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Palladium-Catalyzed C−H Arylation of 2,5-Substituted Pyrroles

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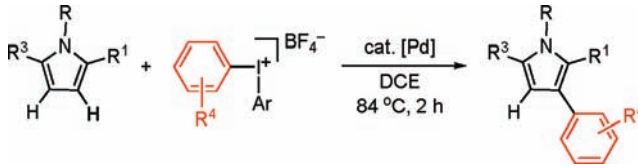
ABSTRACT

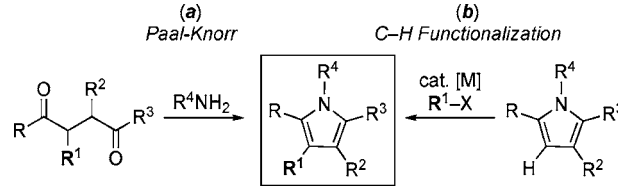


The palladium-catalyzed direct arylation of 2,5-substituted pyrrole derivatives with diaryliodonium salts to generate tri-, tetra-, and penta-substituted pyrrole products is described. The scope and limitations of these transformations are also reported.

Densely substituted pyrroles are an important class of heterocyclic compounds with useful biological and physical properties.[1] For example, tetra- and penta-substituted pyrroles feature prominently in natural products (*e.g.*, the lamellarin, lukianol, ningalin, polycitone, and storniamide classes of natural products),[2] pharmaceuticals (*e.g.*, Lipitor), agrochemicals (*e.g.*, chlorfenapyr), fluorescent dyes (*e.g.*, BODIPY derivatives),[3] and conducting polymers (*e.g.*, polypyrroles).[4] The most common route to pyrrole derivatives involves cyclization reactions, such as the Knorr, Paal−Knorr, and Hantzsch reactions (for example, see Scheme 1a).[5] While these are all robust and versatile transformations, they require preassembly of appropriately substituted carbonyl precursors.[5]

The direct C−H functionalization of preformed pyrroles (Scheme 1b) offers a highly complementary strategy for the synthesis and derivatization of these important heterocycles. In particular, this approach facilitates the late-stage diversification of the pyrrole core into a wide variety of functionalized structures.[6]

Scheme 1. Complementary Strategies for Pyrrole Synthesis



Over the past 5 years, a variety of elegant methods have been developed for the intermolecular C−H arylation,[6,7] olefination,[8] alkynylation,[9] and borylation[10] of pyrrole derivatives. The vast majority of these transformations

(1) Taylor, E. C.; Jones, R. A. *Pyrroles*; Wiley: New York, 1990. (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Kartritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1996; Vol. 4, p 380−382.
(2) Gupton, J. T. *Top. Heterocycl. Chem.* **2006**, *2*, 53.
(3) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891.
(4) (a) Nalwa, H. S. *Advanced Functional Molecules and Polymers: Electronic and Photonic Properties*; CRC Press: New York, 2001.
(5) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095.
(6) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Yu, J. Q.; Shi, Z. *Top. Curr. Chem.* **2010**, 292. (e) Guchhait, S. K.; Kashyap, M.; Saraf, S. *Synthesis* **2010**, *7*, 1166.
(7) For select recent examples of the C2 or C5 arylation of pyrroles, see: (a) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (b) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (c) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (d) Roy, D.; Mom, S.; Beauperin, M.; Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6650. (e) Jafarpour, F.; Rahiminejadan, S.; Hazrati, H. *J. Org. Chem.* **2010**, *75*, 3109.

