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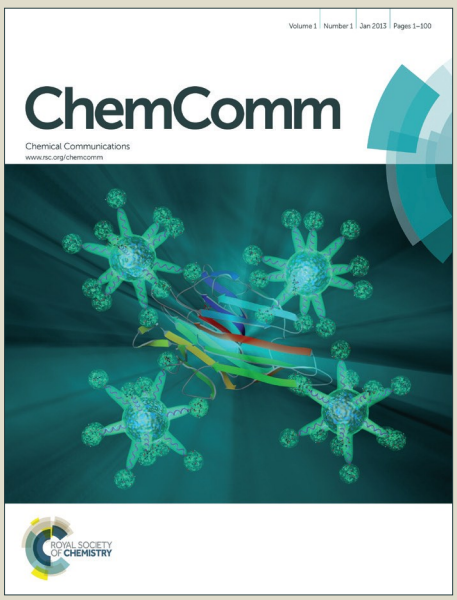

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Palladium-Catalyzed Regioselective C-2 Arylation of 7-Azaindoles, Indoles, and Pyrroles with Arenes

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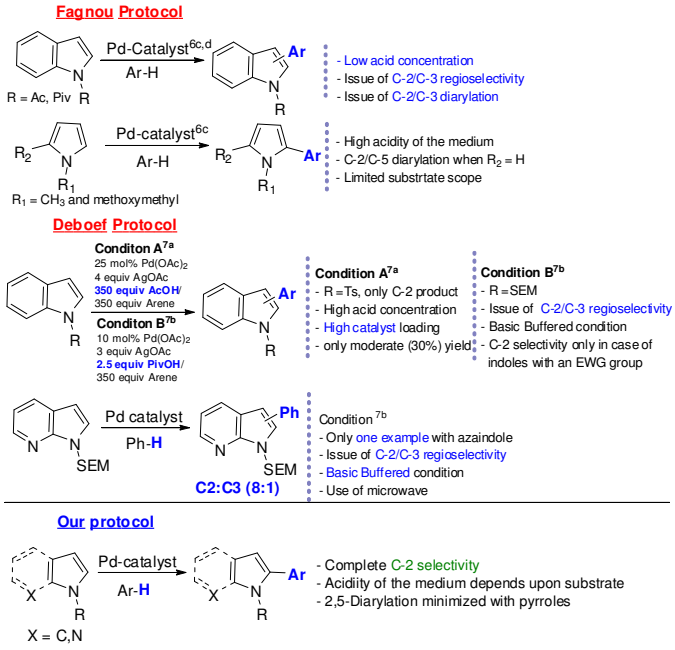
Abstract. A palladium-catalyzed regioselective C-2 arylation of 7-azaindoles, indoles, and pyrroles with arenes has been developed. The study unveils that a critical substrate dependent acid concentration is essential for achieving exclusive C-2 selectivity as well as mono-arylation in pyrroles. Incongruent to the literature, the protocol uses a reduced volume (at least 5 times) of arenes for a workable access to C-2 arylated heterocycles.

7-Azaindoles, indoles, and pyrroles containing a 2-aryl group are privileged molecular scaffolds in therapeutic discovery with a proven track record of drugabililty, while each requiring a 2-aryl group for demonstrated pharmacophoric activities.[1] C-2 arylation of these nitrogen heterocycles have traditionally been effected using transition-metal-catalyzed cross-couplings[2] or direct arylations[3] utilizing either one or both prefunctionalized substrate(s). However, the dependence on these cross-couplings reactions has gradually been reduced since the evolution of oxidative couplings involving double C(sp^2)-H bonds. Unlike traditional cross-couplings, transition-metal-catalyzed oxidative couplings involving double C(sp^2)-H bonds[4] obviate the requirement of prefunctionalized substrates and alleviate the generation of salt-waste substantially, thereby empowering superior sustainability and environmental compatibility. Remarkably, transition-metal-catalyzed oxidative couplings have been proven a powerful variant of traditional couplings enabling rapid C-H arylation on heteroarenes.[5] However, a fundamental challenge intrinsic to these oxidative functionalizations lies in achieving regioselective C-H arylations of nitrogen heterocycles.[5a,c,e,f] Towards this endeavor, a few reports, contributed independently by Fagnou and DeBoef, of regioselective C-2 arylation of indoles and pyrroles with arenes via transition-metal-catalyzed oxidative coupling has successfully been



