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Palladium-Catalyzed Direct α-Arylation of Methyl Sulfones with Aryl Bromides

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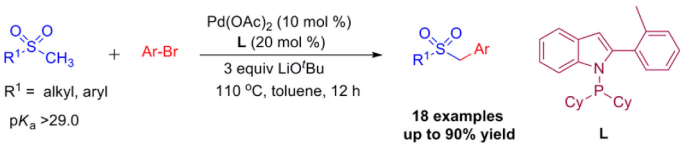
ABSTRACT



A direct and efficient approach for palladium-catalyzed arylation of aryl and alkyl methyl sulfones with aryl bromides has been developed. The catalytic system affords arylated sulfones in good to excellent yields (73−90%).

Sulfones are present in a large number of pharmaceuticals and biologically active compounds.[1] They are also found in natural products[2] and Syngenta's popular herbicide mesotrione.[3] Given the importance of sulfones, more efficient and atom-economical approaches to their synthesis are in demand.

Despite the recent interest in palladium-catalyzed arylation reactions,[4,5] only limited success has been achieved in the α-arylation of sulfones. This may be due to the high pK_a's of sulfones, particularly in the absence of neighboring electron-withdrawing substituents. In 2002, Beletskaya and co-workers described the first example of α-arylation of activated sulfones (Scheme 1, eq 1) using a palladium/triphenylphosphine-based catalyst. Flourinated sulfones, $CF_3SO_2CH_2R$, with their increased acidity (pK_a ∼20), were also good substrates. Unfortunately, unactivated substrates, such as methyl phenyl sulfone, were not suitable for this method.[6] In 2009, Niwa and co-workers reported a protocol for the direct arylation of benzyl sulfones in excellent yield (up to 99%, Scheme 1, eq 2). The pK_a of $PhSO_2CH_2Ph$ in DMSO is 24. More challenging substrates, such as $PhSO_2CH_3$ (pK_a 29), did not react under their conditions.[7]

Subsequently, Zhou described a palladium-catalyzed arylation of alkyl sulfones with aryl halides (Scheme 1, eq 3).[8] A broad scope and good yields were obtained.

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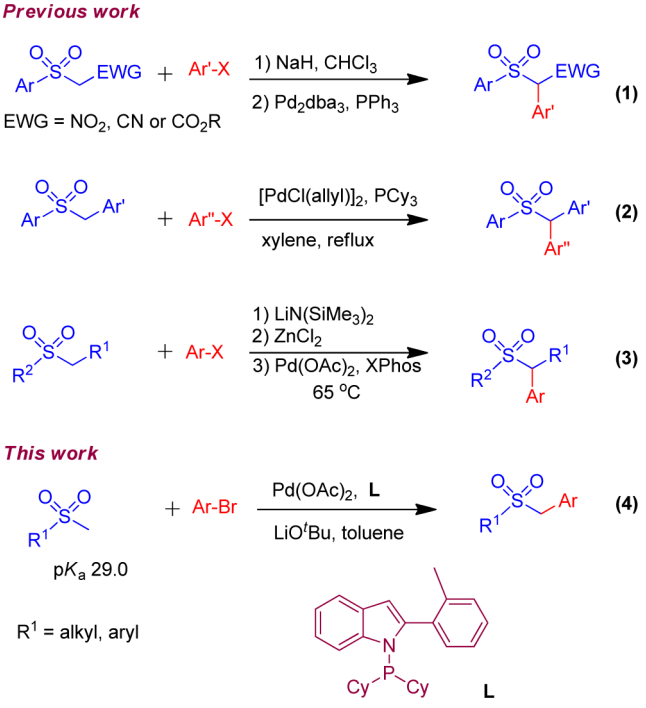
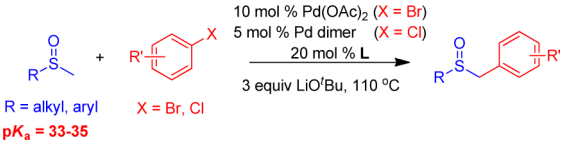
Their method, however, has several experimental drawbacks. It requires multiple changes in temperature (−20 °C to rt to −20 °C to 65 °C), generation of the lithiated sulfone must be followed by transmetalation to $ZnCl_2$, and the limiting reagent was the aryl halide and not the sulfone. Thus, a more atom-econimical and experimentally simpler method to make these valuable compounds would be advantageous.

