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

Simple Amine-Directed Meta-Selective C−H Arylation via Pd/Norbornene Catalysis

Zhe Dong, Jianchun Wang, and Guangbin Dong*

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States

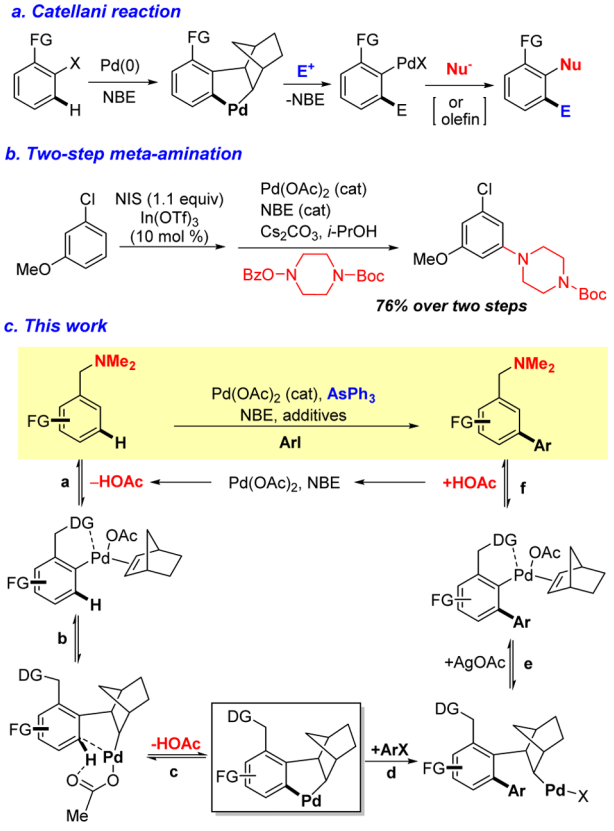
Supporting Information

ABSTRACT: Herein we report a highly meta-selective C−H arylation using simple tertiary amines as the directing group. This method takes advantage of Pd/norbornene catalysis, offering a distinct strategy to control the site selectivity. The reaction was promoted by commercially available $AsPh_3$ as the ligand and a unique "acetate cocktail". Aryl iodides with an ortho electron-withdrawing group were employed as the coupling partner. A wide range of functional groups, including some heteroarenes, are tolerated under the reaction conditions. In addition, the amine directing group can be easily installed and transformed to other common versatile functional groups. We expect this C−H functionalization mode to have broad implications for developing other meta-selective transformations beyond this work.

Site-selective arene functionalization has been continuously impacting the fields of drug discovery, materials science, and chemical industry.[1] While numerous ortho-selective arene functionalization methods have been extensively developed, meta-selective functionalization of electronically unbiased arenes remains a difficult task.[2] Recently, a number of elegant approaches have been developed, including steric-sensitive borylation and silylation,[3] cluster-templated metalation,[4] diaryliodonium salt-mediated arylation,[5] use of a traceless directing group (DG),[6] ortho-metalation-triggered ArS_E,[7] use of a U-shaped template,[8] and others.[9] Despite these seminal efforts, a broadly applicable C−H functionalization strategy that is completely meta-selective, overrides the intrinsic steric and electronic preference of the arene substrates, and tolerates a broad range of functional groups (FGs) remains highly sought.

We foresaw the potential of employing Pd/norbornene (NBE) catalysis, namely, the Catellani reaction,[10] to control the site selectivity for arene C−H functionalization. The Catellani reaction generally uses aryl halides as the substrates and allows ipso and ortho difunctionalization of arenes through an NBE-mediated vicinal C−H metalation reaction (Scheme 1a).[1c,f,10] Seminal work by Catellani and Lautens showed that various carbon FGs can be installed at the ortho position of the arene,[11] which has been employed to prepare meta-substituted arenes.[11f,j] Our group recently demonstrated the first ortho C−N bond-forming transformations with an electrophilic amination reagent and further illustrated a two-step meta-amination sequence via electrophilic halogenation followed by reductive ortho amination (Scheme 1b).[12] In this Communication, we extend our efforts toward developing a direct approach for catalytic meta functionalization of arenes based on the unique features of the Pd/NBE catalysis.[13]

