ORGANIC LETTERS

2012
Vol. 14, No. 17
4358–4361

Decarboxylative Acylation of Cyclic Enamides with α-Oxocarboxylic Acids by Palladium-Catalyzed C−H Activation at Room Temperature

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Received July 1, 2012

ABSTRACT

An efficient catalytic decarboxylative acylation of unactivated sp^2 (alkenyl) C−H bonds has been developed. Various substituted α-oxocarboxylic acids with different electronic properties react under mild conditions to afford a diverse range of β-acyl enamide products in good yields. The reaction is proposed to proceed via a cyclic vinylpalladium intermediate, facilitating the decarboxylative dehydrogenative process with enamide coupling partners.

Palladium-catalyzed decarboxylative cross-coupling reactions using simple carboxylic acids as coupling partners have emerged as a new type of C−C bond formation reaction.[1] In these reactions, using readily available and stable carboxylic acids instead of organometallic reagents enabled the decarboxylative cross-coupling reactions to proceed with good selectivities and tolerance of functional groups. Goossen,[2] Forgione,[3] and others[4−7] demonstrated the palladium-catalyzed decarboxylative cross-coupling of (hetero)aromatic carboxylic,[2−4] alkenyl,[5] and alkynyl acids[6] and monooxalates[7] with organo halides. Myers first discovered a palladium-catalyzed decarboxylative Heck-type coupling of olefin with arene carboxylic acids.[8] This concept was further expanded to decarboxylative C−H bond activation by Crabtree, Glorius, and others who disclosed the palladium-catalyzed direct decarboxylative arylation of unactivated arenes.[9] Despite the great

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10.1021/ol301801r
Published on Web 08/14/2012

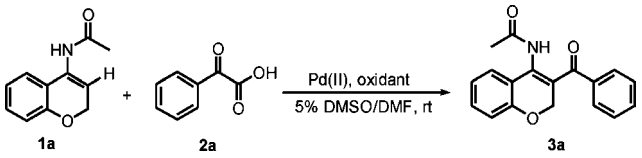
advantages of these reactions, there are still certain limitations including harsh reaction conditions and a narrow range of carboxylic acids. Thus, further development of decarboxylative coupling under mild conditions remains a challenge.

Ketones are important molecules for organic synthesis, and numerous methods for the preparation of ketones have been developed.[10] Recently, Goossen first reported the unsymmetrical diaryl ketone formation using α-oxocarboxylic acid salts as acyl anion equivalents through palladium-catalyzed decarboxylative cross-coupling.[11] Later, related elegant studies on decarboxylative acylation of unactivated arenes with α-oxocarboxylic acid via palladium-catalyzed C−H activation were also reported by Ge.[12] Among these direct decarboxylative dehydrogenative cross-coupling examples, unactivated arene and chelation-assisted sp^2 (aryl) C−H bond activations have been well-documented.[9,12] In sharp contrast, analogous decarboxylative dehydrogenative cross-couplings of alkenes via vinylic C−H bond activation have been scarcely reported to the best of our knowledge. Enamides and their derivatives are intrinsically useful intermediates[13] and have been successfully used as a coupling partner in the palladium-catalyzed C−H bond activation reaction.[14] However, methods for direct olefin functionalization of enamides typically rely on the use of organometallic reagents,[14a,b] acrylate,[14c] or arenes,[14e] and catalytic decarboxylative dehydrogenative couplings of carboxylic acids with enamides have thus far never been investigated. Herein, we report a palladium-catalyzed decarboxylative acylation of cyclic enamides with α-oxocarboxylic acid via alkenyl C−H bond activation under mild conditions.

Our study commenced with the decarboxylative acylation of *N*-(2*H*-chromen-4-yl)acetamide **1a** with phenylglyoxylic acid **2a** to the *N*-(3-benzoyl-2*H*-chromen-4-yl)-acetamide **3a** using $K_2S_2O_8$ as the oxidant and $Pd(OAc)_2$ as the catalyst. Unfortunately, the enamide **1a** readily decomposed when DME, THF, or diglyme was used as the solvent.[15] After many trials, we discovered that **1a** and **2a** in the presence of 10 mol % of $Pd(OAc)_2$ and 3.0 equiv of $K_2S_2O_8$ in 5% DMSO/DMF (2.5 mL) at room temperature for 20 h led to the desired product **3a** in 46% yield (Table 1, entry 1). Variation of the oxidant showed that $K_2S_2O_8$ is superior to other persulfate and silver(I) salts and over oxone (Table 1, entries 2−6). Further optimization demonstrated that the yield could be raised to 55% in the presence of 2.0 equiv of $K_2S_2O_8$ and 1.0 equiv of Ag_2O (Table 1, entry 7). When the amount of $K_2S_2O_8$ was reduced to 1.0 equiv and the amount of Ag_2O was increased to 2.0 equiv, the coupling yield could be further improved (Table 1, entry 8). To our delight, changing the ratio of **1a** and **2a** from 1.0/2.0 to 1.0/1.0 resulted in a satisfactory yield (Table 1, entry 10). A screening of the catalysts indicated that $Pd(TFA)_2$ was also effective (Table 1, entry 11), whereas the others were found to be inferior (Table 1, entries 12−14).

