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Palladium-Catalyzed Direct α-Aryation of Benzyl Thioethers with Aryl Bromides

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Abstract

The arylation of sp^3-hybridized C–H's bonds is a powerful strategy to build molecular complexity and diversity. A novel and efficient palladium-catalyzed direct sp^3 C–H arylation of aryl and alkyl benzyl thioether derivatives with aryl bromides is reported. The reaction involves reversible deprotonation of the benzylic C–H's of the thioether with either $LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$ and subsequent cross-coupling to provide the functionalized products in up to 97% yield.

A screen of 24 of the most successful ligands in cross-coupling chemistry led to the identification of NiXantPhos as the only viable ligand for this challenging coupling.

Keywords

C–H functionalization; Sulfides; Palladium; Arylation; Cross-Coupling

Introduction

The direct arylation of C–H bonds[1] is an appealing alternative to classic coupling of prefunctionalized partners, because it circumvents the use of preformed organometallic reagents. In the context of a broader program to functionalize weakly acidic sp^3 hybridized C–H bonds,[2–4] we became interested in the arylation of C–H bonds situated alpha to sulfur atoms, since sulfur-based compounds are commonplace in the chemistry of life and in medicinal chemistry.[5] Our initial efforts focused on the direct α-arylation of C–H bonds adjacent to sulfur(II), such as found in sulfoxides, including the parent DMSO (Scheme 1A).[6] Based on these results, we then examined α-C–H arylation of sulfur(IV) of methyl and benzyl sulfones.[7] In both cases, the reactions were promoted by a palladium catalyst employing Kwong's indole-based phosphine[8, 9] in the presence of LiO-*t*-Bu at 110 °C (Scheme 1).

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Our development of a successful reaction system for the arylation of sulfoxides and sulfones inspired us to conjecture about the possibility of α-arylation of less oxidized sulfur compounds such as thioethers.[10] The α-C–H's of thioethers are more difficult to metallate than either sulfoxides or sulfones due of their higher pK_a values.[11] Although thioethers can be deprotonated with organolithiums[12] and then quenched with a variety of electrophiles, the in situ metallation/arylation of thioethers has never been achieved. Given the importance of organosulfur small molecule libraries, we set out to develop conditions for the tandem reversible metallation of thioethers with subsequent arylation.

To accomplish this objective, two hurdles would need to be surmounted. First, bases must be identified that are sufficiently strong to deprotonate thioethers, yet are compatible with transition metal arylation catalysts. Second, a catalyst would need to be found that could withstand reactive organolithium,[13] -sodium, or -potassium intermediates. Furthermore, given the known propensity of palladium catalysts to cleave C–S bonds[14] the catalyst must also exhibit a high degree of chemoselectivity.

Herein we report the first examples of C–H arylation alpha to sulfur in thioethers (Scheme 2). Given the distinct chemistry of thioethers relative to sulfones and sulfoxides, and the increased reactivity of metallated sulfides compared to their sulfoxide and sulfone counterparts, it is not surprising that different bases, conditions, palladium precursor and ligand were required for the α-arylation of thioethers.

Results and Discussion

Given the high pKa's of thioethers, it seemed wise to initiate research in this area with a class of thioethers wherein the α-lithiated substrates had been generated and studied. Benzyl phenyl sulfide satisfied our criteria: it can be deprotonated by *n*-BuLi and it is monomeric in solution and the solid state.[15]

Our first step toward development of the arylation of sulfides is to identify base and solvent combinations for the reversible deprotonation of the benzylic C–H's of ArS–CH_2Ar' under conditions amenable to catalysis. To this end, we employ base and benzyl chloride to trap any metallated sulfide. By measuring the yield of the benzylation product, we can determine which bases deprotonate the benzylic C–H's of the substrate over the course of the reaction (Table 1).[3] Thus, we screened 6 bases [LiO-*t*Bu, NaO-*t*Bu, KO-*t*Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$] at room temperature in CPME (cyclopentyl methyl ether). As outlined in Table 1, entries 1–3, alkoxide bases MO-*t*Bu (M = Li, Na, K) did not generate detectable amounts of benzylation products, suggesting they would not be applicable in the arylation of thioethers. Interestingly, these results are in contrast to the arylation of aryl methyl sulfoxides[6] and sulfones,[7] where LiO-*t*Bu was the optimal base (Scheme 1). On the other hand, benzylation products were observed in increasing conversions, with $LiN(SiMe_3)_2 < NaN(SiMe_3)_2 < KN(SiMe_3)_2$ (entries 4–6).

