JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

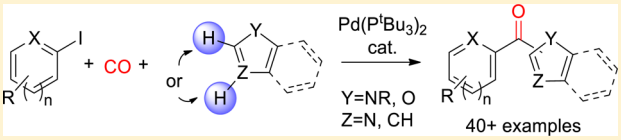
An Electrophilic Approach to the Palladium-Catalyzed Carbonylative C−H Functionalization of Heterocycles

Jevgenijs Tjutrins and Bruce A. Arndtsen*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada

Supporting Information

ABSTRACT: A palladium-catalyzed approach to intermolecular carbonylative C−H functionalization is described. This transformation is mediated by P^{t}Bu$_3$-coordinated palladium catalyst and allows the derivatization of a diverse range of heterocycles, including pyrroles, indoles, imidazoles, benzoxazoles, and furans. Preliminary studies suggest that this reaction may proceed via the catalytic formation of highly electrophilic intermediates. Overall, this provides with an atom-economical and general synthetic route to generate aryl-(hetero)aryl ketones using stable reagents (aryl iodides and CO) and without the typical need to exploit pre-metalated heterocycles in carbonylative coupling chemistry.

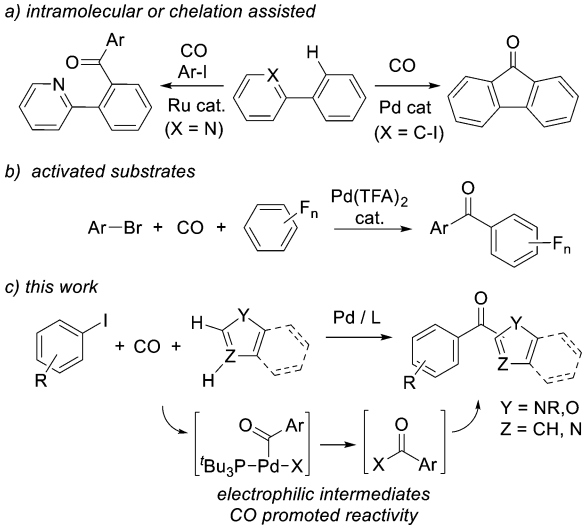


INTRODUCTION

The palladium-catalyzed C−H functionalization of arenes and heteroarenes has emerged as one of the most important new approaches in synthetic chemistry.[1] Extensive research efforts have been directed toward the discovery of new approaches to these transformations, with examples including such powerful platforms as chelation-assisted functionalization,[2] concerted metalation deprotonation (CMD),[3] radical reactions,[4] and others.[5] In contrast, the design of methods to incorporate reactive functionalities such as CO into C−H bond functionalization has to date presented a challenge. Unlike reactions that generate robust and relatively inert aryl-(hetero)aryl, -alkyl, or -heteroatom bonds, palladium-catalyzed carbonylations provide an efficient route synthesize a number of the most easily manipulated functional groups in synthetic chemistry, such as carboxylic acid derivatives or ketones.[6] Unfortunately, carbon monoxide is also a π-acidic and reactive ligand with the potential to interfere with many modes of Pd-based bond activation. In this regard, Fujiwara and others have demonstrated the palladium-catalyzed oxidative carbonylation of arenes and heteroarenes to carboxylic acids and esters.[7,8] More recently, examples of the application of this chemistry to coupling with aryl halides have emerged involving either intramolecular or chelation assisted carbonylations by Larock, Beller, Yu, Lei, and others (Scheme 1a),[9] or the use of activated substrates, such as perfluoroarenes, reported by Skrydstrup (Scheme 1b).[10] However, a general carbonylative coupling of heterocycles and aryl halides, to our knowledge, is not known. These products are instead often prepared via palladium-catalyzed cross coupling reactions,[11] or via Friedel−Crafts acylations with acid chlorides and strong Lewis acids,[12] both of which require the synthesis of high-energy substrates and/or create significant waste.

