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Cationic Palladium(II) Catalysis: C-H Activation/Suzuki-Miyaura Couplings at Room Temperature

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Abstract

Cationic palladium(II) catalyst realized facile C-H activation of aryl urea with arylboronic acids at room temperature. This reaction is extremely mild to carry out aromatic C-H activations through electrophilic substitution.

Notwithstanding the extraordinary progress being made in Pd-catalyzed cross-couplings involving nitrogen or oxygen-based directing groups (DG) for C-H activation chemistry, Suzuki-Miyaura couplings under very mild, room temperature conditions remain very rare.^{1,2} Most of the highly successful approaches to date employ a combination of neutral palladium acetate as catalyst, and high temperatures (>120 °C) in aromatic C-H activations.³ Increased nucleophilicity of reaction partners along with acidic conditions oftentimes aid in the desired bond constructions.⁴ Mechanistic studies indicate that aromatic C-H bonds, independent of temperature, are activated with the aid of carboxylate or carbonate anions.^{5,6} Alternatively, electrophilic C-H activation^{1,5,7} with cationic palladium at room temperature has been advanced (Scheme 1). While not yet of general applicability, it does raise the intriguing notion of tuning the cationicity of the catalyst^{8,9} potentially leading to far milder conditions for C-H activation/coupling with arylboronic acids. Herein, we report Suzuki-Miyaura couplings with aryl ureas catalyzed by a preformed cationic palladium(II) complex, which provide aniline derivatives at room temperature in the absence of metal oxidants or added acid (Scheme 2).

Initially, a study was conducted of several neutral palladium catalysts, such as Pd(OAc)₂, PdCl₂, and Pd₂(dba)₃, but none were effective (<1% biaryl). On the other hand, the combination of anilide **1a** and phenylboronic acid (**2a**, 3 equiv) in the presence of [Pd(MeCN)₄](BF₄)₂ (10 mol %), and 1,4-benzoquinone (BQ, 5 equiv) dramatically improved the extent of product formation (Table 1). While several solvents under otherwise identical conditions gave the desired biaryl in low-to-moderate yields (runs 1-6), C-H activation in EtOAc led to **3a** in 96% isolated yield (run 7). Decreased amounts of both phenylboronic acid (**2a**) and BQ could be used with equal success; lower catalyst loading,

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Supporting Information **Available:** Experimental details are available free of charge via the Internet at <http://pubs.acs.org>.

however, led to far slower reactions. Thus, this cationic palladium(II) catalyst enhances not only the rate of C-H activation,¹⁰ but also that for transmetalation with an arylboronic acid, which otherwise requires *ate* formation.¹¹ The BQ present is known to promote reductive elimination in metal-catalyzed couplings.¹²

Under optimized conditions, various arylboronic acids having electron-donating or –withdrawing groups reacted smoothly with aromatic ureas in high yields (Table 2).¹³ Indications that functional group tolerance appears to be good can be found from products **3d-3f**, and **3k-3m**, likely reflecting the mildness of the C-H activation event. Especially noteworthy is the general trend of selective directed mono-arylation (**3w-3bb**), which is typically not the case with symmetrical coupling partners.^{2,3}

Pd(OAc)₂ is also reactive in this reaction but undergoes C-H Suzuki-Miyaura coupling only in the presence of additional strong acid, HBF₄ (Scheme 3). Under such acidic conditions, Pd(OAc)₂ may release acetate anion to generate cationic Pd(II) species.¹⁴

The dimethylurea moiety was easily removed under general hydrolysis conditions to produce the corresponding amine quantitatively (Scheme 4).

