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Palladium(II)-Catalyzed Dehydrogenative Alkenylation of Cyclic Enaminones via the Fujiwara-Moritani Reaction

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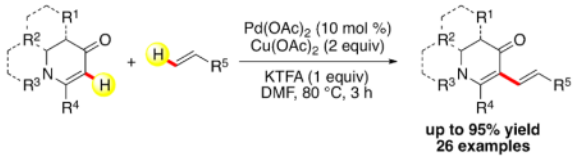
Abstract



A new Pd(II)-catalyzed dehydrogenative alkenylation reaction involving two alkenes was developed. A variety of nonaromatic, cyclic enaminones were successfully coupled to primary and secondary alkenes yielding a series of unique 1,3-dienes. The generality of this transformation presents a useful strategy for directly cross-coupling alkenes and offers an attractive new approach to functionalize enaminones.

Direct C–H functionalization chemistry has seen significant progress during the last decade. [1] Cross dehydrogenative coupling reactions that use two C–H bonds to form a new C–C bond are highly sought after, because these processes do not require pre-funtionalization and as a result have high atom economy.[2] The Fujiwara-Moritani reaction is a process by which aromatic substrates undergo an intermolecular dehydrogenative alkenylation. This reaction was initially developed using stoichiometric amounts of Pd(II) (Figure 1a), [3] but soon thereafter was shown to also take place with catalytic amounts of Pd(II) (Figure 1b).[4] In recent years, the scope of the Fujiwara-Moritani has been expanded to a plethora of aromatic substrates.[5] However, only few cases of alkenylation reactions involving two alkene C–H donors (Figure 1c) are known. They are limited to select substrates, require high Pd loading, and need long reaction time. [6] Herein, we report the development of an efficient Pd(II)-catalyzed Fujiwara-Moritani reaction, featuring nonaromatic cyclic enaminones that react with a variety of alkenes to furnish 5-alkenylated reaction products.

In our quest to generate libraries for biological screening, we were particularly interested in functionalizing the cyclic enaminone nucleus **I** (Figure 2) because of its unique chemical and biological properties.[7] Recently, we reported a Pd(II)-catalyzed direct arylation of cyclic enaminones with aryl trifluoroborates (Figure 2a). [8] Alkenyl trifluoroborates, however, did not furnish the desired alkenylated products. We speculated that the rate of transmetallation with the alkenyl reagents surpassed that of C5-palladation and as a result homocoupling depleted the alkenyl precursors and reoxidants.

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Supporting Information Available. Experimental procedures, detailed reaction optimization data, and results from the mechanistic study, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

To address this problem, we examined the feasibility of a Fujiwara-Moritani reaction (Figure 2b) to access 5-alkenyl enaminone derivatives. Key to this strategy would be the use of alkenes with complementary reactivity. We envisioned that the palladated enaminone **II** could be orthogonally intercepted by an electron-deficient alkene to furnish product **VI**.

We selected enaminone **1** as the substrate and examined its reaction with *tert*-butyl acrylate (**2a**) (Table 1). $Pd(OAc)_2$ (10 mol %) was initially selected because of its well-established reactivity.[8, 9] Next, DMF was identified as the best solvent (entries 1–4). $Cu(OAc)_2$ proved to be the most effective and economical reoxidant (entries 4–7). The incorporation of additives, KTFA specifically, notably increased the yield of the reactions (entries 8–12). Furthermore, the highest yields were observed when the reaction was run at 80 °C (entries 12– 14), and the reaction time was reduced from 24 h to 3 h (entries 12 and 15).

With these optimized conditions, we were pleased to find that this direct alkenylation reaction was amenable to a variety of alkenes (Scheme 1). Acrylate esters and vinyl ketones readily reacted with **1**, providing the desired dienes (**3a–3e**) in excellent yields. Notably, the highest yield (95%) was observed with *N*,*N*-dimethylacrylamide (**3f**). Phosphonates, styrene and sulfones were also viable coupling partners, yet furnished the products (**3g–3i**) in slightly lower yields. Acrylic acid and vinyl ethers, however, failed to afford the desired products **3j** or **3k**. Methyl crotonate, as a multi-substituted alkene, could also be coupled to **1** to produce a single isomer (**3l**), whereas α-methylene-γ-lactones afforded both the conjugated and unconjugated diene products with a greater preference for the latter (**3ma: 3mb**=1:2.5). This preference for unconjugated dienes has been previously noted.[5k, 10] Interestingly, alkenylation of cyclohexene yielded two inseparable, unconjugated dienes (**3na**/**3nb**). Mechanistically, we speculated that **3nb** was generated from **3na** through Pd–H insertion and immediate β-H elimination.[11]