Scheme 1. Regioselective C-2-Arylation of 7-azaindoles, indoles and pyrroles with Arenes.

achieved enabling C-2 arylated indoles/pyrroles in good to excellent yields.[6,7] While a complete C-2 selectivity utilizing *N*-Ts indoles was achieved under a high acid concentration *albeit* in low yield (30%),[7a] only a mixture of C-2/C-3 arylated products could be obtained when *N*-SEM indoles was used under low acid concentration.[7b] In contrast, C-2 arylation of *N*-protected pyrroles required a strong acidic medium.[6c] Although the current literature is quite resourceful warranting applications of oxidative couplings to the preparation of 2-aryl indoles or pyrroles, they still suffer from C-2/C-3 site-selectivities within indoles and mono/2,5-diarylation in pyrroles. Moreover, the application is largely impeded to the preparation of 2-aryl-7-azaindoles. Remarkably, DeBoef et al. included an exotic example of oxidative coupling to the preparation of 2-phenyl-1-SEM-7-azaindole in a report.[7b] However, the limitations may include a) formation of both C-2

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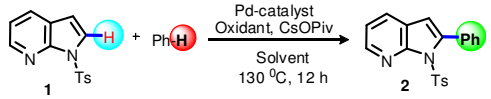
and C-3 regioisomers in a 8:1 ratio, b) use of 350 equivalent of benzene, and c) requirement of microwave use (Scheme 1). To the best of our knowledge, no other report of C-2 arylation on 7-azaindoles using arene as the coupling partner is currently available, despite significant relevance of 2-aryl-7-azindoles as pharmacophores. A defined objective of C-2 arylation of 7-azaindoles that considers a) achieving complete C-2 selectivity, b) avoids usage of a large excess of arenes, c) beneficial effect of acid concentration, and d) conventional heating would be a daunting challenge. Based on our previous experiences on double C(sp^2)-H oxidative couplings in the synthesis of biaryl sultams[8] and heterobiaryl sultams,[9] and regioselective C-3 alkenylation on indoles as well as 7-azaindoles,[10] we embarked on this ambitious objective. Herein, we describe a palladium-catalyzed intermolecular oxidative coupling of 7-azaindoles and arenes under high acid concentration yielding 2-aryl-7-azaindoles in good to excellent yields. Moreover, our protocol is not only useful for 7-azaindoles, but also for indoles and pyrroles, warranting a wide substrates scope. Distinct from the current literature, our protocol uses a high acid concentration for C-2 arylation of 7-azaindoles and indoles, while a low acidity of the reaction medium is essential for successful C-2 mono-arylation of pyrroles.

While *N*-methyl azaindole is largely used as a successful coupling partner in the C-2-arylation,[3c,e] we considered using 7-azaindoles with a *N*-protecting group that could be easily installed and subsequently removed, if desired. Reaction of *N*-Ts 7-azaindole **1** and benzene under the conditions described previously to prepare 2-phenyl-1-SEM-7-azaindole[7b] was ineffective (Table 1, entry 1).