Scheme 1. Meta-Selective Arene C−H functionalization via Pd/NBE catalysis



We postulated that the NBE-bridged five-membered palladacycle, the key intermediate in the Catellani reaction, could also be generated via a C−H metalation-initiated pathway.[14] A proposed meta arylation is depicted in Scheme 1c. Guided by a DG, ortho metalation should give a Pd(II) intermediate (step a), which should be able to undergo an analogous Catellani reaction pathway (steps b and c). The five-membered palladacycle is expected to react with an electrophile (e.g., an aryl halide) through either a Pd(IV) intermediate or a transmetalation pathway,[15] to generate a meta-substituted complex (step d). The resulting Pd(II) intermediate would

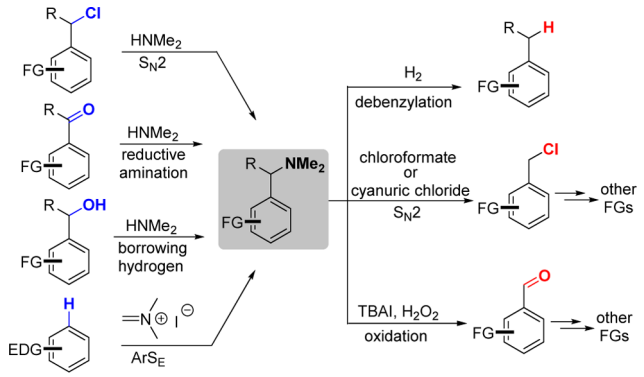
Received: March 17, 2015
Published: April 24, 2015

DOI: 10.1021/jacs.5b02809
J. Am. Chem. Soc. 2015, 137, 5887−5890

then undergo β-carbon elimination followed by reprotonation at the ortho position to furnish the desired meta product (steps e and f). However, the challenges of the proposed pathway are threefold. First, the ortho metalation/deprotonation (step a), its reverse step (demetalation/protonation; step f), and the metalation at the meta position (step c) must be accommodated under the same reaction conditions. Second, the electrophile can possibly react with either the ortho-palladated arene species or the intermediate after meta metalation. Thus, finding an appropriate ligand to control the relative reactivity of these arylpalladium intermediates is nontrivial. Finally, for broad applicability purposes, it would be more attractive to utilize a common and versatile FG as the DG.

Stimulated by the aforementioned challenges, we sought the use of a simple tertiary amine, i.e., dimethylamine, as the DG.[16] A number of benefits of this type of DG can be envisioned: (1) it was demonstrated three decades ago by Ryabov that the dimethylamine can direct a *reversible* ortho metalation under mildly acidic conditions;[17] (2) amines are widely available and frequently found in bioactive and pharma-interesting molecules; (3) it is small and light (the MW of the Me_2N group is only 44); (4) it can be easily installed from a number of common starting materials (e.g., benzaldehydes, halides, etc.) (Scheme 2);[18] (5) it is also known that a dimethylamino group

Scheme 2. Availability and Versatility of the Amine DG

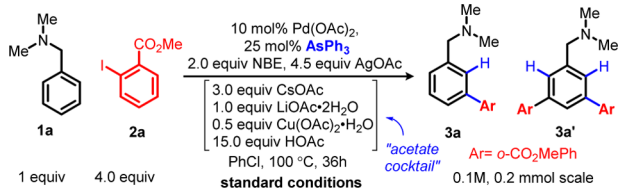


at the benzylic position can be easily removed under hydrogenolysis conditions[16b,c,19] or converted to other FGs (vide infra, Scheme 3).

