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Synthesis of β-, γ-, and δ-Lactams via Pd(II)-Catalyzed C−H Activation Reactions

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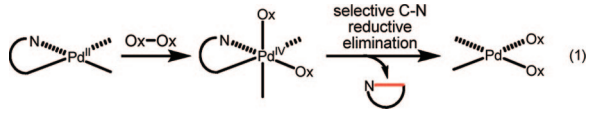
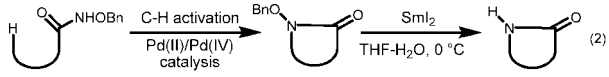
Despite recent progress in the development of Pd-catalyzed C−H activation reactions, amination of C−H bonds using Pd catalysts remains a significant challenge.[1] In previous efforts to explore the recently developed Pd(II)/Pd(IV) catalysis[2] for C−H bond amination, the reductive elimination of the C−halide other than C−N bonds proceeds as the predominant pathway.[3] We turned our attention to tuning the amino group and oxidant to promote the selective reductive elimination of the C−N bonds instead of the C−Ox bonds (eq 1).

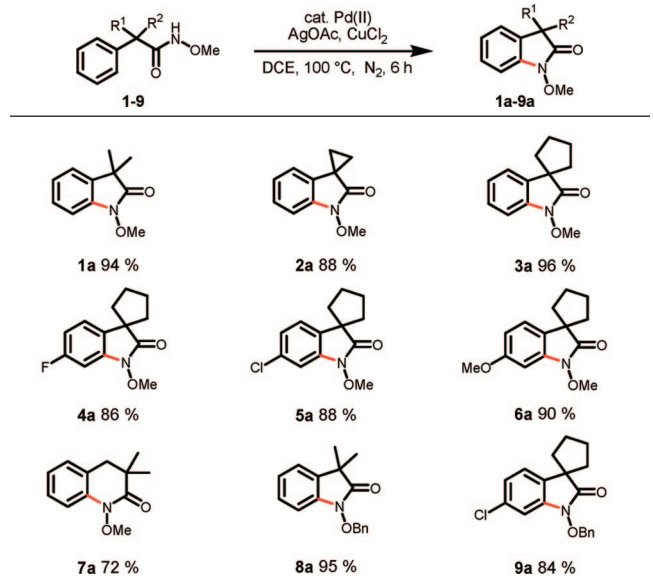


Herein, we disclose a C−H amination procedure for the preparation of β-, γ-, and δ-lactams employing Pd-catalyzed C−H activation reactions (eq 2). Mechanistic observations are consistent with a Pd-catalyzed C−H amination process involving Pd(II)/Pd(IV) catalysis, although an alternative catalytic pathway remains a possibility. A noteworthy feature of this method is the tolerance of double bonds located at the α,β-position of the amide substrate which affords versatility for further synthetic manipulations. This lactamization protocol provides a new synthetic disconnection complementary to other C−H activation/lactam formation approaches.[4,5]



The excellent reactivity of *N*-methoxyhydroxamic acid in sp^3 C−H activation reactions[6] led us to focus on the development of a lactamization reaction using this type of substrates (Table 1). We anticipated that the reductive elimination of aryls and the *N*-alkoxyamides in an intramolecular manner would prove advantageous. We found that treating substrate **1** with 20 mol% $Pd(OAc)_2$ in the presence of 1.5 equiv of $CuCl_2$ oxidant effectively generates 15% of the desired lactam **1a**. Addition of 2 equiv of AgOAc to the reaction increases the yield to 94% (Table 1). To explain this catalysis, we tested the possibility of the C−H insertion Pd(II) intermediate being oxidized to Pd(IV) species by running this reaction using $PhI(OAc)_2$, an established oxidant for Pd(II)/Pd(IV) redox chemistry.[2a] Although the amide substrate was largely decomposed, ∼10% of the desired lactam product was formed. On the basis of this observation, we hypothesize that $CuCl_2$ is providing a chloronium ion[7,8] which oxidizes Pd(II) to Pd(IV) via the Shilov mechanism.[9] It is not clear whether $CuCl_2$ serves as a 2-electron or 1-electron oxidant. In the latter case, 0.5 equiv of AgOAc is consumed to oxidize Cu^+ to Cu^{2+} since only 1.5 equiv of $CuCl_2$ are used. $PdCl_2$ generated from the C−N reductive elimination would presumably be converted back to $Pd(OAc)_2$ through ligand exchange with AgOAc, thus closing the catalytic cycle. As previously proposed in amination of olefins,[10] it is also possible that $CuCl_2$ complexes with

Table 1. Lactamization of Aryl C−H Bonds[a]



[a] Conditions: 0.5 mmol of substrate, 10 mol% $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, 10 mL of dichloroethane, N_2, 100 °C, 6 h.

a Pd(II) intermediate and triggers C−N reductive elimination through transient oxidation of Pd(II) to give $PdCl_2$ and CuCl.