Having identified three potential bases for the catalytic arylation of thioethers, we next turned our attention to the hunt for a catalyst. Based on our experience with deprotonative cross-coupling processes of weakly acidic substrates,[3, 4] we chose to use van Leeuwen's NiXantPhos ligand as a starting point (Figure 1).[16, 17] Eight different palladium sources

[$Pd(OAc)_2$, $[PdCl(allyl)]_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$, $PdCl_2(cod)$, $Pd(acac)_2$, $Pd(tfa)_2$ and $PdCl_2$], the three bases identified in the benzylation screen in Table 1 [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$] and 4 solvents [CPME, THF, DME (dimethoxyethane) and toluene] were examined in the coupling of Ph–S–CH_2Ph (**1a**) with bromobenzene (**2a**). Screens were conducted at 50°C using microscale high-throughput experimentation (HTE) techniques (see Supporting Information for details and complete results). The 7 leading hits in the HTE screen were performed on laboratory scale and the assay yields of **4a** are listed in Table 2. The combination of $[PdCl(allyl)]_2$ and $LiN(SiMe_3)_2$ in THF was the top contender and was employed in a broader screen of ligands, as outlined below. Interestingly, in contrast to the benzylation in Table 1, the results of the catalyst screening (Table 2) indicate the *opposite* efficacy ordering of the bases in the arylation [$LiN(SiMe_3)_2$ ~ $NaN(SiMe_3)_2$ > $KN(SiMe_3)_2$].

Based on the results in Table 2, we subsequently examined 24 sterically and electronically diverse ligands in the arylation of $PhSCH_2Ph$ with bromobenzene using HTE techniques with $[PdCl(allyl)]_2$ and $LiN(SiMe_3)_2$ in THF (see the Supporting Information for details and a full list of ligands tested). Interestingly, of the 24 ligands examined, only NiXantPhos generated the coupling product in meaningful amounts. Structurally similar XantPhos[18] (Figure 1) generated only trace product. Well known dppf derivatives and bulky monodentate phosphines (members of the Buchwald family,[19] Kwong's indole-based phosphine,[8] Q-Phos,[20] etc.) *failed to generate product* under these conditions, attesting to the challenging nature of this cross-coupling reaction. These results further indicate that NiXantPhos, with an N–H that can be deprotonated under the basic reaction conditions, is a uniquely effective ligand.[17]

In order to optimize the reaction conditions with the NiXantPhos/$[PdCl(allyl)]_2$ system, we tested different ratios of thioether (**1a**), bromobenzene (**2a**), $LiN(SiMe_3)_2$ (**3a**) and various reaction times (Table 3). At this point, we did not yet understand the sensitivity of the yield to reaction time (due to product decomposition). The yield of the reaction was higher when 2 equiv each of $LiN(SiMe_3)_2$ and bromobenzene were used (entries 1–3, up to 52% yield).

To minimize byproduct formation, we reduced the reaction temperature from 80 °C to 50 °C and to room temperature with 12 h reaction time. The yield of **4a** increased to 60% at rt (entries 3–5). The effect of the reaction time was next evaluated. The yield of **4a** in entries 6–9 reached a maximum when the reaction was quenched after 30 min (entry 8, 86% yield). We next decreased the palladium and ligand loading from 10 mol % Pd to 5 mol %. Unfortunately, the yield decreased from 86 to 67% (entries 8 vs. 10). Furthermore, increasing the reaction concentration at the lower catalyst loading did not improve the yield of **4a** (entry 11). Substituting other solvents for THF did not lead to the desired product, except in the case of DME where the yield was not improved (entries 12–16).

