

Published in final edited form as:

J Am Chem Soc. 2010 April 14; 132(14): 4978–4979. doi:10.1021/ja910973a.

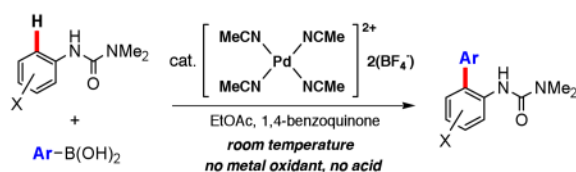
Cationic Palladium(II) Catalysis: C-H Activation/Suzuki-Miyaura Couplings at Room Temperature

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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.

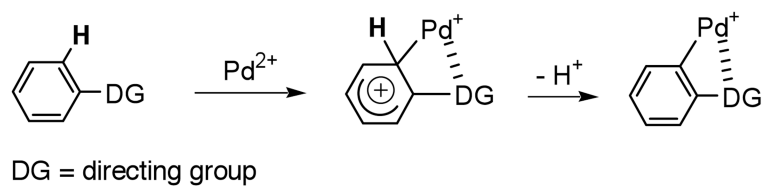
Acknowledgments

Financial support provided by the NIH (GM 86485) is warmly acknowledged as is Johnson Matthey for providing catalyst [Pd(MeCN)₄](BF₄)₂ used in this study.

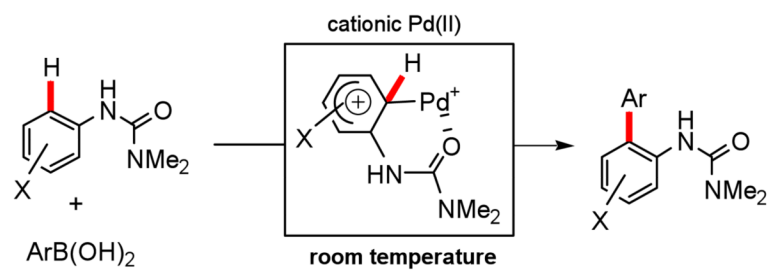
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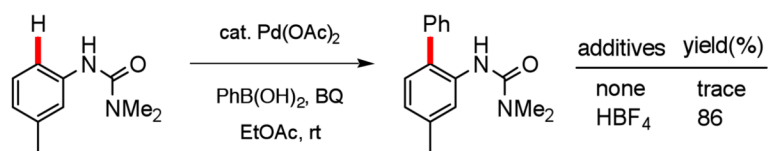
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13. Neither the corresponding acetamides or trifluoroacetamide analogs led to arylated products in useful yields (low conversions).
14. In the absence of Pd(OAc)₂, no reaction takes place.



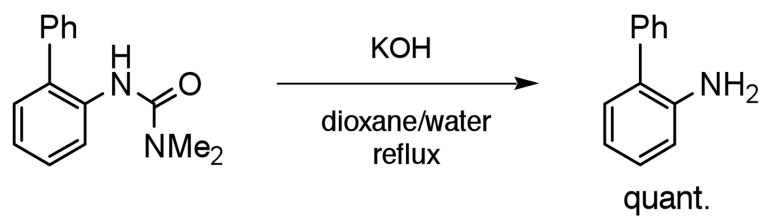
Scheme 1.
Electrophilic C-H activation with cationic Pd(II).



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



Scheme 3.
C-H activation catalyzed by Pd(OAc)₂.



Scheme 4.
Deprotection.

Table 1



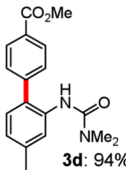


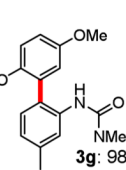
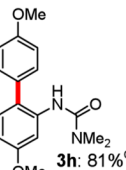





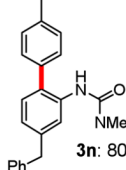
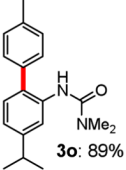


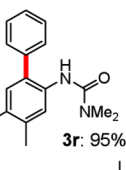

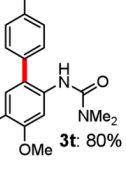
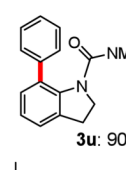
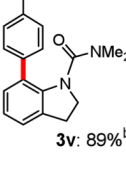
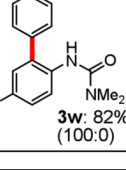
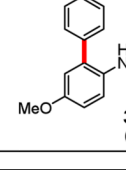
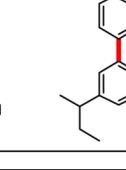
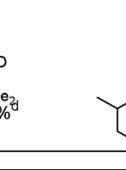
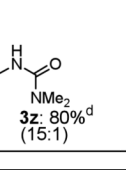
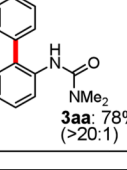
Solvent effects.^a

| 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**.