Organic LETTERS

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Enantioselective [3 + 2] Annulation of Enals with 2-Aminoacrylates Catalyzed by *N*-Heterocyclic Carbene

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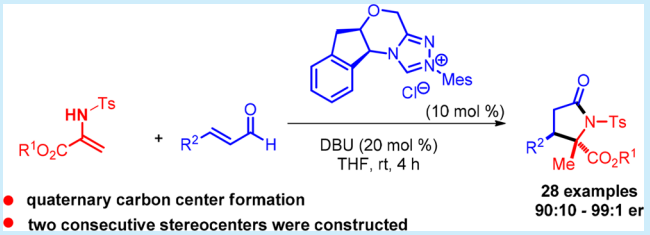
Supporting Information

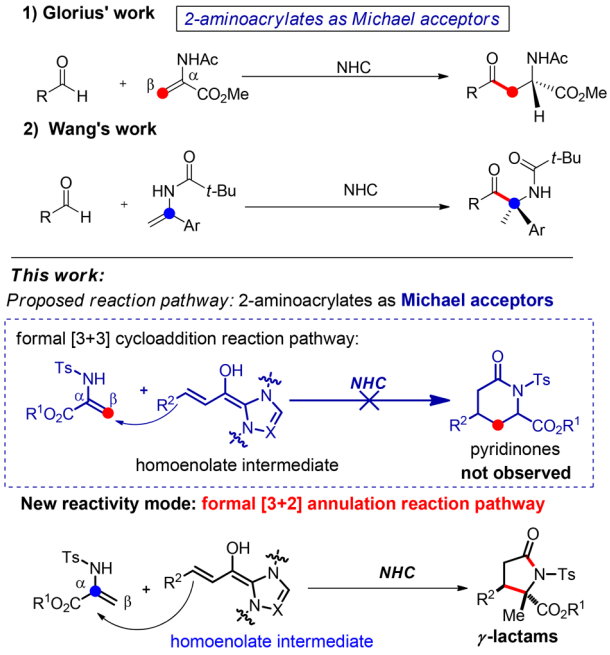
ABSTRACT: A novel and convenient strategy for the enantioselective synthesis of γ-lactam derivatives via *N*-heterocyclic carbene catalyzed formal [3 + 2] annulation of enals with 2-aminoacrylates is disclosed. This activation mode provides a complementary approach to the synthesis of various γ-lactam derivatives in good yields with excellent diastereo- and enantioselectivities. In this process, two consecutive stereocenters are constructed, and a quaternary carbon center is also established.



In the past decade, *N*-heterocyclic carbene (NHC) catalysis has been applied to many organic reactions due to its unique polarity reversal strategy.[1] Acyl anion equivalents and homoenolate equivalents generated from the reaction of aldehydes and enals with NHC have offered unconventional access to various organic transformations.[2] In 2011, Glorius and co-workers reported an elegant NHC-mediated asymmetric Stetter reaction starting from aldehydes and 2-aminoacrylates for the synthesis of α-amino acid derivatives, in which 2-aminoacrylates served as Michael acceptors.[3] Impressively, Wang's group recently designed enamides as a coupling partner in the NHC-catalyzed intermolecular cross-coupling with aldehydes, resulting in the formation of *N*-acyl protected amine derivatives.[4] Although the reactions of acyl anion equivalents with 2-aminoacrylates and enamides have already represented versatile synthetic routes, the direct application of homoenolate equivalents with 2-aminoacrylates remains unexplored in NHC-catalyzed cycloaddition reactions. Motivated by Glorius' work with 2-aminoacrylates as a reactant, we surmised that combining homoenolate equivalents with 2-aminoacrylates in the presence of a NHC catalyst might lead to a Michael-type addition occurring at the β-carbon atom of the 2-aminoacrylate and that this might be accompanied by intramolecular *N*-acylation to afford a pyridinone product. Intriguingly, instead of the proposed formal [3 + 3] annulation, the reaction underwent a formal [3 + 2] annulation to generate a γ-lactam as the product (Scheme 1).

