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Highly Enantioselective Addition of Enals to Isatin-Derived Ketimines Catalyzed by N-Heterocyclic Carbenes: Synthesis of Spirocyclic γ-Lactams

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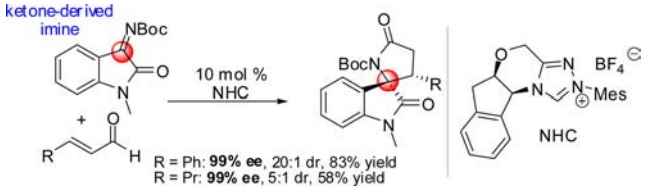
ABSTRACT



An N-heterocyclic carbene (NHC)-catalyzed annulation reaction of isatin *N*-Boc ketimines and enals is developed for the synthesis of spirocyclic oxindole-γ-lactams bearing one quaternary chiral center in good yields and excellent stereoselectivities (up to >20:1 dr and 99% ee).

γ-Lactams are privileged scaffolds found in naturally occurring and synthetic biologically active compounds.[1] The synthesis of γ-lactams has therefore received considerable attention. Examples of the representative methods to γ-lactams include transition metal-catalyzed cyclization,[2] intramolecular carbenoid C−H insertion,[3] hypervalent iodine-promoted intramolecular electrophilic cyclization,[4] a Lewis acid-catalyzed imino Mukaiyama-Aldol reaction,[5] ring expansion of β-lactams,[6] and tandem Aza-Michael initiated cyclization.[7] In recent years, the organocatalytic approaches have become increasingly attractive for γ-lactam synthesis. Under *N*-heterocyclic carbene (NHC) catalysis,[8] the addition of enals (via homoenolate intermediates) to

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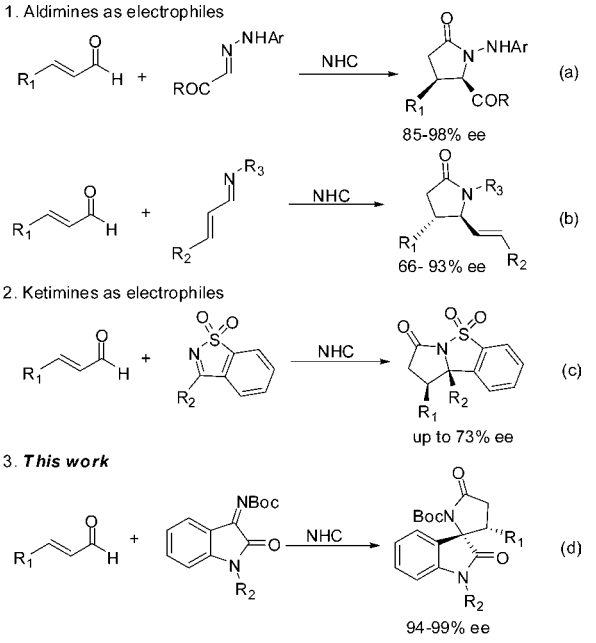
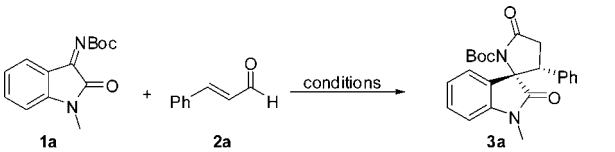
aldehyde-derived imines (aldimines) has provided facile access to γ-lactams.[9] In 2005, Bode and co-workers reported an addition of enals to aldehyde-derived *N*-sulfonylimines to afford racemic γ-lactams.[9a] The enantioselective synthesis of γ-lactams from aldimines have also been developed.[9b,c] Scheidt and co-workers used NHC in combination with a Lewis acid cocatalyst to promote the annulation of enals with hydrazones to afford γ-lactams with high enantioselectivities (Scheme 1a).[9b] Rovis and co-workers demonstrated highly enantioselective umpolung reactions of enals with *N*-aryl α,β-unsaturated aldimines using a cooperative Brønsted acid cocatalyst (Scheme 1b).[9c]

