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Establishment of Broadly Applicable Reaction Conditions for the Palladium-Catalyzed Direct Arylation of Heteroatom-Containing Aromatic Compounds

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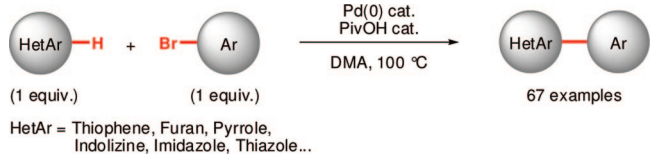
Received December 3, 2008

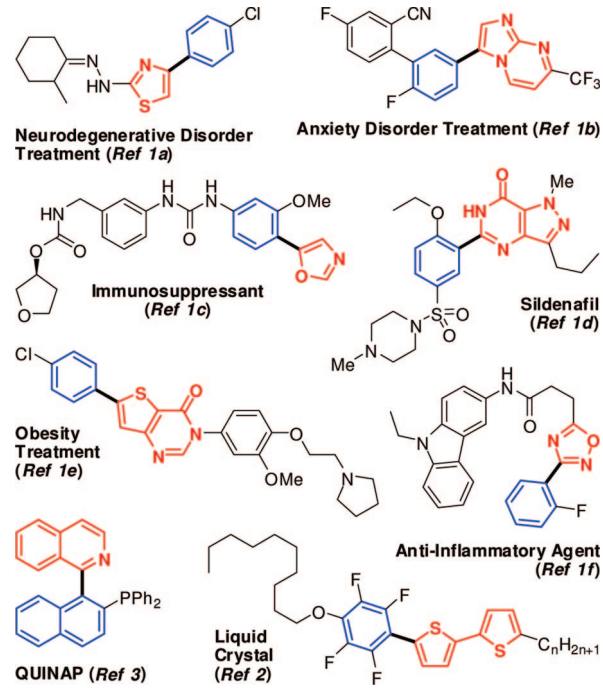


Conditions for the palladium-catalyzed direct arylation of a wide range of heterocycles with aryl bromides are reported. Those conditions employ a stoichiometric ratio of both coupling partners, as well as a substoichiometric quantity of pivalic acid, which results in significantly faster reactions. An evaluation of the influence of the nature of the aryl halide has also been carried out.

Introduction

Heteroatom-containing biaryls are common motifs in biologically active products,[1] in organic materials[2] and in ligands for metal catalysis[3] (Scheme 1). Over the past 30 years, the preparation of these molecules has been dominated by the use of transition-metal-catalyzed processes, where an organometallic species can be cross-coupled with an aryl halide.[4] Over the past decade, however, alternatives are emerging where one of the coupling partners (usually the organometallic component) is

SCHEME 1. Heteroatom-Containing Biaryls[1−3]



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10.1021/jo8026565 CCC: $40.75
Published on Web 02/10/2009

replaced by a simple arene.[5] Since the pioneering work more than a quarter century ago,[6] many research groups, including ours, have been involved in the development of new methods for the preparation of heteroatom-containing biaryl structures.[7] A wide range of electron-rich heterocycles have been successfully employed in palladium-catalyzed cross-coupling reactions, including (benzo)thiophenes,[8] furans,[9] (benz)oxazoles,[10] indoles,[11] pyrroles,[12] (benz)imidazoles,[13] (benzo)thiazoles,[14] triazoles,[15] indolizines,[16] purines,[17] as well as imidazopyrimidine, -pyrazine, and -triazine derivatives.[18−21] Despite the growth, challenges remain including the establishment of generally applicable conditions that can enable the successful cross-coupling of the broadest range of heterocyclic compounds possible and the frequent need to use one of the coupling partners in excess. Underlying the challenges is an inability to point to a single predominant reaction pathway that may be used as a starting point for a more rational approach to reaction development. With a greater mechanistic understanding of these processes should come the establishment of improved reaction conditions and a greater acceptance of this approach in the preparation of heterocycle containing biaryl molecules.

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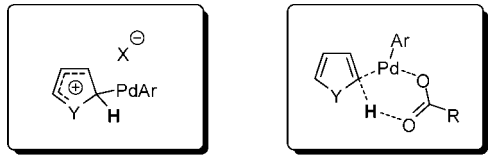
SCHEME 2. Electrophilic Aromatic Substitution (S_EAr) and Concerted Metalation−Deprotonation (CMD) Pathways