γ-Lactams are found in important naturally occurring compounds show biological activity.[5] Consequently, there is a great deal of interest in an efficient synthesis of this core motif.[6] Among these synthetic methods, a versatile and challenging strategy is the generation of homoenolate equivalents from enals with NHCs followed by annulation with an appropriate imine.[7] However, the NHC-catalyzed addition of enals to imine electrophiles has been limited to aromatic aldehyde derived *N*-

Scheme 1. Stetter Reaction and Cross-Coupling Reaction between Aldehydes and 2-Aminoacrylates or Enamides and NHC-Catalyzed formal [3 + 2] Annulation of Enals with 2-Aminoacrylates



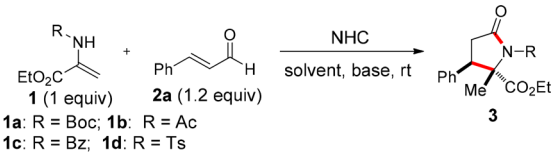
Received: June 22, 2017

DOI: 10.1021/acs.orglett.7b01860
Org. Lett. XXXX, XXX, XXX−XXX

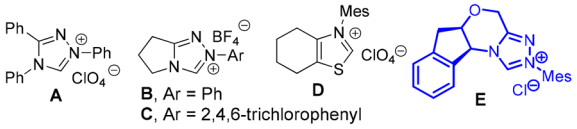
sulfonyl imines, enal-derived imines, cyclic ketimines, and isatin-derived ketimines. Herein, we report a simple and convenient strategy for the synthesis of γ-lactam derivatives via an NHC-catalyzed formal [3 + 2] annulation that uses enals and 2-aminoacrylates as reactants. This strategy provides a complementary approach for the construction of various γ-lactam derivatives in good yield with excellent diastereo- and enantioselectivities. Notably, two consecutive stereocenters were constructed, and a quaternary carbon center was also established.

We began by investigating the reaction between different *N*-protected 2-aminoacrylates **1** and cinnamaldehyde **2a** in the presence of the NHC precatalyst **A**, where THF was initially employed as the solvent and DBU was chosen as the base. Gratifyingly, the *N*-Ts-protected 2-aminoacrylates **1d** exhibited unique reactivity in the reaction and gave the desired cycloaddition product **3a** in 70% yield (Table 1, entry 2).

Table 1. Screening of Reaction Conditions for the Reaction of 1 with 2a[a]



entry	1	NHC	base	solvent	yield (%)[b]	er[c]
1	1a-1c	A	DBU	THF	N.R	-
2	1d	A	DBU	THF	70	-
3	1d	B-D	DBU	THF	trace	-
4	1d	A	DIPEA	THF	<5	-
5	1d	A	Cs_2CO_3	THF	54	-
6	1d	A	K_2CO_3	THF	58	-
7	1d	A	DBU	1,4-dioxane	84	-
8	1d	A	DBU	DCE	82	-
9	1d	E[d]	DBU	1,4-dioxane	60	94:6
10	1d	E[d]	DBU	DCE	58	92:7
11	1d	E[d]	DBU	THF	70	96:4
12	1d	E[d]	DBU	DCM	50	95:5
13	1d	E[d]	DBU	MTBE	55	93:7

