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Domino Palladium-Catalyzed Heck-Intermolecular Direct Arylation Reactions

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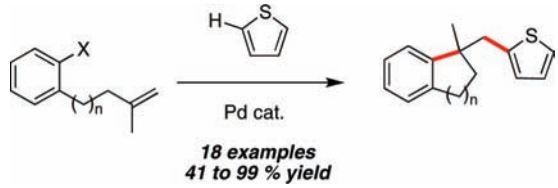
ABSTRACT



A domino palladium-catalyzed Heck-intermolecular direct arylation reaction has been developed, giving access to a variety of dihydrobenzofurans, indolines, and oxindoles. A variety of sulfur-containing heterocycles such as thiazoles, thiophenes, and benzothiophene can be employed as the direct arylation coupling partner in yields up to 99%.

Although the use of aryl halide and organometallic coupling partners is the norm in metal-catalyzed cross-coupling reactions,[1] more efficient processes that can replace the aryl organometallic with a simple arene are emerging as valuable alternatives.[2] The majority of studies done in the past decade have focused on the formation of Csp^2-Csp^2 bonds.[2] Recently, however, important steps have been made dealing with the formation of Csp^3-Csp^2 (alkane−arene) bonds. Building on the first reports that validated this reactivity in intramolecular processes,[3] new intermolecular reactions have been realized with aliphatic and benzylic halides with Pd(0) catalysts[4] as well as with aliphatic halides and Pd(II)[5] or Ru(II) catalysts.[6]

An alternative to the use of aliphatic halides as a means of accessing the alkylpalladium(II) intermediates is to employ a Heck coupling of an aryl halide with an alkene in a domino sequence with a direct arylation step.[7] This strategy has been successfully employed in the preparation of complex organic

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(3) (a) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33. (b) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158.

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(6) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045.

(7) For reviews on domino palladium-catalyzed reactions, see: (a) Patil, N. T.; Yamamoto, Y. *Top. Organomet. Chem.* **2006**, *19*, 91. (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, *21*, 4101. (c) De Meijere, A.; Von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 412. (d) Patil, N. T.; Yamamoto, Y. *Synlett* **2007**, *13*, 1994.

(8) For selected examples, see: (a) Grigg, R.; Sridharan, W.; Zhang, J. *Tetrahedron Lett.* **1999**, *40*, 8227. (b) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 34, 11803. (c) Sukanthini, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *38*, 7525. (d) Lee, C.-W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000**, *2*, 1213. (e) Arthuis, M.; Pontikis, R.; Florent, J.-C. *Tetrahedron Lett.* **2007**, *48*, 6397. (f) Ishikura, M.; Takahashi, N.; Yamada, K.; Yanada, R. *Tetrahedron* **2006**, *62*, 11580.

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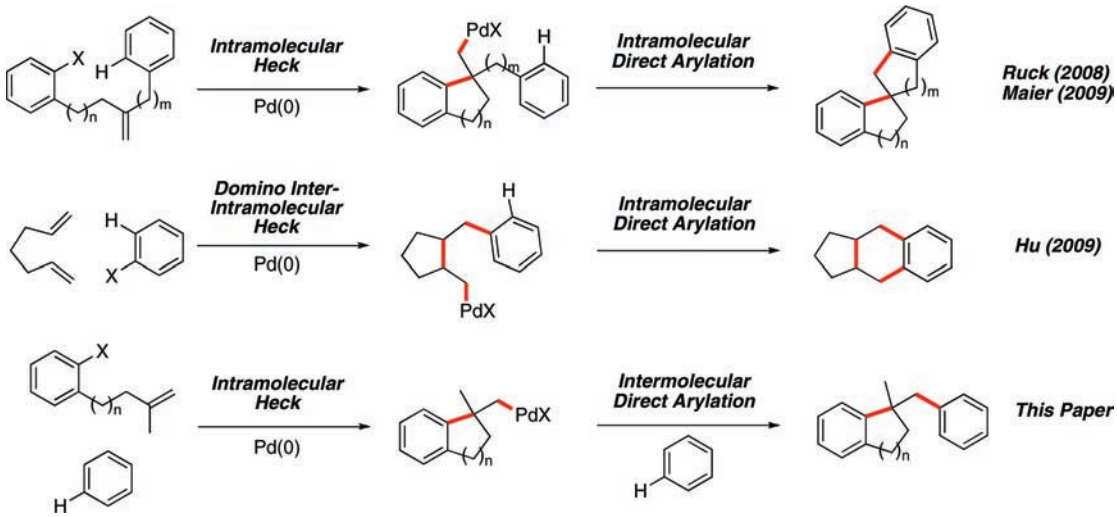
Scheme 1. Precedent in Domino Heck-Direct Arylation Involving Alkylpalladium(II) Intermediates and the Formation of New Csp^3-Csp^2 Bonds

