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Palladium Catalyzed One-Pot Sequential Suzuki Cross-Coupling–Direct C–H Functionalization of Imidazo[1,2-*a*]pyrazines

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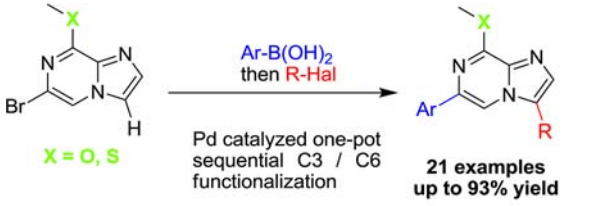
ABSTRACT



An efficient "one-pot" selective functionalization at C3/C6 of imidazo[1,2-*a*]pyrazines has been developed via a palladium-catalyzed sequential Suzuki–Miyaura cross-coupling/direct C–H arylation, vinylation, and benzylation. The procedure remains effective in the presence of a methyl thioether group at C8, which may in turn be successfully engaged in a cross-coupling method to afford 3,6,8-trisubstituted imidazo[1,2-*a*]-pyrazines. This work paves the way for the design of biologically relevant compounds in an imidazo[1,2-*a*]pyrazine series.

One of the most important challenges in organic synthesis is to synthesize efficiently complex molecular structures from trivial compounds. Thus, the development of multistep sequences in a single flask, such as tandem, cascade, or sequential reactions, has been the focus of much attention in the organic chemistry community.[1] A number of advantages of these processes are extremely attractive for synthetic chemists and pharmaceutical companies, such as the reduction of cost, time, and waste. One of the most appealing aspects of this strategy is to produce a large molecular diversity and to introduce a wide degree of complexity in a single transformation. In this context, transition-metal-catalyzed C–H bond activation has recently emerged as a powerful tool that may be advantageously associated with more commonplace cross-coupling methods to develop one-pot sequential functionalization of various relevant fused heterocycles.

The imidazo[1,2-*a*]pyrazine is an important pharmacophore prevalent in a number of biologically active molecules,[2] such as acid pump antagonists,[2c] kinase aurora

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(1) For general references, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (c) Padwa, A. *Pure Appl. Chem.* **2004**, *76*, 1933–1952. (d) Wu, G.; Yin, W.; Shen, H. C.; Huang, Y. *Green Chem.* **2012**, *14*, 580–585.

(2) For selected examples, see: (a) Sablayrolles, C.; Cros, G.; Milhavet, J.-C.; Rechenq, E.; Chapat, J.-P.; Boucard, M.; Serrano, J. J.; McNeill, J. H. *J. Med. Chem.* **1984**, *27*, 206–212. (b) Shimokawa, H.; Yamagishi, T. (Pfizer Inc.). PCT Int. Appl. WO/2008/059373A1, 2008; AN 2008:607625. (c) Zimmermann, P. J.; Brehm, C.; Buhr, W.; Palmer, A. M.; Volz, J.; Simon, W.-A. *Bioorg. Med. Chem.* **2008**, *16*, 536–541. (d) Ken-Ichi, K.; Hiroshi, Y.; Kohei, N.; Hiroshi, H.; Genta, T.; Jun, S.; Yuusuke, T.; Yasunori, M. (Oncotherapy Science, Inc.). US/2012/0059162A1, 2012; AN 2012:346056. (e) Belanger, D. B.; Curran, P. J.; Hruza, A.; Voigt, J.; Meng, Z.; Mandal, A. K.; Siddiqui, M. A.; Basso, A. D.; Gray, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5170–5174. (f) Bartolomé-Nebreda, J. M.; Conde-Ceide, S.; Macdonald, G. J.; Pastor-Fernandez, J.; Van Gool, M. L.; Martin-Martin, M. L.; Vanhoof, G. C. (Janssen Pharmaceutica NV). WO/2011/110545A1, 2011; AN 2011:1164004.

