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One-pot catalysis of dehydrogenation of cyclohexanones to phenols and oxidative Heck coupling: expedient synthesis of coumarins†

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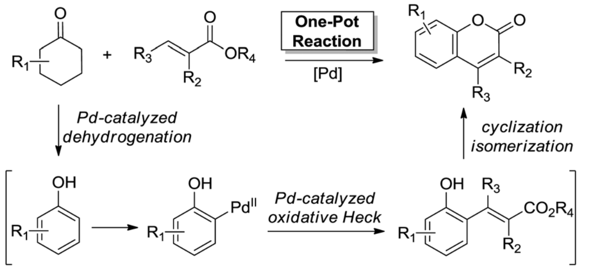
One-pot reactions leading to highly functionalized coumarins have been developed *via* a Pd(II)-catalyzed dehydrogenation–oxidative Heck–cyclization process.

The direct functionalization of C–H bonds in (hetero)arenes is a highly desirable process for enhancing the efficiency of formation of new C–C and C–X bonds in the organic synthesis.[1] Recently, the palladium(II)-catalyzed dehydrogenation of cyclohexanones has been demonstrated to be a highly efficient process for generating substituted phenol derivatives.[2] This route offers a promising alternative to classical procedures because electrophilic aromatic substitutions of phenols are limited to *ortho-* and *para*-positions due to the influence of strong electron directing effects. A one-pot procedure is synthetically and environmentally advantageous for carrying out multistep reactions in one synthetic operation, thereby reducing synthesis time, cost and undesired waste. The development of one-pot catalysis of tandem processes is a desirable strategy for generating molecular complexity from simple starting materials by employing a single catalyst in a single reaction vessel.[3]

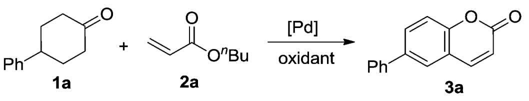
Coumarin derivatives exhibit a broad range of biological activities[4] and also comprise one of the most widely used classes of fluorophores for their outstanding optical properties.[5] Extensive synthetic efforts have therefore been made to introduce a range of groups into the coumarin core.[6] Among them, an efficient synthesis of coumarin from phenol has also been developed.[7] We speculated that the phenol generated *in situ* from the Pd(II)-catalyzed dehydrogenation could be utilized for further oxidative cross-coupling *via* the electrophilic palladation of phenol using the same Pd(II) catalyst system.[8] If successful, the one-pot reaction sequence would represent a practical and exceptionally efficient method for accessing diversely substituted coumarins (Scheme 1). Herein, we report the first example of a sequential Pd(II)-catalyzed dehydrogenation–oxidative Heck[9]–cyclization process using readily available cyclohexanones and alkenes, providing an efficient and straightforward protocol for preparing a variety of coumarins.



Scheme 1 Strategy for a one-pot process involving dehydrogenation–oxidative Heck–cyclization starting from cyclohexanones.

We explored the potential of the proposed sequential reactions by investigating the reactivity of 4-phenylcyclohexanone (**1a**) and butyl acrylate (**2a**) as model substrates (Table 1). The starting material **1a** underwent dehydrogenation to provide appreciable amounts of a phenol intermediate; however, no coumarin product was isolated under 1 atm O_2 in the presence of a Pd(II) catalyst (Table 1, entry 1).

Table 1 Optimization studies of the one-pot process of sequential dehydrogenation–oxidative Heck–cyclization[a]



Entry	Pd	Oxidant	Additive (equiv.)	Yield[b] (%)
1	$Pd(OAc)_2$	—	TsOH (0.2)	—
2	$Pd(OAc)_2$	DDQ	—	Trace
3	$Pd(OAc)_2$	$K_2S_2O_8$	—	Trace
4	$Pd(OAc)_2$	$Cu(OAc)_2$	—	63
5	$Pd(OAc)_2$	$CuCO_3 \cdot Cu(OH)_2$	—	69
6	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc (1)	47
7	$Pd(OAc)_2$	$Cu(OAc)_2$	Ag_2CO_3 (1)	23
8	$Pd(TFA)_2$	$CuCO_3 \cdot Cu(OH)_2$	—	80
9	$Pd(TFA)_2$	CuO	—	68
10	$Pd(TFA)_2$	$CuCl_2$	—	Trace
11	**$Pd(TFA)_2$**	**$Cu(Oac)_2$**	—	81

[a] Reactions were conducted with **1a** (1.0 equiv.), **2a** (1.2 equiv.), PdL_2 (0.2 equiv.), and oxidant (1.0 equiv.) in PivOH at 110 °C for 20 h under 1 atm O_2. [b] Yield of the isolated product. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFA = trifluoroacetate.

