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Cationic Pd(II)-Catalyzed Fujiwara−Moritani Reactions at Room Temperature in Water

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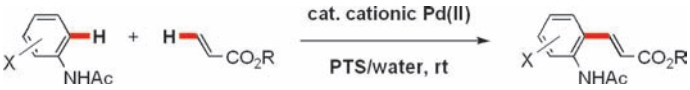
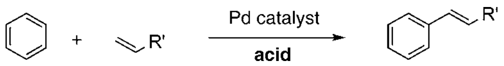
ABSTRACT



Pd^{II}-catalyzed Fujiwara−Moritani reactions can be carried out without external acid at room temperature and in water as the only medium. A highly active cationic Pd^{II} catalyst, [Pd(MeCN)$_4$](BF$_4$)$_2$, easily activates aromatic C−H bonds to produce electron-rich cinnamates in good yields.

C−H activation reactions are very much in focus. Exchanges between aromatic C−H bonds and arenes, aryl halides, olefins, and heteroaromatics continue to be extensively investigated.[1] The Fujiwara−Moritani reaction (Scheme 1), first reported in 1967,[2] is one representative of such Pd-catalyzed couplings. Previous reports on C−H alkenylation reactions indicated that not only are elevated temperatures (80−160 °C) and anhydrous acidic conditions required, but high pressures of CO or O_2 as an oxidizing agent may also be important.[1a,3] Related recent developments of note include reactions with arenes bearing an *ortho*-directing group[4] and a *meta*-selective Fujiwara−Moritani reaction.[5] Nonetheless, traditional Fujiwara−Moritani reactions that can be conducted in the absence of external acid, as well as at ambient temperatures, have yet to be reported.[6] Typically, acids such as HOAc, TFA, and TsOH are used to accelerate these cross-couplings, whereas water has inhibitory properties.[6b] The catalyst is oftentimes palladium acetate, where acetate (or carboxylate) presumably participates in aromatic proton abstraction (Scheme 2).[7] Thus, Pd(OAc)$_2$ has the dual role of electrophilic activation of the arene and intramolecular deprotonation in either a six-membered transition state (A) or alternative (B).[8] Oxidative addition of a metal−substrate complex to an aromatic C−H bond is another possibility.[9] Although electrophilic substitution of an aromatic C−H bond with cationic palladium has

Scheme 1



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(1) See recent reviews: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Ishiyama, T.; Miyaura, M. *Pure Appl. Chem.* **2006**, *78*, 1369. (f) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167, and references therein.

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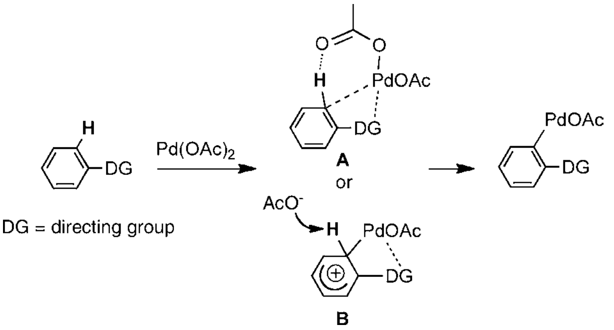
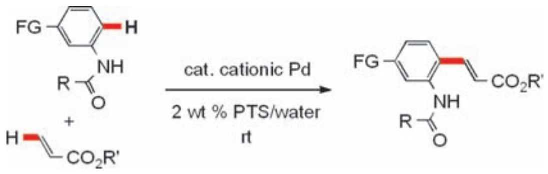
been proposed,[1,3,6d,g,j] use of strongly Lewis acid dicationic Pd^{II} for C−H activation is very rare.[4a]

Scheme 2



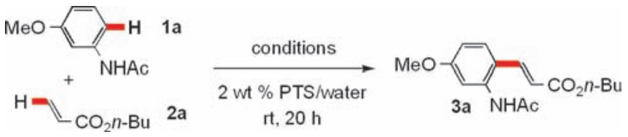
Recently, a weak dicationic palladium species, $[Pd(MeCN)_2](OTs)_2$, has been reported as an effective catalyst for C−H activation of ureas under an atmosphere of CO leading to products of carbonylation.[10] In these cases, the presence of TsOH was essential, and simple acetanilide derivatives gave poor results. Herein, we disclose new technology for effecting Fujiwara−Moritani reactions on anilide derivatives that not only take place at room temperature and in water as the only medium, but most notably without addition of external acid (Scheme 3).

