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Mild Pd-Catalyzed *N*-Arylation of Methanesulfonamide and Related Nucleophiles: Avoiding Potentially Genotoxic Reagents and Byproducts

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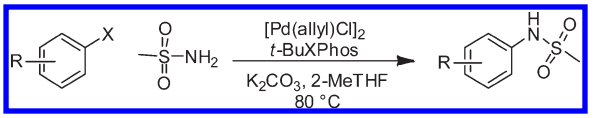
ABSTRACT



A convenient, general, and high yielding Pd-catalyzed cross-coupling of methanesulfonamide with aryl bromides and chlorides is reported. The use of this method eliminates concern over genotoxic impurities that can arise when an aniline is reacted with methanesulfonyl chloride. The application of this method to the synthesis of dofetilide is also reported.

The *N*-arylsulfonamide substructure is quite common among medicinally interesting molecules.[1] Molecules of this type have most frequently been prepared via the reaction of an aniline with a sulfonyl chloride. While generally effective, this approach is less than ideal when one considers it from the perspective of potential genotoxic impurities in the product.[2] Both the aniline and the sulfonyl chloride raise alerts for genotoxicity. Furthermore, exposure of the reaction mixtures to alcohols during workup can yield alkyl sulfonates, which can also be genotoxic.[3]

Given these concerns, a more attractive alternative for the construction of *N*-arylsulfonamides is the metal-catalyzed cross-coupling of an aryl halide with a sulfonamide, Scheme 1. Although couplings under Ullman-type conditions have been known for many years,[4,5] the harsh conditions required for such couplings rendered them impractical for many applications. A major breakthrough came in 1996 when the Pd-catalyzed intramolecular arylation of sulfonamides was described by Buchwald.[6] Since then, significant progress has been made with both Cu and Pd catalysis, but noteworthy issues still exist, including the frequent use of Cs_2CO_3 as the base,[7] relatively high reaction temperatures, and high catalyst loadings.[8−11]

(1) For a list of marketed drugs containing a sulfonamide, see: Smith, D. A.; Jones, R. M. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 72–79.

(2) (a) Snodin, D. J. *Org. Process Res. Dev.* **2010**, *14*, 960–976. (b) Pierson, D. A.; Olsen, B. A.; Robbins, D. K.; DeVries, K. M.; Varie, D. L. *Org. Process Res. Dev.* **2009**, *13*, 285–291.

(3) Teasdale, A.; Delaney, E. J.; Eyley, S. C.; Jacq, K.; Taylor-Worth, K.; Lipczynski, A.; Hoffmann, W.; Reif, V.; Elder, D. P.; Facchine, K. L.; Golec, S.; Oestrich, R. S.; Sandra, P.; David, F. *Org. Process Res. Dev.* **2010**, *14*, 999–1007.

(4) Ullmann, F.; Junghans, W. *Annalen* **1913**, *399*, 330–345.

(5) For a review, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456.

(6) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546.

(7) We choose to avoid Cs_2CO_3 where possible due, in part, to its high molar cost when compared to several other common bases.

(8) For examples employing Cu catalysis, see: (a) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3385–3386. (b) Steinhuebel, D.; Palucki, M.; Askin, D.; Drolling, U. *Tetrahedron Lett.* **2004**, *45*, 3305–3307. (c) Baffoe, J.; Hoe, M. Y.; Touré, B. B. *Org. Lett.* **2010**, *12*, 1532–1535. (d) Han, X. *Tetrahedron Lett.* **2010**, *51*, 360–362.

(9) For examples employing Pd catalysis, see: (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104. (b) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373–7376. (c) Steinhuebel, D.; Palucki, M.; Askin, D.; Drolling, U. *Tetrahedron Lett.* **2004**, *45*, 3305–3307. (d) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13009. (e) Anjanappa, P.; Mullick, D.; Selvakumar, K.; Sivakumar, M. *Tetrahedron Lett.* **2008**, *49*, 4585–4587. (f) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734.

(10) For Cu-catalyzed arylation of sulfonamides with boronic acids, see: (a) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418. (b) Pan, C.; Cheng, J.; Wu, H.; Ding, J.; Liu, M. *Synth. Commun.* **2009**, *39*, 2082–2092.

(11) For arylation of sulfonamides via reaction with benzynes, see: Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673–4675.