In considering these issues, we postulated that the features unique to carbonylation may offer an alternative approach to C−H functionalization. We have recently reported that the highly sterically encumbered ligands such as P^{t}Bu$_3$ can induce the reductive elimination and Pd-catalyzed generation of acid chlorides from aryl halides and CO.[13] In contrast to the moderate reactivity of the palladium-acyl intermediates formed in traditional carbonylations, acid chlorides are highly electrophilic and have allowed the application of carbonylation to a range of new classes of weak nucleophiles. The formation of acid chlorides is driven by the unusual energetics of carbon monoxide, whose reduction is sufficiently exothermic as to allow the formation of a weak aroyl−chloride bond. These results led us to question if carbonylations might be used to create even more high-energy products than acid chlorides,

Scheme 1. An Electrophilic Approach to Pd-Catalyzed Carbonylative C−H Bond Functionalization



Received: July 8, 2015
Published: August 31, 2015

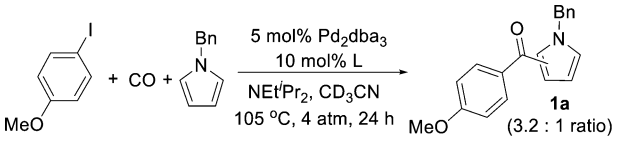
DOI: 10.1021/jacs.5b07098
J. Am. Chem. Soc. 2015, 137, 12050−12054

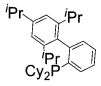
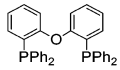
including those sufficiently electrophilic to react directly with aromatic systems (Scheme 1c). We describe here the results of these studies. These have led to the design of what is to our knowledge the first broadly applicable approach to perform carbonylative C−H functionalization of heterocycles, without directing groups, and via a mechanism that is promoted, rather than inhibited, by carbon monoxide.

RESULTS AND DISCUSSION

Our initial studies involved the carbonylation of 4-iodoanisole in the presence of the electron-rich *N*-benzylpyrrole employing the conditions we have reported for the catalytic, *in situ* formation of acid chlorides (Pd/P^{t}Bu$_3$, Bu$_4$NCl). As shown in Table 1, this leads to the generation of the carbonylative arene/

Table 1. Catalyst for Carbonylative Functionalization[a]



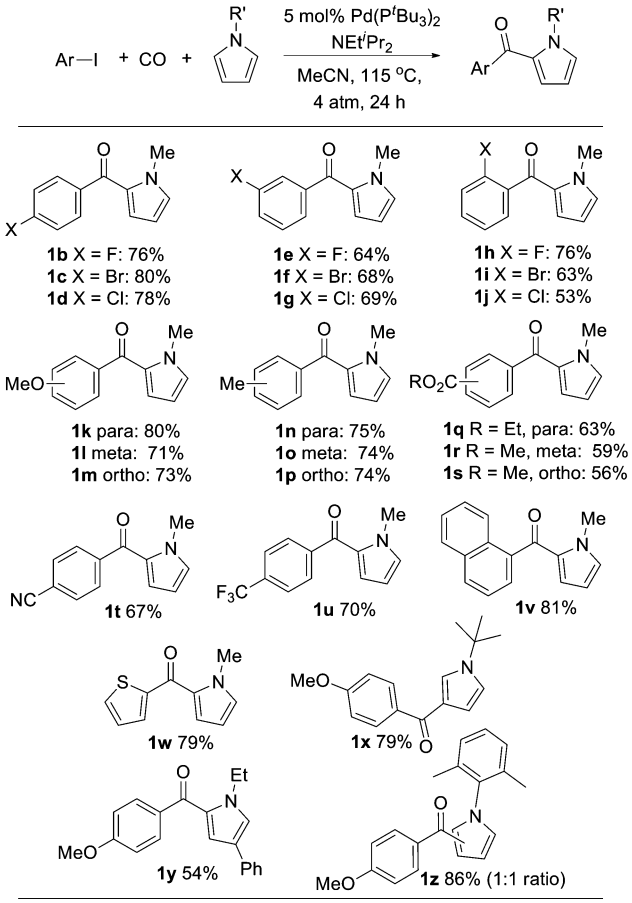
entry	L	additive	% **1a**[c]	entry	L	% **1a**[c]
1	P^{t}Bu$_3$	Bu$_4$NCl	44	12	-	45
2	PPh$_3$	Bu$_4$NCl	0	13	PCy$_3$	15
3	P(*o*-tolyl)$_3$	Bu$_4$NCl	27	14		9
4	PCy$_3$	Bu$_4$NCl	0			
5		Bu$_4$NCl	24	15		21
6	P^{t}Bu$_3$	-	84	16	DPPE	0
7	Pd(P^{t}Bu$_3$)$_2$	-	79	17	DPPP	0
8	PPh$_3$		60	18	DPPF	0
9	P(*o*-tolyl)$_3$	-	62	19	DCPE	0
10		-	64	20		11
11		-	72	21	Pd(P^{t}Bu$_3$)$_2$[b]	97 (73)[d]

