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A Useful Pd-Catalyzed Negishi Coupling Approach to Benzylic Sulfonamide Derivatives

Gang Zhou,* Pauline Ting, Robert Aslanian, and John J. Piwinski

Department of Medicinal Chemistry, Schering-Plough Research Institute, Kenilworth, New Jersey 07033

gang.zhou@spcorp.com

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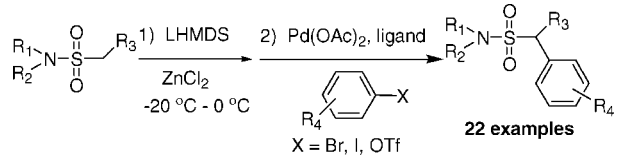
ABSTRACT



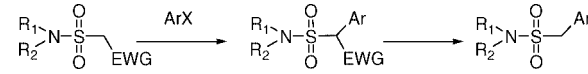
A mild catalytic system to access diversely functionalized benzylic sulfonamides has been developed. Palladium-catalyzed α-arylation by Negishi cross-coupling of sulfonamide-stabilized anions and a wide range of aryl iodides, bromides, and triflates constitutes a practical strategy for the synthesis of various benzylic sulfonamides.

The sulfonamide is an important functional group that is widely found in both natural products and medicines such as Axert for migraine[1] and Zonisamide for seizure.[2] Several conventional approaches have been used to prepare benzylic sulfonamides which include using unstable sulfonyl chloride intermediates, free-radical processes, vicarious nucleophilic substitution, or harsh oxidation conditions.[3] However, substrate dependency and operational practicality have limited the use of these approaches in sulfonamide synthesis. In conjunction with our interest in readily accessing diversified benzylic sulfonamides, we needed to develop an effective method for the construction of benzylic sulfonamides.

Since the pioneering efforts of Buchwald, Hartwig, and Miura in 1997,[4] Pd-catalyzed arylation of ketones has opened a new path to a reliable construction of molecules that were traditionally difficult to synthesize. The scope of arylation reaction has been expanded to include a variety of nucleophilic coupling partners including ketones, esters, amides, nitriles, aldehydes, nitroalkanes, sulfones, and sulfoximines in recent years.[5]

While many reports have appeared detailing arylation of ketone and amide substrates, there are few reports concerning C-arylations of alkanesulfonamide derivatives. In most cases, the nucleophilic component is generally limited to sulfonamides in which the α-H acidity is enhanced by activating groups (e.g., NO_2, CN, CO_2R) that need to be removed if α-unsubstituted sulfonamide was desired (Scheme 1).[6] To our knowledge, only a single literature example exists in which simple methanesulfonamide derivatives lacking such an activating group are converted to a mixture of mono- and bisarylated products.[7]

Scheme 1. General Strategy for Sulfonamide C-Arylations



(1) Bosch, J.; Roca, T; Armengol, M.; Fernandaz-Forner, D. *Tetrahedron* **2001**, *57*, 1041.
(2) Uno, H.; Kurokawa, M.; Masuda, Y.; Nishimura, H. *J. Med. Chem.* **1979**, *22*, 180.
(3) (a) Anderson, K. K. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, p 345. (b) Lee, I.; Kang, H. K.; Lee, H. W. *J. Am. Chem. Soc.* **1987**, *109*, 7472. (c) Wininarski, J.; Makosza, M. *Acc. Chem. Res.* **1987**, *20*, 282.
(4) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

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In our research program, existing methods were found to be inappropriate due to the harsh reaction conditions. It was necessary for us to develop a novel sulfonamide C-arylation protocol that uses mild reaction conditions and is compatible with a variety of functional groups. After several preliminary attempts, we found that use of zinc anions instead of alkali metal anions led to greater functional group compatibility in the α-arylation of sulfonamide reactions.