Benzylamine (**1a**) was employed as the initial model substrate. After extensively examining a range of Pd, ligand, additive, and solvent combinations (for detailed optimization studies, see the Supporting Information), we found to our delight that the desired meta arylation can be achieved using $Pd(OAc)_2/AsPh_3$ as the metal/ligand choice, aryl iodide **2a** as the aryl source, and chlorobenzene as the solvent. Since substrate **1a** has two meta positions, both mono- and diarylation are possible; nevertheless, by controlling the amount of the aryl halide used, the diarylation product **3a′** can be formed as the dominant product (72% yield; Table 1, entry 1).

A series of control experiments were subsequently conducted to understand the role of each reactant (Table 1). In the absence of either the Pd precatalyst or NBE, no desired product was observed (entries 2 and 4). Commercially available $AsPh_3$ proved to be the most efficient ligand to promote the arylation (entry 3); in contrast, use of more electron-rich ligands such as PPh_3 or S-Phos gave significantly lower yields. The silver salt

Table 1. Control Experiments for the Meta Arylation



entry	change from standard conditions	yield (%)[a] 3a	3a′
1	none	2	72
2	no $Pd(OAc)_2$	0	0
3	no $AsPh_3$	11	7
4	no NBE	0	0
5	no AgOAc	6	0
6	no CsOAc	7	34
7	no $LiOAc{\cdot}2H_2O$	3	60
8	no $Cu(OAc)_2{\cdot}H_2O$	8	45
9	no HOAc	19	14
10	no acetate cocktail	21	20
11	HOAc instead of PhCl	0	0
12	12 h instead of 36 h	23	29
13	0.5 equiv of NBE instead of 2.0 equiv	22	13

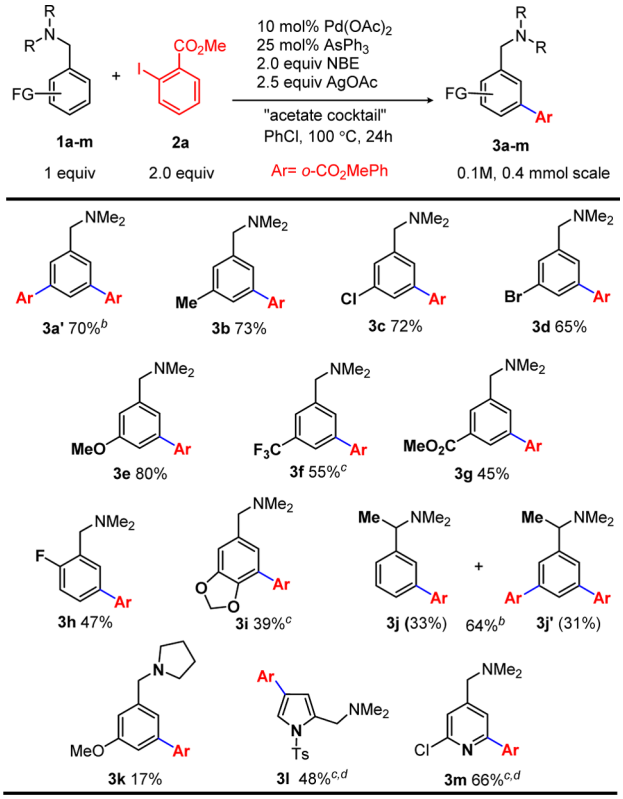
[a]Determined by GC using dodecane as the internal standard.

was employed to accelerate the oxidative addition of the aryl iodide. In the absence of AgOAc, the monoarylation product **3a** can still be obtained in 6% yield (entry 5). We further discovered that the reaction rate can be improved by using an interesting "acetate cocktail" containing $LiOAc{\cdot}2H_2O$, CsOAc, and $Cu(OAc)_2{\cdot}H_2O$ (1:3:0.5) in acetic acid (entries 6–8). Although the exact reason remains to be further explored, we speculate that HOAc and LiOAc help with dechelation of the DG from the palladium (through protonation or complexation) after the initial ortho C–H activation, which is required for the second metalation (vide supra, step b in Scheme 1c); CsOAc might work as a stronger acetate source to assist the deprotonation/metalation step; the Cu(II) salt may act as an efficient Pd(0) scavenger to minimize Pd(0)-mediated reactions. It should be noted that in the absence of the acetate cocktail, the desired meta products can be still be formed, albeit in lower yields (entry 10). Interestingly, while in the absence of acetic acid the reaction became more sluggish, its use as the solvent completely shut down the reaction (entry 11). Finally, shortening the reaction time or using less NBE led to incomplete conversion and more monoarylation product (entries 12 and 13). Further control experiments showed that no ortho- or para-arylation products were observed during the reaction with **1a**.[20] One major side reaction arises from the self-dimerization of aryl ioide **2a** with NBE.[11f,21]