[a]CH$_3$OC$_6$H$_4$I (47 mg, 0.20 mmol), pyrrole (16 mg, 0.10 mmol), Pd (0.010 mmol), L (0.010 mmol), NEt^{i}Pr$_2$ (15 mg, 0.12 mmol), 4 atm CO, 0.7 mL of CD$_3$CN. [b]115 °C, 0.005 mmol of Pd. [c]NMR yield of 2- and 3-isomers, all formed in a 3.2:1 ratio. [d]Isolated yield of 2-aroylpyrrole.

pyrrole coupling product **1a** in 44% yield (entry 1). This reaction proceeds in highest yields with P^{t}Bu$_3$ (entries 2−5), presumably due to its ability to facilitate acid chloride reductive elimination. The formation of **1a** is slow under these conditions and generates a mixture of 2- and 3-substituted isomers (3.2:1 ratio). These features mirror the reactivity of aromatic acid chlorides with pyrroles.[14]

While this reaction is effective, the observed yields are moderate, and the product scope is expected to be limited to substrates reactive toward acid chlorides. In probing methods to increase reactivity, we questioned if acid chloride formation is indeed necessary for carbonylative coupling. A simple experiment in this regard was to omit the addition of chloride from the reaction of aryl iodide, pyrrole, and CO. Rather than

Table 2. Pd-Catalyzed Functionalization of Pyrroles[a]



[a]ArI (1.0 mmol), pyrrole (0.50 mmol), NEt^{i}Pr$_2$ (77 mg, 0.60 mmol), 4 atm CO, and Pd(P^{t}Bu$_3$)$_2$ (13 mg, 0.025 mmol) in MeCN (2 mL) at 115 °C for 24 h. Isolated yield of isomer shown.

inhibiting catalysis, this led to a dramatic *increase* in aroylation and **1a** yield (entries 6 and 7, also in a 3.2:1 isomeric ratio). Examination of ligand effects reveals that the large cone angle P^{t}Bu$_3$ ligand creates the most reactive catalyst for this transformation, and smaller ligands show diminished activity (entries 8−15). Bidentate ligands, which have become common in many Pd-catalyzed carbonylation reactions, almost fully shut down catalysis (entries 16−20). Increasing the reaction temperature to 115 °C with the most active ligand, P^{t}Bu$_3$, allowed us to decrease the catalyst loading to 5 mol% and obtain the near-quantitative formation of ketone (entry 21).

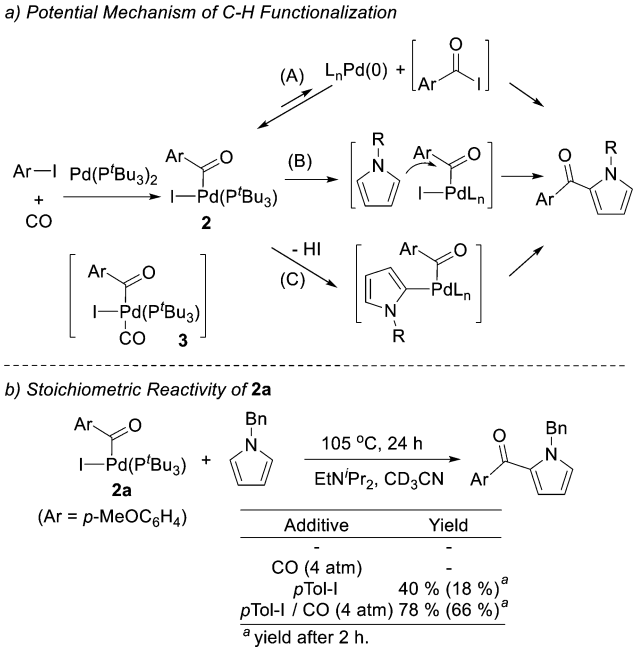
The optimized catalyst system can mediate carbonylative C−H functionalization with a range of aryl iodides and pyrroles (Table 2). Electron-acceptor and electron-donor substituents are tolerated in all positions of the aryl iodide and lead to substituted pyrroles in good yield. This includes a number of palladium-reactive functionalities (**1c,d,f,g,i,j**) and *ortho*-functionalized substrates (**1h-j,m,p,s**). Sterically encumbered arenes are also viable in this transformation (**1v**), and the chemistry can be extended to the use of thiophenyl iodides (**1w**). With *N*-methylpyrrole, the 2-derivatized isomer is obtained in all cases as the isolated product.[16] In the case of the more sterically encumbered *N*-2,6-dimethylphenyl-substituted pyrrole, both regioisomers were observed in moderate yields (**1z**), and further increasing the steric bulk to *N*-*tert*-butylpyrrole leads to the exclusive generation of the 3-

DOI: 10.1021/jacs.5b07098
J. Am. Chem. Soc. 2015, 137, 12050−12054

subsitututed product (**1x**). Substituents can also be incorporated onto the pyrrole backbone (**1y**).