Herein, we report a mild palladium-catalyzed arylation reaction with sulfonamide zinc reagents prepared in situ. LHMDS was used as base to generate a sulfonamide anion, and the sulfonamide zinc reagent was prepared by the reaction of the anion with $ZnCl_2$. The ligand usually plays a critical role in the success of this type of reaction. Accordingly, the effect of sterically and electronically varied phosphine ligands on the model reaction of **5** with bromobenzene was studied, and the reaction conditions were optimized. A set of small ligands and a few sterically hindered and electron-rich monophosphines as well as bisphosphines (Figure 1) were selected for study.[8]

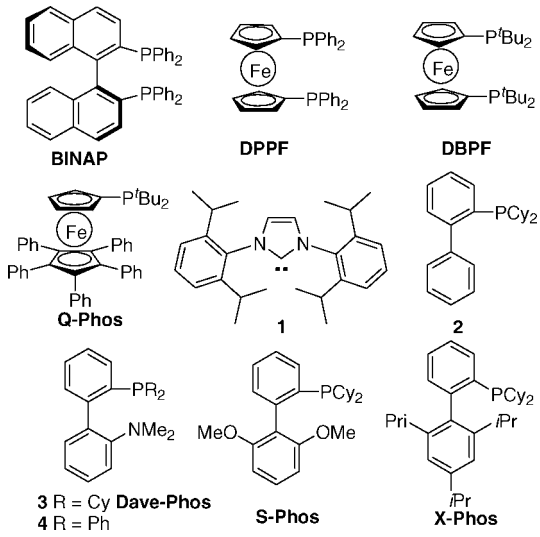
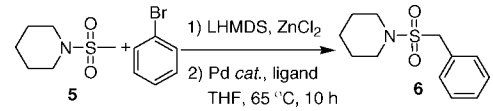


Figure 1. Selected ligand structures.

As shown in Table 1, reactions catalyzed by Pd(0)/ligand combinations or preformed palladium complexes were carried out under mild conditions and required low quantities of catalyst (1.5 mol %).

Table 1. Effect of Ligand Structure on the Arylation



entry	Pd source	ligand	yield (%)[a,b]
1	$Pd(PPh_3)_4$	n/a	<5
2	$[Pd(Pt\text{-}Bu_3)Br]_2$	n/a	<5
3	$Pd(Pt\text{-}Bu_3)_2$	n/a	<5
4	$Pd(OAc)_2$	$n\text{-}Bu_3P\bullet HBF_4$	19
5	$Pd(OAc)_2$	$t\text{-}Bu_3P\bullet HBF_4$	<5
6	$Pd(OAc)_2$	$Cy_3P\bullet HBF_4$	<5
7	$Pd(OAc)_2$	Ph_3P	15
8	$Pd(OAc)_2$	BINAP	<5
9	$Pd(OAc)_2$	DBPF	<5
10	$Pd(OAc)_2$	DPPF	<5
11	$Pd(OAc)_2$	Q-Phos	81
12	$Pd(OAc)_2$	**1**	<5
13	$Pd(OAc)_2$	**2**	55
14	$Pd(OAc)_2$	Dave-Phos **3**	95
15	$Pd(OAc)_2$	**4**	<5
16	$Pd(OAc)_2$	S-Phos	82
17	$Pd(OAc)_2$	X-Phos	99
18	$Pd(dba)_2$	X-Phos	85

[a] Isolated yields based on the bromobenzene. [b] Reactions were conducted with bromobenzene (0.8 mmol), 1-(methanesulfonyl)piperidine (1.0 mmol), LHMDS (1.0 mmol), $ZnCl_2$ (1.2 mmol), Pd reagent (0.012 mmol), ligand (0.024 mmol) in THF (2 mL) at 65 °C for 10 h.