Under the optimized reaction conditions, a variety of substituted phenylglyoxylic acids were found to undergo efficient decarboxylative acylation with cyclic enamide **1a** at room temperature (Scheme 1). Specifically, phenylglyoxylic acids with *p*-substituted electron-rich or -withdrawing groups are all successfully engaged in this reaction (**3b**−**3e**). It is noteworthy that electronic properties do

Table 1. Optimization of the Direct Decarboxylative C−H Acylation of *N*-(2*H*-Chromen-4-yl)acetamide **1a** with Phenylglyoxylic Acid **2a**[a]



1a **2a** **3a**

entry	Pd(II) (mol %)	oxidant (equiv)	yield (%)[b]
1	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (3.0)	46
2	$Pd(OAc)_2$ (10)	$(NH_4)_2S_2O_8$ (3.0)	10
3	$Pd(OAc)_2$ (10)	oxone (3.0)	8
4	$Pd(OAc)_2$ (10)	Ag_2CO_3 (3.0)	<5
5	$Pd(OAc)_2$ (10)	AgOAc (3.0)	38
6	$Pd(OAc)_2$ (10)	Ag_2O (3.0)	44
7	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.0)/Ag_2O (1.0)	55
8	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (1.0)/Ag_2O (2.0)	66
9[c]	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (1.0)/Ag_2O (2.0)	72
10[d]	**$Pd(OAc)_2$ (10)**	**$K_2S_2O_8$ (1.0)/Ag_2O (2.0)**	**80**
11[d]	$Pd(TFA)_2$ (10)	$K_2S_2O_8$ (1.0)/Ag_2O (2.0)	68
12[d]	$Pd(CH_3CN)_2Cl_2$ (10)	$K_2S_2O_8$ (1.0)/Ag_2O (2.0)	30
13[d]	$Pd(PhCN)_2Cl_2$ (10)	$K_2S_2O_8$ (1.0)/Ag_2O (2.0)	20
14[d]	$PdCl_2$ (10)	$K_2S_2O_8$ (1.0)/Ag_2O (2.0)	<5

[a] Reaction conditions: 10 mol % of Pd(II), **1a** (0.25 mmol, 1.0 equiv), **2a** (0.50 mmol, 2.0 equiv), oxidant (3.0 equiv), solvent (2.5 mL), room temperature, 20 h. [b] Yield of isolated product. [c] **1a** (0.25 mmol, 1.0 equiv), **2a** (0.375 mmol, 1.5 equiv). [d] **1a** (0.25 mmol, 1.0 equiv), **2a** (0.25 mmol, 1.0 equiv).

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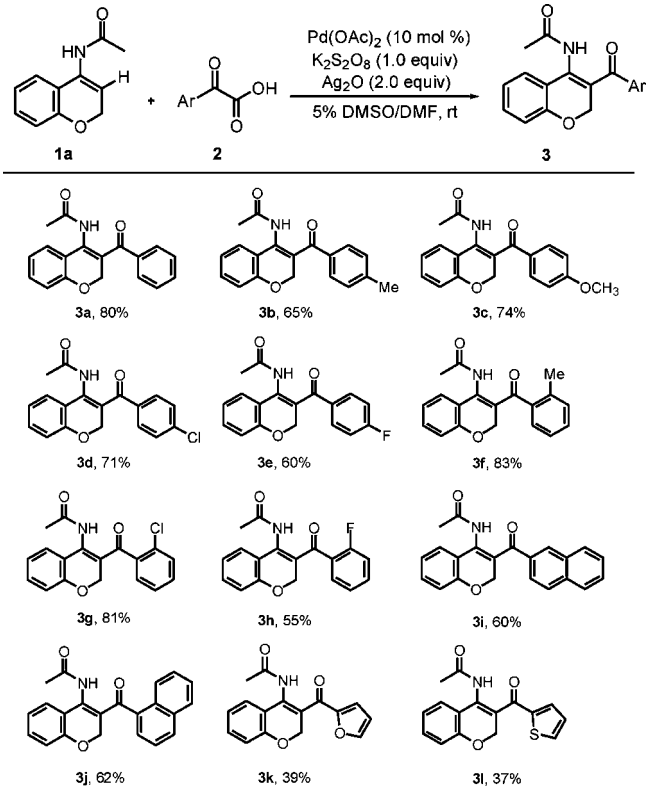
(15) For more details, see the Supporting Information.