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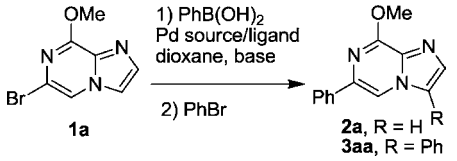
inhibitors,[2e] and phosphodiesterase inhibitors.[2f] Several procedures for transition-metal-catalyzed direct C−H functionalization of imidazoazines have been developed, notably in the imidazo[1,2-*a*]pyridine[3] and imidazo[1,2-*a*]pyrimidine[4] series. Remarkably, Guillaumet et al. have described the first sequential functionalization of imidazo[1,2-*a*]pyridines by implementing Suzuki−Miyaura and direct C−H cross-coupling reactions.[3b] However, the imidazo[1,2-*a*]pyrazine series remains almost unexplored since only one paper reporting on the palladium-catalyzed direct C−H arylation at C3 of the naked imidazo[1,2-*a*]pyrazine skeleton with iodobenzene was recently disclosed by Chatani.[5] Among the available imidazo[1,2-*a*]pyrazine scaffolds, the readily prepared 6-bromoimidazo[1,2-*a*]pyrazine flanked with a methyl ether (**1a**) or a methyl thioether (**1b**) group at C8 position[6] represent attractive candidates for sequential coupling reactions.[3b,7] Herein, we report an efficient procedure for the sequential functionalization of 6-bromoimidazo-[1,2-*a*]pyrazine **1a** and **1b** at C3/C6 positions through a palladium-catalyzed one-pot Suzuki−Miyaura−direct CH cross-coupling sequence. To the best of our knowledge, this work constitutes one of the rare successful palladium-catalyzed direct C−H functionalization conducted in the presence of a sulfide group[8] which could act as a poison of palladium catalyst.[9]

Our study was initiated with the Suzuki−Miyaura coupling reaction between **1a** and phenylboronic acid under a palladium-based catalysis in the presence of $Pd(OAc)_2$/PPh_3 and Cs_2CO_3 base in dioxane at 90 °C (Table 1). These conditions previously proved to be effective in the direct C3-H arylation of imidazoazines.[4a] The complete conversion of the reaction (monitoring by GC−MS) was attained within 3 h, and the expected 6-phenylimidazopyrazine **2a** was further isolated in quantitative yield (entry 1). The first sequential selective C6-Br/C3-H double arylation was then carried out by simply adding bromobenzene in the wake of the initial Suzuki−Miyaura cross-coupling reaction. The resulting reaction mixture was then stirred for a further 18 h while raising the temperature to 120 °C. Pleasingly, the expected diarylated imidazopyrazine **3aa** was obtained in fairly good 67% isolated yield (entry 2), along with a 20% yield of the monoarylated intermediate **2a**. This preliminary result is all the more interesting as no further addition of palladium catalyst is required for the subsequent C3-H functionalization step.

Table 1. Optimization of Reaction Conditions[a]



entry	ligand	base	yield[c] (%) of **1a/2a/3aa**
1[b]	PPh_3	Cs_2CO_3	0/99/0
2	PPh_3	Cs_2CO_3	0/20/67
3	P*o*-Tol_3	Cs_2CO_3	0/50/47
4	$P^tBu_3 \cdot HBF_4$	Cs_2CO_3	0/20/66
5	$PCy_3 \cdot HBF_4$	Cs_2CO_3	0/70/20
6	CyJohnPhos	Cs_2CO_3	0/0/99 (95)[d]
7	CyJohnPhos[e]	Cs_2CO_3	0/0/87 (85)[d]
8	CyJohnPhos[e]	K_2CO_3	0/23/68 (63)[d]

[a] Reaction conditions: A mixture of 10 mol % of Pd source, 20 mol % of phosphine ligand, 0.2 mmol of **1a**, 1 equiv of $PhB(OH)_2$, and 5 equiv of base in 1 mL of dioxane was heated to 90 °C for 3 h, and then 1.5 equiv of bromobenzene was added and the resulting mixture was heated to 120 °C for a further 18 h. [b] 10 mol % of Pd source, 20 mol % of phosphine ligand, 0.2 mmol of **1a**, 1 equiv of $PhB(OH)_2$, 5 equiv of base, 1 mL of solvent, 90 °C. [c] Yields determinated by NMR and GC analysis with internal standard. [d] Isolated yields of **3aa**. [e] 5 mol % of Pd source and 10 mol % of ligand were used.

A survey of different phosphines (entries 3−6) revealed that 2-(dicyclohexylphosphino)biphenyl (CyJohnPhos) displayed the best performance, providing the expected diarylated imidazopyrazine **3aa** in 95% isolated yield (entry 6). Interestingly, no significant drop of the yield (85%) was observed when using a catalyst loading as low as 5 mol % (entry 7). When the reaction was performed in the presence of K_2CO_3, diarylated imidazopyrazine **3aa** was obtained with a somewhat lower yield (63%) together with the monoarylated imidazopyrazine **2a** (23%), pointing out the superiority of Cs_2CO_3 in the C−H bond activation step (entry 8).