Scheme 1. Asymmetric Synthesis of γ-Lactams via NHC Catalysis



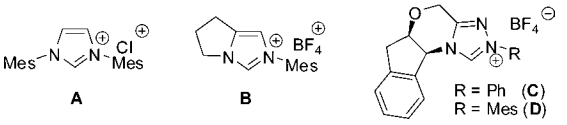
While the use of aldimine electrophiles has shown to be quite successful, a switch to ketone-derived imines (ketimines) becomes challenging. Compared to aldimines, ketimines are typically less reactive, and control of enantioselectivities for ketimines are often more difficult. In 2008, Bode and co-workers made an use of cyclic sulfonyl ketimines for the synthesis of γ-lactams (Scheme 1c).[10] Unfortunately, the control of stereoselectivities remained difficult after considerable efforts (27 catalysts were evaluated, the best results are 73% ee and 6:1 dr).[11] To the best of our knowledge, highly enantioselective organocatalytic reactions using ketimine electrophiles are rare.[12] Here we disclose an efficient addition of enals to isatin-derived ketimines to afford spirocyclic oxindole-γ-lactams with high diastereo- and enantioselectivities (Scheme 1d; typically 99% ee and 20:1 dr).[13]

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	base	solvent	yield (%)[b]	dr[c]	ee[d]
1	**A**	DBU	THF			
2	**B**	DBU	THF	<10		
3	**C**	DBU	THF	39	4:1	99
4	**D**	DBU	THF	83(81)[e]	20:1	99
5	**D**	DBU	CH_2Cl_2	41	20:1	99
6	**D**	DBU	Et_2O	59	20:1	99
7	**D**	DBU	toluene	74	20:1	99
8	**D**	KO^{t}Bu	THF	19	20:1	99
9	**D**	KOAc	THF	89	20:1	95
10	**D**	DIPEA	THF	23	20:1	99
11	**D**	Et_3N	THF	24	20:1	99
12	**D**	**Cs_2CO_3**	**THF**	**87(83)[e]**	**>20:1**	**99**
13[f]	**D**	Cs_2CO_3	THF	35	20:1	99
14[g]	**D**	Cs_2CO_3	THF	48	20:1	99

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), cat. (10 mol %), base (20 mol %), 2 mL solvent, 24 h at rt. [b] NMR yield (1,3,5-trimethoxybenzene as internal standard). [c] Diastereomeric ratio of **3a**, determined via ^{1}H NMR analysis of unpurified reaction mixtures. Absolute configurations of the products were determined via X-ray of **3l** (see Figure 1 and Supporting Information). [d] Enantiomeric excess of **3a**, determined via chiral-phase HPLC analysis. [e] Number in the parentheses is the isolated yield based on **1a**. [f] In presence 4 Å MS. [g] 5 mol % of **D**.



Our investigation began by using isatin *N*-Boc ketimine **1a** and cinnamaldehyde **2a** as model substrates (Table 1). Imidazolium-based NHC precatalyst **A**, previously found effective in enal activations,[14] did not work in our reaction (entry 1). We then evaluated triazolium-based NHC catalysts, and found that achiral precatalyst **B** could lead to the formation of desired lactam product **3a** with low but encouraging yield (typically less than 10% yield, entry 2). We next quickly moved to identify chiral NHC catalysts

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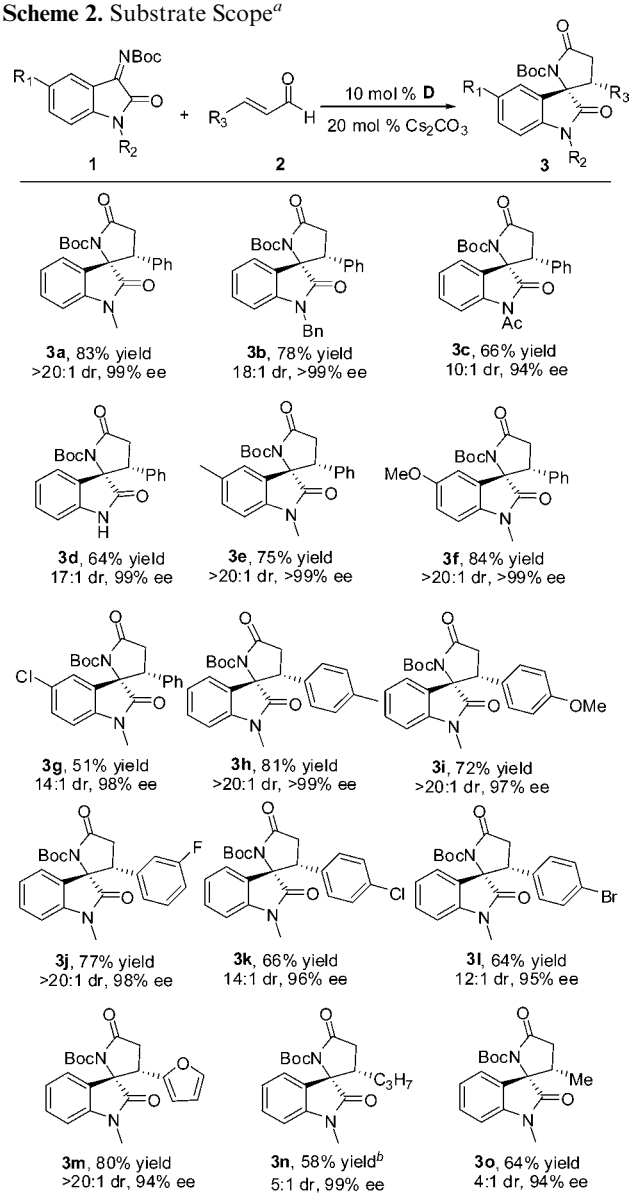
Scheme 2. Substrate Scope[a]