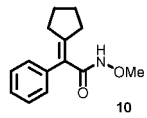
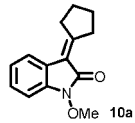
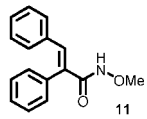
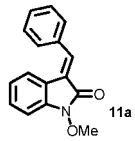
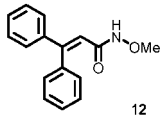
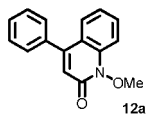
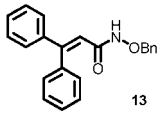
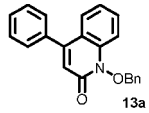
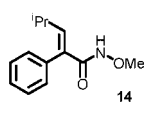
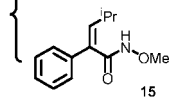
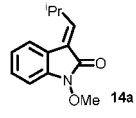
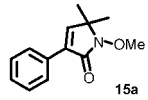
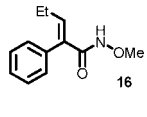
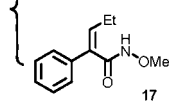
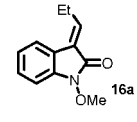
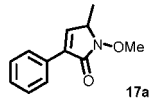
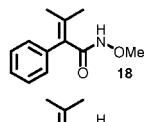
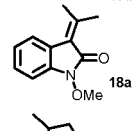
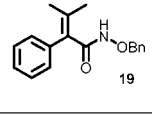
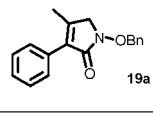
The electronic density of the arene does not affect the yield of the reaction to an appreciable extent (**3a**−**6a**). Moreover, δ-lactams can also be prepared via this method, albeit giving a slightly lower yield (**7a**). Following lactamization, the cleavage of the *N*-methoxy groups in the products can be readily accomplished by reduction with H_2/Pd/C.[11] Alternatively, Romo's deprotection of the *N*-benzyloxy groups using SmI_2 at 0 °C is an especially high-yielding and convenient transformation (**8a**, **9a**; see Supporting Information).[12]

Unlike Kikugawa's intramolecular electrophilic substitution reaction of arenes by *N*-methoxy-*N*-acylnitrenium ions,[11] the presence of hydrogens instead of alkyls adjacent to directing groups severely retards Pd-catalyzed C−H activation due to the Thorpe−Ingold effect (also called dialkyl effect).[13] In view of broad synthetic application, the presence of an α,β-double bond in the substrate could overcome this limitation to a great extent. Gratifyingly, we found that lactamization of α,β-unsaturated substrates proceeds under the established conditions to give γ- and δ-lactams in good yields (Table 2, entries 1−4).

Due to the difficulty of separation, a mixture of *cis*- and *trans*-isomeric amides were used in entries 5 and 6. In addition to the formation of the anticipated lactam as a major product, lactamization of the allylic C−H bonds was also observed. The product ratio suggests that the allylic lactamization only occurs with the *cis* isomer **15**. Substrates **18** and **19** were prepared to further study lactamization of allylic C−H bonds. Remarkably, selective lactamization of the allylic

10.1021/ja807129e CCC: $40.75

Table 2. Expanding the Scope of the Lactamization Reaction[a,b]

entry	substrate	product	isolated yield (%)
1	 **10**	 **10a**	78
2	 **11**	 **11a**	58
3	 **12**	 **12a**	91
4	 **13**	 **13a**	79
5	 **14**  **15**	 **14a**  **15a**	62 21
6	 **16**  **17**	 **16a**  **17a**	60 observed by ^{1}H NMR
7	 **18**	 **18a**	72
8	 **19**	 **19a**	68

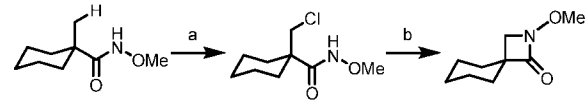
[a] Conditions: 0.5 mmol of substrate, 10 mol% $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, 10 mL of dichloroethane, N_2, 100 °C, 10 h. [b] For entry 5, 4:1 mixture of *E*-*Z* isomers was used. For entry 6, 6:1 mixure of *E*-*Z* isomers was used.

C−H bonds could be achieved by using an *N*-benzyloxy amide. At this stage, the exact mechanistic nature of this sp^3 C−H activation remains to be elucidated.

When substrate **20** was treated with our standard lactamization conditions, only β-chlorinated products were obtained (Scheme 1). This is not surprising since the reductive elimination of the five-membered palladacycle to form four-membered β-lactam is less favored due to a strained transition state structure, and therefore the reductive elimination of the alkyl chloride from the Pd(IV) intermediate occurs. Importantly, β-lactams can be readily obtained by treating the reaction mixture with CsF and triethylbenzyl quaternary ammonium salt in one pot (Scheme 1).

Preliminary mechanistic studies were also carried out. First, the *ortho*-chlorinated substrate **21** (Scheme 2) did not undergo intramolecular amination under treatment with CuCl in DCE at 100 °C.

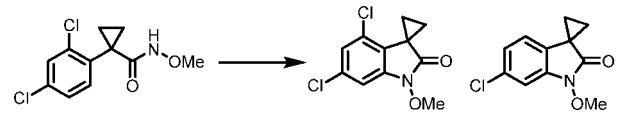
Scheme 1. One-Pot Synthesis of β-Lactams[a]



20 **20a** **20b**, 68%

[a] Reaction conditions: (1) 0.5 mmol of substrate, 10 mol % $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, DCE, 100 °C, N_2, 10 h. (2) 4 equiv of CsF, 0.18 equiv of benzyltriethyl ammonium chloride, 100 °C, 12 h.

Scheme 2. Mechanistic Studies[a]



21 **21a**, 40 % conversion **21b**, not obsverved

[a] Reaction conditions: 0.5 mmol of substrate, 10 mol % $Pd(OAc)_2$, 1.5 equiv of $CuCl_2$, 2.0 equiv of AgOAc, DCE, 100 °C, N_2, 10 h.

Second, lactam **21b** did not form when substrate **21** was subjected to the standard conditions (Scheme 2). These observations argue against a sequential chlorination−amination pathway in these reactions.

In summary, we have developed a novel catalytic C−H lactamization reaction using a Pd(II) catalyst. The reaction provides new access to a range of lactams. We are currently developing an intermolecular C−H amination protocol using this catalysis.

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

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