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Palladium-Catalyzed Dehydrogenation/Oxidative Cross-Coupling Sequence of β-Heteroatom-Substituted Ketones**

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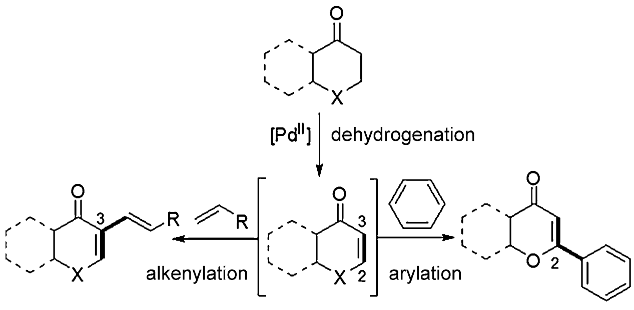
In recent years, impressive achievements have been made toward enhancing the efficiency of a diverse range of C–C bond formations through a direct C–H bond functionalization strategy.[1] The palladium(II)-catalyzed dehydrogenation of ketones has been demonstrated to be a highly efficient process for generating functionalized enone products.[2,3] Cyclic enolone and enaminone motifs are prevalent in a plethora of natural and synthetic compounds which display a variety of biological activities.[4] Recently, synthetic approaches to these heterocyclic scaffolds through the palladium-catalyzed dehydrogenation of the corresponding saturated substrates has been investigated.[3b] Furthermore, Pihko and co-workers have accomplished the oxidative coupling of β-ketoesters and indoles.[5] Despite these important contributions, consecutive reactions of the β-heteroatom-substituted enone functionality formed through a dehydrogenation step in one-pot have yet to be reported.

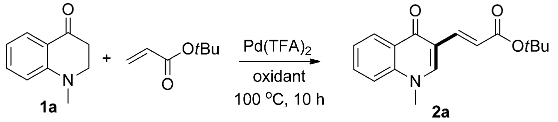
In recent years, a regiocontrolled C–H functionalization of cyclic enolones and enaminones has been disclosed.[6] Driven by the need for a more efficient synthetic route to these derivatives, we were particularly interested in exploring efficient approaches to functionalized cyclic enolone and enaminone scaffolds directly from simple saturated ketones, such as chromanone and dihydroquinolinone. This transformation could be achieved by a two-step sequence involving dehydrogenation of saturated ketones and subsequent oxidative cross-coupling with a suitable coupling partner. We speculated that the cyclic enolones and enaminones generated in situ from palladium(II)-catalyzed dehydrogenation might be utilized for further oxidative cross-coupling using same catalytic systems. Herein, we report the first example of a palladium(II)-catalyzed dehydrogenation/oxidative cross-coupling reaction sequence of readily available β-heteroatom-substituted cyclic ketones in one-pot, thus providing a straightforward protocol for the preparation of functionalized cyclic enolone and enaminone systems (Scheme 1). In this study, palladium(II) was found to play a dual role in catalyzing both the oxidation of the saturated ketones and the C–H functionalization of the resulting enolones or enaminones.



Scheme 1. General strategy for the sequential dehydrogenation/oxidative cross-coupling. The reaction involves successive palladium-catalyzed C–H functionalization, requires no pre-functionalization, and has a broad substrate scope.

To test the hypothesis, we initially focused on the dehydrogenation/oxidative Heck reaction. Since the discovery of direct olefination of benzene by Fujiwara and co-workers,[7] substantial progress of the oxidative Heck reaction has been made to improve the reaction efficiency.[8] Our efforts began by exploring possible reaction conditions for a one-pot reaction of 1-methyl-2,3-dihydroquinolin-4(1*H*)-one (**1a**) with *tert*-butyl acrylate (Table 1). Recent advances in palladium-catalyzed dehydrogenation provide useful starting

Table 1: Optimization of the dehydrogenation/oxidative Heck reaction.[a]



1a **2a**

Entry	Cu	Ag[b]	Solvent	Yield [%][c]
1	Cu(OAc)$_2$	AgOAc	DMF	trace
2	Cu(OAc)$_2$	AgOAc	1,4-dioxane	19
3	Cu(OAc)$_2$	–	1,4-dioxane	23
4	Cu(OAc)$_2$	AgOAc	PivOH	47
5	Cu(OAc)$_2$	–	PivOH	61
6	Cu(OAc)$_2$	–	AcOH	32
7	–	AgOAc	PivOH	5
8	Cu(TFA)$_2$·nH$_2$O	AgOAc	PivOH	18
9	CuCO$_3$·Cu(OH)$_2$	AgOAc	PivOH	57
10	**CuCO$_3$·Cu(OH)$_2$**	**–**	**PivOH**	**83**