In summary, the dramatic effect of cationic palladium in Suzuki-Miyaura reactions has been uncovered, which enables facile aromatic C-H activation and subsequent cross-couplings at room temperature. Mechanistic studies on these highly reactive cationic complexes are ongoing to further elucidate the nature of the active catalyst formed in related C-H activation reactions catalyzed by neutral Pd(OAc)₂ at higher temperatures or in strongly acidic media.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. C-H Suzuki-Miyaura: Shi BS, Zhang YH, Lam JK, Wang DH, Yu JQ. *J Am Chem Soc.* 10.1021/ja909571zChu JH, Tsai SL, Wu MJ. *Synthesis.* 2009:3757. Shi BF, Mangel N, Zhang YH, Yu JQ. *Angew Chem, Int Ed.* 2008; 47:4882. Wang DH, Wasa M, Giri R, Yu JQ. *J Am Chem Soc.* 2008; 130:7190. [PubMed: 18479089] Wang DH, Mei TS, Yu JQ. *J Am Chem Soc.* 2008; 130:17676. [PubMed: 19067651] Kirchberg S, Vogler T, Studer A. *Synlett.* 2008:2841. Vogler T, Studer A. *Org Lett.* 2008; 10:129. [PubMed: 18072783] Shi Z, Li B, Wan X, Cheng J, Fang Z, Cao B, Qin C, Wang Y. *Angew Chem Int Ed.* 2007; 46:5554. Giri R, Mangel N, Li JJ, Wang DH, Breazzano SP, Saunders LB, Yu JQ. *J Am Chem Soc.* 2007; 129:3510. [PubMed: 17335217] Chen X, Goodhue CE, Yu JQ. *J Am Chem Soc.* 2006; 128:12634. [PubMed: 17002342] Kakiuchi F, Kan S, Igi K, Chatani N, Murai S. *J Am Chem Soc.* 2003; 125:1698. [PubMed: 12580585]
2. C-H activation at rt: Xiao B, Fu Y, Xu J, Gong TJ, Dai JJ, Yi J, Liu L. *J Am Chem Soc.* 10.1021/ja909818nNishikata T, Abela AR, Lipshutz BH. *Angew Chem, Int Ed.* 10.1002/anie.200905967Zhang HB, Liu L, Chen YJ, Wang D, Li CJ. *Adv Synth Catal.* 2006; 348:229. Boele MDK, van Strijdonck GPF, de Vries AHM, Kamer PCJ, de Vries JG, van Leeuwen PWNM. *J Am Chem Soc.* 2002; 124:1586. [PubMed: 11853427] Ishiyama T, Takagi J, Hartwig JF, Miyaura N. *Angew Chem, Int Ed.* 2002; 41:3056.
3. For recent reviews on C-H activations, see: Colby DA, Bergman RG, Ellman JA. *Chem Rev.* 10.1021/cr900005nAckermann L, Vicente R, Kapdi AR. *Angew Chem, Int Ed.* 2009; 48:9792. Daugulis O, Do HQ, Shabashov D. *Acc Chem Res.* 2009; 42:1074. [PubMed: 19552413]