Table 1. Optimization study[a]



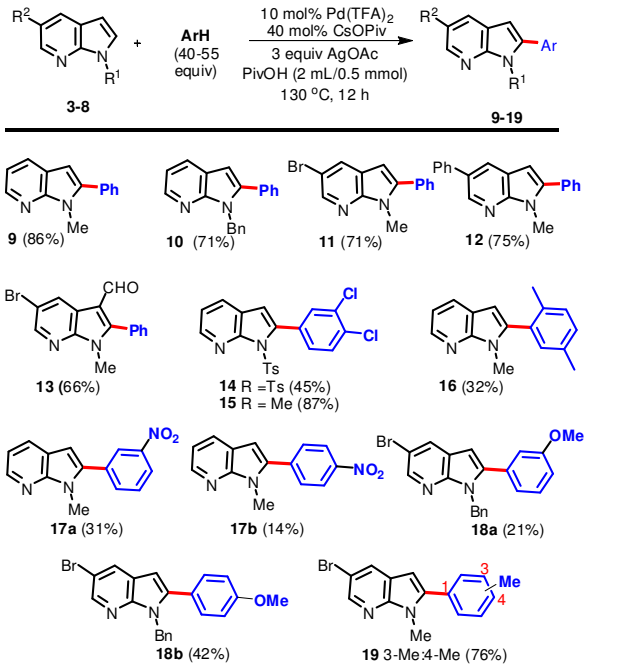
1 2

Entry	Pd-catalyst	Oxidant	PhH	PivOH	Yield of 2 (%)[b]
1[c]	$Pd(OAc)_2$	AgOAc	13 mL	2.5 equiv	<10
2[d]	$Pd(OAc)_2$	O_2	5 equiv		n.r.
3	$Pd(TFA)_2$	AgOAc	2.5 mL	2.5 equiv	Trace
4	$Pd(TFA)_2$	AgOAc	2.5 mL	5.0 equiv	29
5	**$Pd(TFA)_2$**	**AgOAc**	**2.5 mL**	**2 .0 mL**	**65**
6	$Pd(TFA)_2$	AgOAc	1 mL	3.5 mL	51
7	$Pd(TFA)_2$	AgOAc	10 equiv	4.5 mL	44
8[e]	$Pd(TFA)_2$	AgOAc	10 equiv	2 .0 mL	22
9	$Pd(TFA)_2$	AgOAc	1.25 mL	1 mL	35
10	$Pd(OAc)_2$	AgOAc	2.5 mL	2 .0 mL	53
11[f]	$Pd(TFA)_2$	$Cu(OAc)_2.5H_2O$	2.5 mL	2 .0 mL	n.r.
12	$Pd(TFA)_2$	$K_2S_2O_8$	2.5 mL	2 .0 mL	n.r.
13[g]	$Pd(TFA)_2$	$K_2S_2O_8$	2.5 mL	2 .0 mL	n.r.

[a] *N*-Ts azaindole **1** (0.5 mmol), Pd-catalyst (10 mol%), oxidant (3.0 equiv), CsOPiv (40 mol%), benzene, PivOH, 130 °C, 12 h; [b] Isolated yield; [c] Referred to conditions in ref 7b; [d] PPh_3 (20 mol%), $Cu(OTf)_2$ (50 mol%), dioxane (4 mL), DMSO (1 mL); [e] 2.5 mL DMF; [f] rt-80 °C; [g] AgOAc (50 mol%); n.r.= No reaction.

Similarly, a neutral condition largely used for alkenylation of indoles[11] was futile (entry 2). We next investigated the effect of acid concentration, usage of reduced volume of arenes, and overall concentration in the reaction (entries 3-9). Increasing the acid concentration in the reaction improved the yield of the product (entries 3-5). Further increase of acid concentration was detrimental (entries 6-7). Beside acid concentration, the concentration of arenes also plays an important role delivering the product (entry 8). Reducing the total volume of solvent by half is also detrimental (entry 9). The best conditions obtained for C-2 arylation of **1** entailed heating a mixture of **1** and benzene in the presence of $Pd(TFA)_2$ (10 mol%), AgOAc (3 equiv), CsOPiv (40 mol%), and PivOH at 130 °C for 12 h affording **2** in 65% yield (entry 5). A different palladium catalyst or oxidant was not beneficial (entries 10-13). It is important to mention here that C-3 arylated product was not isolated under the optimized condition (entry 5).