The scope and limitation of this Suzuki−Miyaura cross-coupling/C3−H bond activation sequence was then investigated using the optimized procedure; namely $Pd(OAc)_2$ (5 mol %), CyJohnPhos (10 mol %), Cs_2CO_3 (5.0 equiv) in dioxane by using various arylboronic acids and aryl halides (Table 2).

(3) (a) Touré, R. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979–1982. (b) Koubachi, J.; Kazzouli, S. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *J. Org. Chem.* **2007**, *72*, 7650–7655. (c) Koubachi, J.; Kazzouli, S. E.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synthesis* **2008**, 2537–2542. (d) Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Synthesis* **2009**, 271–276. (e) Singhaus, R. R.; Bernotas, R. C.; Steffan, R.; Matelan, E.; Quinet, E.; Nambi, P.; Feingold, I.; Huselton, C.; Wilhelmsson, A.; Goos-Nilsson, A.; Wrobel, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 521–525. (f) Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron* **2010**, *66*, 1937–1946. (g) Kumar, P. V.; Lin, W.-S.; Shen, J.-S.; Nandi, D.; Lee, H. M. *Organometallics* **2011**, *30*, 5160–5169. (h) Cao, H.; Zhan, H.; Lin, Y.; Lin, X.; Du, Z.; Jiang, H. *Org. Lett.* **2012**, *14*, 1688–1691. (i) Fu., H. Y.; Chen, L.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473–4478.

(4) (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835–4837. (b) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584.

(5) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem. Asian J.* **2012**, *7*, 1357–1365.

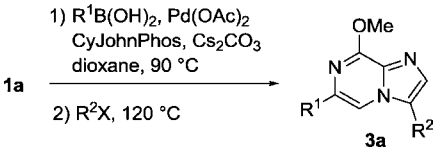
(6) Compounds **1a** and **1b** were prepared according to the literature procedures; see: Bradač, J.; Furek, Z.; Janežič, D.; Molan, S.; Smerkolj, I.; Stanovnik, B.; Tišler, M.; Verček, B. *J. Org. Chem.* **1977**, *42*, 4197–4201and ref 2e.

(7) For selected examples of one-pot palladium-catalyzed coupling reactions, see: (a) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537–1539. (b) Handy, S. T.; Wilson, T.; Muth, A. *J. Org. Chem.* **2007**, *72*, 8496. (c) Zhang, X.; Liu, A.; Chen, W. *Org. Lett.* **2008**, *10*, 3849–3852. Wong, N. W. Y.; Forgione, P. *Org. Lett.* **2012**, *14*, 2738–2741.

(8) For selected examples, see: (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972. (b) Yu, M.; Xie, Y.; Xie, C.; Zhang, Y. *Org. Lett.* **2012**, *14*, 2164–2167.

(9) (a) Hegedus, L. L.; McCabe, R. W. In *Catalyst Poisoning*; Marcel Dekker: New York, 1984. (b) Hutton, A. T. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, U.K., 1984; Vol. 5.

Table 2. Synthesis of Compounds **3a**[a]



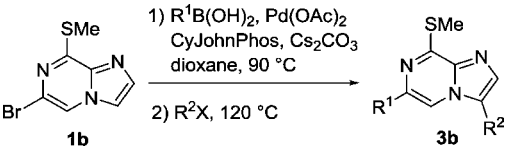
entry	R^1	R^2X	product	yield[b] (%)
1	Ph	PhBr	**3aa**	93
2	4-$MeOC_6H_4$	PhBr	**3ab**	89
3	4-$MeOC_6H_4$	PhCl	**3ab**	81
4	4-$MeOC_6H_4$	PhI	**3ab**	90
5	4-FC_6H_4	PhBr	**3ac**	73
6	3-$CF_3C_6H_4$	4-$Me_2NC_6H_4Br$	**3ad**	81
7	4-$Me_2NC_6H_4$	4-ClC_6H_4Br	**3ae**	56
8	Ph	2-bromo-6-methoxypyridine	**3af**	63
9	Ph	4-NCC_6H_4Br	**3ag**	90
10	Ph	4-$MeSC_6H_4Br$	**3ah**	81
11	Ph	3-$MeO_2CC_6H_4Br$	**3ai**	71
12	Ph	3-bromothiophene	**3aj**	30
13	Ph	BnCl	**3ak**	65
14	Ph	1-bromo-2-methylpropene	**3al**	66[c]
15	Ph	1-chloro-2-methylpropene	**3al**	65[c]
16	3-$NO_2C_6H_4$	2-bromopropene	**3am**	60[c]
17	4-Py[d]			
18	2-thienyl[d]			
19	2-benzofuranyl[d]			