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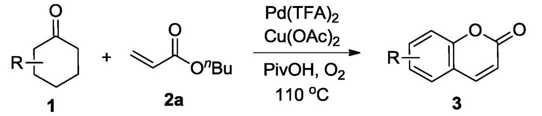
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc41296b

Table 2 Cyclic ketone substrate scope[a]



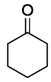
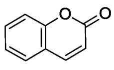
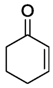
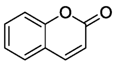
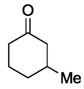
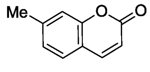
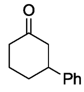
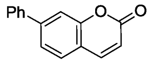
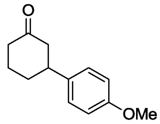
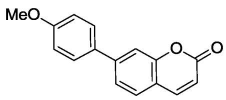
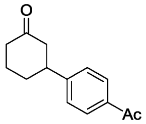
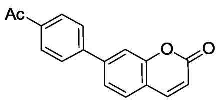
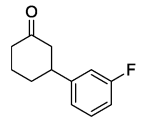
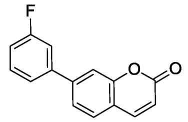
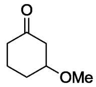
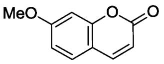
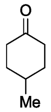
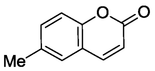
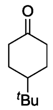
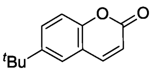
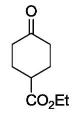
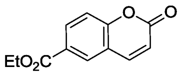
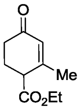
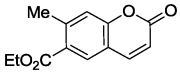
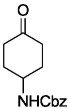
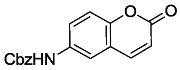
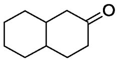
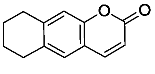
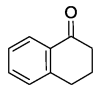
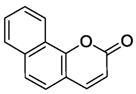
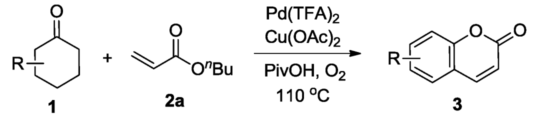
Entry	Substrate	Product		Yield[c] [%]
1			**3b**	67
2			**3b**	72
3			**3c**	59
4			**3d**	56
5			**3e**	52
6			**3f**	70
7			**3g**	46
8[b]			**3h**	56
9			**3i**	77
10			**3j**	78
11			**3k**	81
12			**3l**	85
13			**3m**	38
14			**3n**	48
15			**3o**	56

Table 2 (*continued*)



[a] Conditions: **1** (1.0 equiv.), **2a** (1.2 equiv.), Pd(TFA)$_2$ (0.2 equiv.), Cu(OAc)$_2$ (1.0 equiv.), PivOH, 110 °C, 17–35 h (see the ESI for details), 1 atm O$_2$. [b] Reaction was conducted with PivOH–1,2-dioxane (1 : 5) as a solvent. [c] Yield of the isolated product.

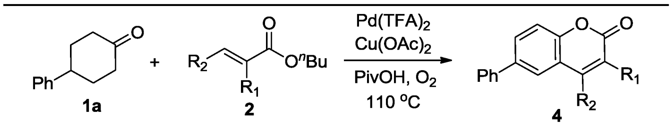
We therefore examined the ability of other oxidizing agents, such as Cu(II), Ag(II), OXONE, DDQ, and $K_2S_2O_8$, to facilitate the re-oxidation of Pd(0) to Pd(II). The copper source was critical to the efficiency of the coupling reaction between the resulting phenol and the butyl acrylate. With a selected set of copper sources, the desired 7-phenylcoumarin (**3a**) was readily produced, proving that the sequential process indeed proceeded (entries 4 and 5). A variety of Cu species were then evaluated, and Cu(OAc)$_2$ was found to be the most effective and economical oxidant for promoting the reactions.[10] Among the palladium sources tested, Pd(TFA)$_2$ displayed the best catalytic reactivity. Under optimized reaction conditions, the sequential dehydrogenation–oxidative Heck–cyclization process of **1a** (1 equiv.), in the presence of butyl acrylate (1.2 equiv.), Pd(TFA)$_2$ (0.2 equiv.), and Cu(OAc)$_2$ (1 equiv.) in pivalic acid at 110 °C, proceeded to provide the best isolated yield of 82%.

