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Palladium-catalyzed Negishi α-arylation of alkylsulfones

Gang Zhou *, Pauline C. Ting, Robert G. Aslanian

Department of Medicinal Chemistry, Merck Research Laboratories, Kenilworth, NJ 07033, United States

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ABSTRACT

A general, mild catalytic system for α-monoarylation of various alkyl sulfones is described that utilizes palladium-catalyzed Negishi cross-coupling approach.

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The sulfone is an important organic structural motif in the total synthesis of natural products and biologically active compounds.[1] The sulfonyl group can facilitate the deprotonation of a neighboring carbon atom and the corresponding carbanion can then be used for a variety of transformations. Afterwards, the auxiliary sulfonyl group can be easily removed by reductive desulfonylation.[1b] Although several synthetic routes to arylmethylsulfones have been reported,[1c] these routes are complex multi-step procedures which have limited use in sulfone synthesis.

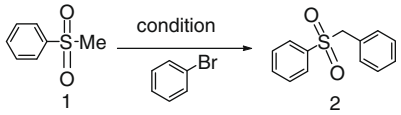
While many reports dealing with α-arylation of ketones exist,[2] there are few reports concerning C-arylations of alkyl sulfone derivatives. To our knowledge, only a single literature reference has studied the C-arylations of methanesulfone derivatives in which the α-H acidity is enhanced by activating groups (e.g., NO_2, CN, and CO_2R).[3]

According to Beletskaya and co-workers, α-functionalized (e.g., NO_2, CN or CO_2R) sulfones can be monoarylated by a Pd-catalyzed reaction with a conventional PPh_3 ligand.[3] However, in the case of arylation of simple methylphenylsulfone **1** without an activating group, these reaction conditions are ineffective despite the use of NaH or NaO*t*Bu as base (Table 1, entries 1 and 2). The lack of reactivity was thought to be due to the higher pK_a of the sulfonyl α-CH-acid (pK_a 29)[4], however, the stronger base *n*-BuLi could not affect this transformation.[3]

Recently we have reported a mild palladium-catalyzed arylation reaction which couples aryl halides with in situ prepared sulfonamide zinc reagents.[5] The ligand plays a critical role in the success of this arylation reaction.[6] A set of sterically hindered and electron-rich phosphines were screened and only the bulky monodentate ligands X-Phos and Dave-Phos, as shown in Figure 1, proved to be applicable for this coupling. Herein, we extend the utility of this system and apply it to the synthesis of benzylsulfones by palladium-catalyzed α-arylation of the related alkylsulfones with aryl halides (Table 1).

Using methylphenylsulfone **1** as a model sulfone and bromobenzene as a typical aryl halide, we optimized the reaction conditions by varying the ligands (Table 1, entries 3–6). Under these conditions, LHMDS was used as the base and arylzinc reagent was prepared in situ by the reaction of aryllithium with anhydrous $ZnCl_2$. The reactions proceeded smoothly with bromobenzene and the best yield of monoarylated sulfone **2** was obtained with X-Phos as ligand (Table 1, entry 6).[7] Using ligands Dave-Phos or S-Phos also gave monoarylated sulfones **2** but in relatively lower yield (Table 1, entries 3 and 5).

Table 1
Arylation of methylphenylsulfone **1**



Entry	Condition[a]	Yield[b] (%)
1	NaH, Pd_2dba_3, $CHCl_3$, PPh_3, dioxane, 70 °C, 3 h	0
2	NaO*t*Bu, $Pd(OAc)_2$, PPh_3, toluene, 110 °C, 12 h	5
3	LHMDS, $ZnCl_2$, $Pd(OAc)_2$, S-Phos, THF, 65 °C, 5 h	20
4	LHMDS, $ZnCl_2$, $Pd(OAc)_2$, Ru-Phos, THF, 65 °C, 5 h	0
5	LHMDS, $ZnCl_2$, $Pd(OAc)_2$, Dave-Phos, THF, 65 °C, 6 h	62
6	LHMDS, $ZnCl_2$, $Pd(OAc)_2$, X-Phos, THF, 65 °C, 5 h	85

[a] Reactions were conducted with aryl bromide (0.7 mmol), substrate **1** (1.0 mmol).
[b] Isolated yield based on bromobenzene.