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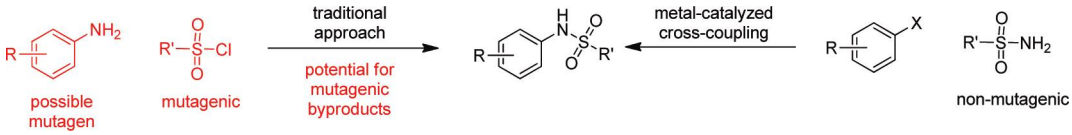
Scheme 1. Alternatives for the Preparation of *N*-Aryl Sulfonamides



Our interest in this area stemmed from a need to couple methanesulfonamide[12] in particular. While several Cu-catalyzed couplings of methanesulfonamide have been published, they each require elevated temperatures (≥100 °C).[13] To the best of our knowledge, there have been no studies focused on Pd-catalyzed couplings of methanesulfonamide and very few isolated examples of such couplings.[14] In each of those cases, Cs_2CO_3 was used as the base, and temperatures of ≥95 °C were employed. This lack of attractive coupling conditions was surprising given that the *N*-arylmethanesulfonamide substructure appears in multiple launched drugs, such as dofetilide and delavirdine (Pfizer's Tikosyn and Rescriptor, respectively), Figure 1.

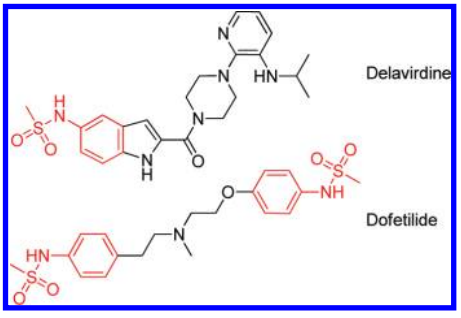
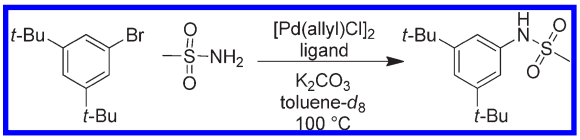


Figure 1. *N*-Arylmethanesulfonamide-containing drugs.

Due to the many recent advances in the design of ligands for Pd-catalyzed aminations,[15] we were very hopeful that we could identify general conditions for the Pd-catalyzed cross-coupling of methanesulfonamide with aryl bromides. Ideally, any such conditions would meet the following goals: (1) A mild base other than Cs_2CO_3 would be used. (2) The reaction temperature would be 100 °C or lower. (3) The catalyst loading would be ≤1 mol %. (4) A safe and convenient solvent would be used. Although residual Pd does require control due to toxicity, we are unaware of any reports of genotoxicity associated with Pd.[16] Furthermore, the measurement and control of Pd-containing impurities is arguably more straightforward than the corresponding challenges associated with genotoxic impurities.[17]

Table 1. Initial Ligand Screen[a]



entry	ligand[b]	yield[c]	entry	ligand[b]	yield[c]
1	DavePhos	8	11	Xantphos[d]	0
2	*t*-BuDavePhos	84	12	CataCXium PtB	90
3	JohnPhos	68	13	Bippyphos	6
4	CyJohnPhos	26	14	CyBippyphos	23
5	XPhos	31	15	QPhos	69
6	*t*-BuXPhos	98	16	cBRIDP	trace
7	Me_4*t*-BuXPhos	92	17	JosiPhos[e]	0
8	SPhos	8	18	(*R*)-MOP	20
9	RuPhos	7	19	P(*t*-Bu)$_3$[f]	0
10	BrettPhos	27	20	IPr[g]	0

[a] Reaction conditions: Aryl bromide (0.25 mmol), methanesulfonamide (0.38 mmol), potassium carbonate (0.5 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), ligand (7.5 mol %), toluene-d_8 (1 mL), 100 °C, 4 h. [b] For ligand structures, see Supporting Information. [c] Yield determined by NMR using phenanthrene as internal standard. [d] 5 mol % of ligand was used. [e] Ligand name = (*R*)-(−)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine. [f] Used as HBF_4 salt. [g] The preformed complex IPrPd(allyl)Cl was used (5 mol %) as the only source of ligand and Pd.