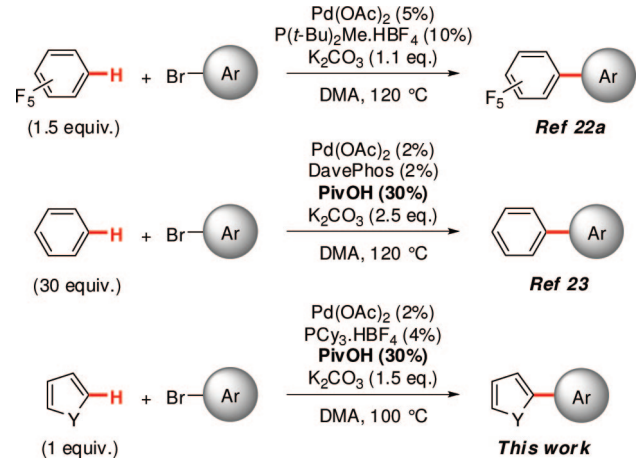


S_EAr Pathway CMD Pathway

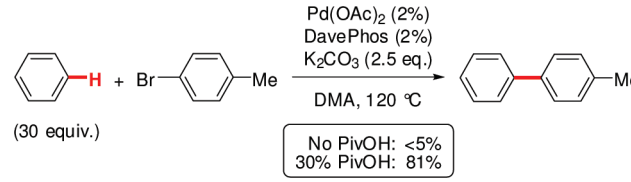
Our research group has been involved in the development of palladium-catalyzed direct arylation reactions with electron-deficient arenes[22,23] and heteroarenes.[24] In these processes, the experimental and computational data support the involvment of a concerted metalation-deprotonation pathway (CMD)[22a,23,25] that accurately predicts both the relative rates as well as the regioselectivity (Scheme 2). Recently, we questioned whether this mode of reaction might also occur with some types of π-excessive aromatics that are more commonly proposed to react via an electrophilic aromatic substitution pathway (S_EAr)[6o,8b,11b,16,18a,26] and, upon evaluation by computational analysis, found a remarkable parallel with the computationally predicted and experimentally observed reaction outcomes.[27]

These studies prompted us to explore the use of the direct arylation conditions developed for CMD-type aromatic coupling partners to π-rich heteroaromatics, with a particular focus on the use of pivalate additives. In this paper, we describe the outcomes of these studies including the establishment of broadly useful direct arylation reaction conditions that enable efficient cross-coupling between a wide range of coupling partners with a 1:1 substrate stoichiometry.

SCHEME 3. Evolution of Reaction Conditions for the Direct Arylation of Electron-Deficient, Electron-Neutral, and Electron-Rich (Hetero)arenes



SCHEME 4. Influence of Pivalic Acid in the Direct Arylation of Benzene[23]



Results and Discussion

Previous work in our group has focused on the use of palladium acetate in conjunction with sterically encumbered alkylphosphine ligands and potassium carbonate as a stoichiometric base for use in direct arylation reactions with a wide range of electron-deficient arenes and (predominantly) aryl bromide coupling partners. While these conditions proved to be successful for several aromatic substrates, extension to arenes such as benzene[23] and nitrobenzene[22b] relied on the use of substoichiometric amounts of pivalate additives (Scheme 3). For example, in the absence of pivalate, no reaction is observed with benzene while the addition of 30 mol % pivalic acid to a reaction run with an excess of potassium carbonate base (generating potassium pivalate in situ) provides greater than 80% yield of benzene direct arylation (Scheme 4).[23] This increased reactivity was initially rationalized by invoking the CMD pathway where the pivalate was serving as a soluble proton transfer agent from the arene and palladium catalyst to the insoluble carbonate base and has been employed in other types of arene/alkane functionalization reactions.[10i,15c,17e,22b,24d,e,25c,d,27−29]

With the finding that the CMD pathway may also apply to heterocyclic aromatic compounds,[27] similar conditions were evaluated for their use. Three arenes were selected to evaluate the impact of added pivalic acid (in situ becoming potassium pivalate), benzothiophene **1**, 4-methylthiazole **2**, and the in-

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(24) For palladium-catalyzed intermolecular direct arylation of pyridine, diazine, and azole *N*-oxide derivatives, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021. (b) Leclerc, J.-P.; Fagnou, K. *Angew., Chem. Int. Ed.* **2006**, *45*, 7781–7786. (c) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. (d) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277. (e) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* . in press. For palladium-catalyzed intermolecular direct arylation of *N*-iminopyridinium ylides, see also: Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52–54.

(25) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 16754–13755. (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067. (c) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886. (d) Pascual, S.; De Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021–6029. (e) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302.

(26) (a) Catellani, M.; Chiusoli, P. *J. Organomet. Chem.* **1992**, *425*, 151–154. (b) González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 1286–1291. (c) Martin-Matute, B.; Mateo, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2001**, *7*, 2341–2348.

(27) For mechanistic insights on palladium-catalyzed intermolecular direct arylation of heteroaromatics, see: Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

(28) (a) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571. (b) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015–6020. (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759–1762. See also ref 25d.

