmol), CPME (40 mL), LiO*t*Bu (24 mmol), 24 h.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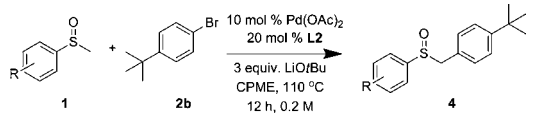
product **3h** was isolated in 85% yield. Sulfoxide **3h** could be used as the key intermediate in the synthesis of an anticancer agent.[1d]

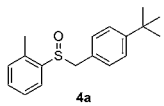
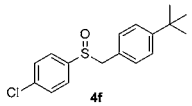
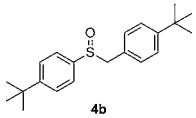
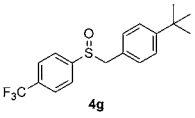
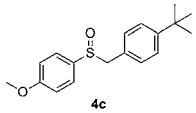
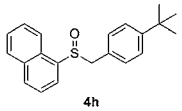
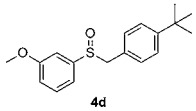
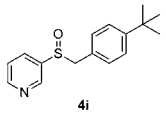
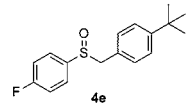
Aryl chlorides are known to be more challenging substrates than aryl bromides for a variety of cross-coupling reactions.[15] When we employed aryl chlorides under our optimized conditions for aryl bromides, only trace products were observed. We suspected that catalyst activation might be problematic and turned to Buchwald-type second-generation catalysts.[16] Thus, addition of **L2** to the palladium dimer (see Table 2) along with 0.33 mmol of $H_2O$ as an additive[17] resulted in an active catalyst toward aryl chlorides (Table 2). Sulfoxide **3a** was isolated using **1a** and chlorobenzene (**2a′**) in 69% yield. Electron-donating (**3b**, **3c**) and electron-withdrawing groups (**3d**) were well-tolerated when the corresponding aryl chlorides were used, as well as 1-naphthyl- (**2g′**) and meta-substituted aryl chlorides (**2f′**, **2i′**). Unfortunately, heterocyclic halides were not viable substrates under these conditions.

We then turned our attention to the aryl methyl sulfoxide substrate scope using 4-bromo-*tert*-butylbenzene (**2b**) as the coupling partner (Table 3). Electron-donating (**4b**, **4c**), withdrawing (**4e**, **4f**, **4g**), *m*-methoxy (**4f**), and *o*-methyl (**4a**) groups all led to good yields (81−87%) under our optimized conditions for aryl bromides. In addition, methyl 1-naphthyl sulfoxide furnished product **4h** in 74% yield. Unfortunately, no product was isolated from 2-pyridyl or 2-pyrimidyl methyl sulfoxide, possibly because of chelation of nitrogen and sulfur or oxygen to palladium. On the basis of this hypothesis, we examined 3-pyridyl methyl sulfoxide and observed the generation of **4i** (77%), a key intermediate in an antivirus compound.[18]

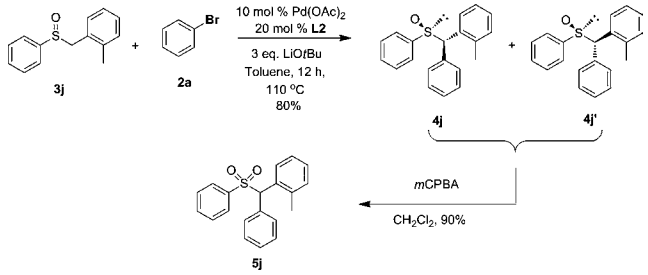
Coupling of sulfoxides with substituents other than methyl may give rise to diastereomers. As anticipated, cross-coupling of benzyl sulfoxide **3j** led to the formation of a mixture of diastereomers in a 1:1.3 ratio. Unfortunately, we were unable to separate the diastereomers by column chromatography. The mixture of sulfoxides was therefore oxidized to sulfone **5j** in 90% yield (Scheme 3).[19]