We next assessed a series of enaminones (Scheme 2). We found that this reaction could be extended to mono-and bicyclic, electronically unattenuated enaminones (**5a–5g**). Importantly, alkenylation of the diastereomeric substrates (**5a**/**5b**) took place without epimerization of the stereocenters and with virtually the same yields. The introduction of a C6-substituent to the cyclic enaminone, however, significantly decreased the yield (of **5h**). *N*-H and *N*-Cbz enaminones also showed poor reactivity (for products **5i** and **5j**) which is consistent with our previous findings.[8] 4-Pyridone was found to furnish a mono-coupling product **5k** albeit in only 7% yield. An *E*-enaminone was also tested, but only a trace amount of product **5l** was observed.

To elucidate the alkenylation process, a mechanistic analysis of the initial interaction of Pd(II) with enaminone **1** was carried out by ^{1}H NMR (in DMSO-d_6 at room temperature, Figure 3). 50 mol % of $Pd(OAc)_2$ with **1** (Figure 3b) furnished intermediate **6** at room temperature along with the same amount of acetic acid and unreacted **1**. With 100 mol % of $Pd(OAc)_2$ (Figure 3c), a complete conversion of **1** was observed after only 20 min, yielding only **6** and acetic acid (See the Supporting Information for the full spectra). 20% of product **3a** was subsequently furnished from intermediate **6** when heated with acrylate **2a** at an elevated temperature (140 °C) (Scheme 3).[12] This suggests that the C–C bond formation is the rate-limiting step. It is worth noting that intermediate **6**, however, was not detected when DMF-d_7 was used as the solvent, presumably because DMF does not stabilize **6** as well as DMSO. [13] The discrepancy of their stabilizing effect as solvents was also reflected in the yield of **3a**, where 78% was produced in DMF compared to 53% in DMSO (Table 1, entries 2 and 4).

Hence, we suggest the following mechanism (Figure 4).[5a] An electrophilic attack of Pd(II) on enaminone **A** followed by deprotonation forms palladated **B**, which then undergoes

alkene insertion to afford **C**. Subsequent *β*-H elimination delivers product **D**. Reductive elimination and reoxidation by Cu(II) regenerates Pd(II).

In summary, we have developed a direct, convenient and highly atom-economic approach for the dehydrogenative coupling of nonaromatic, cyclic enaminones and simple alkenes. The generality of this transformation presents a useful strategy for directly cross-coupling alkenes and offers an attractive new approach to prepare functionalize enaminones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Conversion of **6** required a high temperature, which, however, led to a low yield of **3a** due to its thermal instability. See the Supporting Information for more detail.

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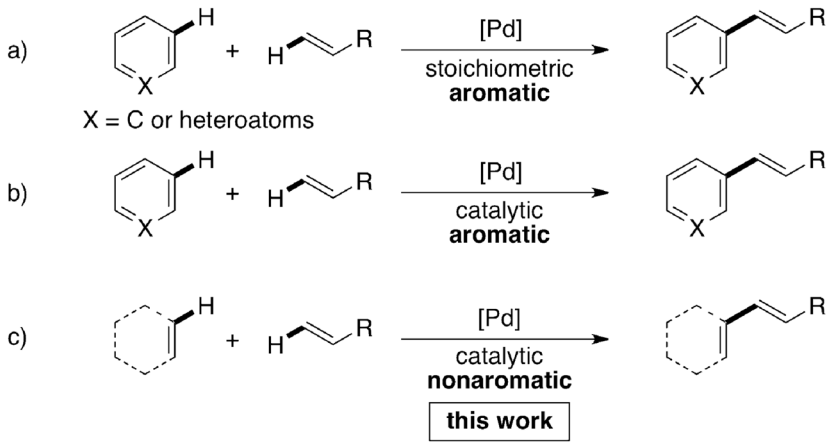


Figure 1.
Development of the Fujiwara-Moritani reaction.

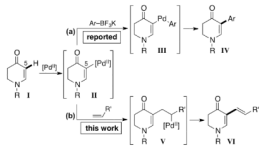


Figure 2.
Pd(II)-cross coupling reactions of cyclic enaminones.

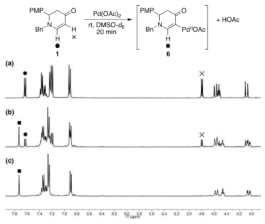


Figure 3.
Detection of palladated intermediate **6** by ^{1}H NMR: (a) Pure **1**; (b) **1** with 50 mol % of $Pd(OAc)_2$; (c) **1** with 100 mol % of $Pd(OAc)_2$.