(29) Similar effects have also been reported in ruthenium-catalyzed direct arylation: (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302. This benefit is likely due to the involvement of an analogous CMD-type mechanism in these reactions; see: (b) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.

dolizine **3**. With the goal of establishing reaction conditions that employ a 1:1 heteroarene/haloarene ratio, both the heterocycle and the aryl bromide were employed in equimolar quantities. For example, reactions of benzothiophene **1** and 4-bromotoluene with palladium acetate (2 mol %), tricyclohexylphosphine (in its bench-stable phosphonium tetrafluoroborate form,[30] $PCy_3 \cdot HBF_4$) (4 mol %) and potassium carbonate as the base (1.5 equiv) in *N*,*N*-dimethylacetamide (DMA, 0.3 M) at 100 °C are outlined in Figure 1. In the absence of pivalic acid, very low conversion was observed (approximately 10% after 3 h). On the other hand, addition of only 10 mol % of PivOH resulted in a dramatic increase in reactivity, giving 65% conversion after the same reaction time. The yield is further improved by increasing the amount of pivalic acid to 30 mol %, which generates greater than 80% GC yield after 3 h. A further increase in the amount of pivalic acid above 30 mol % does not improve the reactivity nor the yield beyond that observed with 30 mol %. Very similar trends were also observed with 4-methylthiazole **2** (Figure 1b). In contrast, the effect of pivalic acid was less pronounced for the highly nucleophilic indolizine **3** that exhibits good reactivity even in the absence of added pivalate (Figure 1c). These trends may hold mechanistic significance and are a focus of continued study. Nonetheless, the observation that the use of a substoichiometric quantity of pivalic acid in conjunction with a stoichiometric amount of insoluble carbonate base should be of broad use in the establishment of generally applicable direct arylation reaction conditions and in the establishment of new reactions.

To evaluate the potential breadth of these reaction conditions, a survey of heterocyclic cross-coupling partners was carried out maintaining a strict 1:1 heteroarene/haloarene stoichiometry (Table 1). Standard reaction conditions for these processes were adopted to involve the use of the heterocycle (1 equiv), an aryl bromide (1 equiv), $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %), PivOH (30 mol %), and K_2CO_3 (1.5 equiv) in DMA (0.3 M) at 100 °C. The use of equimolar arene coupling partner ratios and the use of 2 mol % catalyst (as opposed to 5 mol %, which is more commonly employed when evaluating the scope of these transformations) differentiates many of these entries from previous reports and is more completely delineated for each substrate class below.

C3-Substituted benzothiophenes have recently been employed in direct arylation reactions using a slight excess of the aryl halide substrate (1.1−1.5 equiv).[8c,e] Under the standard conditions developed herein, unsubstituted benzothiophene **1** reacts with numerous aryl bromides, providing the corresponding 2-arylbenzothiophenes **4a**−**i** in synthetically useful yields after 4 h (entries 1−9). A reaction between **1** and 5-acetyl-2-bromothiophene also furnished the heterocyclic biaryl product **4j**, albeit in lower yield (entry 10). C2-Substituted thiophenes are also good substrates for direct arylation. Previous reports employing thiophene derivatives commonly necessitate the use of small to moderate excesses of the thiophene cross-coupling partner (between 1.2 and 3 equiv).[8b,f,k] Under the standard conditions, thiophenes bearing C2 electron-withdrawing groups (**7** and **9**) or electron-donating groups (**11**, **13** and **15**) furnish the 5-substituted products **8**, **10**, **12**, **14**, **16**, and **18** in moderate to very good yields (entries 12−24). With these substrates, longer reaction times were required to reach high conversions (typically 16 h).

(30) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.

