Palladium-Catalyzed Oxidative C—H Bond and C=C Double Bond Cleavage: C-3 Acylation of Indolizines with α,β-Unsaturated Carboxylic Acids
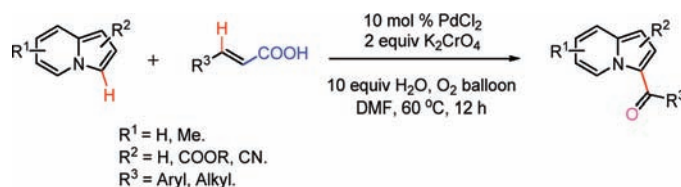
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ABSTRACT

A novel palladium-catalyzed C-3 acylation of indolizines with α,β-unsaturated carboxylic acids via C—H bond and C=C double bond cleavage under oxidative conditions is described. The regioselectivity is assisted by the carboxylic group, and the selection of the oxidant is crucial to the reaction.

Transition-metal-catalyzed reactions involving C—H bond activation have attracted increasing attention currently because they are challenging targets in organic chemistry and capable of providing synthetically useful transformations.[1] Over the past decades, significant progress has been achieved in the transition-metal-catalyzed activation of C—H bonds, which furnishes promising economical alternatives to traditional organic chemistry.[2] Indolizines are an attractive class of heterocycles that are frequently found in bioactive natural products and pharmaceuticals.[3] Direct C—H bond functionalization of indolizines including arylation,[4] alkynylation,[5] and dimerization[6] have been reported. We previously investigated the direct cross-coupling of indolizines and vinylarenes employing a Pd(OAc)$_2$/Ag$_2$CO$_3$ catalytic system to prepare the branched α-olefin products with high regioselectivity.[7] In our ongoing research of direct functionalization of indolizines, we studied the reaction of indolizines with cinamic acids expecting to obtain the linear β-olefinated products.[8] Surprisingly, it was found that the C=C double bond of cinnamic acid experienced palladium-catalyzed

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cleavage in the presence of 2 equiv of K_2CrO_4, which led to the formation of C-3 acylated indolizines. Notably, the reaction was switched to annulation when BQ (1,4-benzoquinone) was used as the oxidant in the presence of 2 equiv of KOAc, affording the annulation product via a decarboxylation process.[9]

Table 1. Screening of the Reaction Conditions[a]
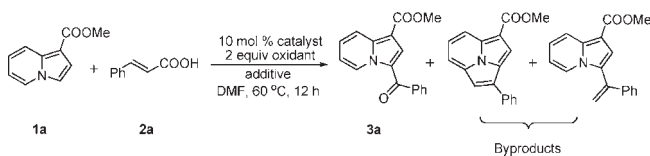
entry	catalyst	oxidant	atmosphere	yield[b] (%)
1[c]	PdCl$_2$	Cu(OAc)$_2$	air	25
2	PdCl$_2$	KMnO$_4$	air	0
3	PdCl$_2$	K$_2$S$_2$O$_8$	air	14
4	PdCl$_2$	K$_2$Cr$_2$O$_7$	air	44
5	PdCl$_2$	K$_2$CrO$_4$	air	52
6	PdCl$_2$	K$_2$CrO$_4$	N$_2$	18
7		K$_2$CrO$_4$	air	0
8[d]	PdCl$_2$	K$_2$CrO$_4$	O$_2$	41
9[e]	PdCl$_2$	K$_2$CrO$_4$	O$_2$	58
10[f]	PdCl$_2$	K$_2$CrO$_4$	O$_2$	36
11[e]	PdCl$_2$	K$_2$CrO$_4$	N$_2$	32
12	Pd(OAc)$_2$	K$_2$CrO$_4$	air	27
13	Pd(PPh$_3$)$_4$	K$_2$CrO$_4$	air	0

[a] Reaction conditions: indolizines (0.4 mmol), cinnamic acids (0.6 mmol), palladium catalyst (0.04 mmol), and oxidant (0.8 mmol) were mixed in 1 mL of DMF at 60 °C for 12 h. [b] Isolated yield of **3a**. [c] 1 equiv of KOAc was added. [d] 5 equiv of H$_2$O was added. [e] 10 equiv of H$_2$O was added. [f] 15 equiv of H$_2$O was added.

