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Palladium-Catalyzed Direct Heck Arylation of Dual π-Deficient/ π-Excessive Heteroaromatics. Synthesis of C-5 Arylated Imidazo[1,5-*a*]pyrazines

Jian-Xin Wang,[†] J. Adam McCubbin,[†] Meizhong Jin,[‡] Radoslaw S. Laufer,[‡] Yunyu Mao,[‡] Andrew P. Crew,[‡] Mark J. Mulvihill,[‡] and Victor Snieckus*[,†]

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6, and OSI Pharmaceuticals, Inc., 1 Bioscience Park Drive, Farmingdale, New York 11735

snieckus@chem.queensu.ca

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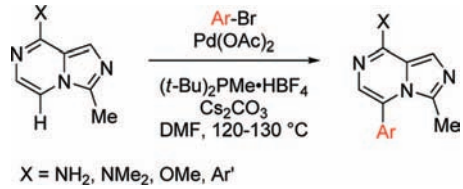
ABSTRACT



A general and efficient synthesis of 5-aryl imidazo[1,5-*a*]pyrazines by palladium-catalyzed coupling of the corresponding 8-substituted derivatives with aryl halides is described. The scope of this new reaction for the imidazo[1,5-*a*]pyrazine ring system was explored using three readily available 8-substituted precursors, X = NH_2, NMe_2, and OMe, as well as 8-aryl derivatives, X = Ar′. On the basis of these results as well as studies using a deuterated derivative, a Heck-like mechanism is proposed for this transformation.

Transition metal catalyzed reactions[1] have assumed a dominant position in C−C as well as C−N and C−O bond-forming reactions of synthetic value, especially for the construction of biaryls of medicinal, natural product, and material science significance.[2] In recent years, a new generation of transition metal catalyzed direct arylation reactions[3] has emerged in which one of the preactivated species of the standard cross coupling mode (ArX or ArMet) is a bare aromatic (ArH)[3a,4,5] (Figure 1) as a prelude perhaps to the ultimate regioselective coupling of two unactivated coupling partners. The Heck reaction, of the same vintage[6] as some of the other cross coupling named reactions[1] and

[†] Queen's University.
[‡] OSI Pharmaceuticals, Inc.

(1) For summaries of state of the art for various, including name, reactions, see: (a) *Metal Catalyzed Cross Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. Dedicated special issue of 30 years of cross-coupling: (b) Tamao, K.; Hiyama, T.; Negishi, E.-i. *J. Organomet. Chem.* **2002**, 653. For recent updated reviews, see Stille: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. Hiyama: (c) Denmark, S. E.; Sweis, T. F. *Acc. Chem. Res.* **2002**, *35*, 835. Suzuki−Miyaura: (d) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(2) (a) *Synthesis of Biaryls*; Cepanec, I., Ed.; Elsevier: Oxford, U.K., 2004. (b) Anctil, E. J.-G.; Snieckus, V. J. *Organomet. Chem.* **2002**, *653*, 150. (c) Echavarren, A. M.; Gomez-Lor, B.; Gonzalez, J. J.; de Frutos, O. *Synlett* **2003**, 585. (d) Hassan, J.; Sevignon, M.; Gozzi, C.; Schultz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Bringmann, G.; Tasler, S.; Pfeifer, R.-M.; Breuning, M. *J. Organomet. Chem.* **2002**, *661*, 49. (f) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (g) Bringmann, G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (h) Zapf, A.; Beller, M.; Riermeier, T. H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 231.

(3) For a rationale for the adoption of this terminology over the currently widely used C−H activation designation: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. See also: (b) Sezen, B.; Sames, D. In *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; p 3.