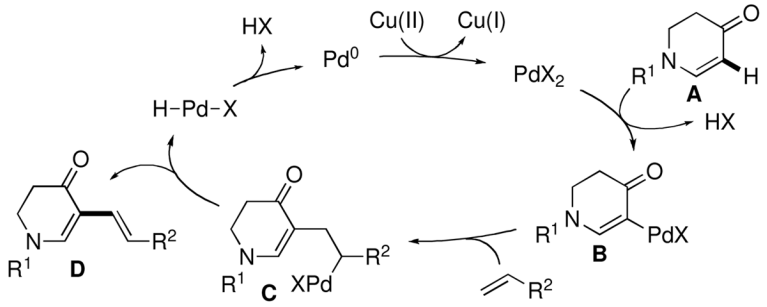
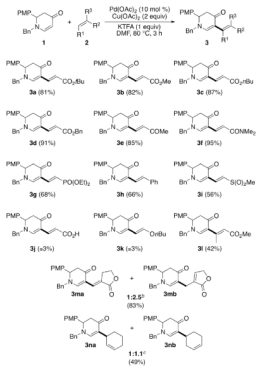


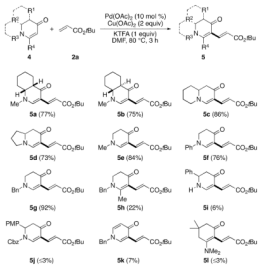
Figure 4.
Suggested mechanism of dehydrogenative alkenylation.



Scheme 1.

Scope of alkenes[a]

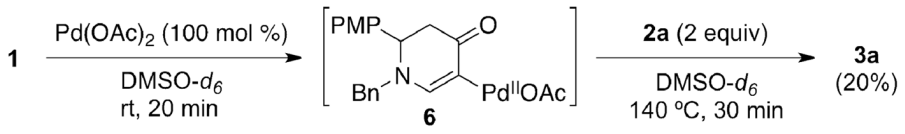
[a] Conditions: **1** (0.2 M), **2** (2 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), KTFA (1 equiv) in DMF under N_2 at 80 °C for 3 h. Isolated yield. [b] Isolated ratio. [c] ^1H NMR ratio.



Scheme 2.

Scope of enaminones[a]

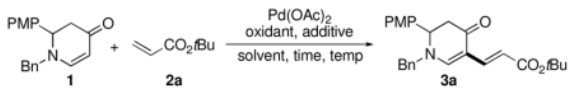
[a] Conditions: **4** (0.2 M), **2a** (2 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), KTFA (1 equiv) in DMF under N_2 at 80 °C for 3 h. Isolated yield.



Scheme 3.
Reaction of **1** with acrylate **2a** in DMSO-d_6

Table 1

Optimization of the reaction conditions[a]



entry	solvent	reoxidant	additive	temp (°C)	3a (%)[b]
1	*t*BuOH	$Cu(OAc)_2$	--	80	55
2	DMSO	$Cu(OAc)_2$	--	80	53
3	DMA	$Cu(OAc)_2$	--	80	70
4	DMF	$Cu(OAc)_2$	--	80	78
5	DMF	$CuCl_2$	--	80	0
6	DMF	AgOAc	--	80	43
7	DMF	$PhCO_3tBu$[c]	--	80	59
8	DMF	$Cu(OAc)_2$	$LiBF_4$	80	80
9	DMF	$Cu(OAc)_2$	$BiCl_3$	80	39
10	DMF	$Cu(OAc)_2$	CsOAc	80	77
11	DMF	$Cu(OAc)_2$	K_2CO_3	80	68
12	DMF	$Cu(OAc)_2$	KTFA	80	85
13	DMF	$Cu(OAc)_2$	KTFA	50	73
14	DMF	$Cu(OAc)_2$	KTFA	110	69
15	**DMF**	**$Cu(OAc)_2$**	**KTFA**	**80**	**87**[d]

[a] Reaction conditions unless otherwise specified: **1** (0.2 M), **2a** (2 equiv), $Pd(OAc)_2$ (10 mol %), reoxidant (2 equiv), additive (1 equiv) under N_2 at 80 °C in 24 h. (PMP=*para*-methoxyphenyl)

[b] ^1H NMR yield *vs.* Ph_3SiMe (1 equiv) as the internal standard.

[c] 1 equiv.

[d] Completed in 3 h. (Detailed optimization is available in the Supporting Information.)