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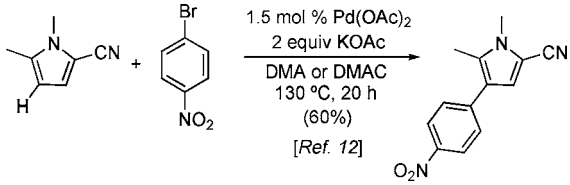
involve functionalization at the 2- and/or 5-positions of pyrroles due to the inherent reactivity of these sites. In marked contrast, very little work has addressed the C−H functionalization of 2,5-disubstituted pyrroles.[8c,9b,11−13] Most relevant to the current studies, Doucet and Santelli have reported the $Pd(OAc)_2$-catalyzed 3-arylation of several 1,2,5-trisubstituted pyrroles with aryl bromides (Scheme 2).[12]

Scheme 2. Previous Example of C3 Arylation of Pyrroles

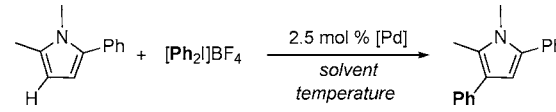


While this was an important advance, the reaction suffers from several key limitations, including (i) a modest scope of pyrrole substrates, (ii) the requirement for electron-deficient aryl bromides, (iii) high reaction temperatures (130 °C), and (iv) moderate yields (typically <65%).

Previous studies from our group have shown that Pd^{II} catalysts promote the 2-arylation of indoles and pyrroles with diaryliodonium salts.[14,15] These reactions proceed with high functional group tolerance and under extremely mild conditions (typically at room temperature). In contrast, most other Pd-catalyzed indole/pyrrole arylation methods require temperatures in excess of 100 °C.[16] On the basis of our prior work, we hypothesized that the combination of a Pd^{II} catalyst and Ar_2IBF_4 might also promote the C−H arylation of 2,5-substituted pyrrole derivatives. We report herein that this is an effective strategy for the synthesis of tri-, tetra-, and even penta-substituted pyrrole products.

Our initial investigations focused on the phenylation of 1,2-dimethyl-5-phenylpyrrole with Ph_2IBF_4. We first examined $Pd(OAc)_2$ as the catalyst in AcOH at room temperature, since these were effective conditions for the C2-arylation of 1-methylpyrrole.[14] Gratifyingly, traces (3%) of the desired product **1** were obtained (Table 1, entry 1). A screen of other

Table 1. Optimization of the Pd-Catalyzed C−H Phenylation of 1,2-Dimethyl-5-Phenylpyrrole with Ph_2IBF_4[a]



entry	[Pd]	solvent	temp (°C)	yield[b]
1	$Pd(OAc)_2$	AcOH	25[c]	3%
2	$(MeCN)_2PdCl_2$	AcOH	25[c]	7%
3	$(MeCN)_2PdCl_2$	DCE	25[c]	11%
4	$(MeCN)_2PdCl_2$	DCE	40[c]	42%
5	$(MeCN)_2PdCl_2$	DCE	60[d]	60%
6	$(MeCN)_2PdCl_2$	DCE	80[e]	84%

[a] 1 equiv (0.5 mmol) of pyrrole, 1 equiv (0.5 mmol) of Ph_2IBF_4, 2.5 mL of solvent, 2.5 mol % of [Pd]. [b] Isolated yields (average of two or three runs). [c] 15 h. [d] 5 h. [e] 2 h.

Pd^{II} catalysts revealed that $(MeCN)_2PdCl_2$[17] provided a significantly higher yield (7%, entry 2). Moving from AcOH to DCE as the solvent and increasing the reaction temperature from 25 to 84 °C further enhanced the yield to 84% (entry 6). Notably, the optimal conditions (2.5 mol % of [Pd], 84 °C, 2 h in DCE) are mild compared to most other Pd-catalyzed pyrrole arylation reactions reported in the literature.[6,7,12,13] In addition, this transformation was highly site selective, providing 1,2-dimethyl-3,5-diphenylpyrrole as the only regioisomer detected by GC and GCMS analysis.