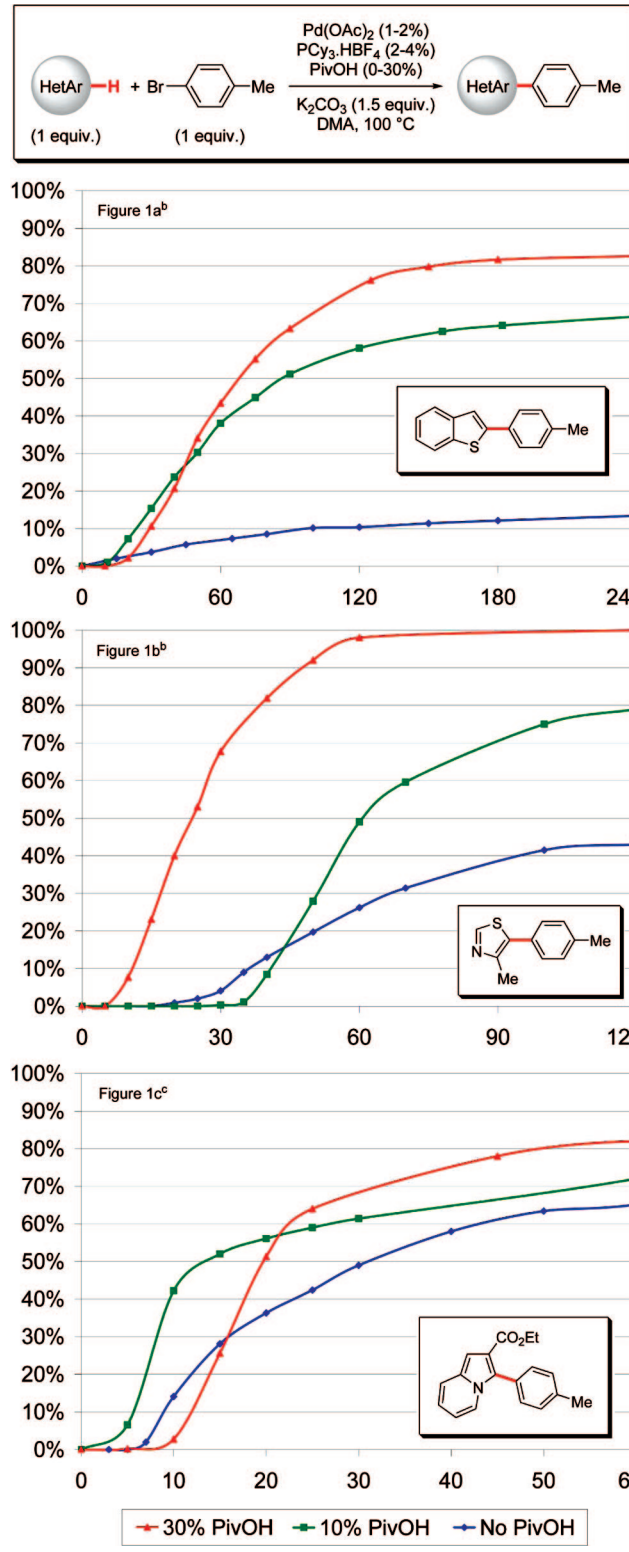


FIGURE 1. Influence of pivalic acid in the direct arylation of heteroaromatics with 4-bromotoluene. (a) GC yield in coupling product overtime (min), using tetradecane as an internal standard. (b) $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %). (c) $Pd(OAc)_2$ (1 mol %), $PCy_3 \cdot HBF_4$ (2 mol %).

Benzofurans have been more rarely examined in direct arylation[6g,j] and were found to be more problematic substrates under these conditions. For example, treatment of benzofuran **17** with 2-bromotoluene results in arylation at C2 in 29% yield (entry 25). Other bromoarenes gave lower yields. On the other

TABLE 1. Scope of the Direct Arylation of Aromatic Heterocycles[a]

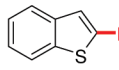
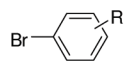
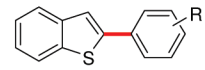
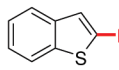
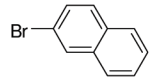
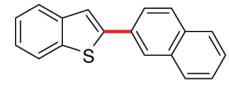
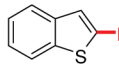
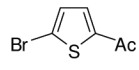
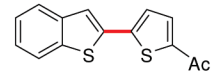
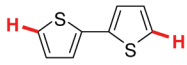
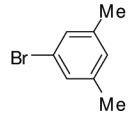
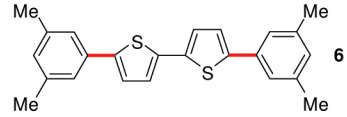
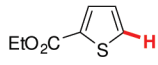
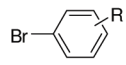
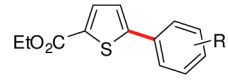
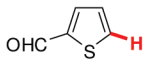
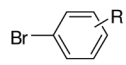
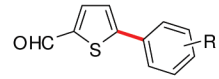
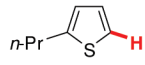
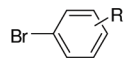
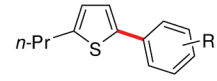
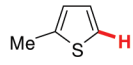
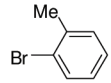
