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Palladium-catalyzed dehydrogenative C–H cyclization for isoindolinone synthesis†

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In this paper Pd-catalyzed intramolecular dehydrogenative C(sp³)-H amidation for the synthesis of isoindolinones is described. This method features the use of a Pd/C catalyst and the addition of a stoichiometric amount of oxidant is not necessary. A mechanistic study suggested the possible formation of H₂ gas during the reaction.

The isoindolinone scaffold occurs frequently in numerous biologically active compounds ranging from designed medicinal agents to natural products, thus constituting an extremely important class of heterocycles.^{1,2} Although a number of synthetic methods exist for the preparation of isoindolinones,³ the development of more general, versatile, and efficient procedures to construct the isoindolinone framework is still an ongoing, intensive research area.

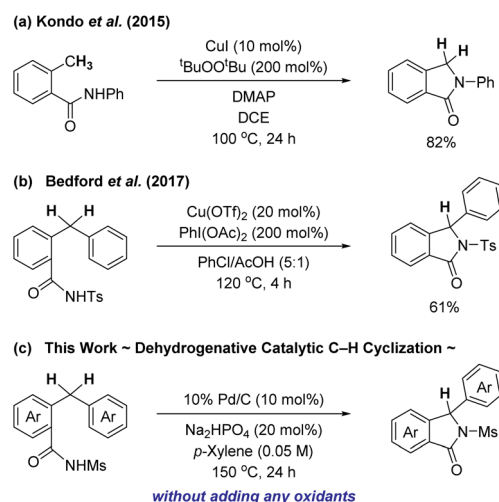
Among a variety of synthetic strategies for isoindolinones, methods that make use of transition metal-catalyzed C–H functionalization represent a remarkable approach.⁴ In this research area, catalytic oxidative annulation of *N*-substituted benzamides and appropriate coupling partners (*e.g.* alkenes, alkynes, isocyanides, diazo compounds) has been extensively studied, most of which employ transition metals such as rhodium,^{4d,g,h,m,o} ruthenium,^{4l} cobalt,^{4a,i,j,k} and palladium.^{4b,m} These precedents often require the use of stoichiometric oxidants or prefunctionalized coupling partners to make the process catalytic.

On the other hand, an approach that involves intramolecular C–H cyclization of benzamide derivatives exploiting a transition metal catalyst could provide another efficient, facile, and direct access to isoindolinones, although less attention has been paid to such a process (Scheme 1). Kondo *et al.* previously reported C(sp³)-H aminative cyclization of 2-methyl-*N*-arylbenzamides in the presence of a copper catalyst along with a stoichiometric amount of di-*tert*-butyl peroxide as an oxidant, which resulted in the formation of 3-unsubstituted isoindolinones (Scheme 1a).^{4c} Bedford's group also developed a copper-based catalytic system composed of 20 mol% of Cu(OTf)₂ and 2 equiv. of PhI(OAc)₂ that successfully effected the intramolecular benzylic C–H sulfamidation of 2-benzyl-*N*-tosylbenzamides for the synthesis of isoindolinones (Scheme 1b).^{4f} In both cases, the choice of an

oxidant should be crucial for the successful construction of the isoindolinone ring.

Herein, we describe a catalytic system that enables cyclization of 2-benzyl-*N*-mesylbenzamides leading to isoindolinone derivatives, in which benzylic C(sp³)-H functionalization in the presence of a palladium catalyst smoothly occurs. It is particularly noteworthy to mention that any stoichiometric oxidants are not necessary for our isoindolinone synthesis. The key to success is the use of Pd/C as a catalyst. In this dehydrogenative process, an only detectable by-product was H₂, which should also be an appealing feature of the process.