As shown in Table 2, a variety of 1,2-dimethyl-5-aryl pyrrole derivatives were effective substrates for this transformation.[18] Electron-withdrawing and -donating substituents as well as *ortho*-substitution on the aryl ring were all well-tolerated (Table 2, entries 2−6). With all of these substrates, excellent (>50:1) selectivity was observed for C−H functionalization adjacent to the CH_3 substituent. The only case in which another isomer was even detected was with the electron-rich *p*-$MeOC_6H_4$-substituted pyrrole (entry 2). Product **2** was formed along with traces (∼0.3%) of a minor isomer. Interestingly, 2-methyl-5-phenylpyrrole also showed modest reactivity to form **7** under these conditions (entry 7).

2,5-Methyl/alkyl substituted pyrroles also underwent efficient C−H arylation with diphenyliodonium tetrafluoroborate (Table 2, entries 8−11). In all cases examined, arylation adjacent to the CH_3 substituent was favored. The selectivity was modest (2.0:1) with R^1 = ethyl but was very good (29:1) with R^1 = cyclohexyl (entries 9 and 10, respectively).

(8) For examples of pyrrole C−H olefination, see: (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (b) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004. (c) Garcia-Rubia, A.; Urones, B.; Arrayas, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676.

(9) For examples of pyrrole C−H alkynylation, see: (a) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Vakul'skaya, T. I.; Kazheva, O. N.; Alexsandrov, G. G.; Dyachenko, O. A.; Mikhaleva, A. I. *Tetrahedron* **2008**, *64*, 5541. (b) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346.

(10) For examples of pyrrole C−H borylation, see: (a) Tse, M. K.; Cho, J. Y.; Smith, M. R., III. *Org. Lett.* **2001**, *3*, 2831. (b) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649. (c) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103. (d) Harrisson, P.; Morris, J.; Marder, T. B.; Steel, P. G. *Org. Lett.* **2009**, *11*, 3586. (e) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N., Jr.; Smith, M. R., III. *J. Org. Chem.* **2009**, *74*, 9199. (f) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(11) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607.

(12) Fall, Y.; Doucet, H.; Santelli, M. *ChemSusChem* **2009**, *2*, 153.

(13) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.

(14) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

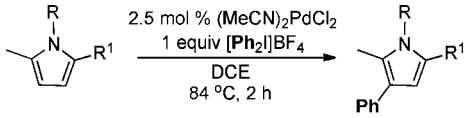
(15) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052.

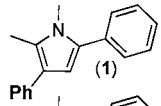
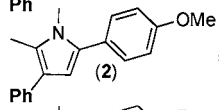
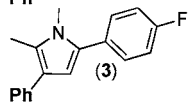
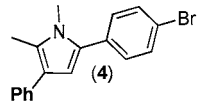
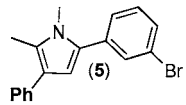
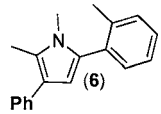
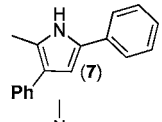
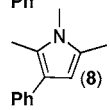
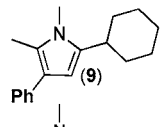
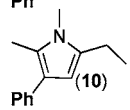
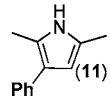
(16) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.

(17) Abrunhosa, I.; Delain-Bioton, L.; Gaumont, A. C.; Gulea, M.; Masson, S. *Tetrahedron* **2004**, *60*, 9263.

(18) Pyrrole substrates were prepared according to the following: (a) Biava, M.; Porretta, G. C.; Poce, G.; De Logu, A.; Meleddu, R.; De Rossi, E.; Manetti, F.; Botta, M. *Eur. J. Med. Chem.* **2009**, *44*, 4734. (b) De, S. *Synth. Commun.* **2008**, *38*, 803.