With the above goals in mind, we chose to launch a broad screen of phosphine ligands employing $[Pd(allyl)Cl]_2$ and K_2CO_3 in toluene at 100 °C.[18] A diverse set of 20 ligands were chosen for our screen. The set included several so-called Buchwald biaryl ligands, but other ligand families previously shown to be effective in C−N cross-coupling were also represented (Table 1). The palladium loading was set at 5 mol % (0.025 equiv of $[Pd(allyl)Cl]_2$) with 7.5 mol % of the ligand.[19,20]

(12) We have verified that methanesulfonamide provides a negative result in a mini-Ames test.

(13) For representative examples, see: (a) Deng, W.; Liu, L.; Zhang, C.; Liu, M.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 7295–7298. (b) Dragovich, P. S.; et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5635–5639. (c) Reference 8a. (d) Reference 8c. (e) Reference 8d.

(14) (a) Briggs, J. R.; Klosin, J.; Whiteker, G. T. *Org. Lett.* **2005**, *7*, 4795–4798. (b) Dinsmore, C. J.; Ortega, A. E. G.; Guerin, D. J.; Jewell, J. P.; Katz, J. D.; Lim, J.; Machacek, M. R.; Otte, R. D.; Young, J. R. U.S. Patent Application 2006/0293358 A1, 2006. (c) Blake, J. F.; Fell, J. B.; Fischer, J. P.; Hendricks, R. T.; Spencer, S. R.; Strengel, P. J. International Patent Application WO2006117306 A1, 2006. (d) Kelly, M.; Lee, Y.; Liu, B.; Fujimoto, T.; Freundlich, J.; Dorsey, B. D.; Flynn, G. A.; Husain, A.; Moore, W. R. Jr. U.S. Patent Application 2008/0280891 A1, 2008.

(15) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.

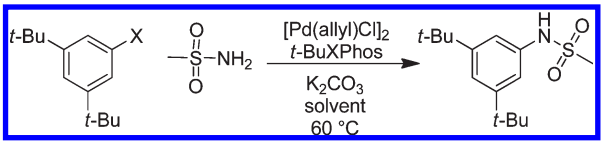
(16) Bünger, J.; Stork, J.; Stalder, K. *Int. Arch. Occup. Environ. Health* **1996**, *69*, 33–38.

(17) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900.

(18) Conditions very similar to these were employed in ref 9f for the coupling of larger sulfonamides with aryl sulfonates.

(19) In the case of Xantphos, only 5 mol % of ligand was used to avoid precipitation of $Pd(Xantphos)_2$; see: Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82–91.

Table 2. Solvent Screen[a]



entry	solvent	conversion (3 h)[b]	conversion (21 h)[b]
1	acetonitrile	38	100
2	*tert*-amyl alcohol	69	100
3	DMF	27	68
4	DMSO	0	52
5	dioxane	100	100
6	NMP	23	71
7	2-Me-THF	100	100
8	toluene	100	100

[a] Reaction conditions: Aryl bromide (1 mmol), methanesulfonamide (1.2 mmol), K_2CO_3 (2 mmol), $[Pd(allyl)Cl]_2$ (1 mol %), *t*-BuXPhos (3 mol %), solvent (4 mL), 60 °C. [b] Conversion determined by GCMS (uncorrected).

We were pleased to see that a clear trend emerged from our screen with *tert*-butylphosphine ligands being more effective than others. Among these, *t*-BuXPhos, Me_4*t*-BuXPhos, Bippyphos, and *t*-BuDavePhos performed best, each providing >80% NMR yield after 4 h. (Figure 2).

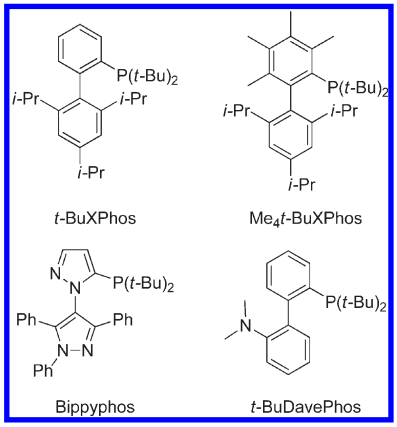


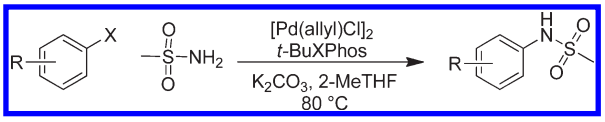
Figure 2. Most Effective *tert*-butylphosphine ligands.