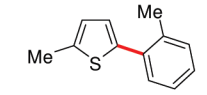
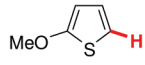
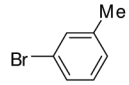
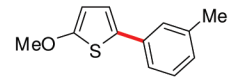
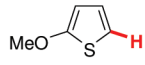
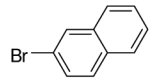
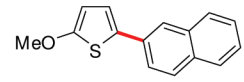
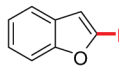
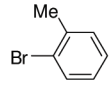
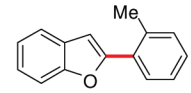
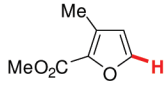
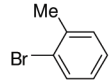
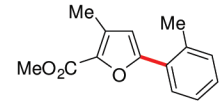
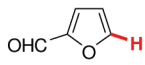
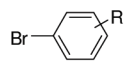
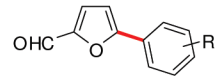
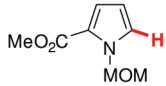
Entry	Heterocycle	Aryl Bromide	Product	Time (h)	Yield (%)
1	 **1**	 R = 4-Me	 **4a**	4	91
2		R = 4-OMe	**4b**	4	65
3		R = 3-OMe	**4c**	4	72
4		R = 3,5-di-OMe	**4d**	4	60
5		R = 4-*t*-Bu	**4e**	4	69
6		R = 4-Cl	**4f**	4	63
7		R = 4-F	**4g**	4	58
8		R = 4-CO_2Et	**4h**	24	63
9	 **1**		 **4i**	4	82
10	 **1**		 **4j**	14	22
11[e,g]	 **5**		 **6**	16	86
12	 **7**	 R = 3-OMe	 **8a**	16	80
13		R = 4-*t*-Bu	**8b**	16	72
14		R = 3-Cl	**8c**	16	74
15		R = 4-CN	**8d**	16	38
16		R = 4-NMe_2	**8e**	22	68
17	 **9**	 R = H	 **10a**	16	58
18		R = 4-OMe	**10b**	16	40
19		R = 3-Cl	**10c**	16	53
20	 **11**	 R = 4-Me	 **12a**	16	54
21		R = 4-CF_3	**12b**	16	40
22	 **13**		 **14**	24	87
23[d]	 **15**		 **16a**	22	61
24	 **15**		 **16b**	16	58
25	 **17**		 **18**	16	29
26	 **19**		 **20**	16	61
27[c]	 **21**	 R = 2-F	 **22a**	16	44
28[c]		R = 2-Ph	**22b**	16	70
29	 **23**		**24**	13	57
30[b]				24	14	69
31[b]	**25**		**26**	14	52
32[b]	**27**		**28**	14	65