With the optimized conditions in hand, we next investigated the scope of substrates that could participate in the reaction. The 7-azaindole substrates **3-8** were either commercially available or prepared using a known procedure (see supporting information). Our protocol worked with different arenes to give C-2 arylated 7-azaindoles **9-19** in good to excellent yields. For example, *N*-Me or *N*-Bn 7-azaindoles **3** and **4** worked eventfully affording **9** and **10** in 71-86% yields.

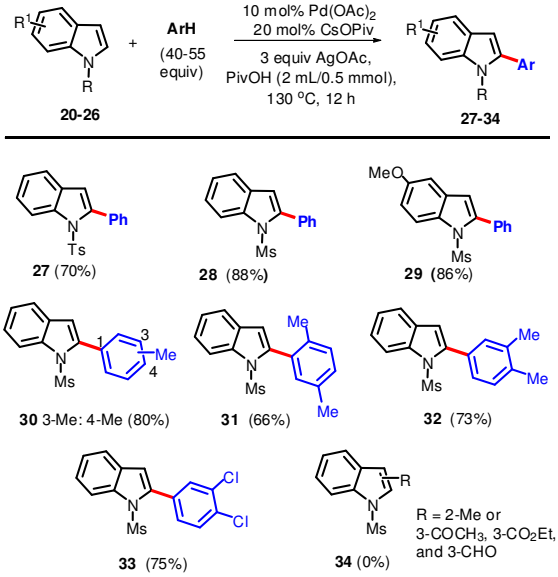


Scheme 2. C-2 Arylation of 7-azaindoles with arenes.

5-Bromo-7-azaindole **5** is especially an attractive substrate for C-2 arylation yielding **11** in 71% yield. The bromo-substituent could serve as a synthetic handle for further functionalizations. Interestingly, 7-azaindole **7** containing a C-3 formyl group was also a viable substrate furnishing **13** in 66% yield. 7-Azaindoles **1** or **3** reacted with disubstituted arenes, for example, 1,2-dichlorobenzene yielding C-2 arylated 7-azaindoles **14** and **15** in varying yields. However, *p*-xylene reacted sluggishly yielding

16 *albeit* in low (32%) yield. 7-Azaindoles **3** or **8** also reacted with mono-substituted arenes such as, nitrobenzene, anisole, and toluene resulting in two regioisomeric products, which required extensive chromatography for isolation of the pure products. The two regioisomers were originated from C-2 arylation of 7-azaindoles at the *meta* and *para*-positions of arenes, irrespective of the nature of substituent.[12] Thus, when **3** reacted with nitrobenzene, two regioisomers **17a** & **17b** were isolated with a 2:1 ratio. Similarly, the reaction of **8** and anisole formed **18a** and **18b** in a 1:2 ratio. On the other hand, toluene gave an inseparable mixture of C-2 arylated 7-azaindole **19** in a combined 76% yield. Perhaps most importantly, our protocol offers exclusive C-2 arylation on 7-azaindoles, overcoming the difficulties encountered previously.[7b]

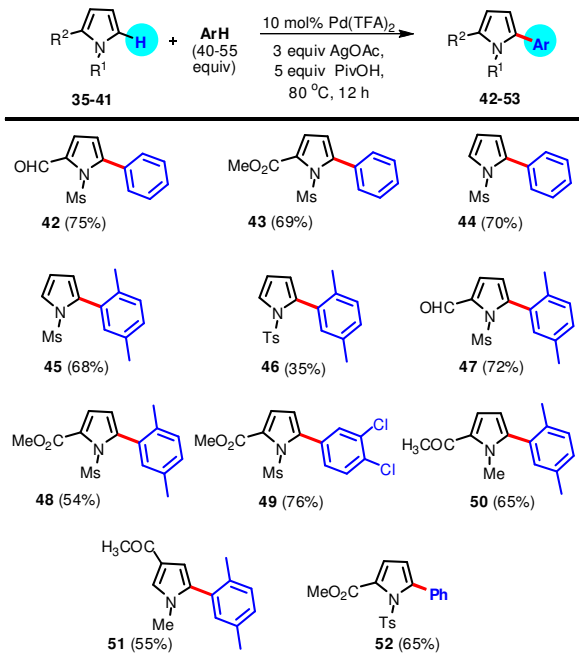
N-tosyl indole **20** reacted with benzene under a slightly modified condition affording **27** in 70% yield (Scheme 3). However, *N*-Ms indole **21** reacted more efficiently with benzene to give **28** in 88% yield.