(4) For other reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (d) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

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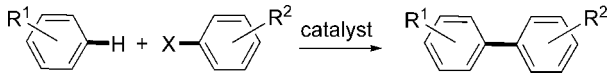


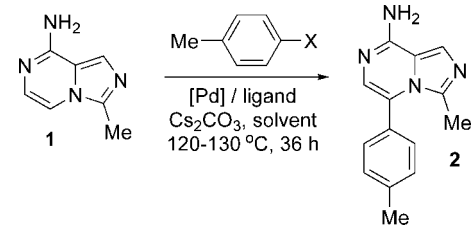
Figure 1. Direct arylation of aromatic compounds.

receiving similar broad adoption in synthesis in inter- and intramolecular processes,[7] has in fact been recently identified in the oxidative mode in which both arene and olefinic partners are unfunctionalized. Such reactions, as yet scattered in the literature, named either oxidative Heck or Heck-type processes, appear to be dependent in terms of rate and regioselectivity on substrate electrophilicity, especially in π-excessive heteroaromatics, and on coordination factors.[8]

As part of the continuing exploration of new chemistry of the imidazo[1,5-*a*]pyrazine core,[9] we discovered a palladium-catalyzed regioselective direct C-5 arylation reaction, **1** → **2**. Herein, we report the first Heck-like reaction on this combined π-deficient/π-excessive ring system which has a broad scope and, in consonance with aims of the evolving nonactivated coupling methods,[3a,4] demonstrates the advantages of minimizing waste and overcomes the requirement for frequently unstable organometallic coupling partners, a factor which is of wide-ranging significance in the construction of heterocyclic systems.[10] Electronic substituent variation on substrates and deuterium isotope studies suggest a Heck-like mechanism for this reaction.

The initial C-5 arylation reaction was observed when the model 8-amino-3-methylimidazo[1,5-*a*]pyrazine **1**[11] was subject to Pd-catalyzed coupling with 4-bromotoluene under Cs_2CO_3/PPh_3/DMF/120 °C conditions. The structure of the product **2** was established by ^{1}H NMR.[11] The low yield of the reaction (Table 1, entry 1) prompted screening studies,

Table 1. Optimization of C-5 Arylation Conditions for **1**[c]



entry	[Pd]/ligand[a]	solvent[b]	X	conversion/%
1	$Pd(OAc)_2/PPh_3$	DMF	Br	25
2	$Pd(PPh_3)_4$	DMF	Br	37
3	$Pd(PPh_3)_4$	DMSO	Br	46
4	$Pd(PPh_3)_4$	DMF	I	30
5	$Pd(OAc)_2/P(tBu)_3{\cdot}HBF_4$	DMF	Br	53
6	$Pd(OAc)_2/PCy_3{\cdot}HBF_4$	DMF	Br	44
7	$Pd(OAc)_2/MeP(tBu)_2{\cdot}HBF_4$	DMF	Br	69
8	$PdCl_2/MeP(tBu)_2{\cdot}HBF_4$	DMF	Br	68
9	$Pd_2dba_3/MeP(tBu)_2{\cdot}HBF_4$	DMF	Br	22
10	$Pd(OAc)_2/MeP(tBu)_2{\cdot}HBF_4$	DMF	Cl	34

[a] Pd:L = 1:2 (molar ratio). [b] Substrate concentration = 0.2 M. [c] Conversion determined by reverse-phase HPLC using 4-methoxy-benzoic acid as an internal standard.

a selection of which is given in Table 1 and deserves brief comment. Use of preformed $Pd(PPh_3)_4$ in DMF or DMSO in reactions of **1** with 4-bromo- or 4-iodotoluene showed modest improvement or little change in the efficiency of the reaction (entries 2−4). Significant improvement resulted

(5) For recent reports categorized by classes of compounds, see, inter alia: simple aromatics: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. ArBr with aromatics bearing Lewis basic directing groups: (e) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (f) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (g) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (h) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. Pyrroles and indoles: (i) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (j) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (k) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (l) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. Thiazoles: (m) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. Intramolecular cases: (n) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (o) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (p) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460.

(6) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

(7) For a review, see: (a) Bräse, S.; de Meijere, A. In *Metal Catalyzed Cross Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 217−317. For insightful mechanistic discussion, see: (b) Beletskaya, I.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(8) For original studies, see: (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *12*, 1119. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranish, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. For recent work, see: (c) Jia, C. G.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (d) Yokta, T.; Tani, S.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (e) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221. For current activity, according to compound type, see carbo- and heterocycles and intramolecular reactions: (f) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (g) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293. (h) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084. (i) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. Thiophenes, furans: (j) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. Pyrroles, indoles: (k) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552. (l) Zhang, H. M.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (m) Grimster, N. P.; Gauntlett, C.; Godfrey, C. D.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (o) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. Indolizines: (p) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. Imidazo[1,2-*a*]pyrimidines: (q) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. Anilides: (r) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (s) Lee, G. T.; Jiang, X.; Prasad, K.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921.

