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Pd-Catalyzed α-Selective C−H Functionalization of Olefins: En Route to 4-Imino-β-Lactams

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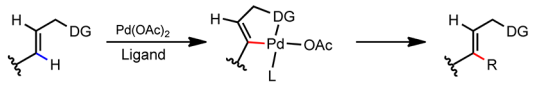
Supporting Information

ABSTRACT: Pd-catalyzed α-olefinic C−H activation of simple α,β-unsaturated olefins has been developed. 4-imino-β-lactam derivatives were readily synthesized via activation of α-olefinic C−H bonds with excellent *cis* stereoselectivity. A wide range of heterocycles at the β-position are compatible with this reaction. The product of 4-imino-β-lactam derivatives can be readily converted to 2-aminoquinoline which exists extensively in pharmaceutical drugs and natural products.

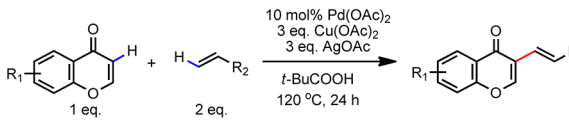
Directed C(sp^2)−H functionalization of various aromatic systems has emerged as a promising tool for arene synthesis.[1] Similarly, β-olefinic C−H activation involving the same five-membered cyclometalation intermediates has been extensively exploited (eq 1).[2−5] To the best of our knowledge,

Directed beta-olefinic C-H Activation:



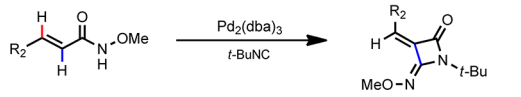
(1)

Non-Directed alpha-olefinic C-H Activation:



(2)

This Work:

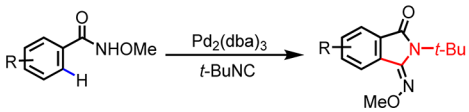


(3)

directed α-C−H activation of simple olefins has not been reported except for nondirected functionalization of electron-rich α-olefinic C−H bonds (eq 2).[6] In addition, construction of β-lactams through olefinic C−H functionalization has not been achieved despite recent reports on β-lactam formation from C(sp^3)−H functionalization.[7] Herein, we report a directed α-selective olefinic C−H activation to construct 4-imino-β-lactam derivatives using air as the sole oxidant (eq 3). The C−H activation step proceeds through a five-membered cyclopalladation of an intermediate formed from the Pd(II)-catalyzed reaction of amide substrate and *t*-BuNC. The tolerance of a wide range of heterocycles at the β-positions renders this reaction valuable for medicinal chemistry.

In directed C−H activation reactions, the hetero atoms in heterocyclic substrates could coordinate with metal catalysts and lead to catalyst poisoning or direct C−H activation at undesired positions, thus limiting its application in heterocycle containing substrates. Recently, we have developed a strategy to tackle this problem by using *N*-methoxy amide group as the directing group, air as sole oxidant, and low-valent Pd(0) to initiate the reaction to avoid the undesired influence from the heterocycles (eq 4).[8]

Previous Related Work:



(4)

Given our success in aromatic systems, we wondered whether β-C−H activation of α,β-unsaturated olefins could take place to give five-membered imino-γ-lactams.

Driven by this idea, we initiated our study by using *N*-methoxy cinnamamide **1a** as the substrate and found that α-C−H activation occurred selectively in the presence of 5 mol % $Pd_2(dba)_3$, 2 equiv of *t*-BuNC in dioxane to give two products **3a** and **3a′** in 16% and 53% yields, respectively (Table 1, entry 2). The structures of the four-membered ring 4-imino-β-lactam **3a** and **3a′** are confirmed by X-ray crystallography (Table 1). For the major product **3a′**, the acyl group is *cis* to the benzene ring in contrast to the *trans* relationship in substrate **1a**.

While both the regioselectivity and the stereochemistry of the products are intriguing, we initially focused on improving the yield of this reaction. In the course of reaction optimization, we found that temperature has significant impact on the yield and the product ratio of *Z*/*E* (Table 1, entries 1−4). When the temperature was increased to 100 °C, yield of **3a′** was improved to 63% with only trace **3a**. However, further increasing the temperature to 120 °C decomposed the substrate (Table 1, entry 4). Scaling up the reaction to 0.2 mmol afforded **3a′** in 58% yield (Table 1, entry 5). Since we observed some decomposition of the starting material, we attempted several modifications of the conditions and found that decreasing the catalyst loading to 2 mol % improved the yield to 72% (Table 1, entry 6). However, the use of 1 mol % $Pd_2(dba)_3$ resulted in low conversion (Table 1, entry 7).

