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Palladium(II)-Catalyzed Direct Alkenylation of Nonaromatic Enamides

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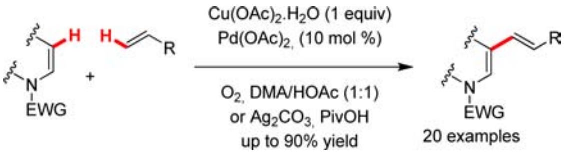
ABSTRACT



A mild and efficient method for the direct alkenylation of nonaromatic enamides was achieved through a palladium(II)-catalyzed C–H functionalization. The reaction scope includes cyclic and acyclic enamides and a range of activated alkenes. This approach represents the first successful direct C(3)-functionalization of nonaromatic cyclic enamides.

Transition-metal-catalyzed regioselective C–C bond formations via C–H bond activation have recently become one of the most attractive research subjects in organic synthesis.[1] Indeed, atom economy, nontoxic and inexpensive solvents, catalytic reagents, and readily available substrates without preliminary functionalization are fundamental criteria for accessing clean reactions.[2] Among these earlier studies, particularly noteworthy is the Mizoroki–Heck reaction which involves aryl halides and alkenes in the presence of transition-metal catalysts to yield π-conjugated aromatic compounds.[3] Alternatively, the Fujiwara and Moritani[4] reaction has recently been widely used to link various aromatic cores directly with activated alkenes via a dehydrogenative process.[5] It constitutes a powerful halogen-free strategy to explore the scope of the alkenylation method. However it is noteworthy that to date only a few studies have reported the direct C–C bond functionalization of nonaromatic substrates with alkenes.[6] In connection with our ongoing project on the development of efficient methodologies to generate an original collection of small nitrogen-containing molecules,[7] we focused on the direct C-3 functionalization of enamides **I** (Figure 1).[8] While the C-2 functionalization was recently developed by direct arylation, especially in the case of acyclic compounds **II**,[9] the regioselective C-3 functionalization of nonsubstituted enamides of type **I** has not yet been described. We therefore envisaged examining the

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direct alkenylation of the appropriate C−H bond to generate conjugated enamides **III**. We report herein our successful results on the direct regio- and stereoselective Pd-catalyzed alkenylation of a range of enamides and demonstrate the cost-effective and high reaction efficiency, excellent functional group compatibility, and mild reaction conditions of our methodology.

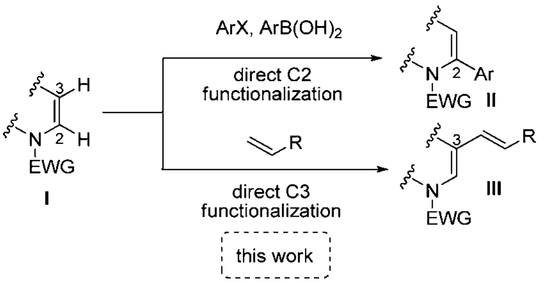
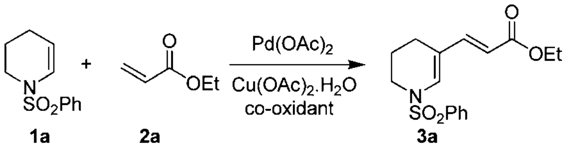


Figure 1. Pd(II) direct functionalization strategy.

In light of recent advances in this area, we began this study by performing the direct alkenylation of enamide **1a** in the presence of 2 equiv of ethyl acrylate **2a**, 10 mol % of $Pd(OAc)_2$ as a catalyst, and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ as oxidant in acetic acid under a slow bubbling of oxygen at 70 °C (Table 1).[6c] As reported in the literature, a co-oxidant (O_2) and an acidic source are both required to carry out the Pd-catalyzed direct alkenylation in good yields.[5g] Under these conditions, the desired conjugated enamide **3a** was isolated as an *E*-isomer in 56% yield (entry 1).[10] No beneficial effect was observed by changing the nature of the acidic source (entries 2 and 3). Owing to the sensitivity of enamides in acidic media, the quantity of acetic acid was reduced by half by using dimethylacetamide as cosolvent; a slight increase in the yield of **3a** (71%) was thus observed (entry 4). The absence of acid dramatically reduced the yield of the reaction (entry 5) by affecting the electrophilicity of the metal ions, highlighting the importance of balancing the two factors. Further optimizing the reaction conditions, we found that satisfying yields could also be achieved by using Ag_2CO_3 as additive (entries 6 and 7). As expected, when the additive was removed, no conversion occurred and starting material is recovered (entry 8). A trace quantity of **3a** was obtained when the reaction was conducted under air rather than a pure oxygen atmosphere (entry 9); in this case the conversion was extremely slow. Moreover, catalytic activity decreased by using lower catalyst loading (entries 10 and 11) or by modifying the copper source (entry 12).