With our optimized conditions (entry 8, Table 3), we examined the substrate scope of the arylation of benzyl phenyl sulfide (**4a**) with aryl bromides (**2a**–**k**, Table 4). The DCCP showed good to excellent yields for alkyl substituted aryl bromides (82–84%, **4b**–**d**, entries 2–4) and those with methoxy substituents in the *para* or *meta* positions (73–93%, **4e**–**f**, entries 5–6). Electron-withdrawing groups in the *para* position led to lower yields (50–63%,

4g–**h**, entries 7–8). Both 1- and 2-bromonaphthalene were good substrates, forming product in 70 and 72% yield (**4i**–**j**, entries 9 and 10, respectively). Nitrogen-protected 5-bromo indole **2k** was also a good coupling partner, producing the heterocyclic product **4k** in 68% yield (entry 11). Reactions with heteroaryl bromides bearing 2- or 3-pyridyl, 2- or 3-furyl, or 2- or 3-thiophenyl did not yield coupling products. This is not totally unexpected given the sensitivity of these heterocycles and the strongly basic conditions in these coupling reactions.

We next turned our attention to the scope of sulfide substrates (Table 5). Sulfides with electron-donating substituents in the S–Ar group resulted in good to excellent yields (**4l**–**n**, 80–97%, entries 1–3) while one with a *para*-CF_3 group gave lower yield (**4o**, 60%, entry 4).

Variation of the benzylic group was also examined. Substitution of 1-naphthyl for phenyl (Ar^2) and coupling with Ph–Br, 3-MeO-C_6H_4–Br, 4-*t*-Bu-C_6H_4–Br resulted in formation of **4i**, **4p**, and **4q** in 77, 70, and 65% yield, respectively (entries 5–7). An electron donating 4-MeO-C_6H_4–CH_2 group is expected to decrease the acidity of the benzylic hydrogens. Nonetheless, coupling with Ph–Br or 3-MeO-C_6H_4–Br resulted in formation of **4e** and **4r** in 60 and 74%, respectively (entries 8 and 9). Electron poor 4-Cl-C_6H_4–CH_2SPh coupled with 3-MeO-C_6H_4–Br to furnish product **4s** in 74% yield (entry 10), illustrating the chemoselectivity of the catalyst for the C–Br bond over the C–Cl bond.

Heterocycle-containing compounds are important in medicinal chemistry.[21] We, therefore, examined heterocycles in the benzylic position of the thioether. Initially, coupling reactions with bromobenzene and Ph–S–CH_2(3-pyridyl) failed due to decomposition of the pyridyl-containing substrate in the presence of $LiN(SiMe_3)_2$. We, therefore, screened alkoxide bases LiO-*t*Bu, NaO-*t*Bu and KO-*t*Bu at room temperature, which led to trace products with NaO-*t*Bu and KO-*t*Bu. Heating reaction mixtures with these bases to 50 °C resulted in generation of the coupling product **4t** in 56% yield with KO-*t*Bu (entry 11). Coupling of Ph–S–CH_2(3-pyridyl) with 3-MeO-C_6H_4–Br, 4-*t*-Bu-C_6H_4–Br, and 4-F-C_6H_4–Br resulted in moderate to good yields of the coupled products **4u**–**4x** (57–71%, entries 12–14).

To examine the scalability of the reaction, we preformed the arylation of benzyl phenyl sulfide (**1a**) with bromobenzene (**2a**) on a 5 mmol (1.00 g) scale (Scheme 3). The desired product **4a** was afforded in 78% isolated yield (1.076 g).

Finally, we wanted to expand our method to arylation of alkyl benzyl sulfides, R–S–CH_2Ar. Under our standard conditions with $LiN(SiMe_3)_2$ and *c*-Hex–S–CH_2Ph the reaction failed and we observed only recovered starting materials. We hypothesized that this was due to the decreased acidity of the alkyl thioether substrate. Based on the difference between estimated pK_a's of dimethyl sulfide (pK_a~45)[22] and Me–S–Ph (pK_a~42),[11] it is likely that *c*-Hex–S–CH_2Ph is about 3 pK_a units less acidic than Ph–S–CH_2Ph (pK_a 30.8 in DMSO).[11] Following this line of reasoning, we tested the more reactive bases $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$.[4] At rt in THF, we observed trace formation of products after 0.5 h with both $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$. Heating reaction mixtures with $NaN(SiMe_3)_2$ or $KN(SiMe_3)_2$ to 50°C for 1 h resulted in coupled product **6a** in 84% yield for the benzyl cyclohexyl sulfide with $NaN(SiMe_3)_2$ (entry 1, Table 6). Coupling of *c*-Hex–S–CH_2Ph with

4-MeO-C_6H_4–Br, 3-MeO-C_6H_4–Br and 4-F-C_6H_4–Br resulted in generation **6b**–**d** in 60–95% yields of the coupled products (entries 2–4). These conditions also worked well with *t*-Bu–S–CH_2Ph, which underwent DCCP with Ph–Br, 4-MeO-C_6H_4–Br, 3-MeO-C_6H_4–Br and 4-F-C_6H_4–Br to provide **6e**–**h** in 75–87% yield (entries 5–8).