With optimized conditions in hand, we subsequently explored the scope with regard to substitutions on the aryl ring (Table 2). Substitutions at the *o*-, *m*-, and *p*-position with a range

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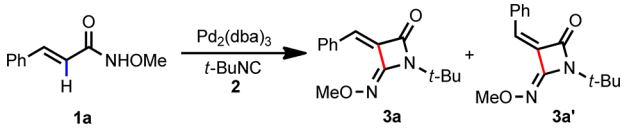
Table 1. Optimization of Reaction Conditions[a,b]



entry	T (°C)	t (h)	$Pd_2(dba)_3$ mol %	solvent (mL)	yield (%) 3a	3a'	1a
1	70	6	5	1	4	0	78
2	80	6	5	1	16	53	0
3	100	6	5	1	6	63	0
4	120	6	5	1	11	23	0
5[c]	100	6	5	2	6	58	0
6[c]	100	6	2	2	2	72 (68)[d]	0
7[c]	100	11	1	2	13	33	23
8[c]	100	4	2	2	9	53	3
9[c]	100	2	2	2	18	17	43

[a]Conditions: **1a** (0.1 mmol), **2** (2.0 equiv), dioxane (x mL). [b]Yield determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c]**1a** (0.2 mmol). [d]Isolated yield.

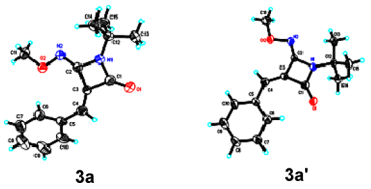
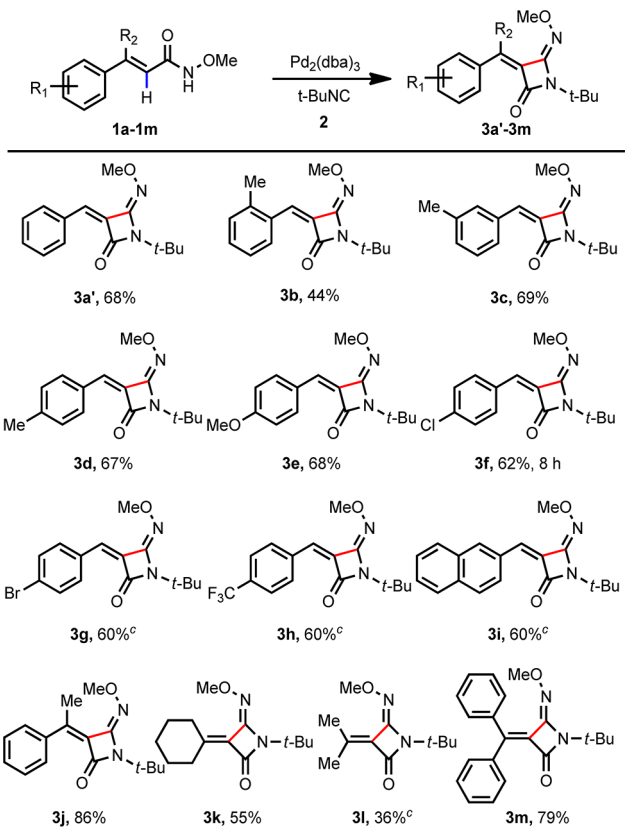


Table 2. α-Olefinic C–H Activation To Construct 4-Imino-β-lactams[a,b]

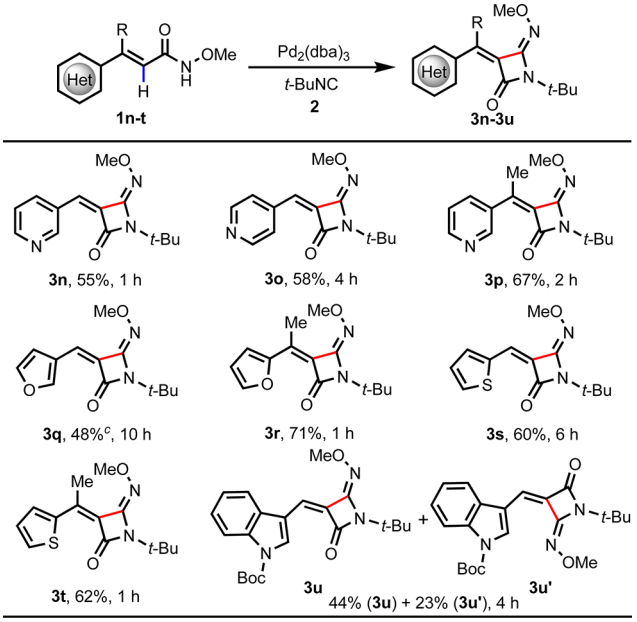


[a]**1** (0.2 mmol), **2** (0.4 mmol), $Pd_2(dba)_3$ (2 mol %), 1,4-dioxane (2 mL), 100 °C, 6 h. [b]Isolated yields are shown. [c]**1** (0.1 mmol), **2** (0.2 mmol), $Pd_2(dba)_3$ (5 mol %), 1,4-dioxane (1 mL).