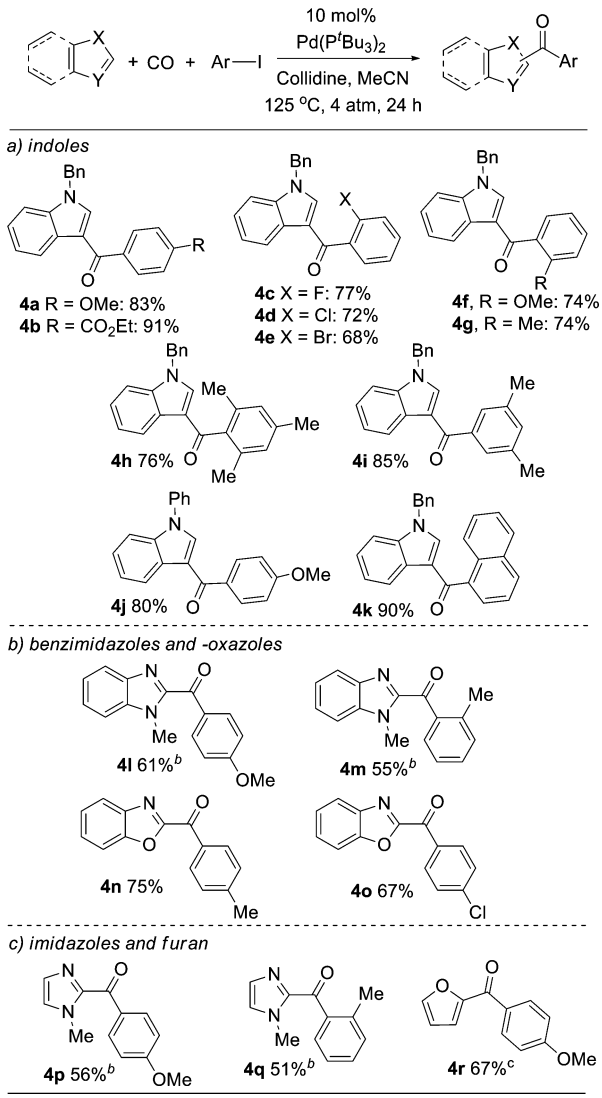
The ability to carbonylatively functionalize pyrroles with aryl iodides opens a number of mechanistic questions. As no chloride salts are present in these transformations, acid chloride is not a viable intermediate. Nevertheless, the reactivity and product selectivity observed are consistent with an electrophilic pathway. In light of our previously observed acid chloride synthesis, one possibility is that without chloride, aroyl iodide (ArCO-I) itself can undergo reductive elimination (Scheme 2a, path A). Although the latter is analogous to acid chloride formation, it is notable that aroyl iodides are much more reactive and electrophilic products and have not been previously observed in Pd-catalyzed carbonylation chemistry. As such, we also consider the potential that the palladium-aroyl intermediates of carbonylation (**2**) could directly react with pyrroles, such as via a Friedel–Crafts reaction with the aroyl ligand (path B), or the electrophilic palladation of pyrrole (path C), in analogy to known non-carbonylative reactions.[16]

Scheme 2. Mechanistic Studies on the Carbonylative Functionalization of Pyrroles



Preliminary studies shed some light on the pathway followed in this reaction. Monitoring the catalytic reaction by *in situ* by ^{1}H and ^{31}P NMR spectrometry reveals the formation of the three-coordinate palladium-aroyl complex **2a** (Scheme 2a) as the major palladium-containing intermediate and presumed catalyst resting state. Complex **2a** can be independently generated from $Pd(P^tBu_3)_2$, aryl iodide, and CO,[17] and its reactivity examined. Interestingly, **2a** does not itself react with the pyrrole at elevated temperatures with or without CO present (Scheme 2b). These data suggest that the palladium-aroyl complex, even with CO coordinated, is not sufficiently electrophilic to directly react with pyrrole, either at the aroyl ligand or palladium. However, the addition of the other reagent present in catalysis, iodotoluene, to the stoichiometric reaction of **2a** initiates a reaction with pyrrole to form the functionalized pyrrole product. In considering the mechanistic postulates,