These results suggest that a variety of alkyl benzyl thioethers can be selectively coupled with aryl bromides at the benzylic position.

Conclusion

Direct and selective functionalization of C–H bonds by transition metal catalysts is a powerful method to facilitate the synthesis of diverse products from simple and readily available precursors. An expanding repertoire of substrates bearing various functional groups is now amenable to such reactions. Herein we have advanced the first method for the arylation adjacent to sulfur of thioethers. This method enables the synthesis of various aryl and alkyl (diarylmethyl) sulfides, which have demonstrated bioactivity.[23]

Our approach involves deprotonative cross-coupling of aryl benzyl sulfides, wherein the weakly acidic sulfide is reversibly metallated by $LiN(SiMe_3)_2$ or $NaN(SiMe_3)_2$ in the presence of a palladium-NiXantPhos-based catalyst. The reaction proved challenging due to the difficult deprotonation of the weakly acidic benzyl thioether. Nonetheless, moderate to excellent yields were obtained (50–97%). This study highlights the compatibility of the NiXantPhos-based palladium catalyst to highly reactive organolithium, -sodium, and -potassium intermediates that are structurally quite different than those employed in prior previously as coupling partners.[3, 18]

Experimental Section

General Procedures for α-arylation of thioethers

General Procedure A—An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $LiN(SiMe_3)_2$ 2 equiv) and the benzyl thioether (1 equiv) under a nitrogen atmosphere. A 1 mL solution (from a stock solution) of $[PdCl(allyl)]_2$ (5 mol %) and NiXantPhos (20 mol %) in dry THF was added to the vial via a syringe. After stirring for 5 min at 24 °C, aryl bromide (2 equiv) was added to the reaction mixture. The reaction mixture was stirred for 30 min at 24 °C, quenched with three drops of H_2O, diluted with 1 mL of dichloromethane, and filtered over a pad of silica. The pad was rinsed with additional dichloromethane, and the solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General Procedure B—An oven-dried 10 mL reaction vial equipped with a stir bar was charged with the benzyl thioether (1 equiv) under a nitrogen atmosphere. A 1 mL solution (from a stock solution) of $[PdCl(allyl)]_2$ (5 mol %) and NiXantPhos (20 mol %) in dry THF was added to the vial via a syringe. After stirring for 5 min at 24 °C, aryl bromide (2 equiv) was added to the reaction mixture followed by slow addition of a solution of $LiN(SiMe_3)_2$ (2 equiv) in 0.5 mL of THF for 40 min. The reaction mixture was stirred for 15 min at 24 °C, quenched with three drops of H_2O, diluted with 1 mL of dichloromethane, and filtered over