Scheme 1. α-Arylation of Sulfones



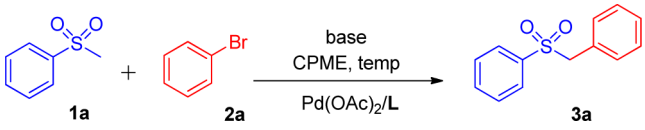
We recently initiated a program in the catalytic functionalization of weakly acidic sp^3-hybridized C−H bonds.[9] Substrates reported to date include diphenylmethanes,[10a,b] benzylic amines,[9] and sulfoxides.[10c] Our α-arylation of sulfoxides is the first example of this reaction and is illustrated in Scheme 2. Given that the α-protons of sulfones (pK_a 29) are more acidic than those of sulfoxides (pK_a 33),[11] we decided to explore the possibility of a palladium-catalyzed deprotonative cross-coupling process (DCCP) for the α-arylation of unactivated sulfones with aryl bromides. We envisioned that one of the challenges would be to minimize the amount of bis(arylation) formed, because the benzyl sulfone product is ∼4 orders of magnitude more acidic than the starting methyl sulfone.

Scheme 2. α-Arylation of Sulfoxides[10c]



We initiated optimization of the sulfone arylation employing conditions for the palladium-catalyzed arylation of sulfoxides (Scheme 2). The sulfoxide arylation was performed at 110 °C in cyclopentyl methyl ether (CPME) with 10 mol % $Pd(OAc)_2$ and 20 mol % of Kwong's ligand **L**.[12] The first and most important variable to be optimized in the sulfone arylation was the base, because the nature of the base would impact the relative rates of the first and second arylations. A screen of six bases [LiO^tBu, NaO^tBu, KO^tBu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] indicated that LiO^tBu performed better for the aryaltion (Table 1, entries 1−6) and provided the monoarylation product with very good selectivity. Both NaO^tBu and KO^tBu did not efficiently promote the arylation reaction (Table 1, entries 2−3), with only trace products observed. Significantly lower yields were obtained with the stronger bases $LiN(SiMe_3)$, $NaN(SiMe_3)$, and $KN(SiMe_3)$ (Table 1, entries 4−6).

Table 1. Optimization of the Base for the α-Arylation of Sulfones with the Bromobenzene[a]



entry	base	time (h)	solvent	temp (°C)	NMR yield (%)
1	LiO^tBu	12	CPME	110	70
2	NaO^tBu	12	CPME	110	trace
5	KO^tBu	12	CPME	110	trace
4	$LiN(SiMe_3)_2$	12	CPME	110	17
5	$NaN(SiMe_3)_2$	12	CPME	110	23
6	$KN(SiMe_3)_2$	12	CPME	75	36

[a] Reactions performed using 1 equiv of **1a**, 2 equiv of **2a**, $Pd(OAc)_2$ (10 mol %), **L** (20 mol %), and 3 equiv of base on 0.1 mmol scale.

With LiO^tBu as the base, four solvents (CPME, 2-MeTHF, dioxane, and toluene), three concentrations (0.1, 0.2, and 0.3 M), and two temperatures (80 and 110 °C) were screened (Table 2). Yields of 70% and 66% were obtained in CPME and toluene, respectively (entries 1 and 4), while

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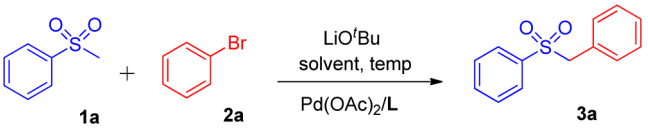
reactions in 2-MeTHF and dioxane gave trace product (entries 2 and 3). When the concentration was increased to 0.2 M, the yield climbed to 88% in toluene (entry 5) and 73% in CPME (entry 7). A lower yield (70%) was observed at 0.3 M in toluene (entry 6). Unfortunately, despite significant effort, reducing the palladium loading from 10 to 5 mol % at 110 °C resulted in a drop in the yield from 88% to 68% (compare entries 5 and 8). Finally, when the reaction temperature was decreased to 80 °C, the yield fell to 50%, despite increasing the reaction time to 24 h (entry 9).