[a] Reactions were conducted with ketone (1.0 equiv), *tert*-butyl acrylate (1.5 equiv), Pd(TFA)$_2$ (0.2 equiv), and Cu^{II} (3 equiv) in PivOH at 100°C for 6–8 h. [b] 3 equiv of silver species was used. [c] Yields of isolated products. DMF = *N*,*N'*-dimethylformamide, Piv = pivaloyl, TFA = trifluoroacetate.

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points for our investigation of reactions.[2,3] Among the palladium sources tested, $Pd(TFA)_2$ displayed the best catalytic reactivity. Low yields of the coupling products were obtained, except under reaction conditions employing pivalic acid[9] as the solvent. The copper source was critical to the coupling efficiency, and a variety of copper species were evaluated as the oxidant. Among the copper species screened, $CuCO_3 \cdot Cu(OH)_2$ was the most effective and economical oxidant for promoting the reactions. An interesting feature of this reaction was that a lower yield of the isolated product was obtained in the presence of AgOAc, presumably as a result of competitive oxidative decomposition of starting substrate **1a** or its intermediate under the highly oxidative conditions. Under the optimized reaction conditions, the dehydrogenation/oxidative Heck reaction of **1a** with *tert*-butyl acrylate proceeded to provide a high yield (83%) of the isolated product.

A preliminary mechanistic analysis of the dehydrogenation/oxidative Heck reaction was performed by monitoring the conversion of 1-methyl-2,3-dihydroquinolin-4(1*H*)-one (**1a**) into 3-vinylquinolinone **2a** under standard reaction conditions (Figure 1). Within 1 hour, the enaminone **3a** was formed (about 50%), and the 3-vinylquinolinone **2a** was subsequently produced with concomitant disappearance of **3a**, thus indicating the intermediacy of **3a** in the course of the alkenylation.

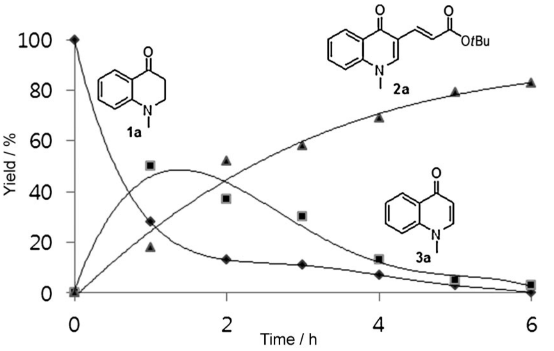
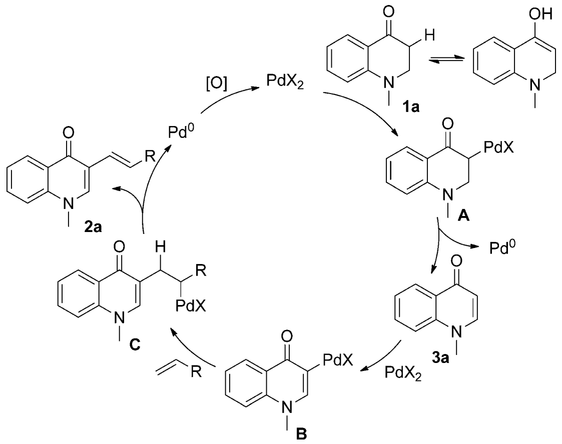


Figure 1. Reaction profile of the palladium(II)-catalyzed dehydrogentation and alkenylation of 1-methyl-2,3-dihydroquinolin-4(1*H*)-one (**1a**).

Based on the above observations, a mechanistic proposal involving a sequential dehydrogenation/oxidative Heck reaction pathway is presented (Scheme 2). First, coordination of **1a** or its enol form to Pd^{II} and subsequent H abstraction provides the Pd^{II}-enolate **A**. Next, β-hydride elimination generates the enaminone intermediate **3a**. Electrophilic palladation of **3a** at the C3-position could proceed because of the more nucleophilic 3-position. In the presence of an alkene substrate, the C3-palladated species **B** inserts into the olefin, and the subsequent reductive elimination of the Pd/alkyl intermediate **C** provides the desired coupled product **2a**. Finally, reoxidation by Cu^{II} regenerates Pd^{II} to complete the catalytic cycle.