a pad of silica. The pad was rinsed with additional dichloromethane, and the solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General Procedure C—An oven-dried 10 mL reaction vial equipped with a stir bar was charged with KO-*t*Bu (2 equiv) and the benzyl thioether (1 equiv) under a nitrogen atmosphere. A 1 mL solution (from a stock solution) of $[PdCl(allyl)]_2$ (5 mol %) and NiXantPhos (20 mol %) in dry THF was added to the vial via a syringe. After stirring for 5 min at 24 °C, aryl bromide (2 equiv) was added to the reaction mixture. The reaction mixture was stirred for 30 min at 50 °C, cooled to room temperature, quenched with three drops of H_2O, diluted with 1 mL of dichloromethane, and filtered over a pad of silica. The pad was rinsed with additional dichloromethane and the solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General Procedure D—An oven-dried 10 mL reaction vial equipped with a stir bar was charged with $NaN(SiMe_3)_2$ (2 equiv) and the benzyl thioether (1 equiv) under a nitrogen atmosphere. A 1 mL solution (from a stock solution) of $[PdCl(allyl)]_2$ (5 mol %) and NiXantPhos (20 mol %) in dry THF was added to the vial via a syringe. After stirring for 5 min at 24 °C, aryl bromide (2 equiv) was added to the reaction mixture. The reaction mixture was stirred for 1 hour at 50 °C, cooled to rt, quenched with three drops of H_2O, diluted with 1 mL of dichloromethane, and filtered over a pad of silica. The pad was rinsed with additional dichloromethane, and the solution was concentrated under reduced pressure. The crude material was loaded onto a silica gel column and purified by flash chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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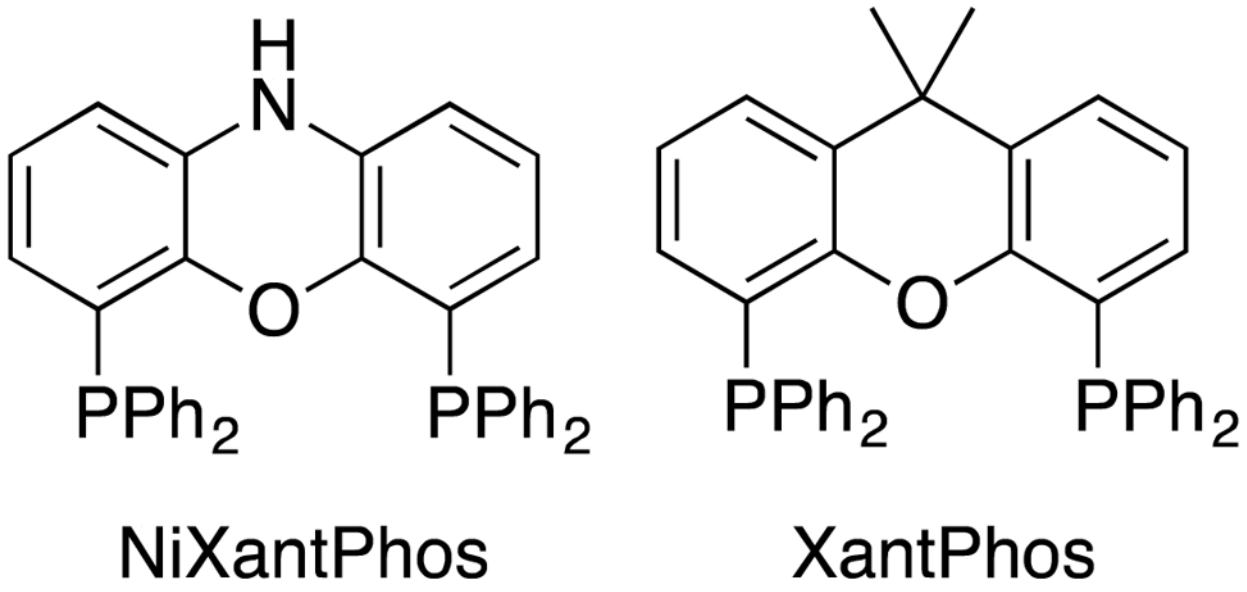
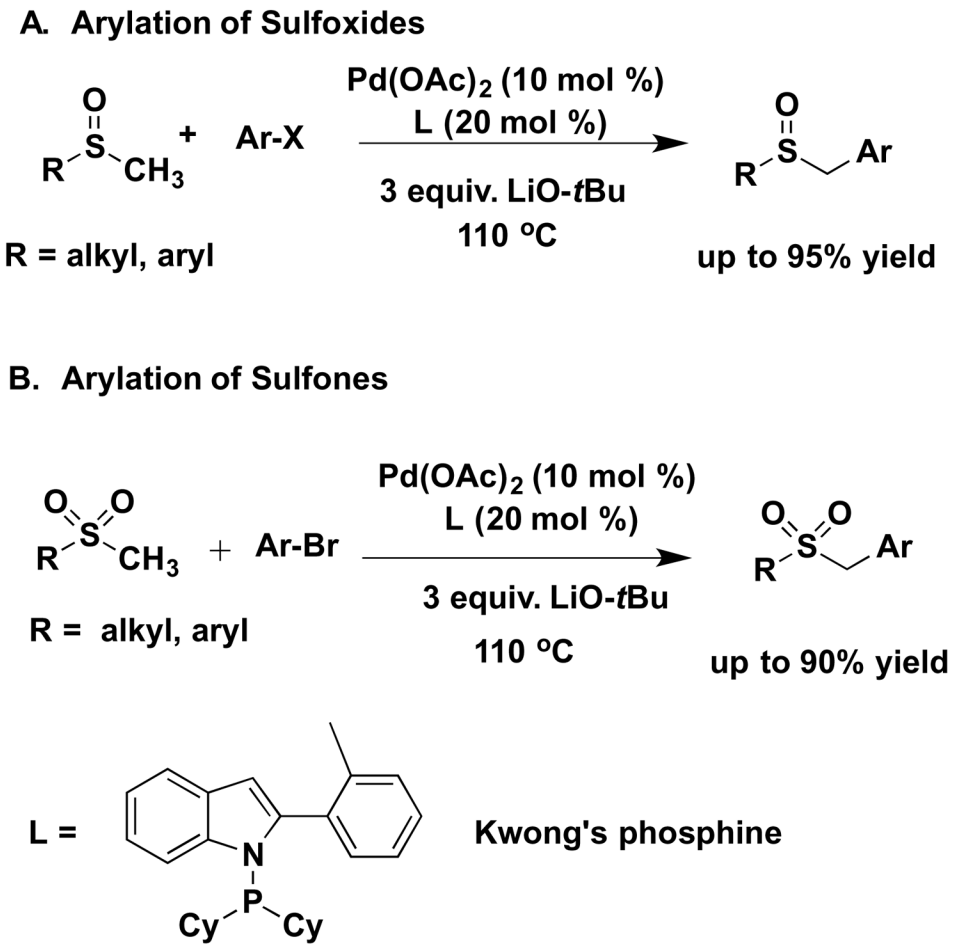
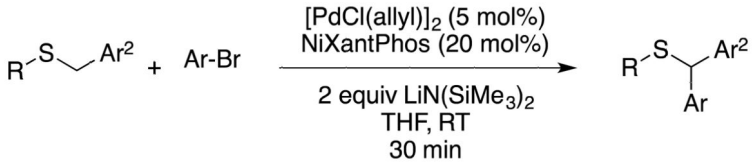