To differentiate these four ligands further, a follow-up screen was done under similar conditions but at 60 °C. Although all four ligands provided >80% NMR yield after 24 h, the 1 h time point showed clear differentiation with *t*-BuXPhos already at >90% NMR yield. Based on this result, we chose to move forward using *t*-BuXPhos.[21]

Using the *t*-BuXPhos ligand, we then screened palladium sources.[22] Among the common Pd sources, $[Pd(allyl)Cl]_2$ and $Pd_2(dba)_3$ both provided good conversion at 60 °C; however, the former was slightly superior. $Pd(OAc)_2$, on the other hand, provided no conversion, likely due to the lack of a viable reduction mechanism. This was even true when the reaction was attempted at 100 °C. We also screened the single component Buchwald precatalyst (chloro(2-di-*tert*-butylphosphino-2′,4′,6′-tri-isopropyl-1,1′-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II))[23] as well as $Pd(OAc)_2$ that had been prereduced with water and excess ligand according to Buchwald's procedure.[24] Although both provided product, neither was as efficient as $[Pd(allyl)Cl]_2$.

Finally, we conducted a small solvent screen (Table 2). Although dioxane, 2-MeTHF, and toluene each provided complete conversion after 3 h at 60 °C, we chose to proceed with 2-MeTHF because it provided better solubility for many substrates of interest. To provide one general set of reaction conditions, we chose to conduct all subsequent reactions at 80 °C, which is the boiling point of 2-MeTHF. This higher temperature allowed us to reduce the catalyst loading to only 1 mol % palladium while maintaining reasonable reaction durations.

Table 3. Halide Scope[a]



entry	R	X	yield (%)[b]	entry	R	X	yield (%)[b]
1	3,5-(*t*-Bu)$_2$	Br	89[c]	8	4-NMe_2	Br	92
2	4-Me	Br	93	9	4-Cl	Br	90[d]
3	2-Me	Br	95	10	4-CF_3	Cl	98
4	2-Me	Cl	88	11	4-CF_3	Br	98
5	4-MeO	Br	96	12	4-Ac	Br	95
6	2-MeO	Br	91	13	4-CO_2Me	Br	96[e]
7	4-CN	Br	98	14	4-CHO	Br	91

[a] Reaction conditions: Aryl halide (5 mmol), methanesulfonamide (6 mmol), K_2CO_3 (10 mmol), $[Pd(allyl)Cl]_2$ (0.5 mol %), *t*-BuXPhos (2 mol %), 2-MeTHF (20 mL), 80 °C. [b] Isolated yield. [c] Residual Pd = 13 ppm. [d] Residual Pd = 470 ppm. [e] Residual Pd = 80 ppm.

To render our coupling reactions more operationally straightforward, we chose to make use of an admixture containing a Pd source, ligand, and base ground together into a fine, nearly homogeneous powder. These mixtures, which we call "catkits," allow the user to conduct fewer

(20) In the case of the IPr ligand, 5 mol % of the preformed (IPr)Pd(allyl)Cl complex was used without an additional ligand; see: Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629–1635.

(21) Although Bippyphos did not result in the fastest reactions, the lack of IP surrounding this ligand could make it an attractive alternative for some applications; see: Singer, R. A.; Doré, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* **2006**, *47*, 3727–3731.

(22) A palladium loading of 2 mol % was used with 3 mol % of ligand.

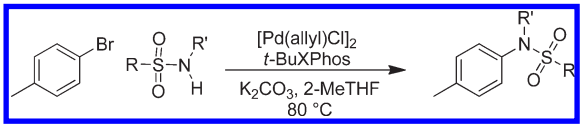
(23) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687.

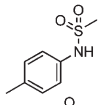
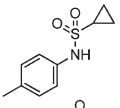
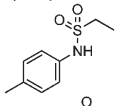
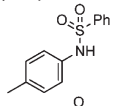
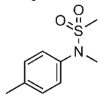
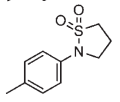
(24) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508.

overall weighing operations, and they provide more precise control of the ligand-to-Pd ratio, particularly on a small scale. In this instance, a mixture containing 0.64 wt % $[Pd(allyl)Cl]_2$, 3.0 wt % *t*-BuXPhos, and 96 wt % K_2CO_3 was used. The use of 289 mg of this catkit per mmol of limiting reagent will deliver 0.5 mol % of $[Pd(allyl)Cl]_2$, 2.0 mol % of *t*-BuXPhos, and 2 equiv of K_2CO_3.[25]