Initially, we examined the reaction of **1a** and cinnamic acid (**2a**) in the presence of 10 mol % of PdCl$_2$, 2 equiv of Cu(OAc)$_2$, and 1 equiv of KOAc at 60 °C for 12 h in the air (Table 1, entry 1). Unprecedently, we isolated the acylated product **3a** in 25% yield, while the desired linear alkenylation product was not found. Considering the acylated product might come from the oxidation of in situ formed alkene, we employed KMnO$_4$ as the oxidant, but there were no products (Table 1, entry 2). By the use of K$_2$S$_2$O$_8$, we isolated the acylated product in 14% yield (Table 1, entry 3). To our delight, the use of K$_2$Cr$_2$O$_7$ as the oxidant obviously improved the reaction (Table 1, entry 4); the yield was further increased to 52% when K$_2$CrO$_4$ was employed (Table 1, entry 5).

The reaction rate was drastically decreased in a nitrogen atmosphere (Table 1, entry 6). It should be noted that the small amount of byproducts (the annulation product and the *gem*-selective alkenylation product) were always observed in these reactions, which had a deleterious effect on the yield of acylation product **3a**. No reaction was observed in the absence of palladium catalyst (Table 1, entry 7).

After the study of reaction conditions, we found that a small amount of water was crucial for switching the reaction to the single acylation product. It was found that the addition of 10 equiv of H$_2$O to the reaction system led to the formation of sole acylated product in 58% yield (Table 1, entries 8−10). Again, the yield was reduced in a nitrogen atmosphere (Table 1, entry 11), showing oxygen is needed to improve the reaction. Among the palladium catalysts investigated, PdCl$_2$ was clearly the best choice (entries 12 and 13). Further investigation of reaction solvents led us to establish the optimized reaction conditions as follows: 10 mol % of PdCl$_2$, 2 equiv of K$_2$CrO$_4$, 10 equiv of H$_2$O, DMF as solvent under O$_2$ at 60 °C for 12 h.
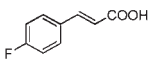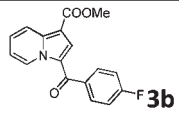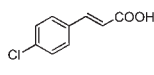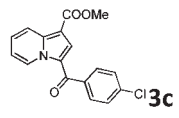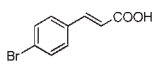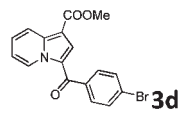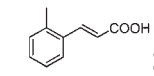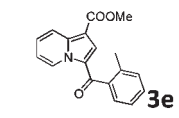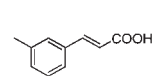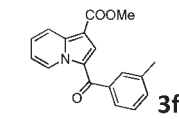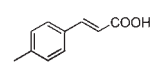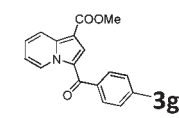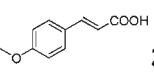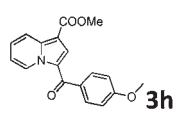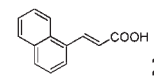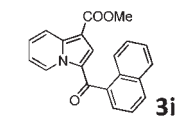
Under the optimized reaction conditions, different α,β-unsaturated carboxylic acids were examined, and the results are presented in Table 2. Both aryl- and alkyl-substituted α,β-unsaturated carboxylic acids showed good reactivity. The cinnamic acids with electron-withdrawing groups in the aryl ring reacted smoothly to give the acylated indolizines in high efficiency (Table 2, entries 1−3). It is noteworthy that the presence of a C−X bond (X = F, Cl, and Br) in the cinnamic acids (**2b**, **2c**, and **2d**) did not alter the reaction pathway, and the produced halo-containing indolizine derivatives could be further functionalized to construct more complicated structures. *Ortho*-substituted cinnamic acid delivered lower yield compared with its *meta*- or *para*-analogues due to the steric hindrance (entries 4−6). Electron-donating substituent (OMe) at the *para*-position of the phenyl ring made the product in 50% yield (entry 7). When (*E*)-3-(naphthalen-1-yl)acrylic acid was employed, the corresponding product **3i** was formed in lower yield (entry 8), possibly due to the steric effect. Importantly, alkyl-substituted α,β-unsaturated carboxylic acids participated in the reaction well to afford the corresponding products (entries 9 and 10).

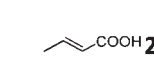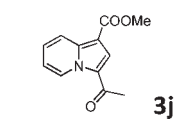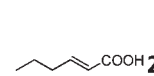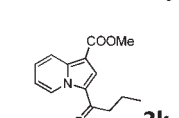The substituent effects of the indolizine on this reaction were studied using cinnamic acid (**2a**) to react with various indolizines (Figure 1). The indolizines bearing electron-withdrawing groups such as COOR and CN on both the C-1 and C-2 positions provided 48−61% yields (**3l−p**). 7-Methylindolizine-1-carbonitrile was also compatible with the reaction conditions, giving the desired product **3q** in 45% yield.

