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Palladium-Catalyzed Intramolecular Coupling of Arenes and Unactivated Alkanes in Air

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Summary: Palladium-catalyzed arene−alkane coupling reactions are described that create a new C(sp^2)−C(sp^3) bond between an azole ring and an unactivated methyl substituent. The reactions employ a simple, readily available palladium catalyst, exhibit high regioselectivity with respect to both the azole and the alkane moieties, and can be performed in an open flask using air as the terminal oxidant.

Most methods for the formation of carbon−carbon bonds depend heavily on substrate activation, requiring the prefunctionalization of both organic coupling fragments.[1] Recently, processes capable of achieving reaction at unactivated C−H bonds have emerged as valuable alternatives, since only one reaction component requires preactivation.[2−7] In contrast, C−C bond forming reactions involving C−H bonds on each coupling partner are rare,[8−10] particularly those at unactivated sp^3 positions.[11] Herein, we describe the development of arene−alkane coupling reactions belonging to this final category that create a new C(sp^2)−C(sp^3) bond between an azole ring and an unactivated methyl substituent using air as the terminal oxidant.

To evaluate the feasibility of these transformations, a range of substrates was evaluated and promising outcomes were obtained with the *N*-pivalylpyrrole **1** (Table 1). An assessment of the important reaction parameters revealed that the quantity of base employed is crucial. In the absence of base, very little reaction is observed (entry 1). With an amount of base equal to or slightly greater than the amount of Pd, the conversion increases to greater than 90%, and good yields of **2** can be achieved. As the amount of base is further increased, the yield of the desired product drops significantly (entries 6 and 7).

Of the terminal oxidants that were evaluated, we were pleased to find that the use of an air atmosphere at ambient pressure provided superior outcomes compared to the use of other common oxidants such as copper(II) acetate and silver(I) acetate (entries 16 and 17). We also found that the use of an oxygen atmosphere provided no benefit to the use of air (entry 15). Under the optimal conditions (10 mol % Pd(OAc)$_2$, 20 mol % NaO-*t*-Bu in PivOH (0.5 M) at 110 °C under an air atmosphere), the [3.3.0] azabicycle **2** could be obtained as one regioisomer in 67% isolated yield (entry 4). The remainder of the mass balance may be accounted for by the presence of unreacted starting material, and in the case of very electron-poor substrates, removal of the pivalyl moiety was also observed; however, the resulting free NH pyrrole proved to have no negative effect on the reactivity.

Additional examples of reactions with other substituted pyrroles are included in Table 2. Electron-rich and -deficient

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(1) For reviews, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 2004. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For reviews, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (e) Satoh, M.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (f) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (g) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (h) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(3) For Pd(0)-catalyzed sp^2−sp^2 couplings, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (c) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (d) Garcı´a-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880.

(4) For Pd(II)-catalyzed sp^2−sp^2 couplings, see: Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066.

(5) For Pd(0)-catalyzed sp^2−sp^3 couplings, see: (a) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (b) Hitce, J.; Baudoin, *Adv. Synth. Catal.* **2007**, *349*, 2054. (c) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759.

(6) For Pd(II)-catalyzed sp^2−sp^3 couplings, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

(7) For other metal-catalyzed couplings, see: (a) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (b) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (c) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364. (d) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (e) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (f) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858.

(8) For a review on Pd(II)-catalyzed oxidative reactions, see: Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

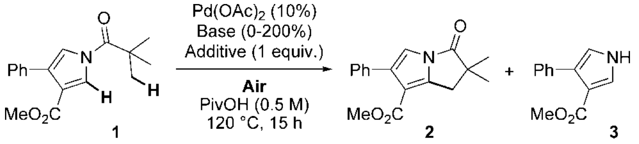
(9) For oxidative Heck reactions, see: (a) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; De Vries, A. H. M.; Kamer, P. C. J.; De Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (c) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (d) Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471. (e) Capito, E.; Browna, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. (f) Kong, A.; Han, X.; Lu, X. *Org. Lett.* **2006**, *8*, 1339. (g) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.

(10) For recent examples, see: (a) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (b) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376. (c) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (f) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (g) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869. (h) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (i) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022, and refs therein.

(11) (a) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376. (b) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278 See also ref 10e.

10.1021/om800780f CCC: $40.75

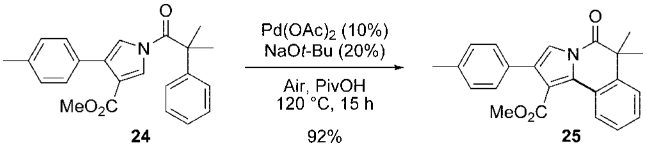
Table 1. Optimization of the Reaction Conditions