Optimized conditions using inexpensive copper salt in association with dioxygen as a co-oxidant, an inexhaustible and nonpolluting resource (Table 1, entry 4), can be applied to different alkene partners (Scheme 1). Electron-deficient alkenes **2** that display a range of functional motifs were investigated, providing conjugated enamides **3a**−**i** in good to excellent yields (70−90%). These newly formed enamides were obtained with absolute regio- and stereoselectivity (*E*-isomers)[10] and polar functional groups were tolerated. To our knowledge this is the first report on the catalytic direct alkenylation in beta position of enamide.[6a,b]

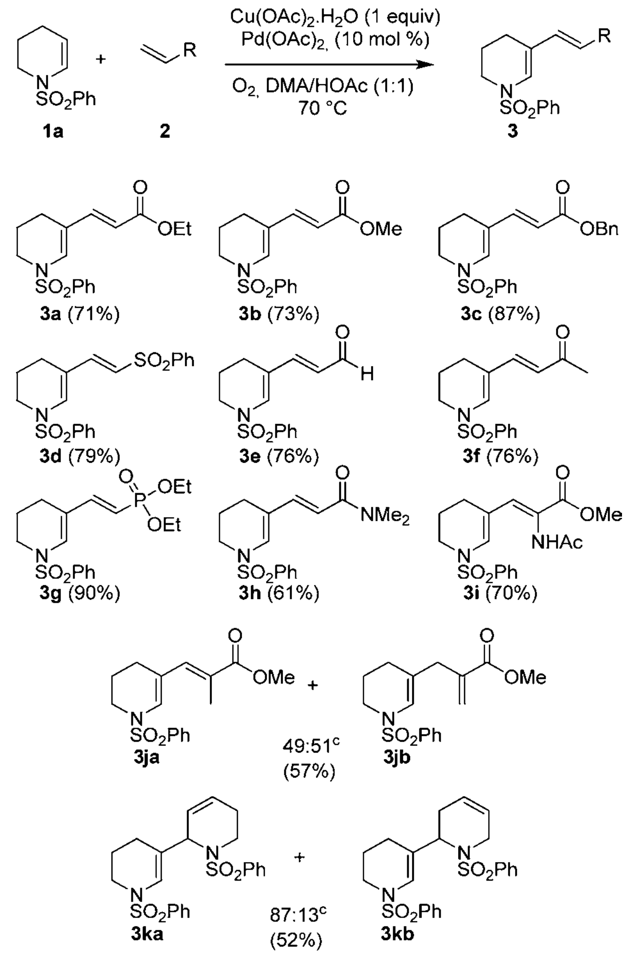
Table 1. Optimization of the Direct Coupling of Enamides[a]



entry	oxidant	solvent	co-oxidant	time[b] (h)	yield[c] (%)
1	$Cu(OAc)_2 \cdot H_2O$	AcOH	O_2	3	56[d]
2	$Cu(OAc)_2 \cdot H_2O$	PivOH	O_2	4	28
3	$Cu(OAc)_2 \cdot H_2O$	TFA	O_2	2	14
4	$Cu(OAc)_2 \cdot H_2O$	AcOH/DMA (1:1)	O_2	5	71
5	$Cu(OAc)_2 \cdot H_2O$	DMA	O_2	6	46
6	$Cu(OAc)_2 \cdot H_2O$	AcOH/DMA (1:1)	Ag_2CO_3	4	67
7	$Cu(OAc)_2 \cdot H_2O$	PivOH	Ag_2CO_3	8	72
8	$Cu(OAc)_2 \cdot H_2O$	AcOH/DMA (1:1)	none	8	0
9	$Cu(OAc)_2 \cdot H_2O$	AcOH/DMA (1:1)	air	8	trace
10	$Cu(OAc)_2 \cdot H_2O$	AcOH/DMA (1:1)	O_2	7	46[e]
11	$Cu(OAc)_2 \cdot H_2O$	AcOH/DMA (1:1)	O_2	7	0[f]
12	$Cu(OTf)_2$	AcOH/DMA (1:1)	O_2	3	67[g]