The annulation product observed in Table 1 is an important member in the family of cyclazines due to its novel structural properties.[10] It might be formed via dual C−H functionalization and decarboxylative coupling in our Pd-catalytic system.[11] Therefore, we optimized the

(8) For recent applications of using α,β-unsaturated carboxylic acids on cross-coupling reactions, see: (a) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 592–595. (b) Wang, Z.; Ding, Q.; He, X.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 863–865. (c) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 68–69.

(9) For recent examples of decarboxylative coupling on C−C bond-forming reactions, see: (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664. (b) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333. (c) Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768–2771. (d) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792–795. (e) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391–14393. (f) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195. (g) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506–5509.

(10) Liang, F.; Hu, J.; Zhang, L.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2001**, *38*, 853–857 and references cited therein.

Table 2. Reactions of Indolizine **1a** with Different α, β-Unsaturated Carboxylic Acids[a]

entry	α, β-unsaturated carboxylic acid	product	yield (%)[b]
1	**2b**	**3b**	64
2	**2c**	**3c**	61
3	**2d**	**3d**	66
4	**2e**	**3e**	45
5	**2f**	**3f**	52
6	**2g**	**3g**	60
7	**2h**	**3h**	50
8	**2i**	**3i**	42
9	**2j**	**3j**	41
10	**2k**	**3k**	45

[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.6 mmol), PdCl$_2$ (0.04 mmol), K$_2$CrO$_4$ (0.8 mmol), H$_2$O (4 mmol) were dissolved in 1 mL of DMF under O$_2$ balloon at 60 °C for 12 h. [b] Isolated yield.

reaction conditions intensely, and the annulation product **4a** was finally successfully isolated in 52% yield in the presence of 10 mol % of Pd(OAc)$_2$, 1 equiv of BQ, and 2 equiv of KOAc under O$_2$ atmosphere (Scheme 1). The effect of the substitution on the aryl ring was also examined. The electron-donating substituent such as −OMe at
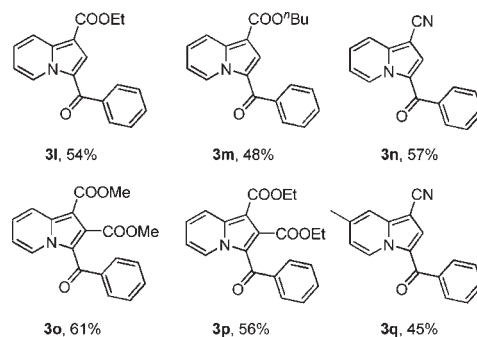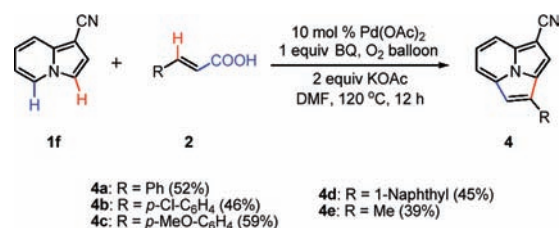

Figure 1. Acylation of various indolizines with cinnamic acid under the optimized reaction conditions.

Scheme 1. Annulations of Indolizine with α,β-Unsaturated Carboxylic Acids

the *para*-position of the phenyl ring gave higher yield than the electron-withdrawing group (46% of **4b** and 59% of **4c**, respectively). (*E*)-3-(Naphthalen-1-yl)acrylic acid showed a relatively lower reactivity to give **4d** in 45% yield. The crotonic acid **2j** participated in the reaction to give the annulation product **4e** in 39% yield.

Control experiments were performed to verify the catalytic pathways (Scheme 2). When indolizine **1a** was treated with methyl cinnamate (Y = Me) or potassium cinnamate (Y = K) under identical conditions, no desired C-3 acylation product was detected. Moreover, using *gem*-selective alkenylation product **5** as the starting material, we failed to get the acylation product or the annulation product. These results may rule out the possibility of Fujiwara-type oxidative vinylation followed by chromium-mediated carbon−carbon double-bond cleavage.[12] Instead, the COOH group could play an important role in this reaction.

On the basis of previous studies[13] and our experimental results, a plausible mechanism for the reactions is illustrated in Scheme 3. The electrophilic palladation first

(11) Other reported annulation reactions include the following. (a) 2-Phenylbenzoic acids by palladium catalysis: Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006–14008. (b) Arylboronic acids by rhodium catalysis: Fukutani, F.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 5198–5201. (c) Benzoic acids by iridium catalysis: Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362–5367. (d) Heteroaromatic acids by palladium catalysis: Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337–2340.