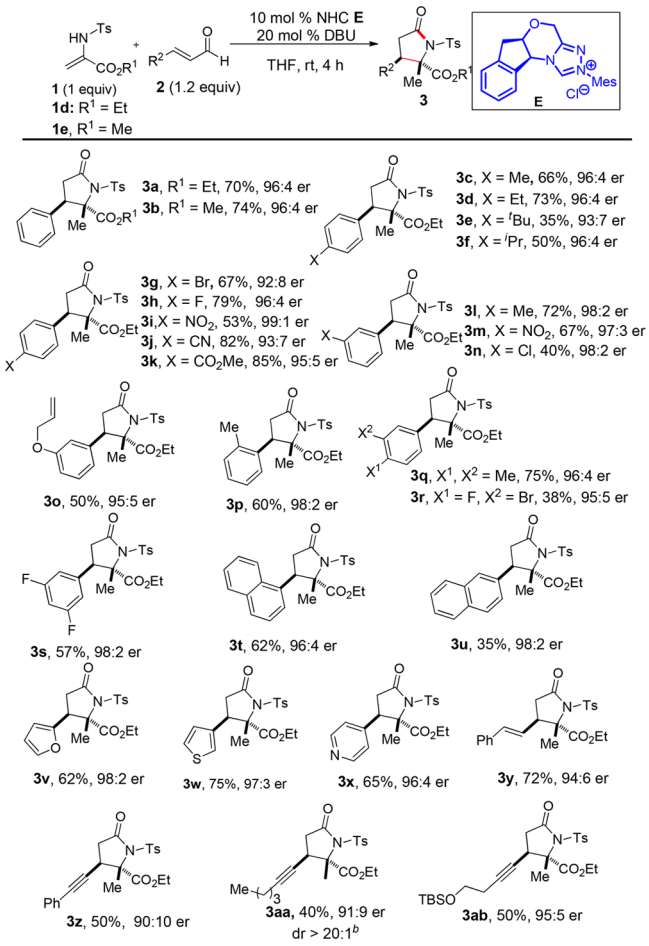


[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (0.24 mmol, 1.2 equiv), NHC (20 mol %), base (20 mol %), solvent (2.0 mL). [b]Yield of isolated product. [c]Determined by chiral-phase HPLC analysis. [d]10 mol % of NHC precatalyst was used. DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, Mes = mesityl, NR = no reaction.

Other commonly used NHCs derived from triazolium salts **B**, **C**, and the thiazolium salt **D** were far less effective (Table 1, entry 3). In comparison to DBU, other bases, such as DIPEA, Cs_2CO_3, and K_2CO_3, furnished the desired products in reduced yield (Table 1, entries 4–6). Changing the solvent to 1,4-dioxane significantly increased the yield to 84% (Table 1, entry 5). With these encouraging results in hand, we turned our attention to the challenges of asymmetric synthesis of γ-lactams using chiral triazolium salt **E** as the precatalyst. To our great delight, the cycloaddition product **3a** was obtained in 60% yield and 94:6 er (Table 1, entry 9). Further optimization showed that the use of THF as the solvent led to a significant increase in both the reaction yield and er value (70% yield, 96:4 er) (Table 1, entry 11). Notably, only *trans*-isomers were generated as the products in all of the reactions, and we did not detect the other isomer during our research.

With the optimized reaction conditions in hand, we next investigated substrate scope using chiral triazolium salt **E** as the precatalyst, as shown in Scheme 2. Changing the ester group

Scheme 2. Substrate Scope[a]



[a]**1** (0.1 mmol), **2a** (0.12 mmol), catalyst (10 mol %), base (20 mol %). Yields given are for the isolated products following column chromatography. [b]dr of product **3aa** was determined via ^{1}H NMR analysis.

from ethyl to methyl did not encumber the reaction, and the corresponding product was obtained in good yield and with excellent er (**3b**). We next focused on examining the scope of the reaction using compound **1d** with various substituted enals. In general, a broad range of differently substituted enals, bearing electron-donating or electron-withdrawing substituents on the aromatic ring, reacted with *N*-Ts 2-aminoacrylates **1d** to form a series of γ-lactams with excellent enantioselectivity (up to 99:1 er) (**3c–p**). Moreover, disubstituted β-aryl enals were also suitable for the reaction, and the high enantioselectivities were maintained (**3q–s**). Replacing the β-phenyl substituent of