[a] Reaction conditions: A mixture of boronic acid (1 equiv), **1a** (0.5 mmol, 1 equiv), $Pd(OAc)_2$ (0.05 equiv), CyJohnPhos (0.1 equiv), and Cs_2CO_3 (5 equiv) in 2.5 mL of dioxane was heated to 90 °C under N_2 for an appropriate time after which R^2X (1.5 equiv) was added, and the resulting mixture was heated to 120 °C for a further 18 h. [b] Isolated yields. [c] 3 equiv of R^2X were used. [d] The Suzuki coupling does not occur.

As first observations, good to high yields of imidazopyrazine **3a** were obtained with a large range of arylboronic acids and aryl halides bearing either electron-donating or -withdrawing groups (entries 2−11). However, Suzuki−Miyaura cross-coupling reactions of **1a** with commercially available heteroarylboronic acids failed to give the desired cross-coupling product under these conditions (entries 17−19). Gratifyingly, the challenging palladium-catalyzed direct C3-H functionalization appeared to be efficient with both 4-iodoanisole and 4-choroanisole (entries 3 and 4) as well as heteroaryl bromides (entries 8 and 12).

More importantly, subsequent to the Suzuki−Miyaura coupling reaction, direct C−H vinylation and benzylation could be successfully achieved using various vinyl bromides and benzyl chloride as electrophiles, affording **3ak**−**am** in fair yields (entries 13−16). In addition, the survival of the palladium during C3−H arylation of **2a** flanked with a sulfide function (entry 10) encouraged us to explore the scope of this sequential C6-Br/C3-H cross-coupling method further with a structural analogue of **1a**, namely the 6-bromo-8-methylthioimidazo[1,2-*a*]pyazine **1b** (Table 3). After checking that the initial Suzuki−Miyaura cross-coupling step afforded 6-phenylimidazopyrazine **2b** in a quantitative yield (entry 1), we were

Table 3. Synthesis of Compounds **3b**[a]



entry	R^1	R^2X	product	yield[b] (%)
1	Ph		**2b**	98
2[c]	Ph	PhBr	**3ba**	30
3	Ph	PhBr	**3ba**	62
4	Ph	3-NCC_6H_4Br	**3bb**	66
5	Ph	3-$MeOC_6H_4Br$	**3bc**	61
6	3-$CF_3C_6H_4$	3,4-MeC_6H_3Br	**3bd**	73
7	3-ClC_6H_4	4-MeC_6H_4Br	**3be**	65
8	4-$EtO_2CC_6H_4$	PhBr	**3bf**	72
9	3-$O_2NC_6H_4$	PhBr	**3bg**	65
10	4-$MeOC_6H_4$	PhBr		0[d]
11	4-$MeOC_6H_4$	PhI	**3bh**	30
12	Ph	1-bromo-2-methylpropene		0[d]
13	Ph	BnCl		0[d]

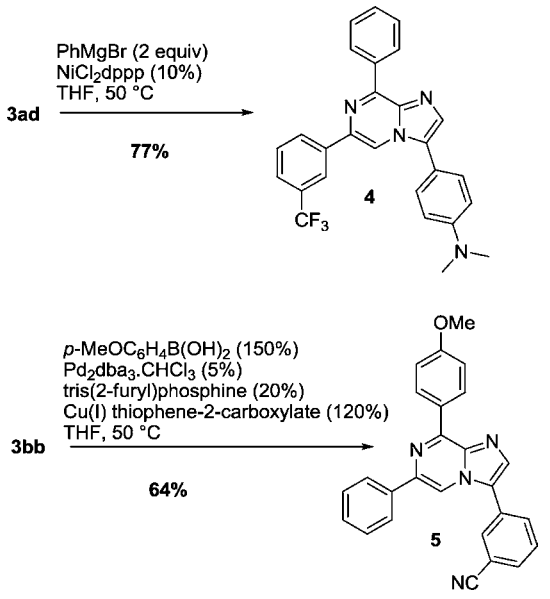
[a] Reaction conditions: A mixture of boronic acid (1 equiv), **1b** (0.5 mmol, 1 equiv), $Pd(OAc)_2$ (0.1 equiv), CyJohnPhos (0.2 equiv), Cs_2CO_3 (5 equiv) in 2.5 mL of dioxane was heated to 90 °C under N_2 for appropriate time after which R^2X (1.5 equiv) was added, and the resulting mixture was heated to 120 °C for a further 18 h. [b] Isolated yields. [c] Reaction performed with 5 mol % of $Pd(OAc)_2$. [d] Only the Suzuki coupling product was isolated.

