

Palladium-Catalyzed Direct Arylation of Nitro-Substituted Aromatics with Aryl Halides

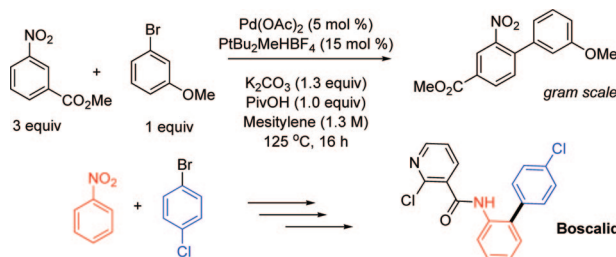
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ABSTRACT



Direct arylation reactions of nitrobenzenes and aryl halides occur in good yield and high ortho regioselectivity. These reactions can be performed on gram scale with as few as 3 equiv of the nitro arene relative to the aryl halide. The synthetic utility of this method is demonstrated via rapid synthesis of a Boscalid intermediate.

Metal-catalyzed cross-coupling reactions of aryl halides with an organometallic reagent constitute the most widely used route to prepare biaryl molecules.¹ While these transformations occur in excellent yield, chemists have begun to question the need for stoichiometric preactivation to achieve the necessary reactivity.² A promising alternative is a class of reactions called direct arylation, where one of the preactivated species is substituted with the simple arene itself (usually the organometallic).^{3–5} A variety of arenes have been demonstrated to undergo reaction, particularly electron-rich heterocycles.⁶ In contrast, electron-deficient arenes have been less extensively investigated. Recently, however, fluoroarenes,^{5k,7} and azine/diazine *N*-

oxides⁸ have been shown to react with aryl halides under palladium(0) catalysis in high yield, allowing a novel entry point into reaction development. This reactivity has been rationalized to occur through a concerted metalation–deprotonation (CMD) pathway^{5d,j,9} which might benefit from the presence of inductive electron-withdrawing groups on the arene ring. This insight prompted us to explore the reactivity of other electron-deficient substrates that may not have warranted consideration under a different mindset.

(1) For reviews on this topic, see: Hassan, J.; Sévignon, M.; Gozzi, C.; Shulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For reviews on C–H activation, see: (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Rittleng, V.; Silin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (f) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979. (g) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987.

(3) For general reviews on direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Lewis, J. C.; Bergman, R. C.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(4) For recent examples using Pd(0), see: (a) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741. (b) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (c) Shabazhova, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (d) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (e) Derridj, F.; Gottumukkala, A. L.; Djebbar, S.; Doucet, H. *Eur. J. Inorg. Chem.* **2008**, 2250. (f) Chuprakov, S.; Chernyak, N.; Dudnik, A.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333.

Our attention was drawn to the potential utility of nitro aromatics which are easily accessible via arene nitration with high degrees of predictable regioselection. Many are commercially available at low cost (for example, the cost of nitrobenzene compares favorably to benzene itself). Furthermore, there are a wide range of methods for either removal or derivatization of the nitro functionality following direct arylation cross-coupling.¹⁰ Herein we show that nitro-substituted aromatics exhibit useful reactivity in direct arylation and may be used in the synthesis of a variety of functionalized biaryl molecules. The successful inclusion of

nitroarenes in the array of aromatic direct arylation coupling partners also demonstrates the value associated with a consideration of CMD entry points into direct arylation.