Table 2. Optimization of the Conditions of the α-Arylation of Sulfones[a]



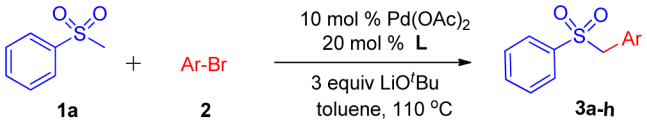
entry	solvent	concn (M)	temp (°C)	time (h)	NMR yield (%)
1	CPME	0.1	110	12	70
2	dioxane	0.1	110	12	5
3	2-MeTHF	0.1	80	12	4
4	Tol	0.1	110	12	66
5	Tol	0.2	110	12	88
6	Tol	0.3	110	12	70
7	CPME	0.2	110	12	73
8[b]	Tol	0.2	110	12	68
9	Tol	0.2	80	24	50

[a] Reactions performed using 1 equiv of **1a**, 2 equiv of **2a**, Pd(OAc)$_2$ (10 mol %), **L** (20 mol %), and 3 equiv of LiO^{t}Bu on 0.1 mmol scale. [b] Pd(OAc)$_2$ (5 mol %) and **L** (10 mol %).

The optimal yield in our study was obtained at 110 °C in toluene using LiO^{t}Bu as the base and a catalyst system generated *in situ* from 10 mol % Pd(OAc)$_2$ and 20 mol % **L**. With optimized conditions in hand, the scope of aryl bromides was examined (Table 3). In general, good to excellent yields (73−90%) were observed for the arylation of methyl phenyl sulfone (**1a**) with aryl bromides. Electron-donating (82−90% yield, entries 2−4) and electron-withdrawing groups (80−83% yield, entries 5−7) were well tolerated. 1-Bromonaphthalene gave the desired product in 73% yield after 24 h (entry 8). Under the optimized conditions, the ratio of mono- to bis-arylation was well controlled (10−20:1) in the reactions of Table 3.

We next explored the scope of substituted methyl sulfones with bromobenzene (Table 4). Electron-donating and -withdrawing substituents at the *ortho*, *meta*, and *para* positions of the sulfone were compatible with the reaction, giving yields in excess of 80% (entries 1−6). Both 3- and 4-methoxy substituted aryl sulfones provided the product in good yields (81−85%, entries 2−3). Sulfones with electron-withdrawing groups underwent coupling in 81−84% yield (entries 4−6). The 1-naphthyl derivative **1h** gave the product in 83% yield (entry 7). The reaction with

Table 3. Substrate Scope of Aryl Bromides in the α-Arylation of Methyl Phenyl Sulfone[a]



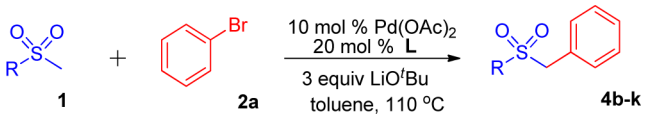
entry	Ar−Br	time (h)	product	isolated yield (%)
1	Ph−Br	12	**3a**	86
2	3-Me−C$_6$H$_4$−Br	12	**3b**	82
3	4-MeO−C$_6$H$_4$−Br	12	**3c**	78
4	4-^{t}Bu−C$_6$H$_4$−Br	12	**3d**	90
5	4-F−C$_6$H$_4$−Br	12	**3e**	83
6	4-Cl−C$_6$H$_4$−Br	12	**3f**	81
7	3-CF$_3$−C$_6$H$_4$−Br	36	**3g**	80
8	1-naphthyl−Br	24	**3h**	73

[a] Reactions performed using 1 equiv of **1a**, 2 equiv of **2**, Pd(OAc)$_2$ (10 mol %), **L** (20 mol %), and 3 equiv of LiO^{t}Bu on a 0.2 mmol scale for 12 h.