With the optimal conditions established, we first examined the scope of benzylamine substrates (Table 2). When substituted benzylamines were employed as the substrate, the amounts of aryl iodide and AgOAc could be reduced to 2 equiv and 2.5 equiv, respectively. To our delight, both electron-rich and -deficient arenes provided the desired meta-arylated products in moderate to good yields. In particular, the highly electron-rich 3-methoxy substrate, with a strong electron bias at the ortho and para positions, still afforded the meta product (**3e**) in 80% yield. Substitutions at various positions of the arenes can be tolerated. Moreover, this transformation is compatible with a number of functional groups, including

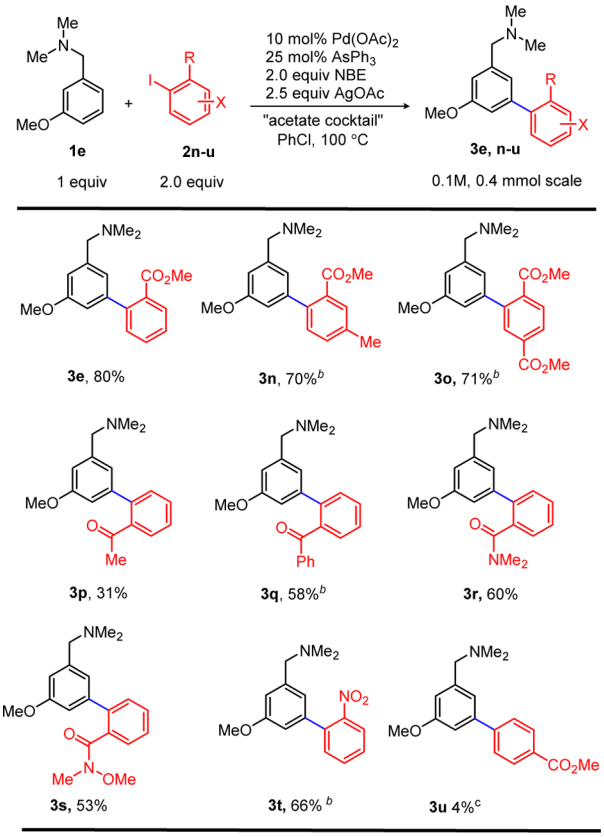
DOI: 10.1021/jacs.5b02809
J. Am. Chem. Soc. 2015, 137, 5887–5890

Table 2. Substrate Scope with Different Benzylamines[a]



[a]All yields are isolated yields. [b]The reaction time was 36 h; 4.0 equiv of **2a** and 4.5 equiv of AgOAc were used. [c]The reaction was run at 130 °C. [d]3.0 equiv of **2a** and 3.5 equiv of AgOAc were used.