Initial screens were performed with 3-bromoanisole in conjunction with 10 equiv of nitrobenzene. In early evaluations, the use of apolar solvents, such as mesitylene or octane provided superior outcomes compared to the more common use of polar aprotic solvents such as *N,N*-dimethylformamide (DMA). While complete consumption of the limiting reagent, 3-bromoanisole was observed in each case, improved regioselectivity in favor of reaction at the ortho-position, and cleaner reactivity is obtained in apolar solvents.¹¹

Further reaction optimization revealed the crucial role of base in these transformations. For example, treatment of 3-bromoanisole with 10 equiv of nitrobenzene in the presence of 5 mol % of Pd(OAc)₂, 15 mol % of P'Bu₂MeHBF₄, 1.3 equiv of base, and 0–0.3 equiv of pivalic acid in mesitylene at 125 °C provides highly variable outcomes depending on the choice of base and the presence/absence of pivalic acid. While the use of K₃PO₄ (Table 1, entry 1) does not induce

(5) For recent examples using Pd(II), see: (a) Beck, E. M.; Hatley, R.; Gaunt, M. *J. Angew. Chem., Int. Ed.* **2008**, *47*, 3004. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (d) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. For recent examples using Rh(I), see: (e) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316. (f) Proch, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3135. (g) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (h) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. For recent examples using Ru, see: (i) Ozdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (j) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (k) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115. (l) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (m) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (n) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081.

(6) For reviews, see refs 3c and 3d. For recent examples, see: (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (b) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. (c) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (e) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (f) Turner, G. L.; Morris, J. A.; Greany, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (g) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543. (h) Požgan, F.; Rogerm, J.; Doucet, H. *ChemSusChem* **2008**, *1*, 404.

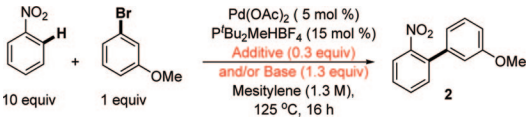
(7) (a) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (b) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.

(8) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (c) Campeau, L.-C.; Schipper, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. See also ref 4e.

(9) (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Davies, D. L.; Donald, S. M. A.; Al-Duaij, O.; Macgregor, S. A.; Polleth, M. *J. Am. Chem. Soc.* **2006**, *128*, 4210. (d) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

(10) For transformations of nitrobiphenyl into indole, see selected examples: (a) Ragaini, F.; Rapetti, A.; Visentin, E.; Monzani, M.; Caselli, A.; Cenini, S. *J. Org. Chem.* **2006**, *71*, 3748. (b) Bartoli, G.; Palmieri, G. *Tetrahedron Lett.* **1989**, *30*, 2129. For transformations of nitrobiphenyl into carbazole, see selected examples: (c) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnáiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713. (d) Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533. For transformation of nitrobiphenyl to 2-hydroxybiphenyl, see selected examples: (e) Boldt, P.; Bruhnke, D.; Gerson, F.; Scholz, M.; Jones, J. G.; Bär, F. *Helv. Chim. Acta* **1993**, *76*, 1739. For transformation of nitrobiphenyl into 2-aminobiphenyl, see selected examples: (f) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035. (g) McLaughlin, M. A.; Barnes, D. M. *Tetrahedron Lett.* **2006**, *47*, 9095. (h) Liu, Y.; Lu, Y.; Prashad, M.; Repiè, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 217. (i) Hanaya, K.; Muramatsu, T.; Kudo, H.; Chow, Y. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, *10*, 2409. (j) Vass, A.; Dudas, J.; Toth, J.; Varma, R. S. *Tetrahedron Lett.* **2001**, *42*, 5347. (k) Huber, D.; ermann, G.; Leclerc, G. *Tetrahedron Lett.* **1988**, *29*, 635. For transformation of nitrobiphenyl into 2-cyanobiphenyl, 2-chlorobiphenyl and 2-bromobiphenyl, see selected examples: (l) Suzuki, N.; Azuma, T.; Kaneko, Y.; Izawa, Y.; Tomioka, H.; Nomoto, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, *3*, 645. (m) Lee, J. G.; Cha, H. T. *Tetrahedron Lett.* **1992**, *33*, 3167. (n) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426. (o) Roe, A.; Graham, J. R. *J. Am. Chem. Soc.* **1952**, *74*, 6297.