**Table 3. Substrate Scope of Aryl Methyl Sulfoxides in Pd-Catalyzed α-Arylation Using 4-Bromo-*tert*-butylbenzene (2b) as the Coupling Partner**




| Product | Isolated yield % | Product | Isolated yield % |
|---|---|---|---|
|  4a | 83% |  4f | 81% |
|  4b | 85% |  4g | 84% |
|  4c | 86% |  4h | 74% |
|  4d | 84% |  4i | 77%[a] |
|  4e | 87% | | |

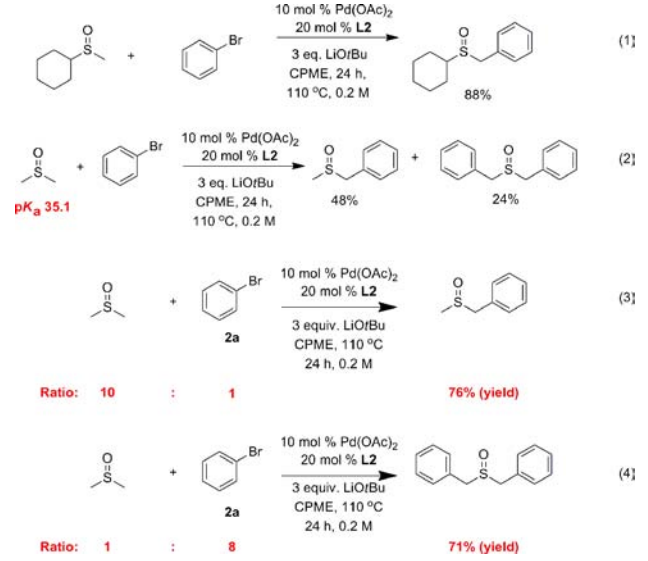
[a]90 °C, 48 h.




**Scheme 3. α-Arylation of 3j with 2a and Subsequent Oxidation to Sulfone 5j**

Alkyl methyl sulfoxides are less acidic than aryl methyl sulfoxides and represent a greater challenge. As shown in Scheme 4, cyclohexyl methyl sulfoxide underwent a DCCP with **2a** to give the desired product in 88% yield after 24 h (eq 1). Interestingly, DMSO, a common organic solvent with $pK_a$ = 35.1,[10a] could be utilized to prepare benzyl sulfoxides. Under the same conditions used for cyclohexyl methyl sulfoxide, mono- and bisarylated products were obtained with DMSO and **2a** in yields of 48 and 24%, respectively (eq 2). To control the selectivity, we adjusted the stoichiometry and optimized the reaction conditions for DMSO. Ultimately, we successfully generated either the mono- or dibenzylated product in isolated yields of 76 and 71% when the DMSO/**2a** ratio was 10:1 or 1:8, respectively (eqs 3 and 4).

**Scheme 4. α-Arylation of Alkyl Methyl Sulfoxides**




In summary, we have developed the first direct α-arylation of unactivated alkyl and aryl methyl sulfoxides with aryl bromides. Aryl chlorides also participate in the reaction when catalyzed by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in situ formation of a Buchwald-type second-generation precatalyst in the presence of $H_2O$ as an additive. The palladium-catalyzed arylation proceeds efficiently in the presence of Kwong's indole-based phosphine and produces benzyl sulfoxides in good to excellent yields. Reversible deprotonation of the weakly acidic $\alpha$-protons of sulfoxides (with p$K_a$'s as high as 35) was achieved using LiO*t*Bu. This direct arylation method provides a novel synthetic route for the generation of sulfoxides, an important class of bioactive compounds. We are currently exploring the mechanism of this reaction and the application of this chemistry to the synthesis of novel ligands. Expanding the substrate scope to heterocyclic halides by using an additive strategy developed by our group[13b] is also under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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