Table 3. Substrate Scope with Different Aryl Iodides[a]



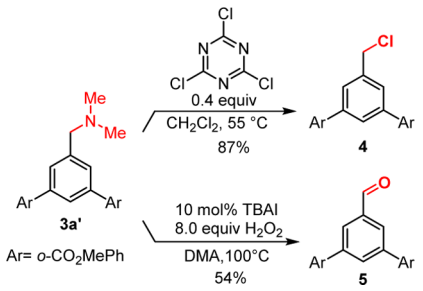
[a]All yields are isolated yields. [b]The reaction time was 36 h. [c]The reaction was run at 130 °C with 4.0 equiv of the aryl iodide and 4.5 equiv of AgOAc.

tertiary amines, aryl fluorides, chlorides, bromides, anisoles, trifluoromethyl and methylenedioxy groups, and esters. In addition, the substrate with a methyl substituent at the benzylic position still provided the desired mono- and diarylation products (**3j** and **3j′**). When enantiopure **1j** was used, no racemization was observed. Besides the dimethylamino group, other tertiary amines[22] can also be employed as the DG (e.g., **3k**), albeit with a lower efficiency. In contrast, use of Ac-protected benzylamines did not lead to the desired products. Further investigation of this transformation with other DGs is ongoing in our laboratory. It is noteworthy that heteroarenes, such as protected pyrrole- and pyridine-derived substrates, are also amenable to this transformation (**3l** and **3m**).

The scope of aryl halides was investigated next (Table 3). Aryl halides containing an ortho electron-withdrawing group (EWG) proved to be most efficient, which is consistent with the previous observation in the typical Catellani arylation reaction.[11g,23] It is likely that the EWG can accelerate oxidative addition of the aryl iodide (step d in Scheme 1c) through a combined electronic and weak-directing effect. Aryl iodides with only a para or meta substituent proved to be much less reactive. For example, when methyl 4-iodobenzoate (**2u**) was used, low conversion was observed (<10%), but the desired meta-arylation product **3u** was still obtained.[24] Nevertheless, besides ester groups, amide, Weinreb amide, alkyl and aryl ketone, and nitro groups were all found to be suitable for this transformation.

Finally, as an example to demonstrate the potential use of this meta-arylation reaction, we showed that the triaryl product **3a′** can be easily transformed to a benzyl chloride or an aldehyde using established procedures (Scheme 3).[25] Both moieties are well-known as versatile synthetic precursors and can be readily transformed to various other FGs.

Scheme 3. Derivatization of the Meta Arylation Product



In summary, we have developed a distinct highly meta-selective arylation using Pd/NBE catalysis. This transformation uses a simple tertiary amine as the DG and commercially available $AsPh_3$ as the ligand. In addition, arenes with various electronic and steric properties can be used as the substrates, and a significant number of FGs, including some heteroarenes, can be tolerated. We expect this mode of reactivity to have high potential to be generalized, allowing other meta functionalizations, e.g., the formation of C−X (X ≠ C) bonds at the meta position. Efforts to expand the reaction scope and detailed mechanistic studies to understand the C−C bond formation

DOI: 10.1021/jacs.5b02809
J. Am. Chem. Soc. 2015, 137, 5887−5890

step (e.g., whether it reacts through a Pd(IV) intermediate or a transmetalation pathway) are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02809.

■ AUTHOR INFORMATION

Corresponding Author

*gbdong@cm.utexas.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank CPRIT for startup funding and the Welch Foundation (F-1781) for research grants. G.D. is a Searle Scholar. We thank Dr. Zhou and Dr. Young for proofreading the manuscript. Mr. Sorey and Ms. Spangenberg are acknowledged for their NMR advice. Johnson Matthey is thanked for a donation of Pd salts.

■ REFERENCES

(1) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (c) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (f) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2010**, *292*, 1. (g) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (h) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (i) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (j) Cheng, C.; Hartwig, J. F. *Chem. Rev.* **2015**, DOI: 10.1021/cr5006414.

(2) Yang, J. *Org. Biomol. Chem.* **2015**, *13*, 1930.

(3) For selected examples, see: (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. *Science* **2002**, *295*, 305. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (c) Maleczka, R. E.; Shi, F.; Holmes, D.; Smith, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (d) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (e) Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853. (f) Cheng, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 592.

(4) For selected examples, see: (a) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3775. (b) Martínez-Martínez, A. J.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T. *Science* **2014**, *346*, 834.

(5) For selected examples, see: (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463.

(6) For selected examples, see: (a) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429. (b) Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109.