Table 3. Pd-Catalyzed Carbonylative Functionalization of Heterocycles[a]



[a]ArI (1.0 mmol), heterocycle (0.5 mmol), collidine (73 mg, 0.6 mmol), Pd(PtBu3)2 (25 mg, 0.05 mmol), 2 mL of MeCN, 125 °C, 24 h. [b]20 atm CO. [c]150 °C, 48 h.

while it is possible that aryl iodide reacts directly with **2a** to form a Pd(IV) intermediate, an alternative role would be for it to trap any Pd(0) generated upon reversible reductive elimination in the rate-determining step (path A). Unlike even acid chlorides, the ArCO–I bond is very weak and reactive, making its formation an equilibrium process that would heavily favor palladium-aroyl complex **2**. In the presence of excess aryl iodide, this palladium can be converted to palladium-aryl complex and allow the subsequent reaction of aroyl iodide with pyrrole.[18] Consistent with this mechanism, the introduction of CO significantly accelerates the stoichiometric reaction (Scheme 2b).[19] The latter has been noted to facilitate reductive elimination by creating a sterically encumbered, electron poor palladium intermediate **3**.[13] Kinetic analysis of the reaction of **2a** with pyrrole in the presence of CO and iodotoluene shows a linear rate dependence on pyrrole concentration (see Supporting Information). While these data are potentially consistent with all three pathways in Scheme 2a, as with the results with iodotoluene, they also suggest that any

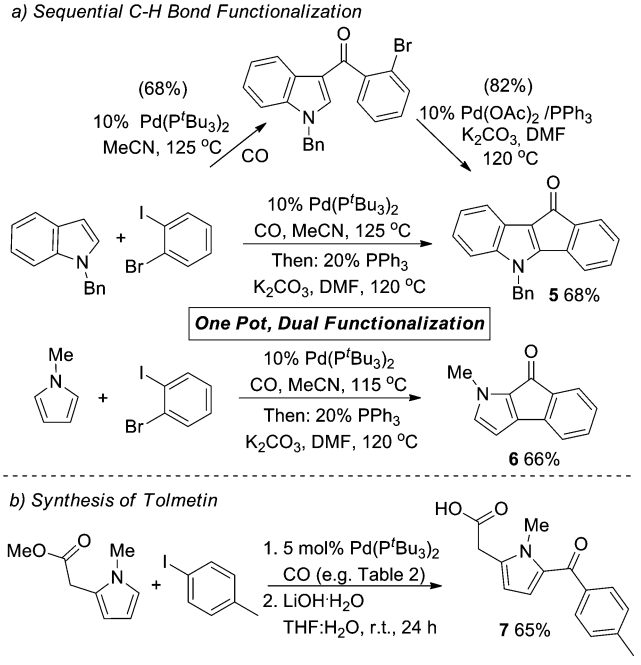
DOI: 10.1021/jacs.5b07098
J. Am. Chem. Soc. 2015, 137, 12050–12054

elimination of aroyl iodide is a rapid equilibrium strongly favoring **2a**.

As far as we are aware, the catalytic formation of potent electrophilic products for carbonylative C−H bond functionalization has not been previously described. This high reactivity provides the ability to functionalize a variety of less reactive heterocycles. As examples, indoles can be converted into ketones in good to excellent yields with this catalyst system (**4a−k**, Table 3). Collidine is required as a base in these reactions to avoid the aroylation of the amine base by these reactive intermediates.[20] In all cases, the 3-substituted indole derivative is generated. The reaction proceeds with electron-rich (**4a,f,j**), electron-poor (**4b−e**), or sterically encumbered (**4f−h**) aryl iodides. Less reactive heterocycles can also be functionalized, such as those containing two heteroatoms. Benzimidazoles undergoes clean carbonylative coupling with aryl iodides to form ketones (**4l,m**). Similar reactivity is observed with benzoxazoles (**4n,o**) and with the monocyclic *N*-methylimidazole (**4p,q**). It is also possible to move beyond nitrogen heterocycles, with simple furan undergoing carbonylative functionalization in good yield (**4r**).