TABLE 1. Continued

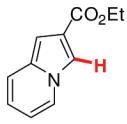
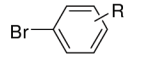
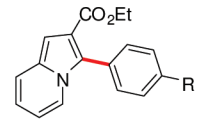
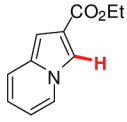
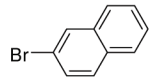
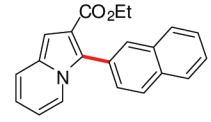
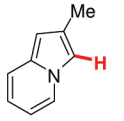
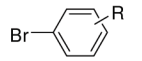
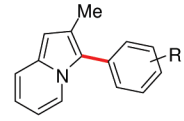
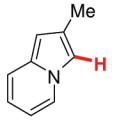
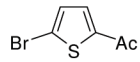
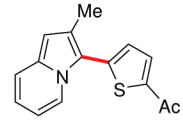
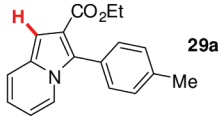
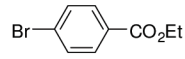
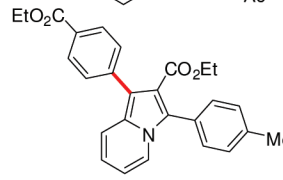
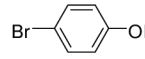
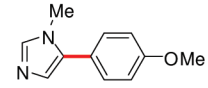
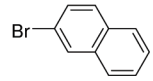
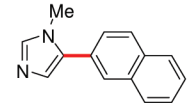
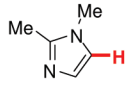
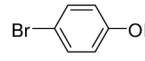
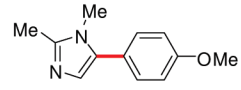
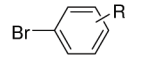
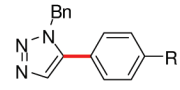
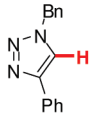
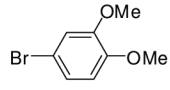
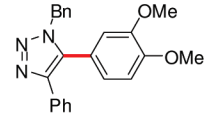
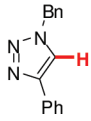
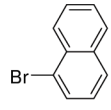
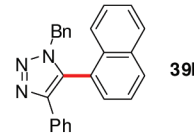
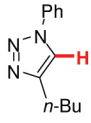
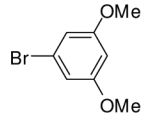
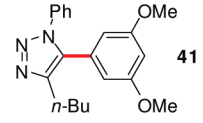
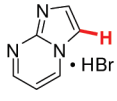
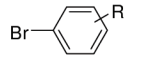
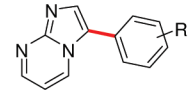
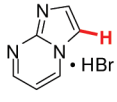
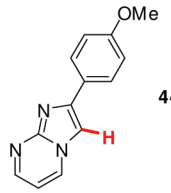
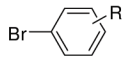
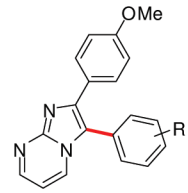
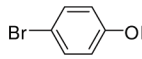
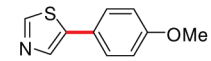
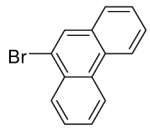
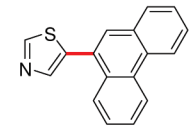
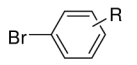
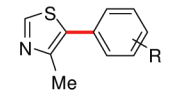
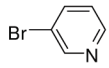
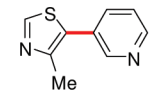
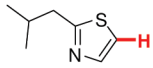
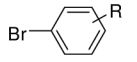
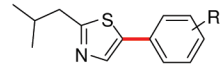
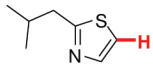
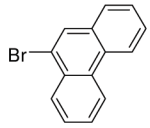
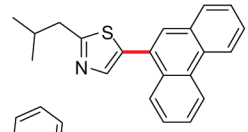
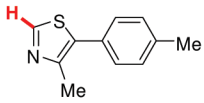
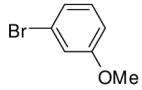
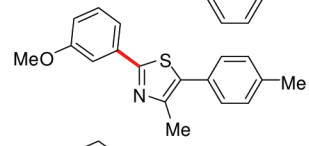
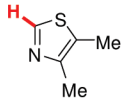
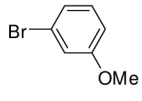
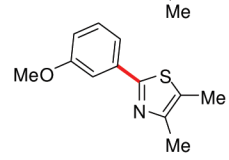
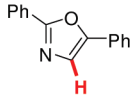
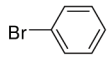
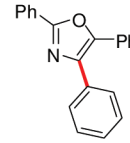
Entry	Heterocycle	Aryl Bromide	Product	Time (h)	Yield (%)
33	 **3**	 R = 4-Me R = 4-CF_3	 **29a** **29b**	4 4	89 82
34	 **3**		 **29c**	4	86
35 36	 **30**	 R = 4-NO_2 R = 2-CO_2Me	 **31a** **31b**	4 24	85 56
37	 **30**		 **31c**	16	81
38 39[e] 40[c]	 **29a**		 **29d** **29d** **29d**	24 24 24	54 63 82
41	 **32**		 **33a**	25	34
42	 **32**		 **33b**	27	40
43	 **34**		 **35**	23	32
44 45	 **36**	 R = 4-OMe R = 4-CO_2Et	 **37a** **37b**	6 6	60 60
46	 **38**		 **39a**	16	62
47	 **38**		 **39b**	16	26
48	 **40**		 **41**	24	87
49[g] 50[g] 51[g]	 **42**	 R = 4-F R = 4-NMe_2 R = 2-NO_2	 **43a** **43b** **43c**	4 4 4	77 80 86
52[g]	 **42**		**43c**	16	46

TABLE 1. Continued

Entry	Heterocycle		Aryl Bromide		Product		Time (h)	Yield (%)
53		**44**		R = 4-Cl		**45a**	4	82
54				R = 2-F		**45b**	4	76
55[b]		**46**				**47a**	19	62
56		**46**				**47b**	18	60
57[b]						**47b**	18	80
58		**2**		R = 4-Cl		**48a**	4	66
59				R = 4-Me		**48b**	1,5	78
60				R = 4-OMe R = 3-OMe		**48c** **48d**	2,5 1,5	65 74
61		**2**				**48e**	25	56
62		**49**		R = 4-H		**50a**	3,5	89
63				R = 4-Me		**50b**	4	77
64		**49**				**50c**	3,5	88
65		**48b**				**48f**	74	54
66		**51**				**52**	42	42
67[b]		**53**				**54**	14	83

[a] Conditions (unless otherwise specified): heterocycle (1 equiv), aryl bromide (1 equiv), $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %), PivOH (30 mol %), K_2CO_3 (1.5 equiv), DMA (0.3 M), 100 °C. [b] Heterocycle (1.5 equiv). [c] Heterocycle (2 equiv). [d] Aryl bromide (1.5 equiv), K_2CO_3 (2 equiv). [e] Aryl bromide (2 equiv), K_2CO_3 (2.5 equiv). [f] $Pd(OAc)_2$ (4 mol %), $PCy_3 \cdot HBF_4$ (8 mol %). [g] K_2CO_3 (2.5 equiv).

hand, substituted furans **19** and **21** were found to participate in these transformations with improved yield when employing a 1:1 or 2:1 furan/aryl bromide stoichiometry—comparing favorable to previous reports where 2−10 equiv of the furan have been used.[9] The yields with many of these reactions were diminished due to the formation of furan/benzofuran arylation regioisomers and to the presence of double arylation as a side reaction. In cases where double arylation is problematic, the use of more sterically hindered arylbromides results in increased yield (entry 28 vs 27).