Figure 1.
Structures of van Leeuwen's NiXantPhos and XantPhos ligands.

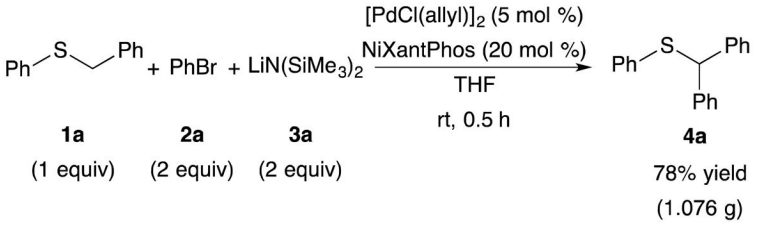


Scheme 1.

Direct α-arylation of sulfoxides (A) and sulfones (B) promoted by a palladium catalyst based on Kwong's indole-based phosphine.



Scheme 2.
Direct α-arylation of sulfides outlined herein.

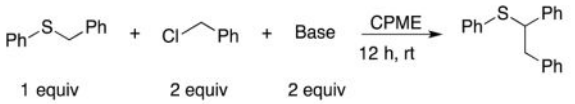


Scheme 3.

Arylation of benzyl phenyl sulfide with bromobenzene on a 5 mmol scale.

Table 1

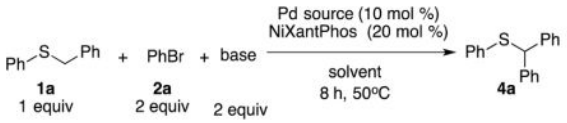
Benzylation of benzyl phenyl sulfide with benzyl chloride.



entry	base	^{1}H NMR assay yield (%)
1	LiO-*t*Bu	0
2	NaO-*t*Bu	0
3	KO-*t*Bu	0
4	$LiN(SiMe_3)_2$	53
5	$NaN(SiMe_3)_2$	60
6	$KN(SiMe_3)_2$	74

Table 2

Laboratory-scale Reactions Using the top HTE Conditions.