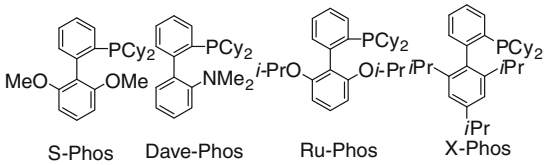


Figure 1. Representative ligand structures.

* Corresponding author. Tel.: +1 908 740 3740; fax: +1 908 740 2252.
E-mail address: gang.zhou@spcorp.com (G. Zhou).

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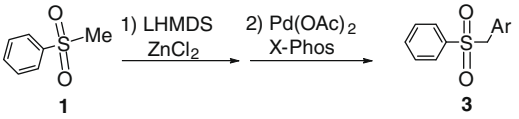
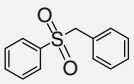
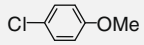
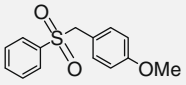
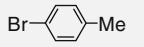
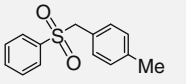
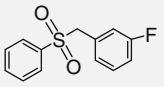
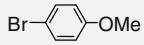
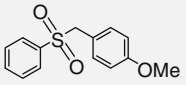
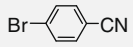
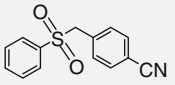
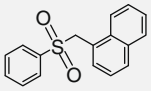
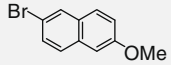
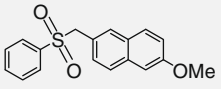
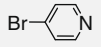
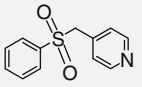
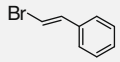
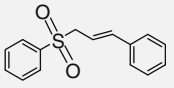
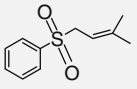
Table 2
Arylation of methylphenylsulfone **1** with various halides[a]



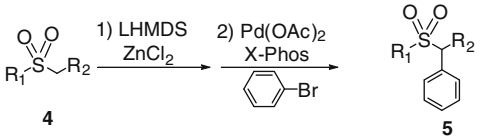
1 3

Entry	Aryl halide	Time (h)	Product	Yield[b] (%)
1		10		20
2		10		65
3		10		90
4		10		82
5		6		98
6		12		63
7		12		74
8		6		94
9		18		62
10		5		68
11		5		54

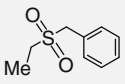
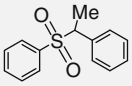
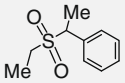
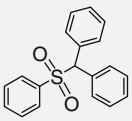
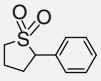
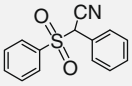
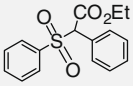
[a] Reactions were conducted with aryl halides (0.7 mmol), substrate **1** (1.0 mmol), LHMDS (1.5 mmol), $ZnCl_2$ (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol) and X-Phos (0.08 mmol) in THF (2 mL) at 65 °C.
[b] Isolated yield based on halide.