of electron-withdrawing and -donating groups are tolerated (**3a′**–**i**). For electron-withdrawing substituted substrates, such as triflormethyl, chloro, and bromo, 5 mol % $Pd_2(dba)_3$ and prolonged time are needed. For these *N*-OMe cinnamic amides, C–H activation all occur at the α-position of the acyl group. Importantly, various 3,3-disubstituted acrylamides are also compatible with this reaction. β,β-Dialkyl-substituted **1k** and **1l** give **3k** and **3l** in 55% and 36% yield, respectively. However, monoalkyl-substituted substrate (*E*)-*N*-methoxyhex-2-enamide gives 17% yield only. For mono- and di-phenyl-substituted acrylamides **1j** and **1m**, the corresponding 4-imino-β-lactams are obtained with good yields up to 86%.

Next, we examined the compatibility of this reaction with substrates containing common heterocycles at the β-positions (Table 3). Pyridine, furan, and thiophene-substituted acrylamides

Table 3. α-Olefinic C–H Activation with Heterocycles[a,b]



[a]**1n**–**1u** (0.1 mmol), **2** (0.2 mmol), $Pd_2(dba)_3$ (5 mol %), 1,4-dioxane (1 mL), 100 °C. [b]Isolated yields are shown. [c]80 °C.

give the corresponding 4-imino-β-lactams in yields from 48% to 71% (**3n**–**t**). Meanwhile, indole-substituted acrylamide gives two separable products in total yield of 67% (**3u** and **3u′**, 44% and 23%, respectively).

When the substrates without α-C–H are employed, C–H activation can also take place at the β-position to give the corresponding 5-imino-γ-lactams products (Table 4). A variety of substituents on the aryl ring are well tolerated (**5a**–**d**). The cyclic olefinic substrates also give good yields (**5e** and **5f**). Moderate yield is obtained with acyclic dialkyl-substituted substrate (**5g**).

Based on these results and our previous work,[8] a probable mechanism is proposed (Scheme 1). First, Pd(0) is converted to Pd(II)X_2 (X = PhCH=CHCONOMe) in the presence of oxygen and **1a**, followed by 1,1-insertion of *t*-BuNC into the Pd–N bond and acyl migration to form intermediate **B**. Subsequently, α-olefinic C–H is activated to form the five-membered cyclopalladated complex **C**. Reductive elimination of **C** produces the initial product **3a**. **3a** is isomerized to give the more stable product **3a′**. This isomerization of **3a** to **3a′** is verified by subjecting **3a** to typical reaction conditions giving **3a′**

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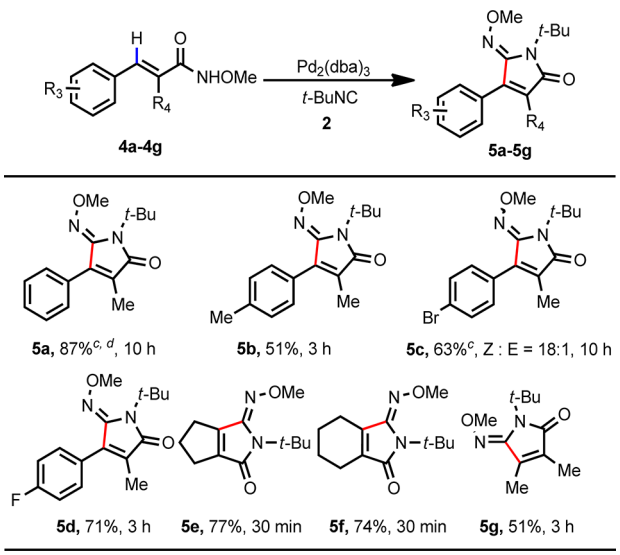
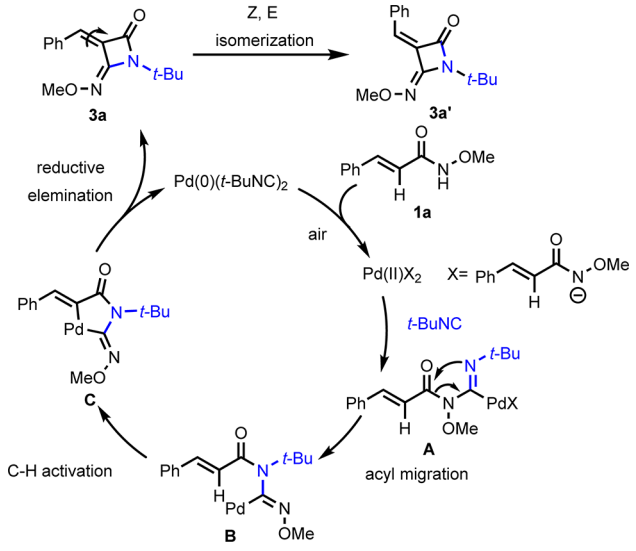
Table 4. β-Olefinic C−H Activation To Construct 5-Imino-γ-Lactams[a,b]