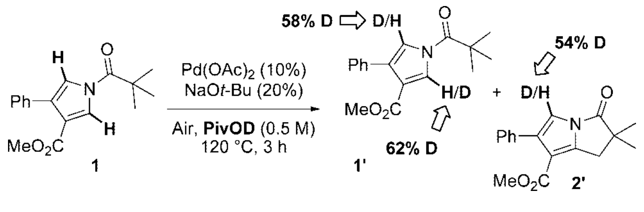
Entry	Base	Additive	SM Consumption[a]	NMR Yield[a,b] 2	NMR Yield[a,b] 3
1			32	15	0
2	NaO-*t*-Bu (5%)		88	75	0
3	NaO-*t*-Bu (10%)		**95**	**81**	**0**
4	NaO-*t*-Bu (20%)		**97**	**82(67)**	**0**
5	NaO-*t*-Bu (50%)		**95**	**76**	**0**
6	NaO-*t*-Bu (100%)		84	52	8
7	NaO-*t*-Bu (200%)		88	32	32
8	Na_2CO_3 (20%)		56	42	5
9	Rb_2CO_3 (20%)		88	34	27
10	NaOPiv (20%)		84	65	2
11	KOPiv (20%)		55	45	3
12	CsOPiv (20%)		90	33	2
13	$(i\text{-Pr})_2EtN$ (20%)		30	18	5
14	DABCO (20%)		43	0	38
15	NaO-*t*-Bu (20%)	dry O_2[c]	83	49	0
16	NaO-*t*-Bu (20%)	$Cu(OAc)_2$[d]	62	25	2
17	NaO-*t*-Bu (20%)	Ag(OAc)[d]	67	35	4

[a] Determined by ^1H NMR analysis of the crude reaction mixture, in acetone d_6, using 1,3,5-trimethoxybenzene as an external standard. [b] Isolated yield in parentheses. [c] Balloon pressure. [d] Reaction conducted in a sealed vial.

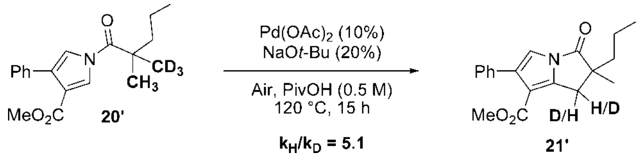
Scheme 1. Six-Membered-Ring Closure Reaction



Scheme 2. Deuterium Incorporation using PivOD as the Reaction Solvent

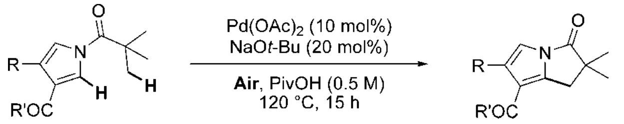


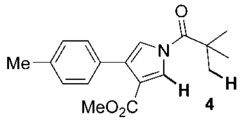
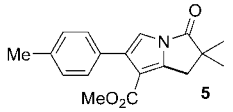
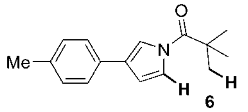
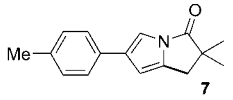
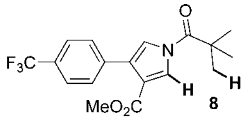
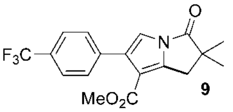
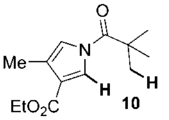
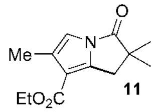
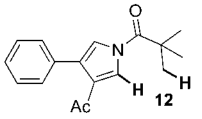
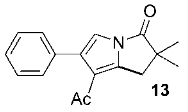
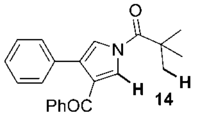
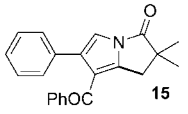
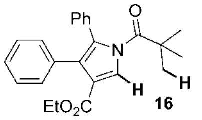
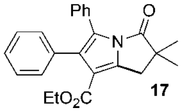
Scheme 3. Kinetic Isotope Effect



arenes as well as esters and ketones may be present. The combined presence of the aromatic and resonance electron-withdrawing groups appears to facilitate the process. If either the arene or the electron-withdrawing group is removed (entries 2 and 4), lower yields are produced under the current conditions. Differentially substituted amides may also be employed (Table 2), and very high selectivity can be achieved with respect to the alkyl substituent. For example, reaction is observed at a methyl group in preference to a methylene of an ethyl or a cyclohexyl group. Similar selectivity has been observed in other aryl−alkane coupling reactions.[5c,6b,c] If a phenyl group is situated close to the pyrrole ring, preferential reaction is observed at an sp^2 aryl position, as illustrated in Scheme 1.[5a,c] While such reactivity is well-known for the formation of five-membered rings,[10i] the formation of a six-membered ring by this method is exceedingly rare,[12] suggesting that this too may merit further attention.

Table 2. Scope of the Reaction with Various Substituted Pyrroles



Entry	Substrate	Product	Yield (%)[a]
1	 **4**	 **5**	65[b]
2	 **6**	 **7**	12[b]
3	 **8**	 **9**	55[b]
4	 **10**	 **11**	29[b]
5	 **12**	 **13**	47[b]
6[c]	 **14**	 **15**	59[b]
7	 **16**	 **17**	69

[a] Isolated yield. [b] Only one isomer detected by GC-MS and ^1H NMR; regioselectivity determined by NOESY experiments. [c] 20 mol % of Pd(OAc)$_2$.