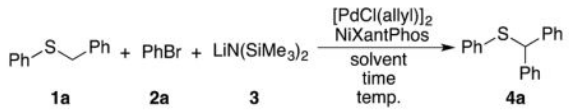


entry	base	Pd source	solvent	assay yield (%)[a]
1	$LiN(SiMe_3)_2$	$[PdCl(allyl)]_2$	THF	61
2	$LiN(SiMe_3)_2$	$PdCl_2(cod)$	DME	57
3	$LiN(SiMe_3)_2$	$PdCl_2(cod)$	toluene	35
4	$LiN(SiMe_3)_2$	$PdCl_2$	toluene	0
5	$NaN(SiMe_3)_2$	$Pd(OAc)_2$	CPME	56
6	$NaN(SiMe_3)_2$	$PdCl_2(cod)$	CPME	58
7	$NaN(SiMe_3)_2$	$[PdCl(allyl)]_2$	toluene	45

[a] Yields determined by ^1H NMR analysis of crude mixture with CH_2Br_2 as internal standard.

Table 3

Optimization of palladium-catalyzed DCCP of benzyl phenyl sulfide.



1a **2a** **3** **4a**

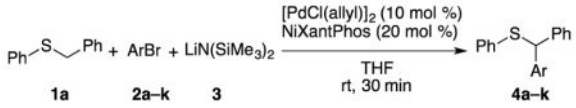
entry	1a:2a:3a	solvent	T (°C)	time (h)	Pd: NiXantPhos (mol %)	4a[a] (%)
1	2:1:2	THF	80	12	10:20	45
2	2:1:3	THF	80	12	10:20	0
3	1:2:2	THF	80	12	10:20	52
4	1:2:2	THF	50	12	10:20	53
5	1:2:2	THF	R.T.	12	10:20	60
6	1:2:2	THF	R.T.	6	10:20	67
7	1:2:2	THF	R.T.	1	10:20	80
8	1:2:2	THF	R.T.	0.5	10:20	86
9	1:2:2	THF	R.T.	0.25	10:20	76
10	1:2:2	THF	R.T.	0.5	5:10	67
11	1:2:2	THF	R.T.	0.5	5:10	64[b]
12	1:2:2	CPME	R.T.	0.5	10:20	0
13	1:2:2	DME	R.T.	0.5	10:20	58
14	1:2:2	dioxane	R.T.	0.5	10:20	0
15	1:2:2	hexanes	R.T.	0.5	10:20	0
16	1:2:2	toluene	R.T.	0.5	10:20	0

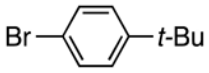
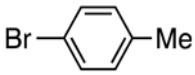
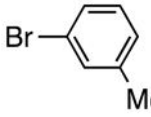
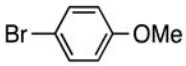
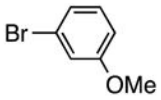
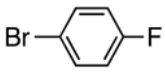
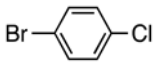
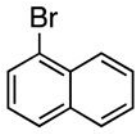
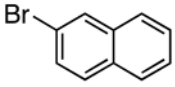
[a] Yields determined by ^{1}H NMR analysis of crude mixture with CH_2Br_2 as internal standard.

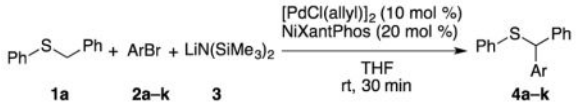
[b] concentration 0.2 M.

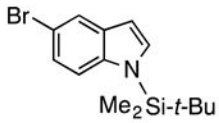
Table 4

Substrate scope of aryl bromides in the α-arylation of benzyl phenyl sulfide.



entry	Br–Ar	product	isolated yield (%)
1	Br–Ph	**4a**	86
2		**4b**	84[a]
3		**4c**	82[a]
4		**4d**	83
5		**4e**	73[b]
6		**4f**	93
7		**4g**	50
8		**4h**	63
9		**4i**	72[a]
10		**4j**	70[a]



entry	Br–Ar	product	isolated yield (%)
11		**4k**	68[c]

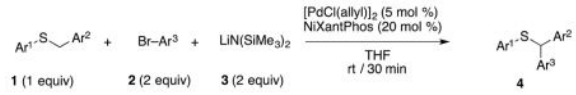
[a] Slow addition of base for 40 min, 30 min reaction time.