(7) For selected examples, see: (a) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298. (b) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877.

(8) (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (b) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567. (c) Lee, S.; Lee, H.; Tan, K. L. *J. Am. Chem. Soc.* **2013**, *135*, 18778. (d) Wan, L.; Dastbaravardeh, N.; Li, G.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 18056. (e) Bera, M.; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *Org. Lett.* **2014**, *16*, 5760. (f) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215. (g) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807. (h) Deng, Y.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 888.

(9) For selected examples, see: (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Zhang, J.; Liu, Q.; Liu, X.; Zhang, S.; Jiang, P.; Wang, Y.; Luo, S.; Li, Y.; Wang, Q. *Chem. Commun.* **2015**, *51*, 1297.

(10) Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 21.

(11) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (b) Motti, E.; Rossetti, M.; Bocelli, G.; Catellani, M. *J. Organomet. Chem.* **2004**, *689*, 3741. (c) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (d) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (e) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759. (f) Deledda, S.; Motti, E.; Catellani, M. *Can. J. Chem.* **2005**, *83*, 741. (g) Motti, E.; Della Ca', N.; Deledda, S.; Fava, E.; Panciroli, F.; Catellani, M. *Chem. Commun.* **2010**, *46*, 4291. (h) Maestri, G.; Della Ca', N.; Catellani, M. *Chem. Commun.* **2009**, 4892. (i) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (j) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053.

(12) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350.

(13) When this article was in preparation, Yu reported a related meta-selective arene alkylation and arylation enabled by a highly optimized pyridine ligand. See: Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334.

(14) For N−H activation-initiated functionalization at the 2-position of indoles and pyrroles via Pd/NBE catalysis, see: (a) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990. (b) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (c) Jiao, L.; Bach, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6080.

(15) (a) Cárdenas, D. J.; Martín-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033. (b) Martín-Matute, B.; Mateo, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2001**, *7*, 2341. (c) Maestri, G.; Motti, E.; Della Ca', N.; Malacria, M.; Derat, E.; Catellani, M. *J. Am. Chem. Soc.* **2011**, *133*, 8574.

(16) For seminal examples of using dimethylamine as the DG in C−H activation, see: (a) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909. (b) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (c) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442. (d) Gao, D.-W.; Shi, Y.-C.; Gu, Q.; Zhao, Z.-L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 86. (e) Feng, R.; Yao, J.; Liang, Z.; Liu, Z.; Zhang, Y. *J. Org. Chem.* **2013**, *78*, 3688.

(17) (a) Ryabov, A. D.; Yatsimirskii, A. K. *Inorg. Chem.* **1984**, *23*, 789. (b) Ryabov, A. D. *Inorg. Chem.* **1987**, *26*, 1252.

(18) For another way to install the directing group, see: Cooper, M. S.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1989**, *45*, 1155.

(19) Cheng, C.; Sun, J.; Xing, L.; Xu, J.; Wang, X.; Hu, Y. *J. Org. Chem.* **2009**, *74*, 5671.

(20) We have synthesized the corresponding ortho- and para-arylation products. Neither of them was observed by GC analysis.

(21) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1985**, *286*, c13.

(22) Primary and secondary amines were found to be unsuitable as DGs for this transformation. The one-carbon homologue of **1a** ($PhCH_2CH_2NMe_2$) did not provide the desired meta-arylation product.

(23) Martins, A.; Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 5186.

(24) Methyl 3-iodobenzoate and 3- and 4-methoxyphenyl iodide all gave low conversions (<10%) and trace amounts of products.

(25) (a) Kolesinska, B.; Kaminski, Z. J. *Tetrahedron* **2009**, *65*, 3573. (b) Gong, J.-L.; Qi, X.; Wei, D.; Feng, J.-B.; Wu, X.-F. *Org. Biomol. Chem.* **2014**, *12*, 7486.

DOI: 10.1021/jacs.5b02809
J. Am. Chem. Soc. 2015, 137, 5887−5890