Several ligands were found to be effective and provided 55−99% yields of the coupled product **6** (Table 1, entries 11, 13, 14, and 16−18). The reactions catalyzed by bulky, electron-rich X-Phos or Dave-Phos afforded the highest yield with $Pd(OAc)_2$ (Table 1, entries 14 and 17), although reaction with S-Phos or Q-Phos also provided a reasonable yield. Interestingly, some ligands such as DBPF and DPPF that have been successfully used in Pd-catalyzed couplings, including arylations of ketones, were less effective for the arylation of sulfonamide **5** (Table 1, entries 9 and 10). $Pd(OAc)_2$ is a better palladium source than $Pd(dba)_2$ is in terms of yield (Table 1, entry 18).[8d]

With the optimal Pd and ligand combination identified, the effects of zinc salt, base, and solvent were examined next (Table 2). A little excess of the organozinc reagent[9] of sulfonamide **5** (1.0 equiv) to bromobenzene (0.8 equiv) apparently gave better conversion, better yield, and reduced bisarylation side product. The zinc salt was also critical. If the alkylzinc reagents were prepared from the corresponding sulfonamide anions and $ZnBr_2$, the coupling reaction became much slower and led to lower yield (Table 2, entries 1 and

(5) (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (b) Jørgensen, M.; Lee, S.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.

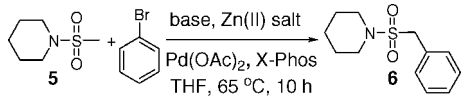
(6) (a) Grimm, J. B.; Katcher, M. H.; Witter, D. J.; Northrup, A. B. *J. Org. Chem.* **2007**, *72*, 8135. (b) Middleton, D. S.; Stobie, A. Patent WO 00/51972; Pfizer Ltd., 2000. (c) Waite, D. C. Patent WO 99/02493; Pfizer Ltd., 1999. (d) Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wife, R. *Tetrahedron Lett.* **2002**, *43*, 2539.

(7) Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2005**, *46*, 1597.

(8) The chosen catalysts have been shown successful in other arylation reactions; see: (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053. (b) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (d) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824. (e) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (f) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

(9) The (sulfonamido)methylzinc chloride could also be generated by reacting of (chloromethanesulfonyl)piperidine with activated zinc powder and LiCl by Knochel's method, which resulted in the arylation product **6** in 30% yield under our Pd-catalyzed coupling conditions; see: (a) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107. (b) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

Table 2. Base and Zinc Source Effect on the α-Arylation of **5**



entry	base	zinc source	yield (%)[a,b]
1	LHMDS	without Zn salt	0
2	LHMDS	$ZnBr_2$	34
3	LHMDS	$ZnCl_2$	99
4	KHMDS	$ZnCl_2$	72
5	NaHMDS	$ZnCl_2$	86
6	*n*-BuLi	$ZnCl_2$	46
7	*sec*-BuLi	$ZnCl_2$	85
8	NaO^tBu	$ZnCl_2$	48
9	*t*-BuLi	$ZnCl_2$	<5

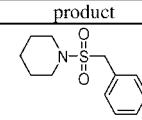
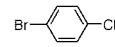
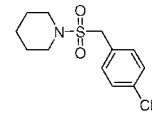
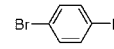
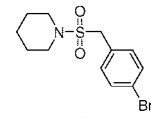
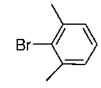
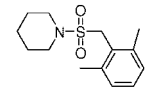
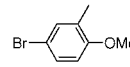
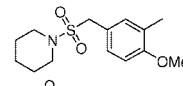
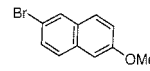
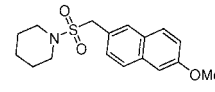
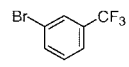
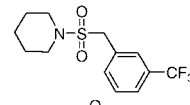
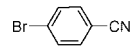
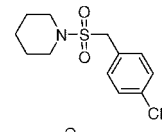
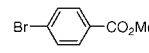
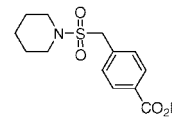
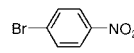
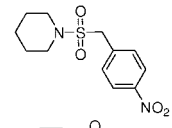
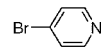
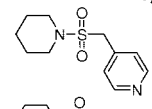
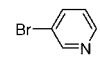
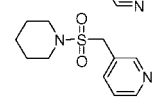
[a] Isolated yield calculated from bromobenzene. [b] For conditions, see Table 1.