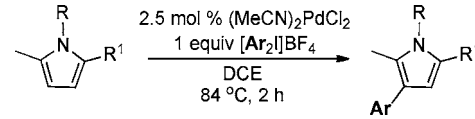
Table 2. Scope of Pyrrole Substrates[a]

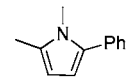
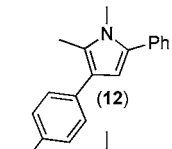
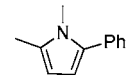
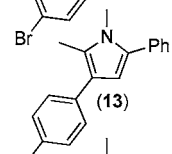
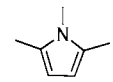
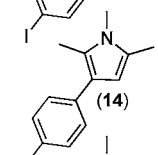
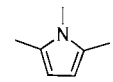
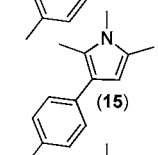
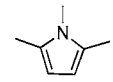
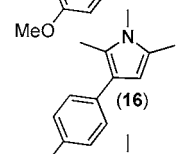
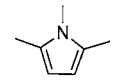
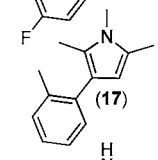
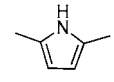
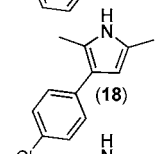
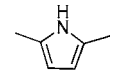
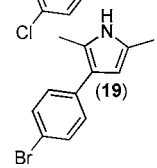


entry	R	R^1	product	yield
1	CH_3	Ph	 (1)	84%
2	CH_3	*p*-$MeOC_6H_5$	 (2)	54%
3	CH_3	*p*-FC_6H_5	 (3)	75%
4	CH_3	*p*-BrC_6H_5	 (4)	70%
5	CH_3	*m*-BrC_6H_5	 (5)	59%
6	CH_3	*o*-$CH_3C_6H_5$	 (6)	83%
7	H	Ph	 (7)	44%
8	CH_3	CH_3	 (8)	54%
9	CH_3	Cy	 (9)	82%[b]
10	CH_3	Et	 (10)	53%[c]
11	H	CH_3	 (11)	55%

[a] 1 equiv (1.0 mmol) of pyrrole, 1 equiv (1.0 mmol) of Ph_2IBF_4, 2.5 mol % $(MeCN)_2PdCl_2$ in 5 mL of DCE at 84 °C for 2 h. All yields represent an average of at least two runs. Mass balance in reactions with moderate yields was generally pyrrole decomposition products (oligomers). Excess hypervalent iodine reagent did not enhance yields. [b] Isomer ratio = 29:1 as determined by ^1H NMR spectroscopy. [c] Isomer ratio = 2.0:1 as determined by ^1H NMR spectroscopy. All results are an average of two runs.

Table 3. Scope of Arylating Reagents[a]



entry	pyrrole	product	yield
1		 (12)	88%
2		 (13)	53%
3		 (14)	74%
4		 (15)	73%
5		 (16)	39%
6		 (17)	34%
7		 (18)	58%
8		 (19)	49%

[a] 1 equiv (1.0 mmol) of pyrrole, 1 equiv (1.0 mmol) of Ph_2IBF_4, 2.5 mol % of $(MeCN)_2PdCl_2$ in 5 mL of DCE at 84 °C for 2 h. All yields represent an average of at least two runs. Mass balance in reactions with moderate yields was generally pyrrole decomposition products (oligomers). Excess hypervalent iodine reagent did not enhance yields.

These results suggest that steric factors are a major contributor to site selectivity in this system.

In contrast to the alkyl and aryl substituted derivatives in Table 2, pyrroles containing highly electron-withdrawing substituents (*e.g.*, 1,5-dimethyl-2-pyrrolecarbonitrile, 1,2-dimethyl-5-pyrrolecarboxylic acid, and 1,5-dimethyl-2-pyrrolecarboxaldehyde) exhibited low reactivity. Under our standard reaction conditions, <5% yields of C−H arylation products were detected, and the mass balance was largely unreacted starting material. As such, the current method is highly complementary to the Doucet/Santelli chemistry (Scheme 2),[12] which works particularly well with 1,5-dimethyl-2-pyrrolecarbonitrile.[19]