Direct arylation of pyrrole substrates, which has previously been achieved with a small excess of the pyrrole chlorozinc anion,[12] or as the SEM-protected pyrrole with a slight excess of aryl halide,[11c] can be accomplished under the standard conditions to give arylated products **24**, **26**, and **28** in moderate to good yields and with good regioselectivity (entries 29−32). Similarly, substituted indolizines, first investigated by Gevorgyan,[16] are excellent substrates for this transformation. For example, indolizines **3** and **30** will react to give the biaryl products **29** and **31** in very good yields, between 80% and 90% (entries 33−37). When these substrates are reacted with electron-deficient aryl bromides (bearing either an ester or a nitro group), or with 2-acetyl-5-bromothiophene, longer reaction times of 16−24 h are required (entries 35, 36, and 37, respectively). This is noteworthy since we have observed diminished reactivity associated with electron-poor aryl bromide partners with other

coupling partners (vide infra). While the reason for this diminished reactivity has not been established, it warrants additional attention. We also determined that indolizine **29a** can undergo a second arylation to provide the corresponding trisubstituted product **29d** (entries 38−40).

Other heterocycles, such as imidazoles **32** and **34**, triazoles **36**, **38**, and **40**, and imidazopyrimidines **42** and **44** also react efficiently with electron-rich and electron-deficient arylbromides to give biaryls **33**, **35**, **37**, **39**, **41**, **43**, and **45** respectively (entries 41−54). In previous reports, these substrates have been successfully coupled using a slight excess of the aryl halide coupling partner (1.5−2 equiv).[13a,f,15a,c,18a,c] Finally, thiazole **46**, 4- and 2-substituted thiazoles **2** and **49**, 4,5-disubstituted thiazoles **48b** and **51**, and oxazole **53** were also found to be suitable components in the direct arylation reaction using our optimized conditions, providing the corresponding products **47**, **48**, **50**, **52**, and **54** in good yields (entries 55−67), with a regioselectivity in favor of the C5 position (when available, entries 55−64). With thiazole, the use of some heterocyclic arylbromides may also be used, such as in the reaction between 4-methylthiazole **2** and 3-bromopyridine which gives **48e** in 56% yield (entry 61).

All of the preceding reactions were performed with aryl bromides since we had noted in previous studies superior outcomes associated with these substrates. To probe the influence of the halide component under these conditions, 4-tolyl chloride, bromide, iodide, and triflate were reacted with heterocycles **1** and **49**. With both substrates, optimal results are achieved with the aryl bromide cross-coupling partner (entry 3). With benzothiophene **1**, use of iodotoluene gave the corresponding product **4a** in 18% and 32% yields in the absence or in the presence of silver carbonate,[31] respectively (entries 1 and 2). We have previously observed an inhibitory effect of iodide anions on direct arylation and a similar inhibition may be occurring here.[31] Despite the use of very electron-rich phosphine ligands, which enable the use of aryl chloride substrates in other types of cross coupling reactions,[14e,15b,c] the use of a less reactive aryl chloride also gives inferior outcomes (entry 4), as does the use of the aryl triflate (entry 5). 2-Isobutylthiazole **49** followed similar reactivity trends as **1**, with yields comprising between 33% and 46% using 4-iodotoluene or 4-tolyltriflate (entries 6, 7, and 10). No product was observed with 4-chlorotoluene (entry 9). The mechanistic reasons for the apparent difference in outcomes observed as the nature of the halide cross-coupling partner is changed merits further attention and is likely not unity for all species. Nonetheless, based on these results, we recommend the use of aryl bromide substrates in direct arylation reaction when such a choice is possible.

While the conditions described in this report were found to be broadly applicable, we also observed very low yields in several cases (Scheme 5). For instance, some electron-deficient haloarenes, bearing a cyano, nitro, or acetyl group, as well as pyridines or their *N*-oxide counterparts, typically give rise to low yields. We were also unable to couple several heterocycles, such as unprotected imidazoles, 2-aminothiazole (unprotected or acyl-protected), isoxazole, benzothiazole, and benzoxazole. For direct arylation to continue to emerge as a viable alternative

(31) It has been previously reported than silver salt additives could overcome the poisoning effect resulting from the accumulation of iodide in the reaction media: Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590.