Scheme 3



Initially, as illustrated in Table 1, reactions under acidic conditions catalyzed by $Pd(OAc)_2$ led to low yields of 1-alkenylated product (**3a**), derived from the reaction of 3-methoxyacetanilide (**1a**) with *n*-butyl acrylate (**2a**) in water (entries 1−6). In the presence of 1,4-benzoquinone (BQ) and surfactant PTS (polyoxyethanyl α-tocopheryl sebacate),[11] C−H activation takes place. Among the acids investigated, excess HBF_4 gave the best yield (entry 6). BQ was critical, without which the reaction essentially did not take place in water (entry 7). Use of an alternative oxidizing agent, such as a silver salt, was of no consequence (entry 8). Ultimately, it was found that a mixture of additives consisting of BQ and $AgNO_3$ in PTS/water gave a 95% yield of the desired product **3a** (entry 10). As expected, acid plays an important role in the reaction catalyzed by $Pd(OAc)_2$ (entry 11). Remarkably, the commercially available dicationic palladium salt $[Pd(MeCN)_4](BF_4)_2$ also smoothly catalyzes the reaction *at room temperature without a large excess of external acid* (entry 13). None of the product from a potentially competitive 1,4-addition pathway was observed.[12,13] Surfactants other than PTS were also studied but found to be less effective: Brij 35 (42%); Triton X-100 (48%); Solutol (65%). In the absence of PTS, the corresponding "on water" reactions were not competitive (entries 9, 12).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additives (equiv)	acid (equiv)	yield (%)
1	$Pd(OAc)_2$	BQ (1.5)	*p*-TsOH (0.5)	39
2	$Pd(OAc)_2$	BQ (1.5)	CSA (0.5)	30
3	$Pd(OAc)_2$	BQ (1.5)	AcOH (6)	16
4	$Pd(OAc)_2$	BQ (1.5)	TFA (1)	trace
5	$Pd(OAc)_2$	BQ (1.5)	HBF_4 aq (1)	47
6	$Pd(OAc)_2$	BQ (1.0)	HBF_4 aq (5)	63
7	$Pd(OAc)_2$	none	HBF_4 aq (5)	0
8	$Pd(OAc)_2$	$AgNO_3$ (2.0)	HBF_4 aq (5)	trace
9	$Pd(OAc)_2$	BQ (1.0), $AgNO_3$ (2.0)	HBF_4 aq (5)	72[b]
10	$Pd(OAc)_2$	BQ (1.0), $AgNO_3$ (2.0)	HBF_4 aq (5)	95
11	$Pd(OAc)_2$	BQ (1.0), $AgNO_3$ (2.0)	none	trace
12	$[Pd(MeCN)_4](BF_4)_2$	BQ (1.0), $AgNO_3$ (2.0)	none	66[b]
13	**$[Pd(MeCN)_4](BF_4)_2$**	**BQ (1.0), $AgNO_3$(2.0)**	**none**	**85**

[a] Conducted at rt for 20 h in 2 wt % PTS/water and 10 mol % catalyst, additives, 3-methoxyacetanilide (**1a**), and *n*-butyl acrylate (**2a**, 2 equiv). [b] Reaction was conducted "on water".

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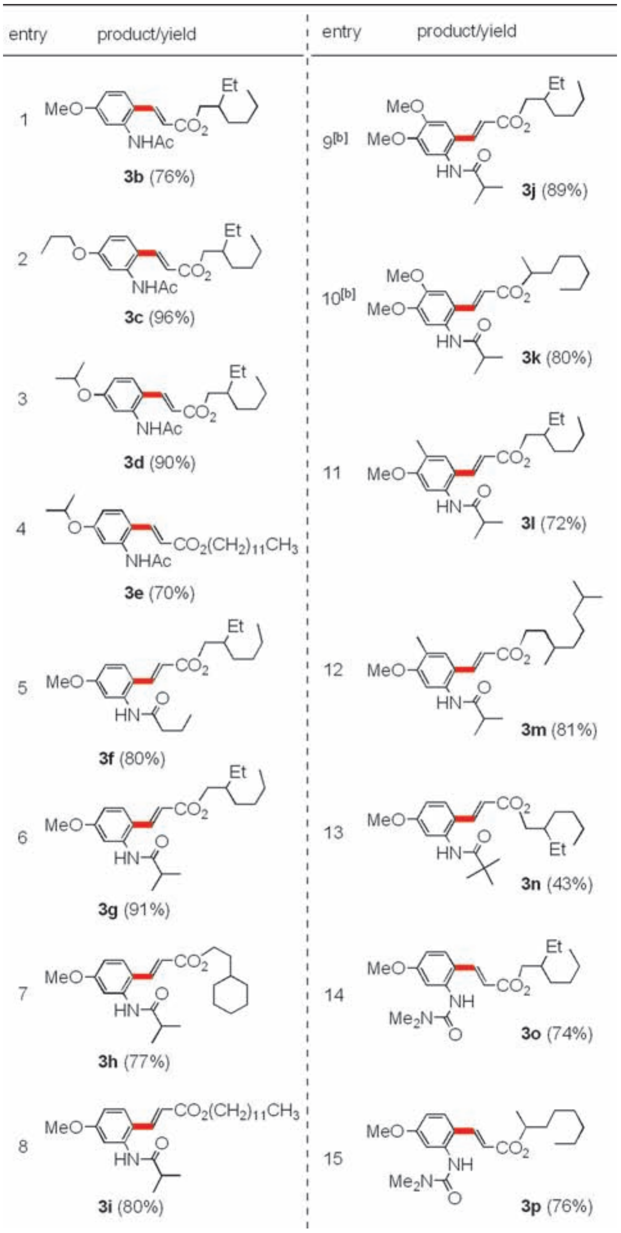
The scope of this transformation is illustrated in Table 2. Reactions of *m*-alkoxy-functionalized anilide derivatives proceed smoothly with acrylates **2** containing a variety of alkyl chains to afford products regiospecifically in 70−96% yields (entries 1−12). Isomeric *p*-alkoxy analogues were found to be unreactive. A pivalamide leading to product **3n** is slower-reacting, presumably due to difficulty in forming a monocationic species from dicationic Pd (entry 13). Although urea derivatives are reported to react only in the presence of excess acid,[10] their reactions under these conditions gave the corresponding vinylated products in good isolated yields (entries 14, 15). Multisubstituted anilides also participated at room temperature, leading to a variety of substituted arenes (entries 9−12).