Scheme 1. Scope of α-Oxocarboxylic Acids[a]



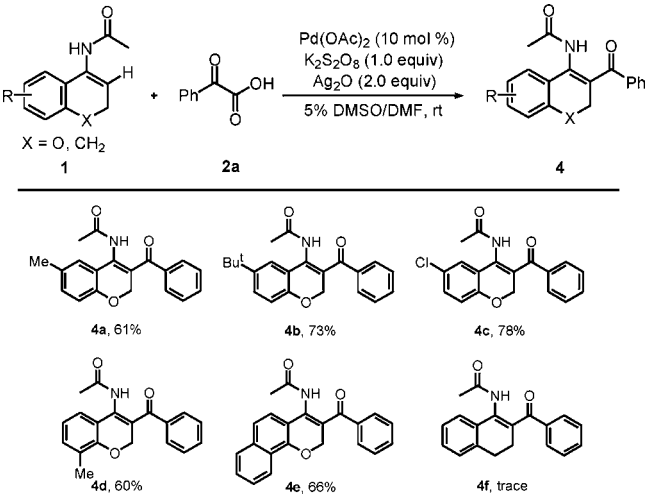
[a] All reactions were performed with **1a** (0.25 mmol) and α-oxocarboxylic acids **2** (1.0 equiv), under standard conditions (Table 1, entry 10) at room temperature. Yields are of the isolated products.

not affect the *o*-substituted phenylglyoxylic acids since both electron-donating and -withdrawing groups gave moderate to good yields (**3f**–**3h**). Satisfactorily, the *β*- and α-naphthyloxoacetic acid also proceeded smoothly to give the desired products **3i** and **3j** in 60% and 62% yields, respectively. Applying furoylformic acid or 2-thienylglyoxylic acid resulted in the desired products in somewhat lower yields under the above conditions (**3k** and **3l**). However, aliphatic α-oxocarboxylic acids, such as pyruvic acid, were inefficient for this decarboxylative C–H acylation.

To expand the scope of this direct acylation reaction further, we next investigated the decarboxylative coupling of phenylglyoxylic acid **2a** with other cyclic enamides. As shown in Scheme 2, all of the 4-chromanone-derived enamides bearing electron-donating or -withdrawing groups on the phenyl ring afforded the desired products in moderate to good yields (**4a**–**4d**). Acylation of enamide **1e** also gave a modest yield of product **4e**. For tetralone-derived enamide, only a trace amount of product was observed due to the decomposition of the starting material (**4f**), whereas protecting the nitrogen atom of the enamide with benzyl group did not significantly improve the yield.

To gain some understanding of the reaction, 1.0 equiv of TEMPO, a radical-trapping reagent, was added into the reaction under the standard conditions. The same yield of

Scheme 2. Scope of Cyclic Enamides[a]

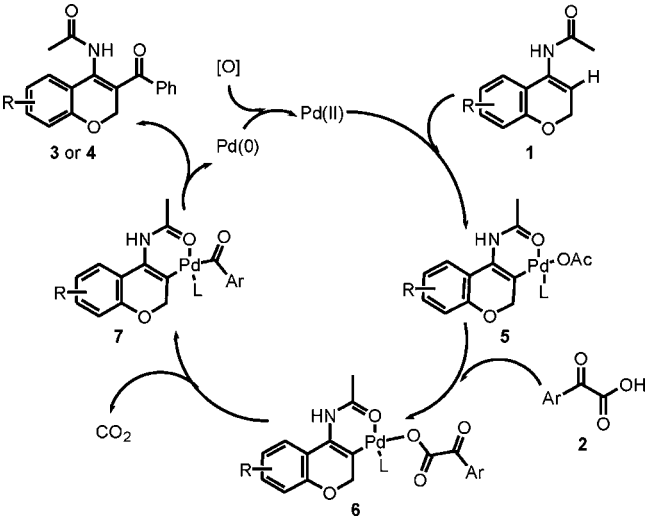


[a] All reactions were performed with cyclic enamides **1** (0.25 mmol) and phenylglyoxylic acid **2a** (1.0 equiv), under standard conditions (Table 1, entry 10) at room temperature. Yields are of the isolated products.

the product **3a** was obtained, suggesting that no free radical intermediate was involved in the reaction.[16] Thus, we proposed the following mechanism for our reaction (Scheme 3).[12,14] The alkenyl C–H bond activation of enamide **1** occurs in the presence of the Pd(II) complex to form a six-membered palladacycle intermediate **5**.[14c] Anion exchange with α-oxocarboxylic acids gave a Pd complex **6**. Decarboxylation of complex **6** to form the complex **7** and then reductive elimination of the complex **7** afforded the desired product **3** or **4**. Pd(0) is then recycled back to Pd(II) by the oxidant.

In summary, we have demonstrated that cyclic enamides participated in efficient intermolecular C–H bond

Scheme 3. Proposed Catalytic Cycle for Direct Decarboxylative Acylation Reaction of Cyclic Enamides



acylation reactions. This novel reaction is the first example of formal vinylic C−H bond direct functionalization via palladium-catalyzed decarboxylative cross-coupling reactions. This process provided a useful method for the preparation of diverse acylated enamides from readily accessible reactants under mild reaction conditions.

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Acknowledgment. Financial support from National Natural Science Foundation of China (Nos. 21102110, 21102111) and the Fundamental Research Funds of the Central Universities are greatly appreciated.

Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.