- Chen X, Engle KM, Wang DH, Yu JQ. *Angew Chem, Int Ed.* 2009; 48:5094. Li CJ. *Acc Chem Res.* 2009; 42:335. [PubMed: 19220064] Kakiuchi F, Kochi T. *Synthesis.* 2008:3013.
4. (a) Yang SD, Sun CL, Fang Z, Li BJ, Li YZ, Shi ZJ. *Angew Chem, Int Ed.* 2008; 47:1473. (b) Lebrasseur N, Larrosa I. *J Am Chem Soc.* 2008; 130:2926. [PubMed: 18278918] (c) Zhao J, Zhang Y, Cheng K. *J Org Chem.* 2008; 73:7428. [PubMed: 18702549]
5. Recent mechanistic studies see. Powers DC, Geibel MAL, Klein JEMN, Ritter T. *J Am Chem Soc.* 2009; 131:17050. [PubMed: 19899740] Racowski JM, Dick AR, Sanford MS. *J Am Chem Soc.* 2009; 131:10974. [PubMed: 19459631] Hull KL, Sanford MS. *J Am Chem Soc.* 2009; 131:9651. [PubMed: 19569623] Desai LV, Stowers KJ, Sanford MS. *J Am Chem Soc.* 2008; 130:13285. [PubMed: 18781752] García-Cuadrado D, de Mendoza P, Braga AAC, Maseras F, Echavarren AM. *J Am Chem Soc.* 2007; 129:6880. [PubMed: 17461585] Lafrance M, Fagnou K. *J Am Chem Soc.* 2006; 128:16496. [PubMed: 17177387] Campeau LC, Fagnou K. *Chem Commun.* 2006:1253. García-Cuadrado D, Braga AAC, Maseras F, Echavarren AM. *J Am Chem Soc.* 2006; 128:1066. [PubMed: 16433509] Davies DL, Donald SMA, Macgregor SA. *J Am Chem Soc.* 2005; 127:13754. [PubMed: 16201772]
6. (a) Lafrance M, Lapointe D, Fagnou K. *Tetrahedron.* 2008; 64:6015. (b) Garcia-Cuadrado D, de Mendoza P, Braga AAC, Maseras F, Echavarren AM. *J Am Chem Soc.* 2007; 129:6880. [PubMed: 17461585] (c) Davies DL, Donald SMA, Macgregor SA. *J Am Chem Soc.* 2005; 127:13754. [PubMed: 16201772] (d) Biswas B, Sugimoto M, Sakaki S. *Organometallics.* 2000; 19:3895. (e) Horino H, Inoue N. *J Org Chem.* 1981; 46:4416.
7. (a) Campeau LC, Bertrand-Laperle M, Leclerc JP, Villemure E, Gorelsky S, Fagnou K. *J Am Chem Soc.* 2008; 130:3276. [PubMed: 18302383] (b) Deprez NR, Kalyani D, Krause A, Sanford MS. *J Am Chem Soc.* 2006; 128:4972. [PubMed: 16608329] (c) Jia C, Piao D, Oyamada J, Lu W, Kitamura T, Fujiwara Y. *Science.* 2000; 287:1992. [PubMed: 10720319]
8. Houlden CE, Hutchby M, Bailey CD, Ford JG, Tyler SNG, Gagné MR, Lloyd-Jones GC, Booker-Milburn K. *Angew Chem, Int Ed.* 2009; 48:1830.
9. Fine tunings of ligands generally enhance ease of C-H activations; see. Wang DH, Engle KM, Shi BF, Yu JQ. *Science.* 10.1126/science.1182512 Stang EM, White MC. *Nat Chem.* 2009; 1:547. [PubMed: 21378935] Reed SA, White MC. *J Am Chem Soc.* 2008; 130:3316. [PubMed: 18302379]
10. A primary isotope effect for a corresponding ortho-benzoate derivative has recently been described suggesting that intramolecular H-atom abstraction is the rate-determining step; see Xiao B, Fu Y, Xu J, Gong TJ, Dai JJ, Yi J, Liu L. *J Am Chem Soc.* 2010; 132:468. [PubMed: 20020760]
11. (a) Miyaura N. *Synlett.* 2009:2039. (b) Nishikata T, Yamamoto Y, Gridnev ID, Miyaura N. *Organometallics.* 2005; 24:5025. (c) Nishikata T, Yamamoto Y, Miyaura N. *Organometallics.* 2004; 23:4317. (d) Nishikata T, Yamamoto Y, Miyaura N. *Angew Chem, Int Ed.* 2003; 42:2768.
12. (a) Chu JH, Chen CC, Wu MJ. *Organometallics.* 2008; 27:5173. (b) Chen MS, Prabakaran N, Labenz NA, White MC. *J Am Chem Soc.* 2005; 127:6970. [PubMed: 15884938]
13. Neither the corresponding acetamides or trifluoroacetamide analogs led to arylated products in useful yields (low conversions).
14. In the absence of Pd(OAc)₂, no reaction takes place.

Scheme 1.
Electrophilic C-H activation with cationic Pd(II).

Scheme 2.
C-H activation/Suzuki-Miyaura coupling catalyzed by cationic Pd(II).

Scheme 3.
C-H activation catalyzed by $\text{Pd}(\text{OAc})_2$.

Scheme 4.
Deprotection.

Table 1

Solvent effects.^a

run	solvent	yield(%)	run	solvent	yield(%)
1	hexane	50	5	DMF	31
2	THF	80	6	2% surfactant/water	trace
3	acetone	38	7	EtOAc	96
4	EtOH	70	8	EtOAc	94 ^b

^aConducted at rt for 20 h with 10 mol % [Pd(MeCN)₄](BF₄)₂, 1,4-benzoquinone(BQ) (5 equiv), **1a** (0.25 mmol), and **2a** (3 equiv).^b1.5 equiv of **2a** and 3 equiv of BQ.

Table 2

Representative couplings.^a

products
3b : 75%	3c : 90%	3d : 94%	3e : 86% ^b	3f : 94% ^b	3g : 98%	3h : 81% ^c
3i : 87% ^c	3j : 93% ^c	3k : 70%	3l : 97% ^b	3m : 80%	3n : 80%	3o : 89%
3p : 86%	3q : 96%	3r : 95%	3s : 65% ^b	3t : 80%	3u : 90% ^b	3v : 89% ^b
3w : 82% ^d (100:0)	3x : 89% ^d (100:0)	3y : 88% ^d (14:1)	3z : 80% ^d (15:1)	3aa : 78% ^d (>20:1)	3bb : 83% (>20:1)	

^aConducted at rt for 20 h with 10 mol % [Pd(MeCN)₄](BF₄)₂, BQ (2 or 5 equiv), **1** (0.25 mmol), and **2** (1.5 or 3 equiv). The ratios of single:double arylation determined by ¹H NMR are shown in the parentheses.

^bRun for 48 h.

^c2 equiv of BQ.

^d1.5 equiv of **2**.