pleased to observe the formation of the desired diarylated imidazopyrazine **3ba**, albeit in a modest 30% yield, when the imidazopyrazine **1b** was subjected to the whole reaction sequence (entry 2). This preliminary result could be significantly improved when 10 mol % of catalyst was used, producing **3ba** in a fair 62% yield (entry 3). With the optimized conditions in hand, we then exemplified this one-pot diarylation process with a variety of arylboronic acids and aryl halides, providing a novel library of 3,6-diarylated 8-methylthioimidazopyrazines **3b** (entries 4−11). In only one case, we found that subsequent to the Suzuki−Miyaura cross-coupling reaction between **1b** and the electron-rich 4-methoxyphenylboronic acid, the resulting monoarylated product **2b** failed to undergo C3−H arylation with bromobenzene (entry 10). However, the desired diarylated imidazopyrazine **3bh** could be formed in a modest 30% yield by using the more reactive iodobenzene (entry 11). In contrast to 6-bromo-8-methoxyimidazopyrazine **1a**, attempts to achieve arylation/C−H vinylation or benzylation sequences from the 8-methylthio analogue **1b** proved unfruitful (entries 12 and 13).

We finally took advantage of the presence of the methoxy and methylthio groups at C8 in both imidazopyrazines **3ad** and **3bb**, respectively, to implement an additional cross-coupling reaction which aimed at providing straightforward access to trisubstituted imidazopyrazines (Scheme 1). Thus, by applying a previously reported nickel-catalyzed cross-coupling method,[10] the triarylated imidazopyrazine **4** was

(10) For examples of C−O activation by Nickel catalyst: (a) Dankwardt, J. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2428–2432. (b) Xie, L.-G.; Wang, Z.-X. *Chem.—Eur. J.* **2011**, *17*, 4972–4975.

Scheme 1. Access to 3,6,8-Triarylated Imidazo[1,2-*a*]pyrazines



isolated in 77% yield from its corresponding 3,6-diarylated methyl ether imidazopyrazine precursor **3ad**. Pleasingly, the palladium- and copper-catalyzed cross-coupling of heteroaromatic thioethers and boronic acids previously reported by Liebeskind[11] has been successfully applied to compound **3bb** and 4-methoxyphenylboronic acid, affording the 3,6,8-triarylated imidazopyrazine **5** in 64% yield.

In summary, an original two-step single flask palladium-catalyzed Suzuki–Miyaura cross-coupling/direct C–H functionalization sequence has been developed from the readily available 8-methoxy- or 8-methylthio-6-bromoimidazo-[1,2-a]pyrazines **1a** and **1b**, allowing the straightforward functionalization at both the C3 and C6 positions of these readily available imidazopyrazine scaffolds. In addition, facile access to 3,6,8-trifunctionalized imidazo[1,2-*a*]pyrazines was also demonstrated by implementing a third cross-coupling reaction. This sequential cross-coupling approach supplies a large range of mono-, di-, or trifunctionalized imidazo[1,2-*a*]pyrazines being potentially pharmaceutically relevant heterocyclic products. Furthermore, this work reports one of the few examples of palladium-catalyzed direct C–H arylation with heteroaryl halides bearing a sulfide group.

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Supporting Information Available. Experimental protocols for the synthesis of compounds **2a**, **2b**, **3aa**–**am**, **3ba**–**bh**, **4**, and **5** and their characterization. Copies of ^{1}H and ^{13}C NMR spectra of the new compounds **2a**, **2b**, **3aa**–**am**, **3ba**–**bh**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979–981. (b) Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002**, 447–450.

The authors declare no competing financial interest.