(12) (a) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639.

Scheme 2. Control Experiments
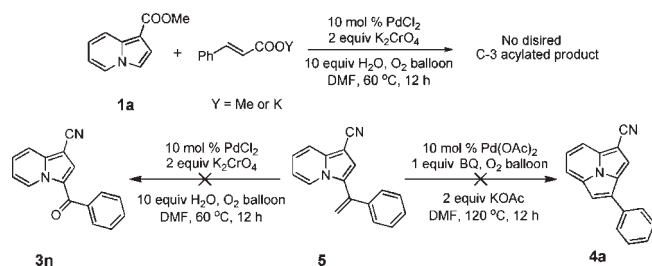
occurs preferentially at the C-3 position of indolizine[5] to form the intermediate **A**, which undergoes the migratory insertion to produce the intermediate **B**. In the presence of K_2CrO_4, the oxidation of the tertiary hydrogen bond occurs to form intermediate **C**,[14] and the subsequent reductive elimination generates the intermediate **D**. The rapid transformation from **C** to **D** might indicate that a small amount of water is necessary for the high yield of acylation product **3** and thus suppresses the formation of **4**. The further oxidation scission of **D** by K_2CrO_4 gives the acylation product, and Pd(0) is oxidized to Pd(II).[15]

In the reactions employing BQ as the oxidant, the intermediate **B** undergoes β-H elimination to form **E**, which is scavenged by BQ/KOAc to form intermediate **F**. The subsequent palladation gives the intermediate **G**, which undergoes decarboxylation and reductive elimination[11a] to form annulated product **4**. The resulting Pd(0) species is oxidized by BQ to regenerate Pd(II). In the absence of base, the decarboxylation and reductive elimination of intermediate **E** afford the *gem*-selective alkenylation product **5** (eq 1).
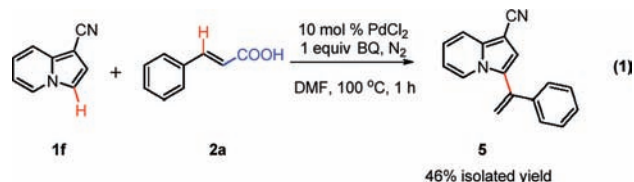
In conclusion, we have developed a novel palladium-catalyzed C-3 acylation of indolizines via C–H bond and C=C double bond cleavage. This reaction provides an

(13) (a) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100–3120. (b) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395–3409.

Scheme 3. Plausible Mechanism
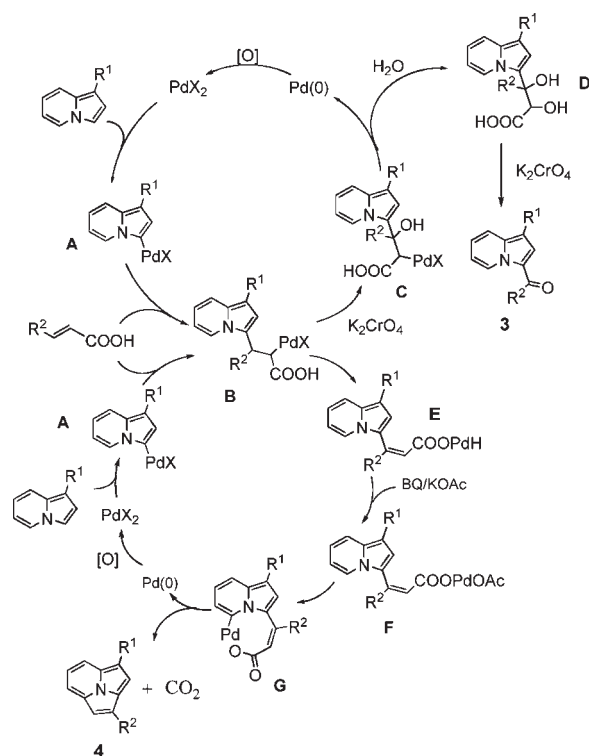
alternative for C-3 acylated indolizine derivatives. The prominent role of the COOH group in this reaction has been disclosed: it may act as a removable group or a coupling partner under properly tuned oxidative conditions, affording an annulation product or an alkenylation product.

Supporting Information Available. Experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Chang, Y. W.; Westheimer, F. H. *J. Am. Chem. Soc.* **1960**, *82*, 1401–1405. (b) Rocek, J.; Westheimer, F. H. *J. Am. Chem. Soc.* **1962**, *84*, 2241–2246. (c) Walker, B. H. *J. Am. Chem. Soc.* **1967**, *89*, 1098–1103.