

N-Heterocyclic Carbene Catalyzed Cyclocondensation of α,β -Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives**

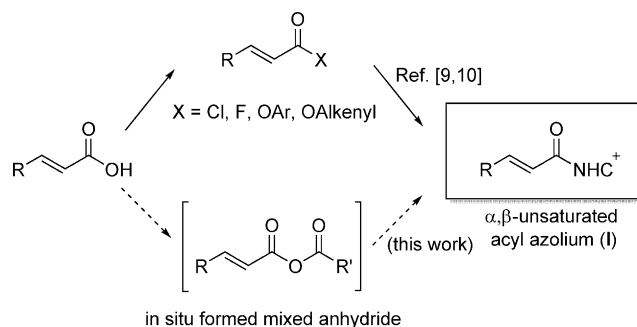
Xiang-Yu Chen, Zhong-Hua Gao, Chun-Yu Song, Chun-Lin Zhang, Zhi-Xiang Wang,* and Song Ye*

Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: The catalytic cyclocondensation of in situ activated α,β -unsaturated carboxylic acids was developed. N-heterocyclic carbenes efficiently catalyzed the generation of α,β -unsaturated acyl azolium intermediates from α,β -unsaturated carboxylic acids via in situ generated mixed anhydrides for the enantioselective [3+2] and [3+3] cyclocondensation with α -amino ketones and alkyl(aryl)imines, respectively. The corresponding pyrrolidinones and dihydropyridinones were isolated in good yields with high to excellent enantioselectivities.

In recent years, N-heterocyclic carbenes (NHCs) have emerged as one of the most powerful organocatalysts for the reactions of various substrates^[1] such as aldehydes,^[2] ketenes,^[3] esters,^[4] and Michael acceptors.^[5] As an important 1,3-biselectrophile intermediate, the NHC-catalyzed generation of α,β -unsaturated acyl azoliums (**I**; see Scheme 1) from enals,^[6] ynals,^[7] α -bromoaldehydes,^[8] α,β -unsaturated acyl fluorides,^[9] and α,β -unsaturated esters^[10] have been well established. Apparently, most of the carboxylate derivatives are prepared from carboxylic acids, which are readily available and easy to handle. However, the direct NHC-catalyzed reaction of a carboxylic acid instead of its derivatives is of great value but remains unexplored. We envisioned that the in situ formed mixed anhydride may afford an alternative direct pathway to generate the NHC-bound α,β -unsaturated acyl azolium (Scheme 1).

The direct catalytic α -functionalizations of carboxylic acids using an amine-based nucleophilic catalyst were well established by Romo et al.^[11] and Smith et al.^[12] Very recently,



Scheme 1. The NHC-catalyzed generation of α,β -unsaturated acyl azoliums from carboxylic acids and its derivatives.

the generation of the α,β -unsaturated acyl ammonium compounds from α,β -unsaturated anhydrides,^[13] acyl chlorides,^[14] and acyl cyanides^[15] have also been successfully explored. We envision that the β -functionalization of α,β -unsaturated carboxylic acids is also possible when the proper nucleophilic catalyst is employed.