Table 1. Effect of Base and Pivalic Acid^{a, 11}

					
entry	base	additive	% conversion	% yield ^c	regioselectivity (o/(m+p)) ^b
1	K ₃ PO ₄	none	0	0	0
2	Cs ₂ CO	none	52	28	27:1
3	K ₂ CO ₃	none	73	43	5.1:1
4	CsOPiv	none	22	10	1.7:1
5	KOPiv	none	19	7.2	1.8:1
6	K ₃ PO ₄	PivOH	65	29	6:1
7	Cs ₂ CO ₃	PivOH	100	69	36:1
8	K ₂ CO ₃	PivOH	100	77	34:1

^a Conditions: PivOH (0 to 0.3 equiv), base (1.3 equiv), Pd(OAc)₂ (5 mol %), and P'Bu₂MeHBF₄ (15 mol %) were added sequentially to the reaction vessel. ArBr (1.0 equiv), nitrobenzene (10 equiv), and mesitylene (1.3 M) were added, and the reaction was heated to 125 °C for 16 h (overnight). ^b Determined by GCMS analysis. ^c Isolated yield.

reaction, the use of carbonate bases leads to partial conversion (Table 1, entries 2 and 3). Similarly, the use of stoichiometric potassium and cesium pivalate provides low conversions and isolated yields (Table 1, entries 4 and 5). In contrast, the combined use of a carbonate base and pivalic acid (generating the metal pivalate in situ) provides 100% conversion and synthetically useful isolated yields of the *o*-arylated biaryl compound (Table 1, entries 7 and 8). Interestingly, the ortho/(meta+para) selectivity is also strongly influenced by these same parameters. While relatively poor

(11) Incomplete peak separation of the meta and para isomers in the crude GCMS analysis prevents a more precise measure of these two isomers separately. In most cases, the meta/para ratio was ~2:1.

reioslectivity is obtained with either K_2CO_3 (5.1: 1) or KOiv (1.8: 1), when K_2CO_3 is combined with a substoichiometric quantity of KOiv, excellent regioselectivity is obtained (34:1). The reasons for this change in selectivity are a focus of ongoing mechanistic evaluation.

Illustrative examples of direct arylation employing nitrobenzene are shown in Table 2. Most cross-coupling pairs

Table 2. Scope of Nitrobenzene and Various Aryl Bromides^a

Entry	Ar-Br	Product	% Yield ^b
1			62
2			77 42 42
3			62
4			54
5			68
6			60
7			76
8			73
9			54
10			56

^a Conditions: PivOH (0.3 equiv), K_2CO_3 (1.3 equiv), $Pd(OAc)_2$ (5 mol %), and $P'Bu_2MeHBF_4$ (15 mol %) were added sequentially to the reaction vessel. ArBr (1.0 equiv), nitrobenzene (10 equiv) and mesitylene (1.3 M) were added and the reaction was heated to 125 °C for 16 h (overnight).
^b Isolated yield. ^c 0.5 equiv of Ag_2CO_3 added.

went to 100% conversion and provided moderate to good isolated yields of pure *o*-arylated compound. This isolated

yield is influenced principally by the ease or difficulty with which the major isomer could be separated in pure form from the small amounts of the other minor isomers by chromatography and is a property that may improve when working on larger scale.

Table 3. Scope of Substituted Nitrobenzene^a

entry	nitrobenzene	aryl bromide	product % yield ^b
1			61
2			45
3			60
4			65
5			45
6			59
7			40
8			49
9			72 ^c
10			50

^a Conditions: PivOH (0.3 equiv), K_2CO_3 (1.3 equiv), $Pd(OAc)_2$ (5 mol %), $P'Bu_2MeHBF_4$ (15 mol %), and nitroarene (5.0 equiv) were added sequentially to the reaction vessel. ArBr (1.0 equiv) and mesitylene (1.3 M) were added, and the reaction was heated to 125 °C for 16 h (overnight).
^b Isolated yield. ^c Reaction was performed on a 1 g scale using 3.0 equiv of nitrobenzene.