(9) This ring system shows remarkable antitumor, antimicrobial, and cardiovascular activities. See: (a) Beck, P. A.; Cesario, C.; Cox, M.; Dong, H.-Q.; Foreman, K.; Mulvihill, M. J.; Nigro, A. I.; Saroglou, L.; Steinig, A. G.; Sun, Y.; Weng, Q.; Werner, D.; Wilkes, R.; Williams, J. U.S. Patent 0084654, 2006. (b) Mulvihill, M. J.; Ji, Q.-S.; Coate, H. R.; Cooke, A.; Dong, H.; Feng, L.; Foreman, K.; Rosenfeld-Franklin, M.; Honda, A.; Mak, G.; Mulvihill, K. M.; Nigro, A. I.; O'Connor, M.; Pirrit, C.; Steinig, A. G.; Siu, K.; Stolz, K. M.; Sun, Y.; Tavares, P. A. R.; Yao, Y.; Gibson, N. W. *Bioorg. Med. Chem.* **2008**, *16*, 1359. See also (c) Demrayak, S.; Kayagil, I. *J. Heterocycl. Chem.* **2005**, *42*, 319.

(10) Tyrrell, E.; Brooks, P. *Synthesis* **2003**, 469.

(11) See Supporting Information.

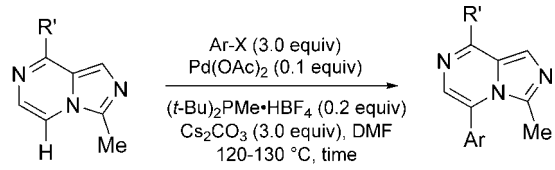
when the reactions were carried out using catalytic $Pd(OAc)_2$[5b] and the stable and easily handled phosphonium-BF_4 salts[12] as ligands (entries 5−7) with the $MeP(tBu)_2{\cdot}HBF_4$ (entry 7) showing the best conversion.[13] Variation of the Pd source in the coupling of **1** with 4-bromotoluene resulted in either no significant change or a decrease in yield of product (entries 8 and 9). The lower yields in reactions of aryl iodide compared to aryl bromide (entries 2 and 4) are consistent with previous observations in similar reactions[5b] as is the lower reactivity of aryl chlorides (entry 10).[14]

With optimized conditions in hand, the scope of the C-5 arylation reaction was investigated (Table 2). First, the hypothesis that the 8-amino primary amine functionality may compromise yields[15] was tested by changing the substrate to the corresponding 8-dimethylamino derivative **3**[11] (Table 2). Using the same conditions, product **4** was obtained in significantly improved yields (entry 2). Extension to two other aryl bromides gave products **4b** and **4c** (entries 3 and 4) in good yields. Generalization was then extensively carried out on the 8-methoxy derivative **5**.[11] As gleaned from Table 2, synthetically useful yields of products were observed for coupling reactions of a variety of aryl bromides. As was the case for **3**, the 8-methoxy system **5** underwent smooth coupling at accelerated rates compared to the corresponding 8-amino imidazopyrazine **1** (entries 2 and 5 vs entry 1).

Using EWG (entries 6−10) and EDG (entries 11−15) bearing aryl bromide coupling partners gave products in very good to excellent yields. However, while strong EDG 3- and 4-OMe substitution (entries 17 and 18) was well tolerated, the corresponding 2-OMe and 2,4-diOMe derivatives (entries 16 and 19) provided product with decreased efficacy. Ester and amide EWG substituted coupling partners gave moderate yields of products (entries 21−24), while cyano and nitro substituted aryl bromides were found to be unstable to the reaction conditions and resulted in decomposition. The sterically hindered mesityl bromide[16] failed to react under the specified conditions (120 °C, 36 h). Unequivocal confirmation of the structure of a representative C-5 arylated product was obtained in the form of the X-ray structure of compound **6a** and **6n**.