DOI: 10.1021/acs.orglett.7b01860
Org. Lett. XXXX, XXX, XXX–XXX

the enal moiety with a naphthyl (**3t**,**u**) or a heteroaryl (**3v**, **3w**, and **3x**) unit did not have a significant impact on the yields and enantioselectivities. This method was also compatible with β-vinyl or ynal enals, giving the desired products in good yields and excellent enantioselectivities (**3z**, **3aa**, and **3ab**).[8] Notably, we did not detect the *cis*-isomer in any of the examples except **3aa** (dr >20:1). To determine the stereochemistry of the γ-lactams formed from this unique strategy, the absolute configuration of the product **3a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).[9]

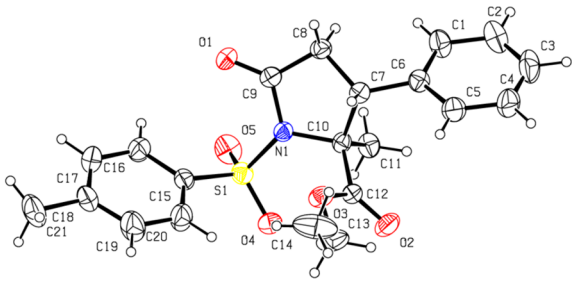
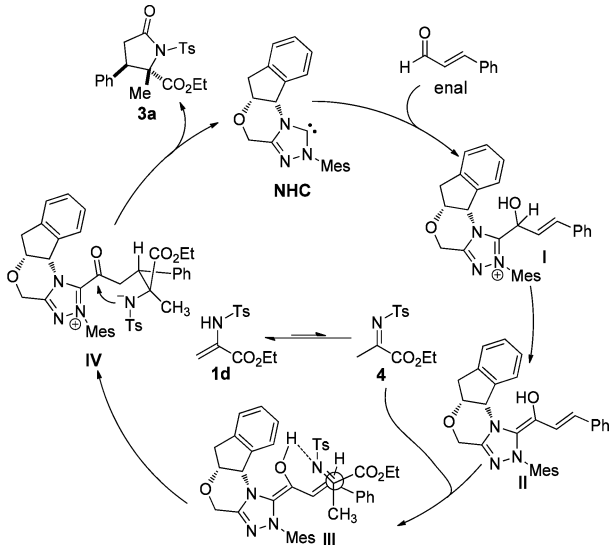


Figure 1. X-ray crystal structure of **3a**. Thermal ellipsoids were shown at 30% probability.

Our proposed mechanism is illustrated in Scheme 3. The catalytic cycle begins with addition of NHC **E** to