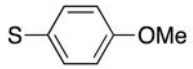
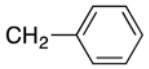
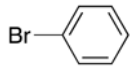
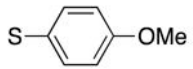
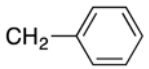
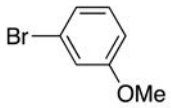
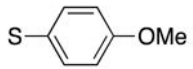
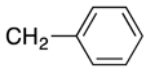
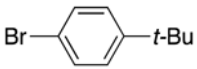
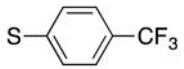
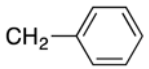
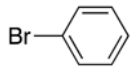
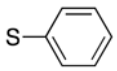
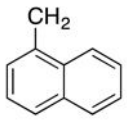
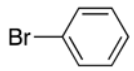
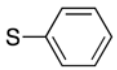
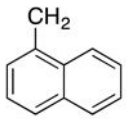
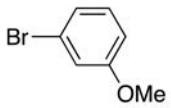
[b] Slow addition of base for 40 min at 10 °C, 15 min reaction time.

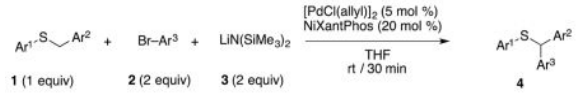
[c] 4 h reaction time.

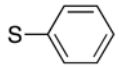
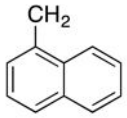
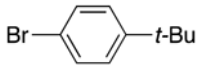
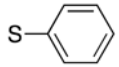
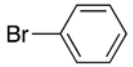
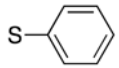
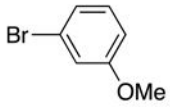
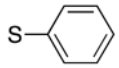
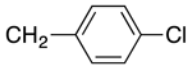
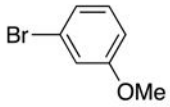
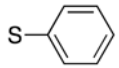
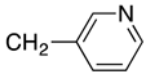
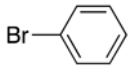
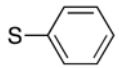
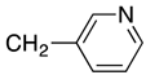
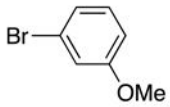
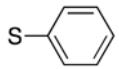
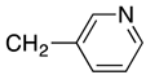
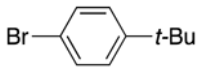
Table 5

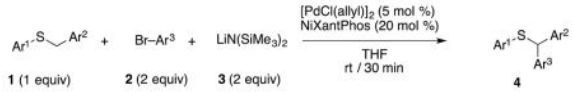
Substrate scope of aryl bromides in the α-arylation of aryl benzyl thioethers.

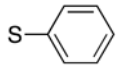
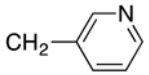
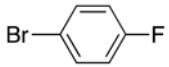


entry	S–Ar	–CH_2–Ar	Br–Ar	product	yield (%)
1				**4l**	80[a]
2				**4m**	97[a]
3				**4n**	83[b]
4				**4o**	60
5				**4i**	77[b]
6				**4p**	70



entry	S–Ar	–CH_2–Ar	Br–Ar	product	yield (%)
7				**4q**	65[b]
8				**4e**	60[a]
9				**4r**	74[a]
10				**4s**	74
11				**4t**	56[c]
12				**4u**	70[c]
13				**4v**	71[c]



entry	S–Ar	–CH_2–Ar	Br–Ar	product	yield (%)
14				**4x**	57[c]

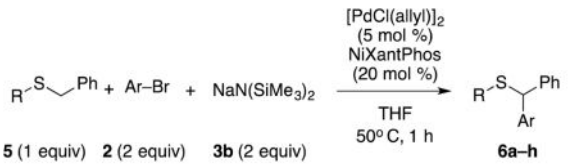
[a] 1 h.

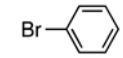
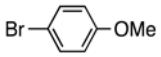
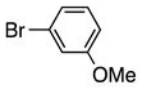
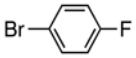
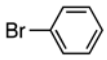
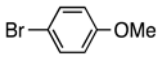
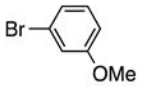
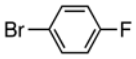
[b] Slow addition of base for 40 min, 15 min.

[c] KO-*t*Bu as base, 50°C for 30 min reaction time.

Table 6

Substrate scope of aryl bromides in the α-arylation of alkyl phenyl sulfides.



entry	S–R	Ar–Br	product	yield (%)
1			6a	84
2			6b	95
3			6c	68
4			6d	60
5			6e	87
6			6f	89
7			6g	75
8			6h	76