To understand the mechanism of the direct arylation reaction, the 8-arylimidazopyrazines **8a**−**d**, positing EDGs

Table 2. Scope of Coupling of 8-Substituted Imidazopyrazines

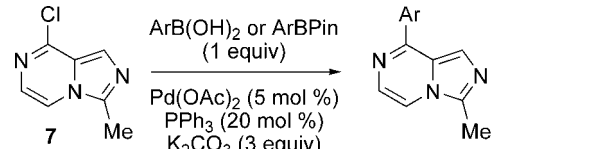


1 R′ = NH_2
3 R′ = NMe_2
5 R′ = OMe

2 R′ = NH_2
4 R′ = NMe_2
6 R′ = OMe

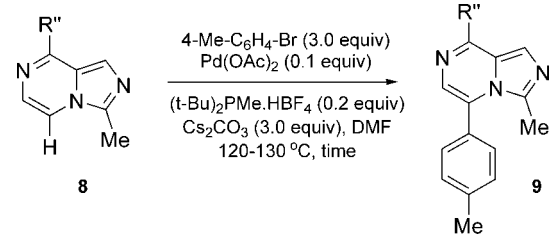
entry	R′	Ar-X	time/h	product (% yield)
1	NH_2	4-Me-C_6H_4Br	36	**2** (61)
2	NMe_2	4-Me-C_6H_4Br	12	**4a** (85)
3	NMe_2	4-F-C_6H_4-Br	24	**4b** (88)
4	NMe_2	4-MeO-C_6H-Br	36	**4c** (74)
5	OMe	PhBr	12	**6a** (85)
6	OMe	4-F-C_6H_4Br	12	**6b** (95)
7	OMe	2-F-C_6H_4Br	12	**6c** (87)
8	OMe	4-CF_3-C_6H_4Br	12	**6d** (80)
9	OMe	3-CF_3-C_6H_4Br	12	**6e** (87)
10	OMe	4-Cl-C_6H_4Br	12	**6f** (85)
11	OMe	4-Me-C_6H_4Br	24	**6g** (81)
12	OMe	3-Me-C_6H_4Br	12	**6h** (92)
13	OMe	2-Me-C_6H_4Br	36	**6i** (84)
14	OMe	2-Me -C_6H_4I	12	**6i** (73)
15	OMe	4-Ph-C_6H_4Br	12	**6j** (84)
16	OMe	2-MeO-C_6H_4Br	24	**6k** (45)
17	OMe	3-MeO-C_6H_4Br	12	**6l** (80)
18	OMe	4-MeO-C_6H_4Br	12	**6m**(89)
19	OMe	2,4-diMeO-C_6H_3Br	24	**6n** (65)
20	OMe	4-Me_2N-C_6H_4Br	12	**6o** (51)
21	OMe	4-MeO_2C-C_6H_4Br	12	**6p** (70)
22	OMe	3-MeO_2C-C_6H_4Br	12	**6q** (66)
23	OMe	2-MeO_2C-C_6H_4Br	36	**6r** (47)
24	OMe	3-Me_2NOC-C_6H_4Br	36	**6s** (55)

Scheme 1. General Synthesis of 8-Aryl-3-Substituted Imidazo[1,5-*a*]pyrazines



8a Ar = 4-MeO-C_6H_4 (99%)
8b Ar = 4-F-C_6H_4 (99%)
8c Ar = 3-NO_2-C_6H_4 (98%)
8d Ar = 4-NO_2-C_6H_4 (97%)

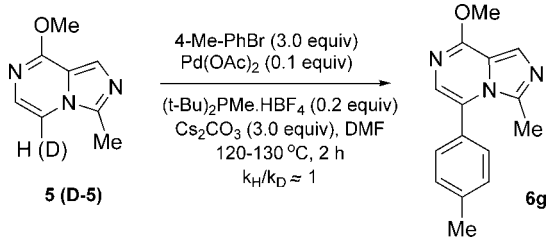
Table 3. EWG and EDG Substituent Effects on Coupling of **8**



entry	substrate	R″	time/h	product (yield/%)
1	**8a**	4-MeO-C_6H_4	11	**9a**(99)
2	**8b**	4−F-C_6H_4	10	**9b**(99)
3	**8c**	3-NO_2-C_6H_4	8	**9c**(98)
4	**8d**	4-NO_2-C_6H_4	4	**9d**(97)

(12) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
(13) Increasing the ligand to catalyst ratio to 4:1 had no significant effect, whereas decreasing it to 1:1 resulted in a ca. 30% decrease in conversion. Changing the concentration of the reaction to 0.4 M and to 0.8 M resulted in a moderate but steady decrease in conversion.
(14) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
(15) For a proposal in the reaction of aminopyrimidine, see: Itoh, T.; Mase, T *Tetrahedron Lett.* **2005**, *46*, 3573.