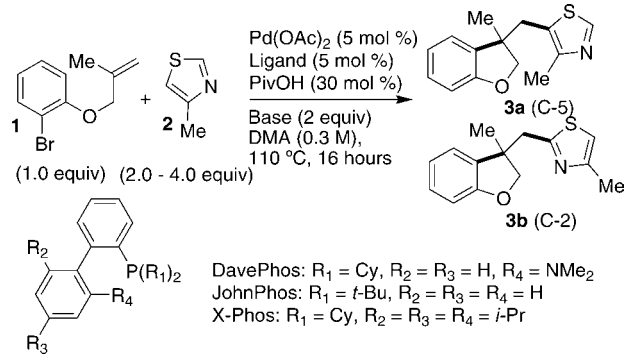


molecules using traditional techniques,[8] and the first examples of successful Heck-intramolecular direct arylation involving alkyl palladium(II) intermediates have recently been described (Scheme 1).[9] To our knowledge, no reports have appeared where a challenging intermolecular direct arylation-terminating step has been used. For this reaction class to function, the catalyst must undergo selective intermolecular direct arylation in the presence of unreacted alkene that may participate in a competitive intermolecular Heck-type addition to give unwanted byproduct. By building on previous advances in catalyst design in palladium-catalyzed direct arylation, our hope was that intermolecular direct arylation at an alkylpalladium(II) intermediate may become a favored process. Herein, we describe several examples demonstrating that such reactivity is indeed possible, providing rapid access to highly functionalized heterocyclic compounds. These results build on past success and should further inspire confidence in the use of direct arylation techniques as a viable alternative to the use of stoichiometric organometallic reagents in an ever widening range of commonly employed palladium(0)-catalyzed organic transformations.

Initial reaction development and optimization was performed with bromoarene **1** and 4-methylthiazole **2**. Two factors were found to exert a dramatic influence on both the yield and the regioselectivity of arylation: the base and the ligand.

For example, with DavePhos, the use of Cs_2CO_3 or K_3PO_4 as the base did not yield significant amounts of desired product (Table 1, entries 1 and 2). A noteworthy improvement was observed with K_2CO_3, giving rise to product **3a** in 21% yield with low regioselectivity (Table 1, entry 3).

Table 1. Optimization of the Reaction with 4-Methylthiazole[a]



entry	base	ligand	equiv. HetAr	yield (%) (**3a**/**3b**)[b]
1	Cs_2CO_3	DavePhos	2.0	2:2
2	K_3PO_4	DavePhos	2.0	4:1
3	K_2CO_3	DavePhos	2.0	21:9
4	K_2CO_3	JohnPhos	2.0	22:6
5	K_2CO_3	$P^tBu_3{\cdot}HBF_4$	2.0	10:31
6	K_2CO_3	X-Phos	2.0	33:4
7	K_2CO_3	X-Phos	4.0	57:5

[a] Reaction conditions: aryl bromide (1.0 equiv), heterocycle (2 or 4 equiv), $Pd(OAc)_2$ (5 mol %), ligand (5 mol %), PivOH (30 mol %), base (2.0 equiv), dimethylacetamide (0.3 M), 110 °C, 16 h. [b] Determined by GC analysis relative to tetradecane as an internal standard.

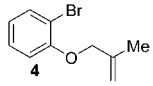
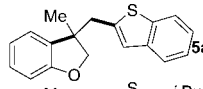
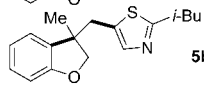
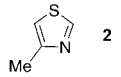
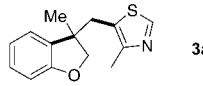
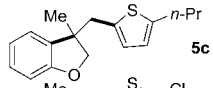
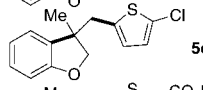
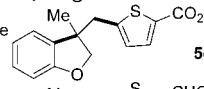
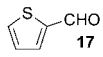
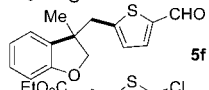
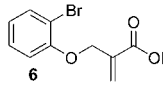
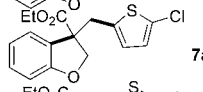
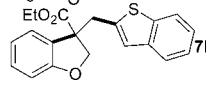
While the use of JohnPhos did not provide any notable change on the reaction outcome (Table 1, entry 4), the use of tri-*tert*-butylphosphine gave an inversion in direct arylation regioselectivity at the thiazole, providing regioisomer **3b** in 31% yield with a 3:1 regioisomeric ratio (Table 1, entry 5). X-Phos, on the other hand, gave a slightly improved yield

