

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

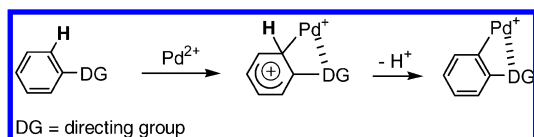
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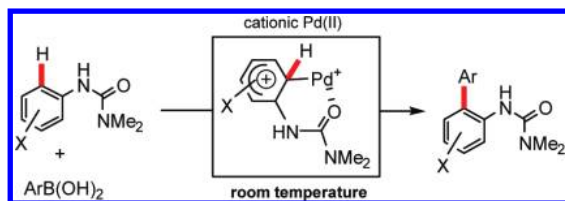
Notwithstanding the extraordinary progress being made in Pd-catalyzed cross-couplings involving nitrogen- or oxygen-based directing groups (DG) for C–H activation chemistry, Suzuki–Miyaura couplings under very mild, room temperature conditions remain very rare.^{1,2} Most of the highly successful approaches to date employ a combination of neutral palladium acetate as catalyst and high temperatures (>120 °C) in aromatic C–H activations.³ The increased nucleophilicity of reaction partners along with acidic conditions often assist 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 cationicity of the catalyst,^{8,9} potentially leading to far milder conditions for C–H

Scheme 1. Electrophilic C–H Activation with Cationic Pd(II)



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).

Scheme 2. C–H Activation/Suzuki–Miyaura Coupling Catalyzed by Cationic Pd(II)



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, however, led to far slower reactions. Thus, this cationic palladium(II) catalyst enhances not only the rate of C–H activation¹⁰ 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

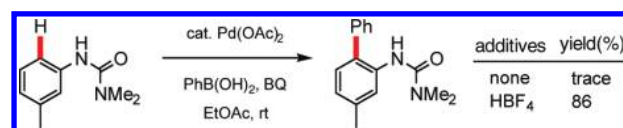
Table 1. Solvent Effects^a

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

^a Conducted 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).
^b 1.5 equiv of **2a** and 3 equiv of BQ.

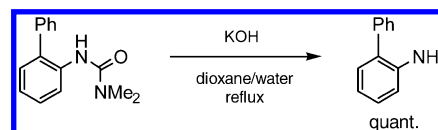
Under optimized conditions, various arylboronic acids having electron-donating or -withdrawing groups reacted smoothly with aromatic ureas in high yields (Table 2).¹³ Indications that functional group tolerance appears to be good can be found from products **3d–3f** and **3k–3m**, likely reflecting the mildness of the C–H activation event. Especially noteworthy is the general trend of selective directed monoarylation (**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 an additional strong acid, HBF₄ (Scheme 3). Under such acidic conditions, Pd(OAc)₂ may release an acetate anion to generate cationic Pd(II) species.¹⁴

Scheme 3. C–H Activation Catalyzed by Pd(OAc)₂

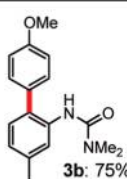
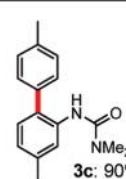
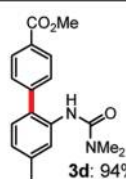
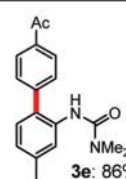
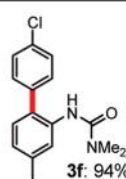
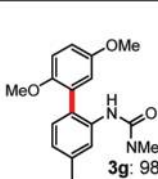
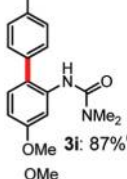
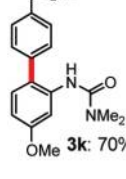
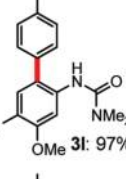
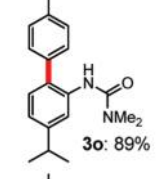
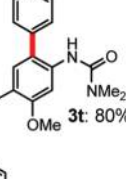
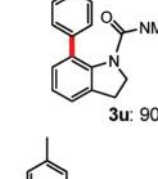
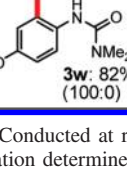
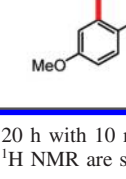
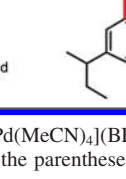
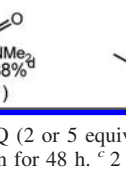
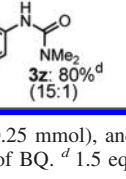
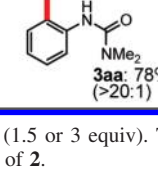
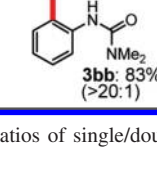
The dimethylurea moiety was easily removed under general hydrolysis conditions to produce the corresponding amine quantitatively (Scheme 4).

Scheme 4. Deprotection



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

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)	3bb: 83% (>20:1)			

^a Conducted 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. ^b Run for 48 h. ^c 2 equiv of BQ. ^d 1.5 equiv of **2**.

in related C–H activation reactions catalyzed by neutral Pd(OAc)₂ at higher temperatures or in strongly acidic media.

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

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- (13) Neither the corresponding acetamides or trifluoroacetamide analogues led to arylated products in useful yields (low conversions).
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