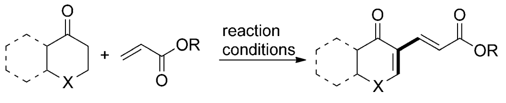


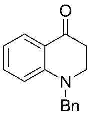
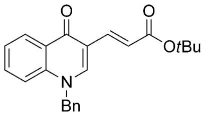
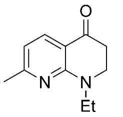
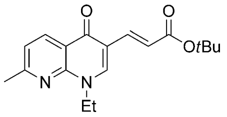
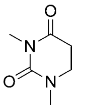
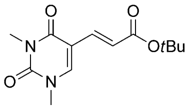
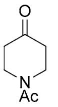
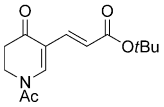
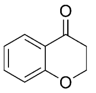
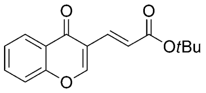
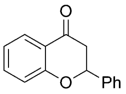
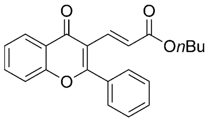
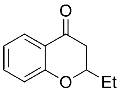
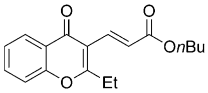
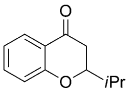
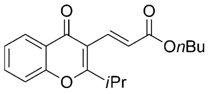
Scheme 2. Proposed mechanistic pathways underlying the present reactions.

With the optimized reaction conditions in hand, we next investigated the substrate scope of the ketones (Table 2). To our delight, our methodology was amenable to a variety of cyclic β-amino ketone types. For example, the reaction of 1-ethyl-7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one proceeded with complete regioselectivity to provide the C3-functionalized quinolinone **2c** (Table 2, entry 2). The dihydropyrimidine dione and *N*-acylpiperidone derivatives successfully yielded the corresponding vinyl products (**2d** and **2e**). Expanding the scope from the cyclic β-amino ketone to the cyclic β-oxo ketone system was also possible, thus leading to the formation of the 3-vinyl chromone **2f**. In addition, the procedure was successfully applied to a series of C2-substituted chromanones which are readily accessed by 1,4-addition to chromones.[10] This strategy thus allows the C2/C3 selective installation of substituents and provides access to highly functionalized chromone derivatives by catalytic methods (**2g**, **2h**, and **2i**).

After successfully achieving a one-pot sequential dehydrogenation/alkenylation, we preliminarily investigated the possibility of extending this catalytic system to other transformatons. Based on the above mechanistic proposal, which suggests the formation of enolone intermediates (Scheme 2), we envisaged that the sequential dehydrogenation/arylation of chromanones would be possible because the resulting chromones would be prone to undergo oxidative cross-coupling with simple arenes through a twofold C−H bond functionalization. Indeed, we were delighted to observe that the sequential processes were very facile under slightly altered reaction conditions in which $Cu(TFA)_2 \cdot n\,H_2O$ (0.2 equiv) and AgOAc (3 equiv) were employed as oxidants.[11] The reaction site switched to the C2-position,[6h] and the C2 phenylchromones were obtained in moderate to good yields with excellent regioselectivity (Table 3).[12] Although at this stage we cannot be certain of the mechanism underlying the process, we believe that the arylpalladium species, which is formed by the concerted metallation/deprotonation process, adds to the 2-position of the chromones, and subsequent β-hydride elimination generates Heck-type products. The catalyst tolerated useful substrate functional groups. Notably, a chromanone bearing a triflate substituent resulted in the isolation of the synthetically versatile **4p** with an intact triflate moiety under the reaction conditions, thus providing an

Table 2: The one-pot dehydrogenation/oxidative Heck reactions of β-heteroatom-substituted ketones.[a]

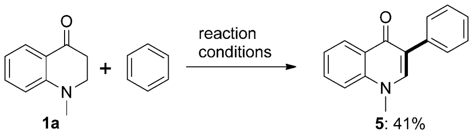


Entry	Arene	Product		Yield [%][d]
1			**2b**	79
2			**2c**	93
3			**2d**	67
4[b]			**2e**	64
5[c]			**2f**	78
6[c]			**2g**	50
7[c]			**2h**	61
8[c]			**2i**	54

[a] Reactions were conducted with ketone (1.0 equiv), *tert*-butyl acrylate (1.5 equiv), $Pd(TFA)_2$ (0.2 equiv), and $CuCO_3{\cdot}Cu(OH)_2$ (3 equiv) in PivOH at 100 °C for 6–8 h. [b] Reaction was conducted with PivOH/1,2-dichloroethane (1:10) as the solvent. [c] Reactions were conducted with chromanone (1.0 equiv), *n*-butyl acrylate (1.5 equiv), $Pd(OAc)_2$ (0.2 equiv), $Cu(OAc)_2$ (3 equiv), and Ag_2CO_3 (3 equiv) in PivOH at 110 °C for 10–16 h. [d] Yields are those of the isolated products.