[a] Reaction conditions: Same as in Table 1, entry 12 at 40 °C (**3a**, **3b** and **3h** at rt). [b] 1.0 Equiv of enal was added after 12 h.

for enantioselective transformations. Aminoindanol-derived catalysts (e.g., **C** and **D**, Table 1), initially pioneered by Rovis,[15] were found to induce >99% enantioselectivities (e.g., entries 3 and 4). A switch from NHC precatalyst **C** to **D** led to excellent yield and dr as well (entry 4). Further evaluations with regards to solvents and bases indicated that both THF and toluene (entries 4 and 7) could be used, and DBU, KOAc and Cs_2CO_3 (entries 4, 9 and 12) behaved well as the bases. It is interesting to note that the addition of molecular sieve led to deminished yield with no changes on dr and ee (entry 13), suggesting the presence of trace water in the solvent was beneficial for the catalytic conversions. Finally, we chose 10% catalyst **D** with Cs_2CO_3 in THF as an optimal condition to evaluate the substrate scope.

As briefed in Scheme 2, a broad range of isatin-derived *N*-Boc ketimines and enals that exhibit diverse electronic and steric properties could readily participate in this reaction under the optimized condition (Table 1, entry 12). The *N*-protecting groups for the amide in the isatin ring had very mild influence only on the reaction yields (Scheme 2, **3a**–**c**). Notably, the amide *N*-unprotected ketimine could also react well (**3d**). Substitution patterns on both the ketimines and enals affected the yields and selectivities of the products to some extent. In general, ketimines with electron-donating substituents (**3e** and **3f**) could afford spiro-γ-lactams in better yields and selectivities compared to the one with −withdrawing substituents (**3g**). Similar substitution effects were observed for β-aryl enals (**3h**–**l**). β-heteroaryl enal also worked well (**3m**). Significantly, β-alkyl enals were also tolerated and gave the products in good to moderate yields and excellent enantioselectivities albeit, with relatively lower diastereoselectivities (**3n** and **3o**).

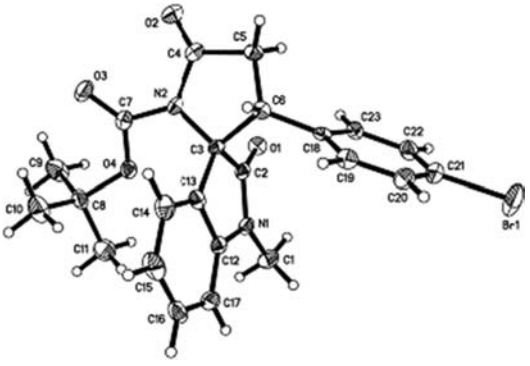
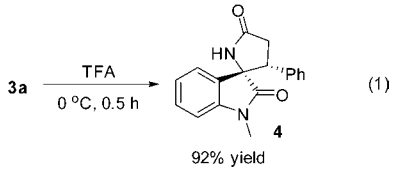


Figure 1. X-ray crystal structure of **3l**.

The resulting *N*-Boc protected γ-lactam **3** could be easily deprotected under acidic condition to afford the free γ-lactam **4** in high yield (eq 1). The absolute configurations of all the spirocyclic oxindole-γ-lactam products **3** were unambiguously assigned on the basis of X-ray crystallographic analysis of **3l** (Figure 1).[16]



In summary, we have developed a highly enantioselective reaction using ketone-derived imines as the electrophiles.

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(16) CCDC 892219 contains the supplementary *X*-ray crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

This catalytic protocol allows for a rapid construction of spirocyclic oxindole-γ-lactams with excellent diastereo- and enantioselectivities. Further investigation into using other sterically demanding and stereochemically challenging electrophiles for stereoselective reactions is being pursued in our laboratory.

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

The authors declare no competing financial interest.