[a] Reaction conditions unless otherwise specified: enamide **1a** (1 equiv), ethyl acrylate **2** (2 equiv), oxidant (1 equiv), $Pd(OAc)_2$ (0.1 equiv), and additive (bubbling or 2 equiv) at 70 °C. [b] Reactions were carried out until disappearance of the starting material. [c] Yield of pure product after purification by column chromatography. [d] By using 0.5 equivalent of $Cu(OAc)_2 \cdot H_2O$, **3a** was isolated in 47% yield. [e] $Pd(OAc)_2$ (0.05 equiv) was used. [f] Reaction conducted without palladium catalyst. [g] $Cu(OTf)_2$ was used as oxidant.

Scheme 1. Direct Coupling of Enamides with Different Alkenes[a,b]

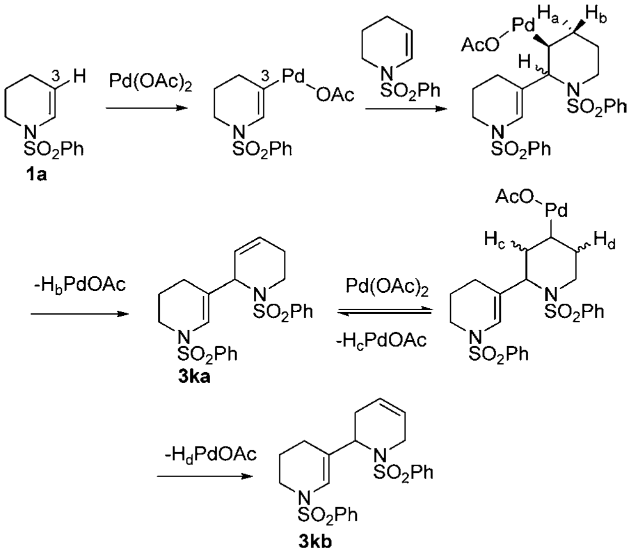


[a] Reaction conditions: **1a** (1 equiv), **2** (2 equiv), $Cu(OAc)_2.H_2O$ (1 equiv), $Pd(OAc)_2$ (0.1 equiv), and O_2 (bubbling) at 70 °C in AcOH/DMA (1:1) for 2−8 h. [b] Yield of pure product after purification by column chromatography. [c] Ratio determined by ^1H NMR.

Interestingly, conducting the coupling with methyl methacrylate provided compounds **3ja** and **3jb**, isolated in 57% yield as inseparable 49:51 regioisomers.[11] The *β*-hydride elimination derivative **3jb** was in fact observed when the methyl group was present at the α-position of the acrylate.

In addition, it is noticeable that in the presence of a simple unactivated alkene as cyclohexene, homocoupling compounds **3ka** and **3kb** were isolated. The reaction was accordingly conducted without additional alkene and the inseparable unconjugated dimers **3ka** and **3kb** were thus isolated in 52% yield as a 87:13 ratio. The nature of **3ka** and **3kb** was demonstrated by NMR. On the basis of the preliminary studies and observations, an electrophilic palladation pathway involving an alkenyl Pd complex was envisaged (Scheme 2). Nucleophilic attack of this palladium species onto the enamide bond and subsequent *β*-hydride elimination furnished the homocoupling product **3ka**, and reoxidation by Cu(II) regenerated Pd(II). **3kb** was provided from **3ka** through Pd−H insertion and immediate *β*-H elimination.[11] As previously noted,[5i] unconjugated dienes were favored.

Scheme 2. Plausible Mechanism for the Homocoupling Reaction



Different enamide derivatives **1** were then screened under these optimized alkenylation conditions in the presence of benzyl acrylate **2b** (Scheme 3). Modifications concerning both the protecting group on the nitrogen atom and the size of the heterocycle were thus envisaged. Conjugated enamides **3l**−**n** were isolated with good yields. Endoenamides furnished the desired dienes **3o**,**p** in excellent yields. However, the introduction of a C2-electron-rich phenyl substituent to the cyclic enamide significantly decreased the yield (of **3q**); pleasingly, in this case, the use of Ag_2CO_3 in pure pivalic acid gave **3q** in 60% yield. These conditions were amenable to other electron-rich enamides substituted with a heteroatom (O or S) in the beta position. Substrates **3r**,**s** were thus isolated in moderate yields.