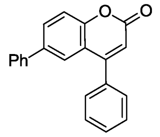
With this one-pot procedure in hand, the scope and generality of this methodology were explored using a variety of cyclic ketones (Table 2). A variety of cyclic ketone substrates were compatible with the one-pot conditions, affording modest to good yields of the desired coumarin products. A slightly higher product yield was obtained when cyclohexenone was used as a substrate (entries 1 and 2). The reaction of the C3-substituted cyclohexanones, which are readily accessed *via* the 1,4-addition to the cyclohex-2-enone proceeded with complete regioselectivity to provide the C7-functionalized coumarins (Table 2, entries 3–7). The introduction of electron-donating groups, such as OMe, at position 7 on the coumarin core triggers a bathochromic shift with strong charge transfer character. The methodology was successfully applied to 3-methoxycyclohexanone to enable the C7 installation of a methoxy group on the coumarin core under slightly modified reaction conditions in which dioxane was employed as a co-solvent (Table 2, entry 8). The scope of the reactions could be expanded from the cyclohexanones to bicyclic ketone systems, leading to the formation of coumarins **3n** and **3o** (entries 14 and 15).[11]

Encouraged by the successful transformation of cyclohexanones to coumarins, we turned our attention to the alkene substrate scope to introduce more structural diversity around the coumarin core. We were pleased to observe that alkene substrate variations were viable under optimized conditions, leading to the formation of synthetically and biologically useful C3- or C4-phenyl coumarins in moderate to good yields (Table 3). Notably, expanding the scope from a phenyl to a naphthyl substituted system **4n**, it was also possible to facilitate the process, and highlight the generality of this method.

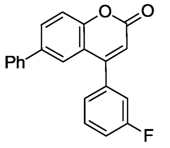
As an extension of these studies, we preliminarily investigated the potential of this catalytic system to catalyze further

Table 3 Alkene substrate scope[a]

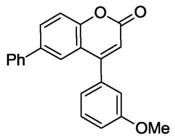




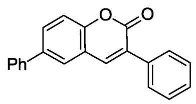
4a, 59%



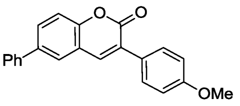
4b, 57%



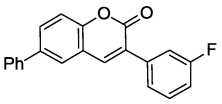
4c, 62%



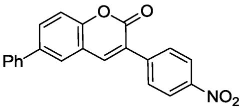
4d, 67%



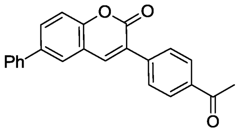
4e, 73%



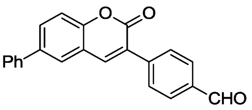
4f, 75%



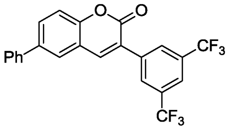
4g, 62%



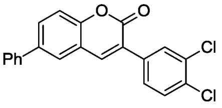
4h, 63%



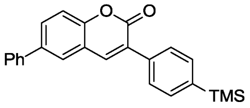
4i, 70%



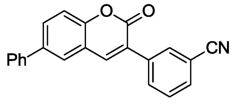
4j, 56%



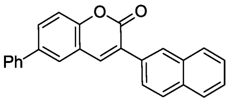
4k, 65%



4l, 58%



4m, 41%

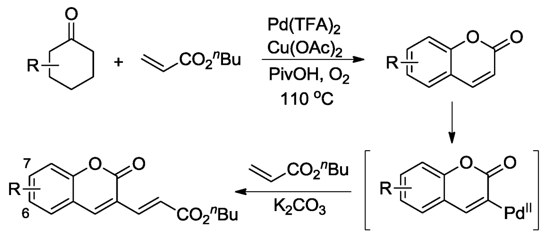


4n, 61%

[a] Conditions: cyclohexanone (1.0 equiv.), alkene (1.2 equiv.), Pd(TFA)$_2$ (0.2 equiv.), Cu(OAc) (1.0 equiv.), PivOH, 110 °C, 15–30 h, 1 atm O$_2$. Yield of the isolated product.

sequential transformations. Our group recently reported the Pd(II)-catalyzed direct alkenylation of coumarins at the C3 position to extend the π-electron system.[6f] Based on the mechanistic pathway, we envisaged that a further consecutive reaction would be possible because the resulting coumarins were susceptible to electrophilic palladation at the C3 position (Scheme 2). Indeed, we were delighted to observe that the further C3-alkenylation process worked well by sequential addition of alkene (2 equiv.) and K$_2$CO$_3$ (3 equiv.) to provide 3-vinylcoumarins **5a** and **5b**.

In summary, we presented the first example of a one-pot process involving dehydrogenation–oxidative Heck–cyclization in the presence of the Pd(II) catalyst system, offering an efficient route to highly functionalized coumarins starting from readily available cyclohexanones in a single synthetic operation. The substrate scope is broad and permits the construction of a variety of substituted coumarins. The methodology is synthetically useful and presents considerable advantages in both simplicity and efficiency.



5a: R = 7-OMe, 33%
5b: R= 6-Ph, 38%

Scheme 2 Strategy for a one-pot process involving dehydrogenation–oxidative Heck–cyclization–alkenylation starting from cyclohexanones.

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Notes and references

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11 The parent cyclohexanone substrates bearing an *ortho* substituent decomposed under the optimized one-pot conditions, and a two-step procedure was required to yield the coumarins.