A range of functional groups are tolerated on the aryl halide including electron poor (Table 2, entries 5, 6, 8, and 9) and electron rich (entries 2, 4, and 7) substrates. The use of an aryl iodide (entry 2) is tolerated when 0.5 equiv of silver carbonate is used. This diminished reactivity with aryl

iodides has been observed in other direct arylation reactions and may be due to competitive iodide inhibition of the palladium catalyst.^{8b,12} Chlorides may also be employed, but lower yields are obtained under the current conditions when compared to the use of aryl bromides (entry 2).

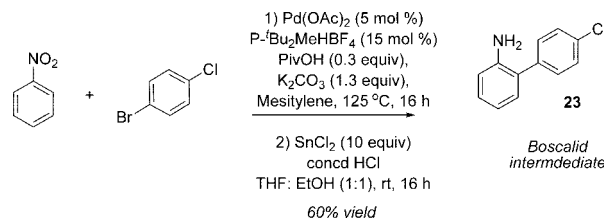
The effect of substitution on the nitroarene was also examined; in many cases, high levels of regioselection were obtained (Table 3). When an ortho substituent is present, 1,2,3-trisubstituted arenes are generated in moderate to good yields (entries 1–3, 5, and 7). Similarly, a para substituent may also be present (entry 10). Interestingly, when meta-functionalized nitroarenes are employed, the regiochemical outcome of direct arylation is governed by both substituents. For example, when a *m*-methyl or methyl ester group is present, arylation occurs ortho to the nitro substituent at the more sterically accessible position (entries 4, 6, and 9). On the contrary, when a meta nitrile functionality is present, arylation occurs at the more sterically encumbered position between the two substituents indicating that other influences on regioselectivity must be at play (entry 8).

While the initial reactions employing substituted nitrobenzenes were performed with 5–10 equiv of the nitroarene, it was subsequently discovered that as few as 3 equiv of the nitroarene may be employed while maintaining good yields. For example, treatment of 1 g of 3-bromoanisole with 3 equiv of 3-methylnitrobenzoate under the standard reaction conditions produces the *o*-arylated product in 72% isolated yield (Table 3, entry 9).

To further investigate the potential utility of this chemistry, we investigated its use in the rapid preparation of a key intermediate **23** in the synthesis of Boscalid, a commercially available agrochemical compound.¹³ 4'-Chlorobiphenyl-2-amine **23** is easily prepared in 60% isolated yield (over two steps) by treatment of nitrobenzene with 4-bromochlorobenzene under the standard conditions followed by reduction of the nitro group to the amine by treatment of the crude reaction mixture with SnCl₂ and concentrated HCl.

To probe the reactivity imparted by the nitro functionality, two competition reactions were performed. In one case, nitrobenzene was reacted in the presence of an equimolar

Scheme 1. Boscalid Intermediate



quantity of methylbenzoate, and in another, in the presence of anisole. In both instances, arylation of nitrobenzene is highly favored.¹⁴ These observations as well as the experimentally observed reversal in regioselectivity are a focus of ongoing experimental and computational analysis. Nonetheless, the successful inclusion of electron-deficient nitrobenzenes in palladium-catalyzed direct arylation reactions, and the observed preferential reactivity over both ester and methoxy-substituted benzenes point to a useful and potentially broad reaction scope outside the traditional nucleophilic arene substrate class. Important from a practical perspective, these reactions have been scaled to gram levels and may be performed with a slight excess of the nitrobenzene if desired. As the mechanism of direct arylation becomes better understood, it is anticipated that many, otherwise disregarded arenes will emerge as useful coupling partners in the preparation of useful biaryl building blocks for use in medicinal chemistry and materials science.

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Supporting Information Available: Complete characterization data for all new biaryl products as well as experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) See the Supporting Information for details.

(12) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

(13) (a) Ehrenfreund, J.; Lamberth, C.; Tobler, H.; Walter, H. WO pat. 2004, 058723. (b) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.