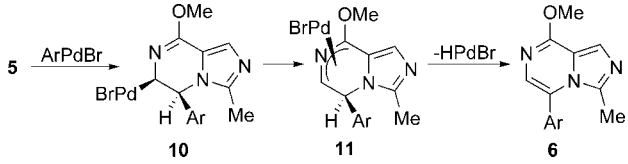
Scheme 2



and EWGs, were prepared by treatment of 8-chloro derivative **7**[17] with the corresponding aryl boronic acids by the venerable Suzuki−Miyaura cross coupling protocol (Scheme 1) and evaluated. As recognized from examination of Table 3, **8a**−**d** underwent rapid arylation under the standard conditions to afford products **9a**−**d** in quantitative yields. The lack of an electronic effect (entry 1 vs entry 4) on the reactivity suggests that an electrophilic palladation mechanism, which is frequently suggested to rationalize arylation of this type,[5l,8j,k,q] is not operating in the present case.

To further probe the mechanism of C-5 arylation, the 5-deutero analogue **D-5** was prepared[18] and subjected to the optimum conditions using a 1:1 mixture of **5** and **D-5** (Scheme 2). This experiment revealed no isotope effect ($k_{H/D} \sim 1$),[19] a result consistent with a Heck-type mechanism[8g] consisting of rate-determining carbopalladation (Scheme 3,

Scheme 3



10) followed by formation of an unprecedented π-azaallyl intermediate **11**[20] and rapid reductive elimination to product **6**. To the contrary, the observation of such a lack of a primary KIE is inconsistent with C−H oxidative addition,[21] proton abstraction,[5a,c,8f] and σ-bond metathesis.[8h,21] In addition, an electrophilic substitution[5j,8i,j,p,q] mechanism, which would be expected to give an inverse secondary KIE, is ruled out on the basis of the results in Table 3.[22] For the imidazopyrazine core bearing EDGs, the controlling features may be associated with facile carbopalladation reactivity which is due to a balance of electronic (combined π-deficient/π-excessive) and N-coordination features.

In summary, an efficient, regioselective, and direct C-5 arylation of imidazo[1,5-*a*]pyrazines **1**, **3**, and **5** has been developed. A general methodology has been developed allowing the synthesis of diverse substituted derivatives (Table 2) in good to excellent yields. In contrast to direct arylation of the imidazo[1,2-*a*]pyrimidines,[8q] arylation occurs in the electron-deficient albeit EDG-containing ring. A Heck-like mechanism, rather than alternative currently proposed mechanisms for similar reactions, is consistent with reactivity and KIE studies. This work, together with other contributions in this area,[5a,d,f,i,n,8j,p] allows anticipation that transition metal catalyzed coupling reactions in which one or both partners are unactivated, thereby eliminating wasted steps and stability issues, will increasingly appear in the tool box of the synthetic chemist.

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Supporting Information Available: Preparation of starting materials, experimental procedures, and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800761R

(16) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(17) Attempts to prepare the strongly electron-withdrawing 8-NO_2 and 8-CN variants of **1** were unsuccessful.

(18) Treatment of **5** with *n*-BuLi followed by quench with MeOD afforded **D-5**,[11] a suprising result in view of the expected acidity of the C-2 methyl hydrogens which is being experimentally pursued.

(19) The ratio of **5**:**D-5** in recovered starting material was determined by peak integration in the ^{1}H NMR spectrum.[11]

(20) This intermediate is analogous to those proposed for similar systems. See for example, refs 8j and 4a. Acyclic 2-aza-π-allyl palladium intermediates have been proposed previously. See, for example: O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A. *J. Org. Chem.* **1997**, *62*, 3962.

(21) For computational studies, see: (a) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171. (b) Davies, D. L.; Donald, S. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754.

(22) Furthermore, electrophilic bromination of such derivatives affords the C1 bromination product only, which indicates that the imidazole ring has the highest HOMO population: Abushanab, E.; Bindra, A. P.; Lee, D.-Y. *J. Org. Chem.* **1975**, *40*, 3373.