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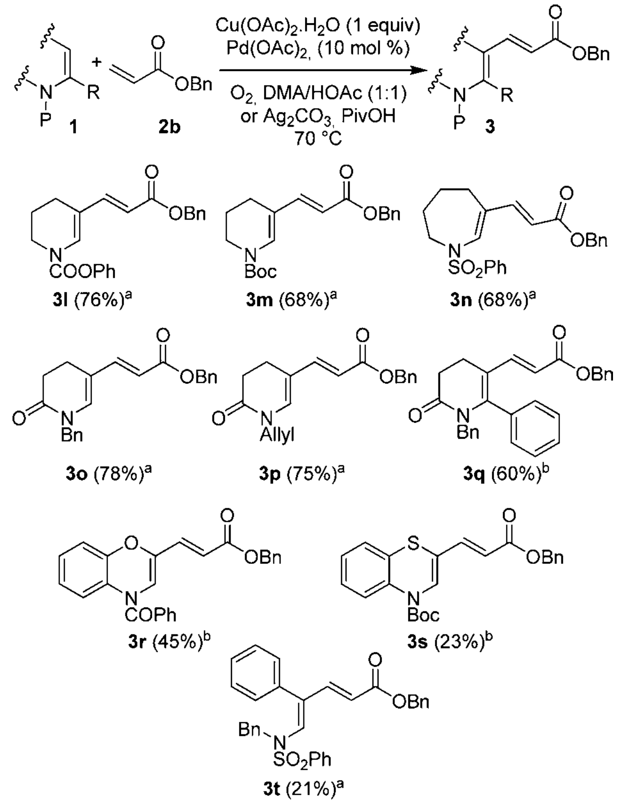
Scheme 3. Direct Coupling of Different Enamides **1** with Benzyl Acrylate **2b**[a]



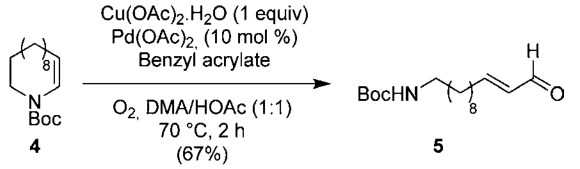
[a]a Reaction conditions: **1** (1 equiv), **2b** (2 equiv), $Cu(OAc)_2.H_2O$ (1 equiv), $Pd(OAc)_2$ (0.1 equiv) and O_2 (bubbling) at 70 °C in AcOH/DMA (1:1) for 2–8 h. [b] Reaction conditions: **1** (1 equiv), **2b** (2 equiv), $Cu(OAc)_2 \cdot H_2O$ (1 equiv), $Pd(OAc)_2$ (0.1 equiv), and Ag_2CO_3 (2 equiv) at 70 °C in PivOH for 3–8 h. [c] Yield of pure product after purification by column chromatography.

Recent reports have proposed that carboxylate-assisted C–H bond transformations proceed via a deprotonative metalation mechanism leading to a decrease of the transition-state energy.[12] The preference for pivalic acid compared to acetic acid, which is less voluminous, is explained by both a greater encumbrance and the increased basicity of its conjugate base.[12] Moreover, the use of pivalic acid in conjunction with oxygen proved to be inefficient, showing the good and unique correlation between the carboxylic acid and the silver salt. Finally, acyclic enamide was found to perform direct alkenylation (**3t**) albeit in low yield (21%) and with slow conversion.[13]

An attempt was also made with the macrocyclic enamide **4** (Scheme 4). Interestingly, the acyclic α,ω-aminoaldehyde **5**, which could be considered as a useful linker,[14] was isolated because of the high sensitivity of this enamide to oxidative conditions.[15]

In summary, we have developed an efficient methodology for the direct palladium(II)-catalyzed alkenylation of nonaromatic enamides. The generality of this approach provides a useful access to C-3 functionalized enamides, stable enamine surrogates, with absolute regio- and stereoselectivity and good functional group compatibility. Further applications of this methodology for the generation of suitably functionalized key scaffolds are in progress and the results of these investigations will be reported in due course.

Scheme 4. Synthesis of α,ω-Aminoaldehyde **5**



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Supporting Information Available. Full characterization details including ^1H and ^{13}C NMR, IR, MS, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The *E* configuration of the alkenes was confirmed from the NOESY spectra and/or the trans coupling constants (J = 15–16 Hz) (see the Supporting Information for details). It is noteworthy that traces of homocoupling compounds were also oberved.

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(13) 62% of the starting material was recovered after 8 h.

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The authors declare no competing financial interest.