As an illustration of the potential utility of this chemistry, we noted that the carbonylative C−H functionalization is mechanistically orthogonal to many of the more established Pd-based methods for heterocycle derivatization. The latter can be exploited for the selective, sequential functionalization of heterocycles. As examples, the carbonylative functionalization of indole with *o*-bromoiodobenzene followed by direct arylation can allow the selective generation of polycyclic **5** (Scheme 3a).

Scheme 3. Application of Palladium-Catalyzed Carbonylative Heterocycle Functionalization



As both of these steps are palladium-catalyzed, this reaction can be extended to a one pot, sequential C−H functionalization reaction, where the same palladium-catalyst is employed in both steps via the stepwise addition of ligands (Pd(P^{t}Bu$_3$)$_2$ and PPh$_3$/K$_2$CO$_3$) for each functionalization. We see no evidence for crossover in functionalization in this chemistry (e.g., noncarbonylative coupling), presumably due to the distinct mechanisms for the two processes. The same transformation is available with pyrroles (**6**) and allows the selective functionalization of two C−H bonds via differing methods in one pot. Alternatively, this chemistry can be applied in synthesis, such as the preparation of Tolmetin (**7**, Scheme 3b), a potent nonsteroidal anti-inflammatory agent, in two steps using available 4-iodotoluene and CO.[21]

CONCLUSIONS

In conclusion, we have reported a new approach to palladium-catalyzed carbonylative C−H functionalization. This provides an efficient method to synthesize functionalized heterocycles with high atom economy, using stable reagents (aryl iodides and CO), and without the need to prefunctionalize the heterocycle, install directing groups, or exploit high energy building blocks. Considering the high electrophilicity of the intermediates in this chemistry and the CO-promoted, rather than diminished, reactivity, this suggests the potential application of carbonylation in a range of new products classes. Studies directed toward the latter are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07098.

Experimental procedures and spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

*bruce.arndtsen@mcgill.ca

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank NSERC, the Canadian Foundation for Innovation (CFI), and the FQRNT supported Centre for Green Chemistry and Catalysis for funding this research.

REFERENCES

(1) (a) Yu, J. Q.; Shi, Z. *C-H Activation*; Springer: Berlin/Heidelberg, 2010. (b) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (d) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (f) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

(2) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.

(3) (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Gorelsky, S. I. *Coord. Chem. Rev.* **2013**, *257*, 153.

(4) (a) White, M. C. *Science* **2012**, *335*, 807. (b) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (c) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070. (d) Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2015**, *47*, 1195. (e) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381.

(5) (a) Haibach, M. C.; Kundu, S.; Brookhart, M.; Goldman, A. S. *Acc. Chem. Res.* **2012**, *45*, 947. (b) Pérez, P. J. *Alkane C-H Activation by Single-Site Metal Catalysis*; Springer: The Netherlands, 2012. (c) Kuhl,

DOI: 10.1021/jacs.5b07098
J. Am. Chem. Soc. 2015, 137, 12050−12054

N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (d) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874.

(6) For recent reviews on palladium-catalyzed carbonylations, see: (a) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (c) Fang, W.; Zhu, H.; Deng, Q.; Liu, S.; Liu, X.; Shen, Y.; Tu, T. *Synthesis* **2014**, *46*, 1689. (d) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (e) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.

(7) (a) Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 220. (b) Fujiwara, Y.; Tabaki, K.; Taniguchi, Y. *Synlett* **1996**, *1996*, 591. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (d) Itahara, T. *Chem. Lett.* **1983**, *12*, 127. (e) Jaouhari, R.; Dixneuf, P. H.; Lécolier, S. *Tetrahedron Lett.* **1986**, *27*, 6315. (f) Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004**, *6*, 2437.

(8) For non-palladium-catalyzed approaches to arene carbonylation, see: (a) Kunin, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **1986**, *108*, 535. (b) Kunin, A. J.; Eisenberg, R. *Organometallics* **1988**, *7*, 2124. (c) Rosini, G. P.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1994**, *116*, 9498. (d) Sakakura, T.; Sodeyama, T.; Sasaki, K.; Wada, K.; Tanaka, M. *J. Am. Chem. Soc.* **1990**, *112*, 7221. (e) Zhuo, G. L.; Jiang, X. Z. *Catal. Lett.* **2003**, *87*, 225. (f) Werner, H.; Höhn, A.; Dziallas, M. *Angew. Chem.* **1986**, *98*, 1112.