2). With X-Phos as the ligand and THF as the solvent, reactions carried out with LHMDS, NaHMDS, or *sec*-BuLi as the base gave the best results (Table 2, entries 3, 5, and 7), while reactions with NaO^tBu, BuLi, and *t*-BuLi led to lower conversions. With LHMDS as base, reactions in THF, dioxane, or THF−NMP (1:1) proceeded smoothly, while reactions in toluene, MTBE, or diethyl ether were rather sluggish.

Having identified the optimal conditions, we then examined the scope of this sulfonamide arylation by coupling a variety of aryl halides and triflates with **5** (Table 3). Aryl bromides, iodides, or triflates were employed as the electrophilic partner. Reactions of aryl iodides or triflates gave comparable yields to aryl bromides (Table 3, entry 1). Furthermore, couplings of chloro- and iodo-substituted aryl bromides were highly halogen-selective, providing exclusively chlorophenylated and bromophenylated products, respectively (Table 3, entries 2 and 3). The sterically challenging 2,6-disubstituted aryl bromide also coupled smoothly to give the desired product in 94% yield (Table 3, entry 4).

The electronic properties of the reactants affected the reactions to some extent. Electron-rich aryl bromides proved to be good substrates under our coupling condition, as exemplified by 4-bromo-2-methylanisole and 6-bromo-2-methoxylnaphthalene (Table 3, entries 5 and 6). However, a number of other aryl bromide components with electron-withdrawing groups were also coupled with substrate **5** and resulted in monoarylated product with moderate yields (Table 3, entries 7−10). The arylation reaction with substrates bearing an acidic proton such as 4-bromoaniline did not proceed under our optimized conditions. Alternatively, the nitro-substituted aryl bromide reacted smoothly to provide the product in 77% yield. The product was easily converted to an amino product under hydrogenation conditions (H_2, 10% Pd−C in MeOH, 10 h) in quantitative yield (Table 3, entry 10). Heterocyclic halides such as 3- or 4-bromopyridine were also tolerated in this system (Table 3, entries 11 and 12).

Table 3. Substrate Scope for α-Arylation of Sulfonamide **5**

entry	aryl bromide	product	yield (%)[a,b]
1	 X=I, OTf		95 (X = I) 93 (X = OTf)
2			89
3			75
4			94
5			92
6			91
7			85
8			73
9			70
10			77
11			76
12			83

[a] Isolated yields based on the aryl halides or triflates. [b] Reactions were conducted with aryl halides or triflates (0.8 mmol), **5** (1.0 mmol), LHMDS (1.0 mmol), $ZnCl_2$ (1.2 mmol), $Pd(OAc)_2$ (0.012 mmol), X-Phos (0.024 mmol) in THF (2 mL) at 65 °C for 10 h.

Generally, only monoarylated sulfonamides were obtained as single products for substrates in Table 3. For some substrates, further arylation to form an bisarylated benzylic sulfonamide was observed. The bisarylated benzylic sulfonamides **7**−**9** (Figure 2) were formed along with the monoarylated benzylic sulfonamides (Table 3, entries 7−9). Bisarylated product **7** was formed in trace amount (<5%), while the bromobenzenes with electron-withdrawing substituents at the *para* position, such as *p*-NCC_6H_4Br and *p*-$MeO_2CC_6H_4Br$ (Table 3, entries 8 and 9), gave more bisarylated products (12 and 15% yield, respectively).