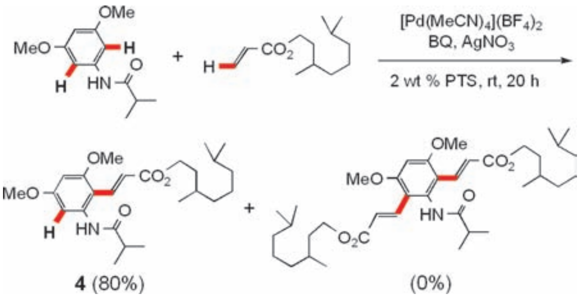
Table 2. Fujiwara−Moritani Reactions with Anilide Derivatives[a]



[a] Run at rt for 20 h in 2 wt % PTS/water (1 mL) and 10 mol % $[Pd(MeCN)_4](BF_4)_2$, BQ (1 equiv), $AgNO_3$ (2 equiv), anilide **1** (0.25 mmol), and acrylate ester **2** (2 equiv). [b] 48 h.

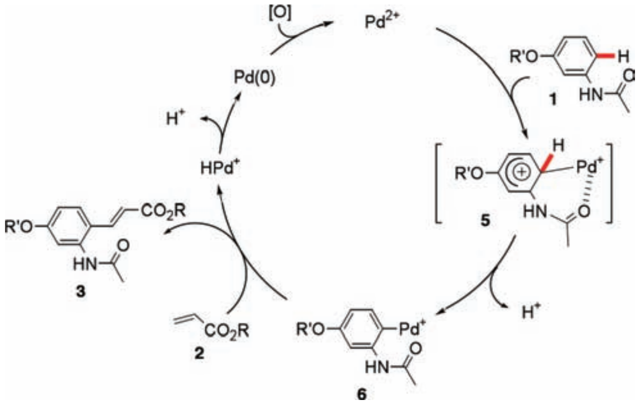
Although *ortho*-directed C−H activation remains a very attractive approach to cross-coupling chemistry, it can result in double functionalization, with reactions oftentimes occurring at both sites *ortho* to the directing group.[1] In such situations, 2-substituted arenes need to be employed so as to avoid this undesired competing pathway. Since an *ortho*-substituent in a product such as **4** appears to sterically prevent these secondary couplings, this can be used to advantage. Hence, our standard conditions for C−H activation lead to a single, regiospecifically *ortho*-positioned product of C−H substitution (**4**; Scheme 4).

Scheme 4. Selective Coupling



One proposed pathway to account for these cationic palladium(II)-catalyzed reactions is offered in Scheme 5, although details await further investigation. Initial electrophilic attack by cationic Pd[II6g,j,14] occurs on an aromatic C−H bond in **1** with the aid of the directing group, proceeding via Wheland-like species **5**[15] to generate monocationic species **6**. The resulting product **3** is obtained after carbopalladation by **6** of acrylate **2**, followed by *β*-hydride

Scheme 5. Proposed Mechanism



elimination. Pd^0 is then oxidized back to Pd^{II} by 1,4-benzoquinone and silver salts, notwithstanding the potential for BQ to competitively ligate the active cationic Pd^{II} catalyst.[16]

In conclusion, Fujiwara−Moritani reactions of anilides can now be run without external acids, at room temperature, and in water as the only medium. A general strategy based on highly reactive dicationic palladium catalysts for the synthesis of valued cinnamates has been established.

Acknowledgment. Financial support provided by the NIH (GM 86485) is gratefully acknowledged, as is Johnson Matthey for providing catalyst $[Pd(MeCN)_4](BF_4)_2$ used in this study.

Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) **Typical Procedure.** Anilide **1** (0.25 mmol), acrylate ester **2** (0.5 mmol), $AgNO_3$ (0.5 mmol), 1,4-benzoquinone (0.25 mmol), and $[Pd(MeCN)_4](BF_4)_2$ (0.025 mmol) were sequentially added in air to a reaction tube equipped with a stir bar and capped with a septum. An aqueous solution containing PTS (1.0 mL, 2 wt %) was added by syringe, and the reaction mixture was vigorously stirred for 20 h. After completion, the contents of the flask were quenched with aq $NaHCO_3$ and extracted with EtOAc. The solution obtained was filtered through a plug of silica gel and anhydrous $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the desired product.