(9) (a) Campo, M. A.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3675. (b) Tlili, A.; Schranck, J.; Pospech, J.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6293. (c) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (d) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (e) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (f) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5204. (g) Zhang, H.; Liu, D.; Chen, C.; Liu, C.; Lei, A. *Chem. - Eur. J.* **2011**, *17*, 9581.

(10) (a) Lian, Z.; Friis, S. D.; Skrydstrup, T. *Chem. Commun.* **2015**, *51*, 1870. For carbonylative coupling with *in situ* generated organocuprates with stoichiometric copper, see: (b) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7316. For in situ halogenation of heterocycles for carbonylative coupling, see: (c) Zhao, M.-N.; Ran, L.; Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *ACS Catal.* **2015**, *5*, 1210. (d) Lang, R.; Shi, L.; Li, D.; Xia, C.; Li, F. *Org. Lett.* **2012**, *14*, 4130. (e) Li, D.; Shan, S.; Shi, L.; Lang, R.; Xia, C.; Li, F. *Chinese J. Catal.* **2013**, *34*, 185.

(11) (a) Beletskaya, I. P.; Cheprakov, A. V. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mings, D. M. P., Eds.; Elsevier: Oxford, 2007; p 411. (b) Beller, M.; Wu, X. F. *Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C-X Bonds*; Springer: Berlin/Heidelberg, 2013.

(12) (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Interscience Publishers: New York, 1963. (b) Olah, G. A. *Friedel-Crafts Chemistry*; John Wiley-Interscience: New York, 1973.

(13) (a) Quesnel, J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2013**, *135*, 16841. (b) Quesnel, J. S.; Kayser, L. V.; Fabrikant, A.; Arndtsen, B. A. *Chem. - Eur. J.* **2015**, *21*, 9550.

(14) The reaction of *N*-benzylpyrrole (16 mg, 0.1 mmol) and *p*-anisoyl chloride (21 mg, 0.12 mmol) with NEt^iPr_2 (16 mg, 0.12 mmol) in CD_3CN (0.7 mL) at 115 °C for 24 h leads to the 2- and 3-substituted pyrrole in 43% yield (in an identical 3.2:1 ratio.

(15) ^1H NMR analysis of reaction crude shows generation of ca. 4:1 ratio of 2- and 3-substituted *N*-methylpyrrole. Only the major isomer is isolated and characterized.

(16) (a) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471. (b) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047. (c) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (d) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (e) Wagner, A. M.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 288. (f) Zhao, L.; Bruneau, C.; Doucet, H. *ChemCatChem* **2013**, *5*, 255.

(17) Bontemps, S.; Quesnel, J. S.; Worrall, K.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8948.

(18) While ArCOI selectivity between Pd(0) and pyrrole would not be affected by iodotoluene, ArCOI presumably reacts much more rapidly with Pd(0). The analogous reaction of benzoyl chloride and $Pd(P^tBu_3)_2$ occurs within 1 h at ambient temperature (ref 13), while reaction with pyrrole requires 115 °C and 24 h (ref 14). Iodotoluene reaction with Pd(0) could therefore allow small concentrations ArCOI to build up for a slower reaction with pyrrole.

(19) While the reaction between pyrrole and **2a** in the absence of CO is not quantitative, the initial rate of this reaction is much slower ($k_{obs} = 1.5 \times 10^{-3}$ min^{-1}) than that in the presence of CO ($k_{obs} = 1.0 \times 10^{-2}$ min^{-1}).

(20) Anisoyl iodide reacts with NEt^iPr_2 at 125 °C to form *N*-ethyl-*N*-isopropyl-4-methoxybenzamide via a Hofmann-type elimination.

(21) (a) Carson, J. R.; McKinstry, D. N.; Wong, S. *J. Med. Chem.* **1971**, *14*, 646. (b) Reddy, L. A.; Chakraborty, S.; Swapna, R.; Bhalerao, D.; Malakondaiah, G. C.; Ravikumar, M.; Kumar, A.; Reddy, G. S.; Naram, J.; Dwivedi, N.; Roy, A.; Himabindu, V.; Babu, B.; Bhattacharya, A.; Bandichhor, R. *Org. Process Res. Dev.* **2010**, *14*, 362.

DOI: 10.1021/jacs.5b07098
J. Am. Chem. Soc. 2015, 137, 12050−12054