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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](BF₄)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 O₂ 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 (A)- or four (B)-membered transition state.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 been proposed,^{1,3,6d,6g,6j} use of strongly Lewis acid dicationic Pd^{II} for C-H activation is very rare.^{4a}

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).

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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>.

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 HBF₄ 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 AgNO₃ in PTS/water gave a 95% yield of the desired product **3a** (entry 10). As expected, acid plays an important role in the reaction catalysed by Pd(OAc)₂ (entry 11). Remarkably, the commercially available dicationic palladium salt [Pd(MeCN)₄](BF₄)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).

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 analogs were found to be unreactive. A pivalamide leading to product **3n** is slower-reacting, presumably due to difficulty in forming a mono-cationic species from dicationic Pd species (entry 13). Although urea derivatives are reported to only react under adding excess acids,¹⁰ their reactions under these conditions gave the corresponding vinylated products in good isolated yields (entries 14, 15). Multi-substituted substrates also participated at room temperature, leading to a variety of substituted arenes (entries 9–12).

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 as substrates to avoid this undesired competing pathway. However, since the presence of an *ortho*-substituent in an educt (**4**) appears to sterically prevent these 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).

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^{II} 6g,6j,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 *mono*-cationic species **6**. The resulting product **3** is obtained after carbopalladation by **6** of acrylate **2**, followed by β -hydride elimination. Pd⁰ 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 for the synthesis of valued cinnamates has been established based on highly reactive dicationic palladium catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- (17). A typical procedure. Anilide **1** (0.25 mmol), acrylate ester **2** (0.5 mmol), AgNO₃ (0.5 mmol), 1,4-benzoquinone (0.25 mmol), and [Pd(MeCN)₄](BF₄)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. NaHCO₃ and extracted with EtOAc. The solution obtained was filtered through a plug of silica gel and anhydrous MgSO₄, and concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the desired product.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Table 1

Optimization of Reaction Conditions.^a

entry	catalyst	additives(equiv)	acid (equiv)	yield (%)
1	Pd(OAc) ₂	BQ (1.5)	<i>p</i> -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

^aConducted 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).

^bReaction was conducted on water.

Table 2Fujiwara-Moritani Reactions with Anilide Derivatives.^a

entry	product/yield
1	3b (76%)
2	3c (96%)
3	3d (90%)
4	3e (70%)
5	3f (80%)
6	3g (91%)
7	3h (77%)
8	3i (80%)
9 ^[b]	3j (89%)

entry	product/yield
10 ^[b]	3k (80%)
11	3l (72%)
12	3m (81%)
13	3n (43%)
14	3o (74%)
15	3p (76%)

^aRun at rt for 20 h in 2 wt % PTS/water (1 mL) and 10 mol % [Pd(MeCN)₄](BF₄)₂, BQ (1 equiv), AgNO₃ (2 equiv), anilide **1** (0.25 mmol) and acrylate ester **2** (2 equiv).

^b48 h.