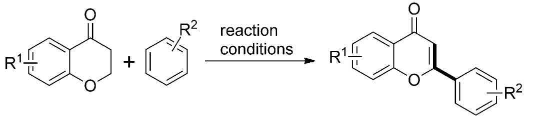
opportunity for the formation of additional C–C or C–heteroatom bonds.

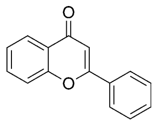
We also observed that **1a** reacted with benzene under the same reaction conditions, and a 41 % yield of the C3-product **5** was provided [Eq. (1)]. The switch in the regioselectivity seems to indicate that electrophilic palladation of enaminone at the C3-position proceeds through a pathway similar to that of the alkenylation.[6a]



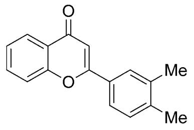
1a **5**: 41% (1)

Table 3: Sequential dehydrogenation/arylation of chromanones.[a]

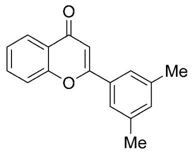




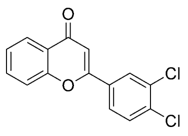
4a: 89 %



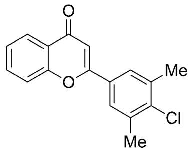
4b: 75 %



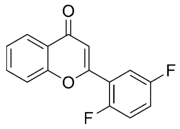
4c: 81 %



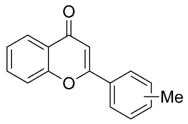
4d: 69 %



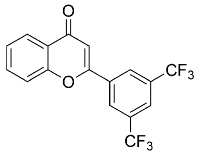
4e: 64 %



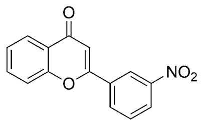
4f: 61 %



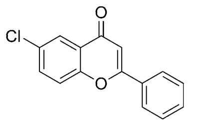
4g: 79 % (*m*/*p* = 2:1)



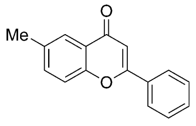
4h: 42 %



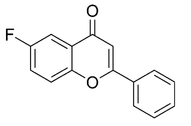
4i: 53 %



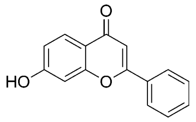
4j: 71 %



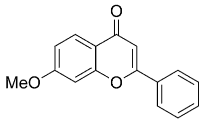
4k: 76 %



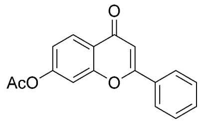
4l: 83 %



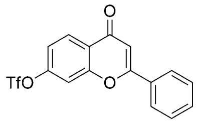
4m: 68 %



4n: 69 %



4o: 71 %



4p: 79 %

[a] Reactions were conducted with chromone, arene (30 equiv), $Pd(TFA)_2$ (0.2 equiv), $Cu(TFA)_2{\cdot}nH_2O$ (0.2 equiv), and AgOAc (3 equiv) in PivOH at 100 °C for 48 h. [b] Yields are those for the isolated products. Tf = trifluoromethanesulfonyl.

In summary, we developed the palladium(II)-catalyzed sequential dehydrogenation/oxidative cross-coupling reaction, which offers an unprecedented one-pot route to highly functionalized cyclic enaminones and enolones from readily accessible β-heteroatom-substituted cyclic ketones. The process is desirable because of considerable advantages in both simplicity and efficiency. The substrate scope was broad and permitted the construction of a variety of C3-vinyl-substituted cyclic enaminones and chromones. In addition, a slightly altered catalytic system was successfully applied to the C2-regioselective arylation of chromones for the generation of flavone derivatives. Additional studies to broaden the scope to include related heterocycles and applications are currently ongoing.

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Keywords: C−H functionalization · cross-coupling · dehydrogenation · heterocylces · palladium

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[11] See the Supporting Information for more details.

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