[a]**4a**–**4g**(0.1 mmol), **2** (0.2 mmol), 1,4-dioxane (1 mL), $Pd_2(dba)_3$ (5 mol %), 100 °C. [b]Isolated yields are shown. [c]80 °C. [d]**4** (0.3 mmol).

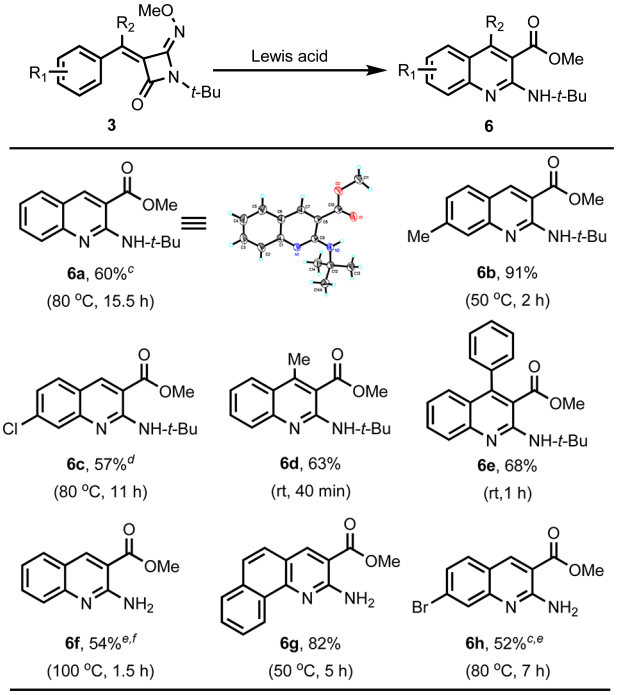
Scheme 1. Proposed Mechanism



in 94% yield (see Supporting Information). Furthermore, reaction of the *Z*-isomer **1a′** under the same conditions gives the same product **3a′** being consistent with the proposed mechanism (see Supporting Information).

The synthetic utility of the 4-imino-β-lactams is also demonstrated by various subsequent transformations. **3a′** could be hydrogenated quantitatively with Pd/C under pressured H_2 and deoximinated with ceric ammonium nitrate at room temperature to give 2,4-azetidine dione. Cleavage of *t*-butyl group and deprotection of the oxime of the γ-lactams to give the imide were also performed under known conditions (see Supporting Information). Interestingly, we found **3a′** could be transformed to 3-substituted quinoline **6a** in the presence of Lewis acid $BF_3{\cdot}OEt_2$ in 60% isolated yield (Table 5). The potential utility of this procedure in the synthesis of 2-aminoquinoline-based pharmaceuticals and natural products is evident from the literature reports.[9] The reaction is found to be compatible

Table 5. Lewis Acid Promoted Rearrangement[a,b]



[a]**3**(0.05 mmol), BF_3OEt_2 (2 equiv), DCM (2 mL). [b]isolated yields. [c]$BF_3{\cdot}OEt_2$ (4 equiv). [d]$AlCl_3$ (2 equiv). [e]**3** (0.1 mmol). [f]TMSOTf (2.0 equiv), DCE (1 mL).

with electron-withdrawing and -donating groups on the aryl ring, and the desired quinoline derivatives are formed in moderate to excellent yields (**6b** and **6c**). For β-methyl or phenyl-substituted substrates, this transformation occurs at room temperature to afford the products in good yields (**6d** and **6e**). In some cases, the *t*-butyl group is deprotected in one-pot (**6f**–**h**). While detailed mechanism of this reaction remains unclear, one possible pathway involves Lewis acid-induced ring opening and nitrene insertion into C−H bond (see Supporting Information).[10]

In conclusion, we have developed a directed regioselective α-olefinic C−H activation to construct 4-imino-β-lactam derivatives using air as the sole oxidant. This operationally simple transformation features excellent regioselectivity and compatibility with heterocycles. Further transformations of the products also indicate potential synthetic utility.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13353.

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Notes

The authors declare no competing financial interest.

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