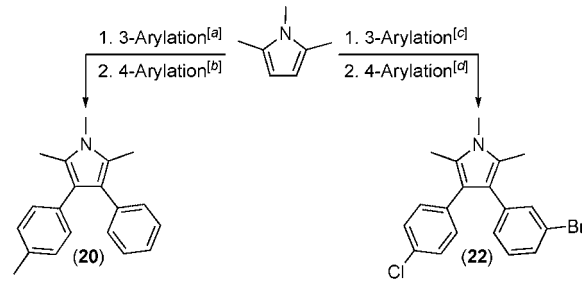
We next evaluated the scope of this transformation with respect to the hypervalent iodine coupling partner. A series of diverse reagents of general structure Ar_2IBF_4 were

prepared from the corresponding ArI and $ArB(OH)_2$ using a versatile one-pot procedure developed by Olofsson and coworkers.[20] As summarized in Table 3, these reagents were effective for the 3-arylation of 1,2-dimethyl-5-phenyl pyrrole, 1,2,5-trimethylpyrrole, and 2,5-dimethylpyrrole. Remarkably, chloride, bromide, and iodide substituents were all well-tolerated on the oxidant (entries 1, 2, and 7). These serve as valuable synthetic handles for further manipulation of the products. In addition, good to excellent yields of C−H arylation products were obtained with Ar_2IBF_4 containing electron-donating methyl and methoxy substituents (entries 4 and 5). This is in marked contrast to the Doucet/Santelli system,[12] which requires electron-deficient aryl bromide electrophiles. Finally, even the sterically congested *ortho*-methyl substituted iodine(III) reagent provided a modest yield of C−H arylated product **17** (entry 6).

A final set of investigations focused on further functionalization of the 3-arylated pyrrole products. Specifically, we sought to examine whether these species underwent Pd-catalyzed C4-arylation with Ar_2IBF_4 to generate 1,2,3,4,5-substituted pyrrole derivatives. We were pleased to find that the reaction of **14** and **21** with Ar_2IBF_4 in the presence of 5 mol % of $(MeCN)_2PdCl_2$ at 84 °C in DCE provided penta-substituted pyrroles **20** and **22** in 44% and 32% yield, respectively (Figure 1). Despite the relatively modest yields, this type of reaction is quite valuable because it provides access to pyrroles with different aryl groups at the 3- and 4-positions, a difficult substitution pattern to achieve using the Paal−Knorr synthesis.

(19) Differences in substrate scope and reactivity between the current reaction and the Doucet/Santelli system may be due to a change in mechanism from a $Pd^{0/II}$ to a $Pd^{II/IV}$ catalytic cycle. Studies to more fully understand electronic effects and the mechanism in this system are underway.

(20) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602.



[*a*] 2.5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[(p\text{-}MeC_6H_4)_2I]BF_4$, DCE, 84 °C, 2 h; (73%, **14**)
[*b*] 5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[Ph_2I]BF_4$, DCE, 84 °C, 2 h; (44%, **20**)
[*c*] 2.5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[(p\text{-}ClC_6H_4)_2I]BF_4$, DCE, 84 °C, 2 h; (37%, **21**)
[*d*] 5 mol % $(MeCN)_2PdCl_2$, 1 equiv $[(m\text{-}BrC_6H_4)_2I]BF_4$, DCE, 84 °C, 2 h; (35%, **22**)

Figure 1. Sequential diarylation to form penta-substituted pyrroles.

In conclusion, this paper demonstrates the Pd-catalyzed monoarylation and sequential diarylation of 2,5-substituted pyrrole derivatives with Ar_2IBF_4. These reactions provide an attractive and selective method for synthesizing polysubstituted pyrroles under mild conditions. Efforts to expand the scope of this reaction with respect to a pyrrole substrate as well as to develop improved catalysts for accessing penta-substituted pyrroles are underway and will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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