Scheme 3. C-2 Arylation of indoles with arenes.

Generally, mono- or di-substituted indoles or arenes are good coupling partners irrespective of the nature of substituents affording various substituted 2-arylindoles **29-33** in 66-86% yields. Similar to the reaction of 7-azaindole and toluene, reaction of indole **21** and toluene gave an inseparable mixture of 2-arylated indole **30** resulting from functionalization at the *meta*- or *para*-position of the methyl group. Notably, the formation of 3-arylated indoles was not observed in any of these oxidative coupling reactions. Unlike 7-azaindole **7**, a 3-substituted indole did not give any C-2 arylated product. More interestingly, a substitution at the 2-position of indole also did not give any 3-arylated product **34.**

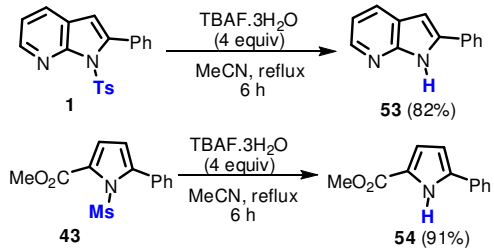
Reaction of 2-formyl-*N*-mesylpyrrole (**35**) and benzene under a slightly acidic condition gave **42** in 75% yield (Scheme 4). More importantly, C-2 unsubstituted pyrroles reacted with arenes to give mono-arylated products **44-46** in varying yields. This constitutes a rare report of mono-arylation of unsubstituted pyrroles via double C-H functionalizations. Pyrroles containing an electron -withdrawing or -donating group reacted smoothly with different arenes to give 2-arylpyrroles **47-52** in good yields.



Scheme 4. C-2 Arylation of pyrroles with arenes.

A 3-substituted pyrrole underwent arylation at the less sterically hindered 5-position. It is also important to mention that 2,5-diarylated pyrroles were not obtained in any of these cases.

Finally, fluoride ion assisted deprotection of sulfonyl group from **1** and **43** under a mild condition further demonstrates the synthetic utility of the protocol. (Scheme 5)



Scheme 5. Deprotection of sulfonyl group

In conclusion, we have developed, for the first time, an efficient protocol for exclusive C-2 arylation of *N*-protected 7-azaindoles. Incongruent to the literature, a high acid concentration in the reaction medium is essential for complete C-2 selectivity in 7-azaindoles and indoles. A low acidity of the reaction medium largely impedes the formation of 2,5-diarylpyrroles yielding 2-arylpyrroles in good to excellent

yields. Further applications of this protocol to the intramolecular cyclizations is currently under investigation.

Acknowledgements

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Notes and references

1 (a) J. Y. Merour, F. Buron, K. Ple, P. Bonnet and S. Routier, *Molecules,* 2014, **19**, 19935; (b) F. R. de Sa Alves, E. J. Barreiro and C. A. Fraga, *Mini Rev. Med. Chem.,* 2009, **9**, 782.

2 For Cross-coupling reviews, see: (a) A. J. Burke and C. S. Marques, Wiley-VCH verlog GmbH & Co. 2015, 1-94; (b) F.-S. Han, *Chem. Soc. Rev*., 2013, **42**, 5270; (c) C. S. G. Modha, V. P. Mehtaz and E. V. Van der Eycken, *Chem. Soc. Rev*., 2013, **42**, 5042. (d) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev*., 2011, **111**, 1780; (e) N. Kambe, T. Iwasaki and J. Terao, *Chem. Soc. Rev.*, 2011, **40**, 4937.