3-(methylsulfonyl)pyridine was performed in toluene at 90 °C (due to decomposition of starting materials at 110 °C) and provided the product (**4i**) in 70% yield after 24 h (Table 4, entry 8).

Dialkyl sulfones are more challenging substrates due to their higher pK_a (~31[13]). Nonetheless, under the optimized conditions, alkyl methyl sulfones underwent coupling at the less sterically hindered methyl group in similar yields to other substrates examined (83−84%, entries 9 and 10).

Table 4. Substrate Scope of Sulfones in the α-Arylation of Benzene Bromide[a]



entry	R	time (h)	product	isolated yield (%)
1	2-Me−C$_6$H$_4$ (**1b**)	12	**4b**	86
2	3-MeO−C$_6$H$_4$ (**1c**)	12	**4c**	85
3	4-MeO−C$_6$H$_4$(**1d**)	12	**4d**	81
4	4-F−C$_6$H$_4$ (**1e**)	12	**4e**	82
5	4-Cl−C$_6$H$_4$ (**1f**)	24	**4f**	81
6	4-CF$_3$−C$_6$H$_4$ (**1g**)	12	**4g**	84
7	1-naphthyl (**1h**)	24	**4h**	83
8	3-pyridyl (**1i**)	24	**4i**	70
9	*c*-hexyl (**1j**)	12	**4j**	83
10	*tert*-butyl (**1k**)	12	**4k**	84

[a] Reactions performed with 1 equiv of **1**, 2 equiv of **2a**, Pd(OAc)$_2$ (10 mol %), **L** (20 mol %), and 3 equiv of LiO^{t}Bu on a 0.2 mmol scale.

We evaluated the scalability of coupling by performing the reaction with bromobenzene on a 6 mmol (0.94 g) scale.

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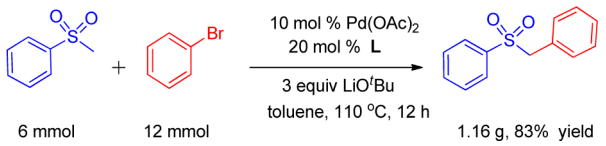
Scheme 3. α-Arylation of Methyl Phenyl Sulfone on Gram Scale

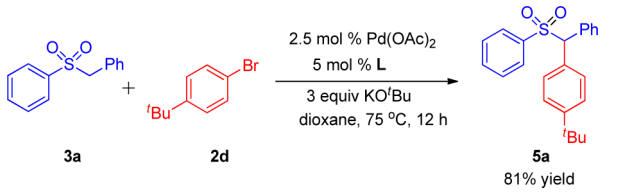


The desired product was afforded in 83% yield (1.16 g, Scheme 3).

Coupling of the more acidic benzyl phenyl sulfone (**3a**) was investigated with 4-*tert*-butylbromobenzene (**2d**) (Scheme 4). We examined six bases [LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu, LiN(SiMe$_3$)$_2$, NaN(SiMe$_3$)$_2$, and KN(SiMe$_3$)$_2$] for this reaction and found that KO^{t}Bu gave the best results. The catalyst loading could be reduced to 2.5 mol % Pd(OAc)$_2$ and 5 mol % of **L** with the more acidic substrate. Furthermore, the reaction could be conducted at lower temperature (75 °C). Under these conditions, the diarylmethyl phenylsulfone (**5a**) was isolated in 81% yield. The excellent reactivity observed in this arylation is attributed to the change in base and solvent.

In summary, we report the first deprotonative cross-coupling process for the direct monoarylation of aryl methyl and alkyl methyl sulfones with aryl bromides. The catalyst afforded products with good to excellent yields (73−90%). Importantly, very high selectivity for the monoarylation products is observed, despite the increased acidity and reactivity of the benzyl sulfone moiety.

Scheme 4. α-Arylation of Benzyl Phenyl Sulfone (**3a**)



It is noteworthy that weakly acidic alkyl methyl sulfones, with pK_a's as high as 31 in DMSO, also proved to be good substrates under our optimized conditions. The challenging nature of this transformation, however, requires the use of 10 mol % catalyst. Future directions include use of a recently developed additive approach[10b] to identify more efficient catalysts and milder reaction conditions.

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Supporting Information Available. Procedures, characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.