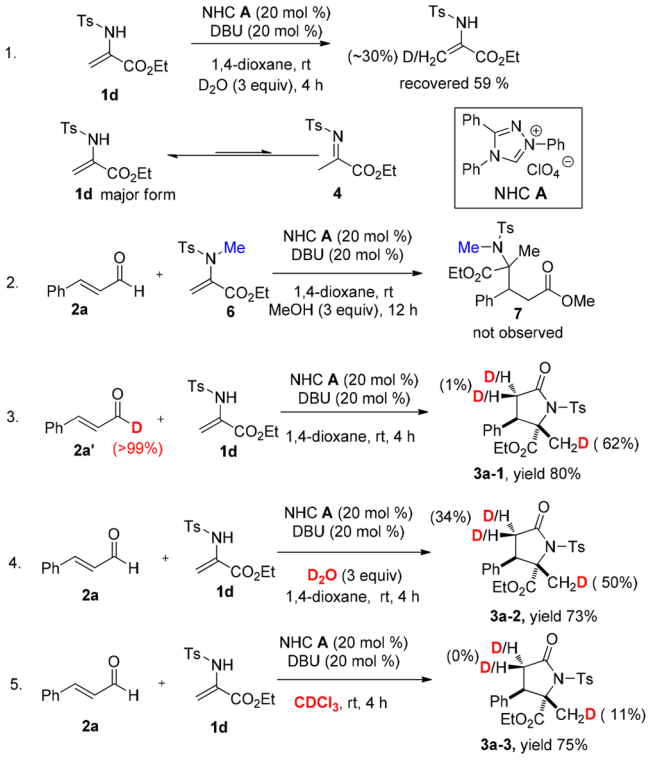
Scheme 3. Proposed Reaction Pathways



cinnamaldehyde **2a** to afford enal catalyst adduct **I** and followed by a deprotonation process to form Breslow intermediate **II**, which acts as a homoenolate equivalent.[10] Upon the tautomerization of 2-aminoacrylate **1d** to its imine form **4**, the homoenolate intermediate undergoes a nucleophilic addition to the imine substrate **4** to create a new carbon–carbon bond and a quaternary stereocenter (intermediate **III**). Then the resulting acyl azolium species **IV** undergoes an intramolecular *N*-acylation to release the NHC catalyst and form the γ-lactam **3a** as the product.

To investigate the mechanism, several additional experiments were carried out, as shown in Scheme 4. The labeling experiment of **1d** demonstrated that the tautomerization between 2-aminoacrylate **1d** and its imine form **4** is possible

Scheme 4. Deuterium-Labeling Experiments



under the reaction conditions, but the 2-aminoacrylate is the major form (Scheme 4, eq 1). Notably, the combination of *N*-methyl-protected 2-aminoacrylates **6** with enal **2a** failed to afford any products under the reaction conditions (Scheme 4, eq 2). These two results support the tautomerization–enal–[3 + 2] cycloaddition mechanism. Several deuterium-labeling experiments were carried out to further explore the reaction mechanism. When deuterated cinnamaldehyde **2a**′ was used as the starting material, the deuterium was incorporated exclusively into the methyl group to give the product **3a-1**, and 62% deuterium was detected in the methyl group (Scheme 4, eq 3). This result could be explained by rapid proton exchange in a bimolecular fashion. To further determine the reaction pathway, the standard reaction was carried out in the presence of 3 equiv of D_2O; the deuterium on the α-carbon atom increased to 34%, while 50% deuterium was incorporated into the methyl group (Scheme 4, eq 4). Furthermore, when the reaction was carried out using chloroform-*d* as the solvent, the deuterium could also be detected in the methyl group (11%, Scheme 4, eq 5). These phenomena further confirmed the equilibrium between 2-aminoacrylates **1d** and its imine form **4** and also indicated that multiple proton exchange reactions occur during this process. Based on current experimental evidence, we believe that the tautomerization–enal–[3 + 2] cycloaddition mechanism is reasonable.[11]

In summary, we have successfully developed an NHC-catalyzed formal [3 + 2] annulation of enals with 2-aminoacrylates to generate a diverse set of γ-lactams in good yields with excellent diastereo- and enantioselectivities. In this novel strategy, two consecutive stereocenters are constructed in one step, and a quaternary carbon center is also established. Further exploration of the reaction mechanism and investigation of the generality of this catalytic process are currently ongoing in our laboratory.

DOI: 10.1021/acs.orglett.7b01860
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01860.

Details on experimental procedure, characterization data of all compounds, HPLC data (PDF)

Single-crystal X-ray data of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for generous financial support from the National Natural Science Foundation of China (21402037), the Natural Science Foundation of Hebei Province (B2015201175), and the Foundation of Hebei Education Department (QN2014106). We thank Prof. Wei Li (Hebei University) and Dr. Shu-Ying Huo (Hebei University) for excellent HPLC support.

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(8) At prescent stage, the aliphatic enals and β-substituted 2-aminoacrylates did not work under the standard conditions.

(9) CCDC 1504028 (**3a**) contains the supplementary crystallographic data for this paper. These data are available free of charge from the Cambridge Crystallographic Data Centre.

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(11) For more details on the mechanism investigation, see the Supporting Informations.

DOI: 10.1021/acs.orglett.7b01860
Org. Lett. XXXX, XXX, XXX−XXX