With this optimized condition in hand, we further investigated this sulfone arylation by coupling a variety of aryl and vinyl halides with methylphenylsulfone **1** (Table 2). Aryl bromides or chlorides were employed as the electrophilic partner. Substituted aryl bromides smoothly gave the desired monoarylation products (Table 2, entries 3, 4 and 7) while the aryl chlorides showed relatively lower reactivity (Table 2, entries 1 and 2). The electronic properties of the reactants also influenced the reaction. Electron-rich aryl halides are good substrates under our coupling conditions, exemplified by 4-chloroanisole, 4-bromoanisole, and 6-bromo-2-methoxylnaphthalene (Table 2, entries 2, 5 and 8). However, aryl bromide components with electron-withdrawing groups resulted in a mono-arylated product with moderate yield (Table 2, entries 6). A heterocyclic halide such as 4-bromopyridine is also tolerated in this system (Table 2, entry 9). Vinyl bromides such as bromostyrene and bromo-2-methylpropene can be used to generate the corresponding α-vinylation products (Table 2, entries 10 and 11).

Table 3
Arylation of sulfone substrates via the palladium-catalyzed Negishi coupling[a]



4 5

Entry	R_1	R_2	Time (h)	Product	Yield[b] (%)
1	Me	H	3		60
2	Et	Me	10		52
3	Ph	Me	12		68
4	Ph	Ph	24		82
5	$-CH_2R_2$	$-CH_2CH_2-$	12		53
6	Ph	CN	6		72
7	Ph	CO_2Et	6		70

[a] Reactions were conducted with aryl halides (0.7 mmol), substrate **4** (1.0 mmol), LHMDS (1.5 mmol), $ZnCl_2$ (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol) and X-Phos (0.08 mmol) in THF (2 mL) at 65 °C.
[b] Isolated yield based on bromobenzene.

While the arylation reactions described in Table 2 employed various substituted aryl halides with methylphenylsulfone **1**, additional alkylsulfones **4** were also subjected to arylation under our optimized reaction conditions (Table 3). The reactions of a variety of sulfones **4** with bromobenzene were generally complete at 65 °C and consistently afforded mono-arylated products **5** in moderate to good yields (Table 3, entries 1–7) along with a minor amount of the bisarylation side products (<20%).

In conclusion, we have developed an efficient method for the synthesis of functionalized benzylic sulfones, using the palladium-catalyzed Negishi coupling reaction of various alkylsulfones and aryl halides.

Acknowledgments

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7. *General experimental procedure for compound* **2**: To a stirred solution of methylphenylsulfone **1** (1.0 mmol, 1.0 equiv) in THF (0.5 mL) at −20 °C in a sealed tube under nitrogen was added a solution of LiHMDS (1.5 mL, 1.5 equiv, 1.0 M in THF). After stirring for 30 min at room temperature, a freshly prepared solution of $ZnCl_2$ (0.206 g, 1.5 mmol, 1.5 equiv) in THF (0.5 mL) was added at −20 °C. The reaction mixture was slowly warmed from −20 °C to room temperature over 60 min then bromobenzene (0.70 mmol, 0.7 equiv) and a solution of the ligand (0.08 mmol, 11.4 mol %) with $Pd(OAc)_2$ (0.04 mmol, 5.7 mol %) in THF (0.5 mL) were added successively. The solution was then degassed under vacuum for 20 min and recharged with nitrogen. The resulting reaction mixture was heated in an oil bath at 65 °C for the stated time, cooled to room temperature, quenched with aqueous NH_4Cl (1 mL) and 1 N HCl (0.5 mL) then extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography with an eluant of hexanes/ether (20:1) to afford the desired product **2** as a white solid (138 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61–7.66 (m, 3H, Ar–H), 7.55–7.57 (m, 1H, Ar–H), 7.47 (t, J = 7.5 Hz, 2H, Ar–H), 7.33–7.36 (m, 1H, Ar–H), 7.29 (t, J = 6.0 Hz, 2H, Ar–H), 7.10 (d, J = 7.5 Hz, 1H, Ar–H), 4.34 (s, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.1, 131.2(2C), 130.4, 129.3 (2C), 129.2, 129.1 (3C), 128.9 (2C), 63.3; HRMS (EI) calcd for [C13H12NaO2S] ($[M+Na]^+$): 255.0456; found 255.0695.