(9) (a) Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711. (b) Satyanarayana, G.; Maichle-Mössmer, C.; Maier, M. E. *Chem. Commun.* **2009**, *12*, 1571. (c) Hu, Y.; Yu, C.; Ren, D.; Hu, Q.; Zhang, L.; Cheng, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 5448. (d) For a slightly different variant of this process where the direct arylation occurs at the aryl halide fragment, see: Beaudoin, M.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3073.

of 33% but favored the formation of regioisomer **3a** in an 8:1 ratio (Table 1, entry 6). We also found that by using 4 equiv of the heterocyclic coupling partner,[10] the isolated yield of **3a** could be further improved to 57% with an 11:1 regioselectivity (Table 1, entry 7).

Pivalic acid, which has previously been shown to be a beneficial additive in palladium-catalyzed direct arylation,[11] also results in increased yields and reproducibility in these reactions. For example, dihydrobenzofurans **5a** and **5b** (Table 2, entries 1 and 2) are obtained in 76% and 72% yields in

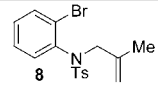
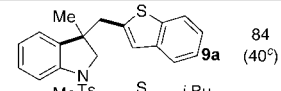
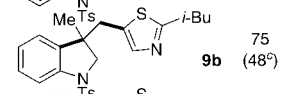
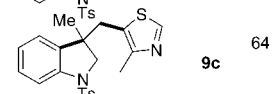
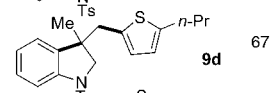
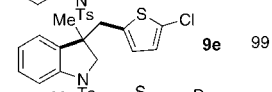
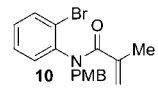
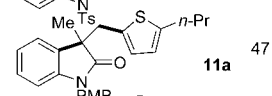
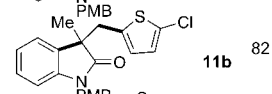
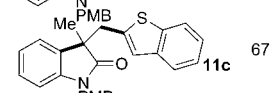
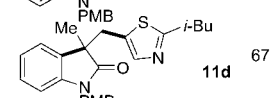
Table 2. Scope of the Reaction for the Formation of Dihydrobenzofurans[a]

entry	aryl bromide	heterocycle	product	yield (%)[b]
1	 **4**	 **12**	 **5a**	76 (66[c])
2	**4**	 **13**	 **5b**	72 (50[c])
3	**4**	 **2**	 **3a**	58 (58[c])
4	**4**	 **14**	 **5c**	76
5	**4**	 **15**	 **5d**	92
6	**4**	 **16**	 **5e**	47
7	**4**	 **17**	 **5f**	41
8	 **6**	**15**	 **7a**	55 (54[c])
9	**6**	**12**	 **7b**	61

[a] Reaction conditions: aryl bromide (1.0 equiv), heterocycle (4.0 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), PivOH (30 mol %), K_2CO_3 (2.0 equiv), dimethylacetamide (0.3 M), 110 °C, 16 h. [b] Yield of isolated product. [c] No PivOH added.

the presence of 30 mol % of PivOH, while 66% and 50% yields, respectively, are observed in its absence. The beneficial effect of pivalic acid is even more marked in the preparation of indolines **9a** and **9b** where yields of 84% and 75% are reduced to 40% and 48% when the use of pivalic acid is omitted (Table 3, entries 1 and 2). While the addition

Table 3. Scope of the Reaction for the Formation of Indolines and Oxindoles[a]

entry	aryl bromide	heterocycle	product	yield (%)[b]
1	 **8**	**12**	 **9a**	84 (40[c])
2	**8**	**13**	 **9b**	75 (48[c])
3	**8**	**2**	 **9c**	64
4	**8**	**14**	 **9d**	67
5	**8**	**15**	 **9e**	99
6	 **10**	**14**	 **11a**	47
7	**10**	**15**	 **11b**	82
8	**10**	**12**	 **11c**	67
9	**10**	**13**	 **11d**	67

[a] Reaction conditions: aryl bromide (1.0 equiv), heterocycle (4.0 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), PivOH (30 mol %), K_2CO_3 (2.0 equiv), dimethylacetamide (0.3 M), 110 °C, 16 h. [b] Yield of isolated product. [c] No PivOH added.