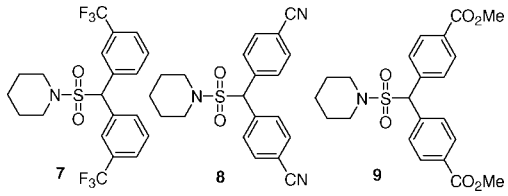
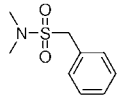
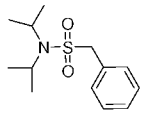
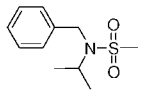
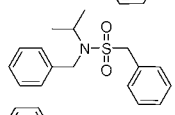
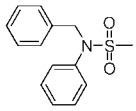
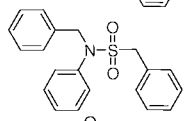
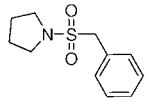
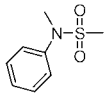
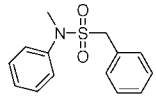
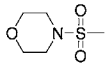
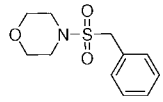
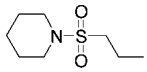
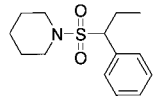


Figure 2. Bisarylation products.

While the arylation reactions described in Table 3 employed various substituted aryl halides with 1-(methanesulfonyl)piperidine **5**, additional unactivated sulfonamides can be arylated under our optimized reaction conditions (Table 4). Reactions of a spectrum of sulfonamides with

Table 4. Arylation of Various Sulfonamides

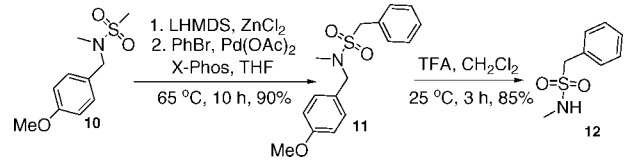
entry	sulfonamide	product	yield (%)[a,b]
1			92
2			94
3			90
4			95
5			98
6			85
7			94
8			66[c]

[a] Isolated yield based on bromobenzene. [b] Reactions were carried out with sulfonamide (1.0 mmol), bromobenzene (0.8 mmol), LHMDS (1.0 mmol), $ZnCl_2$ (1.2 mmol), $Pd(OAc)_2$ (0.012 mmol), X-Phos (0.024 mmol) in THF (2 mL) at 65 °C for 10 h. [c] Reaction was conducted at 70 °C for 24 h.

bromobenzene were generally complete within 10 h at 67 °C and consistently afforded monoarylated products in good to excellent yields (Table 4, entries 1−8, 66−98%) under the described condition.

Importantly, the sterically hindered *n*-propanesulfonamide underwent a smooth cross-coupling reaction with bromobenzene to afford the arylated sulfonamide in 66% yield, although an extended reaction time was required (24 h, Table 4, entry 8). Furthermore, a mild procedure for the generation of primary sulfonamides was also developed and afforded products in good yield. As shown in Scheme 2, *p*-methoxy-

Scheme 2. Protocol to Generate Primary Sulfonamide **12**



benzyl (PMB)-protected sulfonamide **10** was converted to the corresponding benzyl sulfonamide **11** under our arylation conditions in 90% yield. Deprotection of PMB group in **11** was readily achieved in the presence of TFA in dichloromethane at room temperature to give the primary sulfonamide **12** in 85% yield.[10]

This protocol has been successfully applied to our medicinal chemistry program. A series of functionalized benzylic sulfonamides, which were difficult to access with other methods, have been synthesized using our method.[11]

In conclusion, we have developed an efficient method for the synthesis of functionalized benzylic sulfonamides, using the palladium-catalyzed Negishi coupling reaction of unactivated methanesulfonamides and aryl halides. This protocol has the advantage of using readily available starting materials, mild conditions, low catalyst loading, high yields, and good functional group tolerance while providing important synthetic potential for generating a variety of benzylic sulfonamides. Further studies on the enantioselective α-arylation of sulfonamides, such as ethanesulfonamide derivatives, using chiral ligands under our optimal conditions are in progress.

Acknowledgment. Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday. We would like to thank our colleagues at Schering-Plough Co., Mr. Ibrahim Daaro for mass spectrometry assistance, Drs. Jared Cumming and George Sun for helpful discussion, Drs. Michael Wong and Xiaolei Gao for proofreading, and Dr. John Piwinski for strong support of the program.

Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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