Scheme 4. Proposed Mechanism

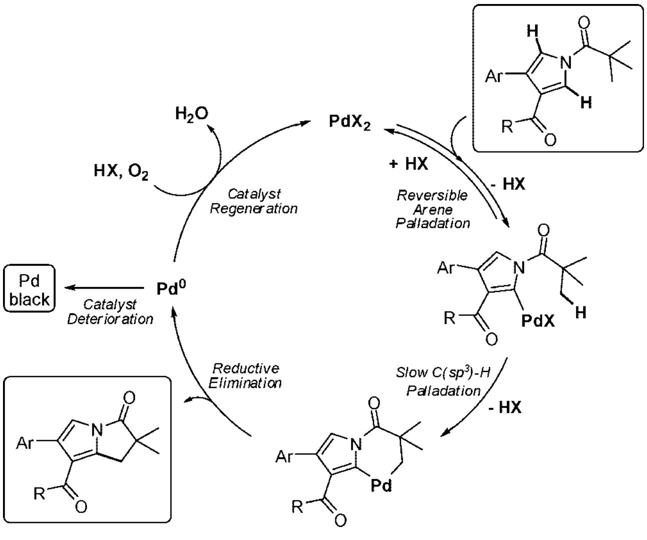
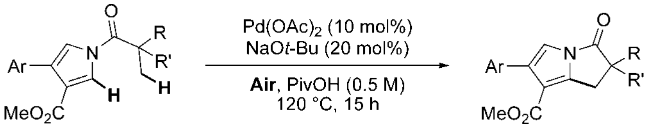
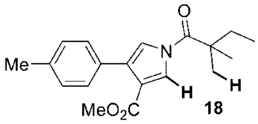
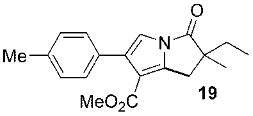
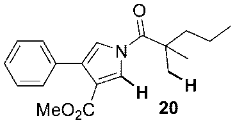
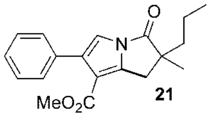
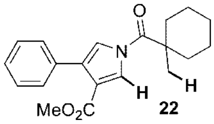
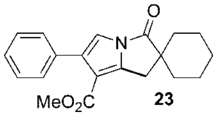


Table 3. Scope of the Reaction with Various Substituted Amides



Entry	Substrate	Product	Yield (%)[a]
1	 18	 19	41[b]
2	 20	 21	59[b]
3	 22	 23	45[c]

[a] Isolated yield. [b] Only one isomer detected by GC-MS and ^{1}H NMR; regioselectivity determined by NOESY experiments. [c] ^{1}H NMR of the crude product revealed the presence of a 7:1 mixture of isomers, in favor of **23**.

As an initial probe of the underlying reactivity and selectivity, deuterium-labeling experiments were performed. Interestingly, when **1** was subjected to the standard reaction conditions using PivOD as the solvent (over 3 h), significant deuterium incorporation was observed at both the 2- and 4-positions of the unreacted pyrrole starting material as well as on the pyrrole ring of the product (Scheme 2).[13] When the same reaction was performed in the absence of palladium catalyst, no deuterium incorporation was noticed. We also observed a large primary kinetic isotope effect (KIE) of 5.1 at the methyl (Scheme 3). A KIE of comparable magnitude has previously been reported in other palladium-catalyzed aliphatic C−H bond cleaving processes.[5c] These results point to a reversible pyrrole palladation−proto(deuterio)depalladation step that is followed by an irreversible alkane C−H bond cleavage step leading to product formation (Scheme 4). This may also imply that the regioselectivity and reactivity with respect to the pyrrole moiety may be governed not by the ability of the catalyst to induce selective C−H bond cleavage but by the persistence of one of the aryl−palladium intermediates, allowing a slower aliphatic C−H bond cleavage to occur.[14]

In conclusion, oxidative couplings of an arene with an unactivated methyl group can be achieved under palladium catalysis employing air as the terminal oxidant. The knowledge that such processes are possible should prompt a greater evaluation of their application in organic synthesis as well as the establishment of improved conditions for their use. The reasons for the observed selectivity are interesting and merit further attention, as is a greater evaluation of the substrate scope. These studies are underway.

Acknowledgment. We thank the NSERC, the University of Ottawa and the American Chemical Society (PRF Type AC) for support of this work. The Research Corporation, Boehringer Ingelheim (Laval), Merck Frosst Canada, Merck Inc., Eli Lilly, Amgen, and Astra Zeneca Montreal are thanked for additional unrestricted financial support.

Supporting Information Available: Text and figures giving experimental procedures, spectroscopic characterization data for all new compounds, and NMR spectra related to Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) To the best of our knowledge,[10i] the formation of six-membered rings by Pd-catalyzed intramolecular oxidative coupling has not yet been reported.

(13) For a recent review on H/D exchange, see: Atzrodt, J.; Derdau, V.; Fey, T.; Zimmermann, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2.

(14) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616.