of pivalic acid is not a crucial prerequisite for product formation, given the improved outcomes associated with its use, we adopted the addition of 30 mol % of pivalic acid as a standard procedure in the evaluation of scope. The role of the potassium pivalate, generated in situ from the stoichiometric potassium carbonate base, is plausibly that of a ligand on the palladium metal that is involved in the transition state for heterocycle C−H bond cleavage.[11a]

llustrative examples of the scope are shown in Tables 2 and 3. Using aryl bromides **4** and **6**, the reaction affords 3,3-disubstituted dihydrobenzofurans with a variety of sulfur-containing heterocycles in yields up to 92% (Table 2). The transformation is compatible with benzothiophene (Table 2, entry 1), alkyl-substituted thiazoles at the 2 or 4 positions (Table 2, entries 2 and 3), and 2-propylthiophene (Table 2, entry 4) producing the dihydrobenzofuran products in good yields ranging from 58% to 76%. Chlorothiophene **15** is also an excellent substrate resulting in a 92% yield (Table 2, entry 5). Electron-withdrawing substituents on the thiophene such

(10) The excess heterocycle remains unreacted and can be recovered in the purification process.

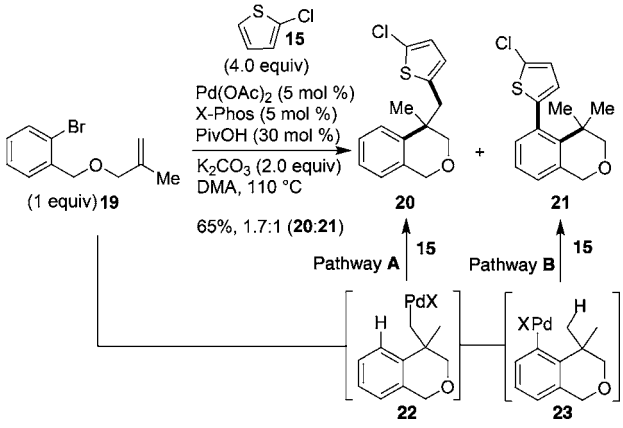
(11) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (c) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (e) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (f) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (g) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. (h) Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042. (i) Ackermann has found that other carboxylic acid additives improve outcomes in Ru-catalyzed direct arylation; see: Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201.

as a methyl ester and an aldehyde are also tolerated, albeit in more modest yields of 47% and 41%, respectively (Table 2, entries 6 and 7). Entries 8 and 9 show that dihydrobenzofurans can also be substituted by an ester at the 3 position in yields ranging from 55% to 61% using 2-chlorothiophene and benzothiophene as the second coupling partner.

Indolines and oxindoles are prevalent in natural products and medicinal compounds;[12] therefore, the establishment of methods enabling their rapid access remains an important goal. We were pleased to find that the domino Heck-direct arylation reaction may be used to access a variety of 3,3-disubstituted indoline and oxindole compounds (Table 3). For the formation of indolines, the reaction is compatible with benzothiophene (Table 3, entry 1), alkyl-substituted thiazoles (Table 3, entries 2 and 3), and 2-propylthiophene (Table 3, entry 4) with yields ranging from 64% to 84%. 2-Chlorothiophene is an ideal coupling partner, providing the desired indoline product in 99% yield (Table 3, entry 5). The formation of oxindoles is also possible with yields ranging from 47% with 2-propylthiophene (Table 3, entry 6) to 82% with 2-chlorothiophene (Table 3, entry 7). Benzothiophene **12** and thiazole **13** both gave product in 67% yield (Table 3, entries 8 and 9).

The formation of isochroman heterocycles was also investigated by the homologation of the phenyl ether to benzyl ether **19**. In this case, the formation of the two regioisomers **20** and **21** in a 1.7:1 ratio was obtained in 65% isolated yield for the mixture. This outcome is most likely the result of palladium migration from the alkyl group to the adjacent aromatic ring. As shown in Scheme 2, intermediate **22**, produced after the intramolecular Heck reaction may undergo two competitive processes: intermolecular direct arylation to give product **20** or migration to the neighboring aromatic ring to form a new arylpalladium(II) intermediate **23**. Once formed, **23** may then participate in an arylation process with the thiophene coupling partner to give regioisomer **21**. Larock and co-workers have demonstrated that such migratory processes can occur when the alkylpalladium intermediate and the adjacent C−H bond on the aromatic ring are in a favorable geometry.[13]

Scheme 2. Regioselectivity of the Formation of Isochromans



In conclusion, we have developed a domino Heck-intermolecular direct arylation to furnish a variety of dihydrobenzofurans, indolines, and oxindoles. The reaction conditions are general for a variety of sulfur-containing heterocycles as the direct arylation coupling partner and excellent yields can be obtained. In addition to synthetic utility, the demonstrated ability to combine direct arylation into this class of tandem process should raise confidence in the viability of other domino processes involving alkylpalladium(II) reactive intermediates.

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

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