Based on our fruitful results of the heterocycles synthesis *via* transition metal-catalyzed C–H cyclization,⁵ our investigation began by examining the conversion of *N*-tosyl-protected benzamide **1a** to the corresponding isoindolinone **2a**. During the screening studies utilizing a range of transition metal catalysts as well as various oxidants, it was found that **2a** did produce even in the absence of an oxidant when Pd/C was used as a catalyst. Indeed, the use of 10 mol% of Pd/C along with



Scheme 1 C–H cyclization strategies for isoindolinone synthesis.

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20 mol% of KOAc enabled the desired cyclization process, providing **2a** in 42% yield (Table 1). Intrigued by this unexpected oxidant-free process, the effect of the protecting group on the nitrogen atom of an amide moiety was briefly evaluated. We are pleased to find that the reaction of **1f** possessing a mesyl group (–Ms) efficiently occurred and the isoindolinone **2f** was obtained in fairly good yield (75%).⁶

Settled in –Ms for the protecting group, further examination of the reaction parameters was performed employing **1f** (Table 2). Use of Na₂HPO₄ gave a slightly better result (entry 2), while reactions with other bases led to lower yields (entry 3). Among a variety of solvents tested, *p*-xylene was found to be the best (entry 4). Varying the concentration of the reaction did not enhance the process (entry 5). Performing the reaction under an oxygen atmosphere dreadfully diminished the yield (entry 6). In contrast, use of the degassed conditions by means of Ar bubbling afforded the desired **2f** with excellent yield (entry 7). In addition, it was found that the yield decreased when the reaction was carried out in the absence of a base (entry 8).^{7,8}

Our new method for isoindolinone synthesis can be applied to cyclization of a wide range of substrates (Table 3). Substituents such as an electron donating methyl or methoxy group as well as an electron withdrawing halogen atom on the benzene ring are well tolerated under the reaction conditions, and the corresponding products **2j–l** are successfully obtained. It is also noteworthy that heterocycles such as thiophene and indoles are compatible during the process (**2n–q**). Remarkably, benzamides **1o–q** possessing an indole nucleus that can be easily oxidable were suitable under our oxidant-free conditions.⁹ An attempt to obtain 3-alkylisoindolinone **2r** unfortunately failed. On the other hand, the reaction of **1f** can be easily scaled up: in this case, **2f** was obtained in 92% yield.¹⁰

To further demonstrate the synthetic utility of the method we have developed, several transformations of isoindolinone **2f** obtained were carried out (Scheme 2). Deprotection of a mesyl group with AIBN and Bu₃SnH afforded the N-free isoindolinone

Table 2 Optimization of reaction parameters^a

Entry	Variation from "standard conditions"	Yield ^{b,c} (%)
1	None	(75)
2	Na ₂ HPO ₄ instead of KOAc	86 (80)
3	NaOAc, LiOAc, K ₂ CO ₃ or Cs ₂ CO ₃ instead of KOAc	61–70
4	DMA, DMI or DMSO instead of <i>p</i> -xylene	0–28
5	0.25 M instead of 0.05 M	67
6 ^d	O ₂ atmosphere instead of Ar atmosphere	4
7 ^d	Degassed (bubbling with Ar)	92 (86)
8 ^d	In the absence of KOAc	72

^a Reactions were run on a 0.25 mmol scale. ^b Yields were determined by ¹H NMR using an internal standard. ^c Isolated yields in parentheses. ^d Na₂HPO₄ was used instead of KOAc.

3 in high yield. Reduction of the carbonyl group of **2f** using LiAlH₄ also successfully preceded, giving rise to isoindoline **4** in excellent yield (97%).

Table 3 Substrate scope^{a,b}

Substrate	Product	Yield (%)
1f,j-r	2f,j-r	86% (92%) ^c
1a	2a	42%
1b	2b	24%
1c	2c	33%
1d	2d	6%
1e	2e	0%
1f	2f	75%
1g	2g	46%
1h	2h	0%
1i	2i	0%
1j	2j	91%
1k	2k	92%
1l	2l	44%
1m	2m	82%
1n	2n	37%
1o	2o	95%
1p	2p	74%
1q	2q	23%
1r	2r	trace

^a Reactions were run on a 0.25 mmol scale. ^b Isolated yields. ^c 1 mmol scale.