3 For Direct arylation, see: (a) S. E. Kazzouli, J. Koubachi, N. E. Brahmi and G. Guillaumet, *RSC Adv.,* 2015, **5**, 15292; (b) J. Feng, G. Lu, M. Lv and C. Cai, *J. Organomet. Chem*., 2014, **761**, 28; (c) P. Kannaboina, K. Anilkumar, S. Aravinda, R. A. Vishwakarma and P. Das, *Org. Lett.,* 2013, **15**, 5718; (d) P. B. Arockiam, C. Bruneau and H. P. Dixneuf, *Chem. Rev.,* 2012, **112**, 5879; (e) L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente and R. Sandmann *Org. Lett.,* 2011, **13***,* 2358; (f) M. P. Huesti and K. Fagnou, *Org. Lett.,* 2009, **11**, 1357; (g) Y. Zhu, M. Baner, J. Ploog and L. Ackermann *Chem. Eur. J.*, 2014, **20**, 13099-13102.

4 (a) S. H. Cho, J. Y. Kim, J. Kwak, and S. Chang *Chem. Soc. Rev*. 2011, **40**, 5068. (b) S. L. You and J. B. Xia *Top. Curr. Chem.,* 2010, **292**, 165. (c) Y. Fujiwara, O. Maruyama, M. Yoshidomi and H. Taniguchi, *J. Org. Chem.,* 1981, **46**, 851.

5 (a) Z. Wang, F. Song, Y. Zhao, Y. Huang, L. Yang, D. Zhao, J. Lan and J. You, *Chem. Eur. J.*, 2012, **18**, 16616; (b) G. Meng, H. Y. NIu, G. R. Qu, J. S. Fossey, J. P. Li and H. M. Guo, *Chem. Commun.*, 2012, **48**, 9601; (c) A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun.,* 2011, **47**, 10257; (d) C. C. Malakar, D. Schmidt, J. Conard and U. Beifuss, *Org. Lett.,* 2011, **13**, 1378; (e) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. Deboef, *Org. Lett.,* 2007, **9**, 3137; (f) T. Itahara, *J. Chem. Soc., Chem. Commun.,* 1981, 254.

6 (a) B. Liegault, D. Lee, M. P. Huestis, D. R. Stuart and K. Fagnou, *J. Org. Chem.*, 2008, **73**, 5022; (b) B. Liegault and K. Fagnou, *Organometallics*, 2008, **27**, 4841; (c) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.,* 2007, **129**, 12072; (d) D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172.

7 (a) S. Potavathri, A. S. Dumas, T. A. Dwight, G. R. Naumice, J. M. Hammann and B. Deboef, *Tetrahedron Lett.,* 2008, **49**, 4050; (b) S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. Lebris and B. Deboef, *J. Am. Chem. Soc.,* 2010, **132**, 14676.

8 J. K. Laha, K. P. Jethava and N. Dayal, *J. Org. Chem.,* 2014, **79**, 8010.

9 J. K. Laha, N. Dayal, K. P. Jethava and D. V. Prajapati, *Org. Lett.,* 2015, **17**, 1296.

10 J. Laha and N. Dayal, *Org. Lett.*, 2015, **17**, 4742.

11 (a) L. Zhou, B. Xu and J. Zhang, *Angew. Chem. Int. Ed.,* 2015, **54**, 1; (b) T. Guo, Q. Jiang, F. Huang, J. Chen and Z. Yu, *Org. Chem. Front.,* 2014, **1**, 707; (c) X. Zheng, L. Lv, S. Lu, W. Wang and Z. Li, *Org. Lett.,* 2014, **16**, 5156.

12 For arylation trend with mono-substituted arenes see; (a) Z. Yang, F. C. Qiu, J. Gao, Z. W. Li and B. T. Guan, *Org. Lett.*, 2015, **17**, 4316; (b) Y. Wei and W. Su, *J. Am. Chem. Soc.*, 2010, **132**, 16377.

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