Table 3 shows the results of applying our optimized coupling conditions to a range of aryl halides on a 5 mmol scale. Excellent isolated yields were obtained with all aryl bromides examined including those that are electron rich (entries 5, 6, and 8), those that are electron deficient (entries 7, 12, and 13), and those bearing ortho substituents (entries 3 and 6). Furthermore, excellent functional group tolerance was observed with a nitrile (entry 7), a ketone (entry 12), an ester (entry 13), and even a free aldehyde (entry 14) all being well tolerated. In the case of 4-chlorobromobenzene, excellent chemoselectivity was observed, and *N*-(4-chlorophenyl)methanesulfonamide was isolated in 90% yield (entry 9).[26] While selectivity for bromide over chloride can be achieved, aryl chlorides do also couple efficiently under these conditions (entries 4 and 11).

Table 4. Sulfonamide Scope[a]



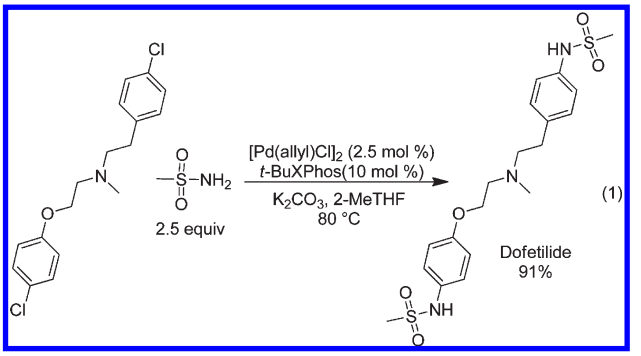
entry	product	yield (%)[b]	entry	product	yield (%)[b]
1		93	4		89
2		86	5		93
3		80	6		87

[a] Reaction conditions: Aryl halide (5 mmol), sulfonamide (5.5 mmol), K_2CO_3 (10 mmol), $[Pd(allyl)Cl]_2$ (0.5 mol %), *t*-BuXPhos (2 mol %), 2-MeTHF (20 mL), 80 °C. [b] Isolated yield.

Although bromo- and chlorobenzenes appear to be excellent substrates for cross-coupling with methanesulfonamide under these conditions, our efforts to couple heteroaryl halides have thus far been disappointing. While boc protected 5-bromoindole coupled in 95% yield, all efforts to couple substrates in which the halide is bound directly to the heterocyclic ring have failed.[27]

We also briefly explored the scope of the sulfonamide coupling partner. As shown in Table 4, we were pleased to find that a range of sulfonamides could be coupled to 4-bromotoluene in high yield under our conditions.

To demonstrate the utility of our coupling conditions on a more medicinally interesting substrate, we chose to attempt the synthesis of dofetilide directly from the previously described dichloroprecursor.[28] To our delight, we were able to promote the double coupling in 91% yield using 2.5 equiv of methanesulfonamide and 5 mol % of palladium (eq 1).[29]



In conclusion, we have developed mild, efficient, and general conditions for the preparation of *N*-arylmethanesulfonamides and other *N*-arylsulfonamides via Pd-catalyzed cross-coupling with aryl bromides and chlorides. Our conditions were designed to minimize the risk of mutagenic impurities often found in more traditional sulfonamide preparations. We have applied our conditions to the preparation of the bissulfonamide drug dofetilide.

Acknowledgment. We would like to acknowledge Barry Phelps (Eli Lilly), Marija Popovic (Eli Lilly), Larry Patterson (Eli Lilly), Dana Laird (Eli Lilly), and Jeff Petkus (Eli Lilly) for helpful discussions. B.R.R. would also like to acknowledge Kevin Hudziak (Eli Lilly) and the Lilly Research Laboratories Summer Internship Program for their support.

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

(25) We have confirmed that the use of freshly prepared catkit provides results equivalent to those obtained when each component is added separately; however, this particular mix does turn gray over days to weeks and should no longer be used once that is observed.

(26) No evidence of *N*-(4-bromophenyl)methanesulfonamide was observed in the crude GCMS of the reaction.

(27) See Supporting Information for list of failed haloheterocycles.

(28) Shagufta; Guo, D.; Klaasse, E.; de Vries, H.; Brussee, J.; Nalos, L.; Rook, M. B.; Vos, M. A.; van der Heyden, M. A. G.; IJzerman, A. P. *ChemMedChem* **2009**, *4*, 1722–1732.

(29) The Pd level in our isolated dofetilide was 535 ppm.