SCHEME 5. Representative Unsuccessful Coupling Products (Reactions Performed Using Standard Conditions; Conversions Determined by GC−MS by Consumption of the Limiting Starting Material)

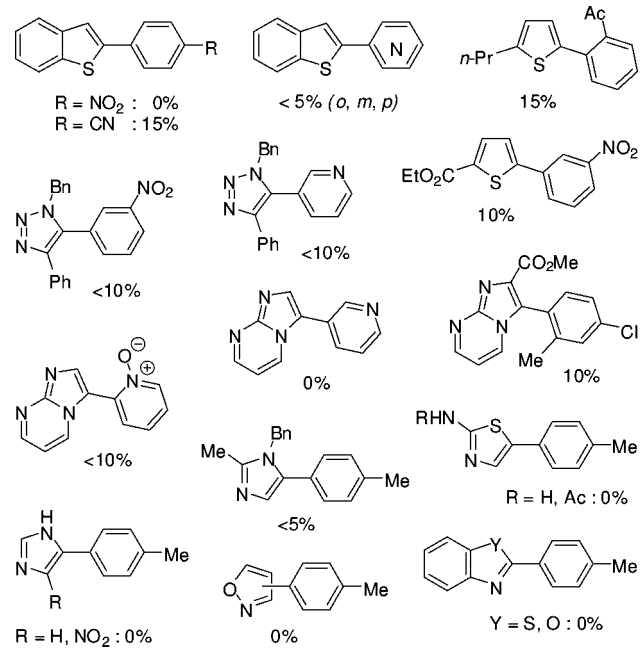
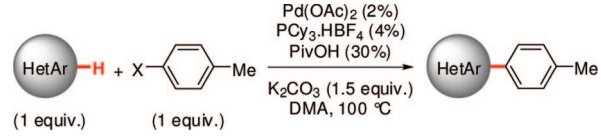


TABLE 2. Effect of the (Pseudo)halide on the Direct Arylation of Aromatic Heterocycles[a]



Entry	Heterocycle	X	Time (h)	Yield (%)[a]
1		I	8	18
2[b]		I	8	32
3	**1**	Br	4	91
4		Cl	24	9
5		OTf	16	19
6		I	24	46
7[b]		I	24	33
8	**49**	Br	4	77
9		Cl	24	0
10		OTf	24	34

[a] Isolated yields. [b] 0.5 equiv of Ag_2CO_3 was added.

to traditional cross-coupling reactions, such limitations must increasingly be identified and resolved. These limitations also point to the continued need for further methodological developments to overcome these challenges.

Conclusion

In summary, we have established broadly applicable reaction conditions for the palladium-catalyzed direct arylation of a very wide variety of heteroatom-containing aromatic compounds with arylbromides. These conditions highlight the utility associated with the use of substoichiometric quantities of pivalic acid (in situ generated potassium pivalate) in accelerating direct arylation and improving reaction outcomes across a broad range of arene classes. This establishment of these conditions should provide a valuable starting point to those wishing to examine the use of

direct arylation in biaryl synthesis and facilitate the discovery of other novel cross-coupling partners in this type of chemistry.

Experimental Section

General Procedure for the Direct Arylation of Heterocycles. K_2CO_3 (1.5 equiv), $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %), and PivOH (30 mol %) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heterocycle (1 equiv) and the aromatic halide (1 equiv) were added at this point if solids. The vial was purged with argon, and DMA (0.3 M) was added. The heterocycle (1 equiv) and the aromatic halide (1 equiv) were added at this point if liquids. The reaction mixture was then vigorously stirred at 100 °C over the indicated time. The solution was then cooled to rt, diluted with EtOAc, washed with H_2O (3 times), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.

2-(*p*-Tolyl)benzothiophene 4a. Compound **4a** was synthesized according to the general procedure and exhibited identical spectral data according to previous report:[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br d, J = 7.8 Hz, 1H), 7.75 (br d, J = 7.6 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 0.5 Hz, 1H), 7.33 (ddd, J = 8.1, 7.2 and 1.3 Hz, 1H), 7.29 (ddd, J = 8.2, 7.2 and 1.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 140.8, 139.3, 138.3, 131.5, 129.6, 126.4, 124.4, 124.1, 123.4, 122.2, 118.8, 21.2.

(32) Baziard-Mouysset, G.; Tchani, G. W.; Stigliani, J. L.; Payard, M.; Bonnafous, R.; Tisne-Versailles, J. *Eur. J. Med. Chem.* **1993**, *28*, 539–546.

Acknowledgment. We thank NSERC, the University of Ottawa, and the ACS (PRF Type AC) for support of this work. The Research Corporation, Boehringer Ingelheim (Laval), Merck Frosst Canada, Merck Inc., Eli Lilly, Amgen, and Astra Zeneca Montreal are thanked for additional unrestricted financial support. Elisia Villemure is kindly acknowledged for the loan of pyrrole compounds.

Supporting Information Available: General considerations; synthesis of starting materials **23**, **25**, and **27**; characterization of all compounds; copies of NMR spectra of all coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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