Table 1 Effect of protecting group^{a,b}

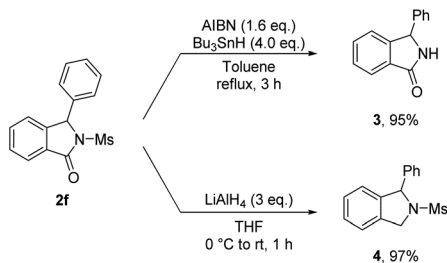
Substrate	Product	Yield (%)
1a–i	2a–i	
1a	2a	42%
1b	2b	24%
1c	2c	33%
1d	2d	6%
1e	2e	0%
1f	2f	75%
1g	2g	46%
1h	2h	0%
1i	2i	0%

^a Reactions were run on a 0.25 mmol scale. ^b Isolated yields (yield determined by ¹H NMR using an internal standard in parentheses).

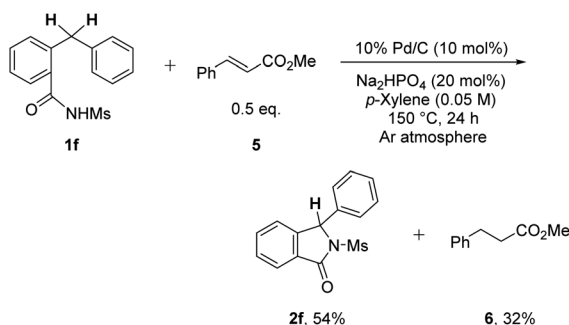
^a Reactions were run on a 0.25 mmol scale. ^b Isolated yields (yield determined by ¹H NMR using an internal standard in parentheses).

^a Reactions were run on a 0.25 mmol scale. ^b Isolated yields. ^c 1 mmol scale.





Scheme 2 Further transformation of isoindolinone 2f.

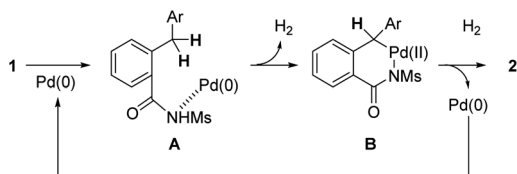


Scheme 3 Mechanistic studies.

To gain insight into the reaction mechanism of the process, C–H cyclization of **1f** in the presence of 0.5 equiv. of methyl cinnamate (**5**) was performed under the optimized conditions (Scheme 3). In addition to isoindolinone **2f**, methyl 3-phenylpropanoate (**6**) was observed in 32% NMR yield, implying that the formation of H₂ gas is possibly occurring during the reaction.¹¹

On the basis of the finding above, a tentative reaction pathway shown in Scheme 4 is proposed. The reaction is likely initiated by the coordination of the nitrogen atom of an amide moiety to give complex **A**. Subsequently, the insertion of Pd(0) into the benzylic C(sp³)–H bond leading to the formation of six-membered palladacycle **B** accompanied with the evolution of H₂ gas and the following reductive elimination process affords the desired isoindolinone **2**.

In summary, we have developed intramolecular Pd-catalyzed dehydrogenative C(sp³)–H amidation for isoindolinone synthesis. The addition of oxidants is not necessary and the Pd/C catalyst along with a catalytic amount (20 mol%) of base is the only reagents required for this C–H cyclization. The method developed provides a simple, facile, and efficient access to



Scheme 4 Plausible reaction mechanism.

a biologically important isoindolinone nucleus. Further studies to broaden the substrate scope of the process as well as to improve the catalytic efficiency are vigorously underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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- 10 It was also found that our catalytic system can be reused without a significant loss of reactivity. For details, see the ESI.†.
- 11 For detailed results of the mechanistic studies, see the ESI.†.