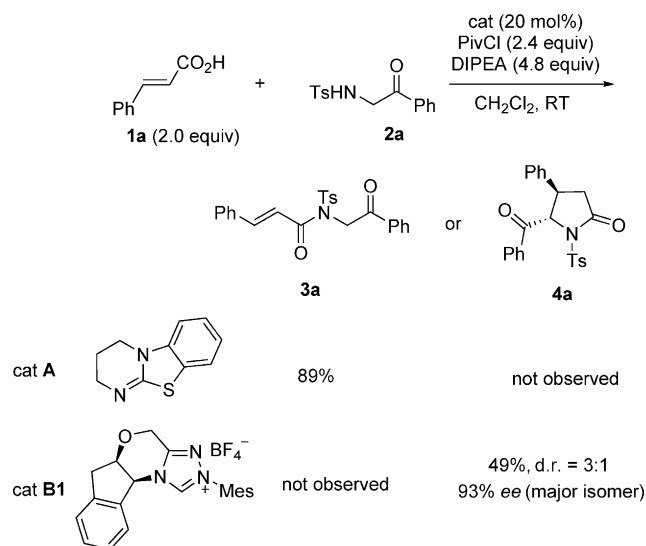
Considering the wide applications of chiral γ -butyrolactams,^[16,17] we are interested in employing α -amino ketones as the possible 1,2-bis(nucleophile) to react with the in situ generated α,β -unsaturated acyl azolium intermediate from an α,β -unsaturated acid, for the synthesis of γ -butyrolactams. Initially, the isothiourea DHPB (3,4-dihydro-2H-pyrimido-[2,1-b]benzothiazole; **A**) was employed as the catalyst for the reaction of cinnamic acid (**1a**) with the α -amino ketone **2a** in the presence of pivaloyl chloride as the reagent for generating the mixed anhydride (Scheme 2). However, the reaction catalyzed by **A**, which works well for the α -functionalization of carboxylic acids,^[12] gave none of the desired cyclocondensation product **4a**, but the amide **3a** was generated in 89% yield. Interestingly, the same reaction catalyzed by the NHC **B1**^[18] afforded the desired cycloadduct **4a** in 49% yield without the formation of **3a**. We proposed that the relatively unfavored amidation of the NHC-bound acyl azolium compared to isothiourea-bound one makes the cyclocondensation feasible.^[19]

The NHC-catalyzed model reaction was then optimized (Table 1). The yield was improved to 60% when the reaction was carried out at 40 °C (entry 1). The screening of solvents revealed that the reaction gave the best results in toluene as

[*] X.-Y. Chen, Z.-H. Gao, C.-L. Zhang, Prof. Dr. S. Ye
Beijing National Laboratory for Molecular Sciences
CAS Key Laboratory of Molecular Recognition and Function
Institute of Chemistry, Chinese Academy of Sciences, Beijing
100190 (China)
E-mail: songye@iccas.ac.cn
C.-Y. Song, Prof. Dr. Z.-X. Wang
College of Chemistry and Chemical Engineering
University of Chinese Academy of Sciences
Beijing 100049 (China)
E-mail: zzwang@gucas.ac.cn

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Scheme 2. Catalyst-dependent reaction results. DIPEA = *N,N*-diisopropylethylamine, PivCl = pivaloyl chloride, Ts = 4-toluenesulfonyl.

Table 1: Optimization of reaction conditions.

Entry	Cat.	Solvent	Yield [%] ^[a]	d.r. ^[b]	ee [%] ^[c]
1	B1	CH ₂ Cl ₂	60	3:1	93
2	B1	CHCl ₃	trace	–	–
3	B1	THF	31	4:1	93
4	B1	toluene	64	5:1	96
5	B2	toluene	trace	–	–
6	B3	toluene	9	n.d.	n.d.
7	B4	toluene	7	n.d.	n.d.
8	B5	toluene	20	3:1	79
9	C	toluene	trace	–	–

[a] Yield of the isolated mixture of two diastereoisomers. [b] Determined by ¹H NMR (300 MHz) spectroscopy of the unpurified reaction mixture. [c] Determined by HPLC using a chiral stationary phase. Mes = 2,4,6-trimethylphenyl, n.d. = not determined, TBS = *tert*-butyldimethylsilyl.

compared to that in dichloromethane, chloroform, and tetrahydrofuran (entries 2–4). A series of NHCs (**B1–B5**) with different *N*-aryl groups was investigated, thus showing that the NHCs **B2–B5**, having *N*-phenyl, benzyl, 2-isopropylphenyl, and 2,6-diethylphenyl groups, respectively, were inferior to **B1** which bears an *N*-mesityl group (entries 4–8). The NHC **C** derived from pyroglutamic acid was not effective for the reaction under the current reaction conditions (entry 9).

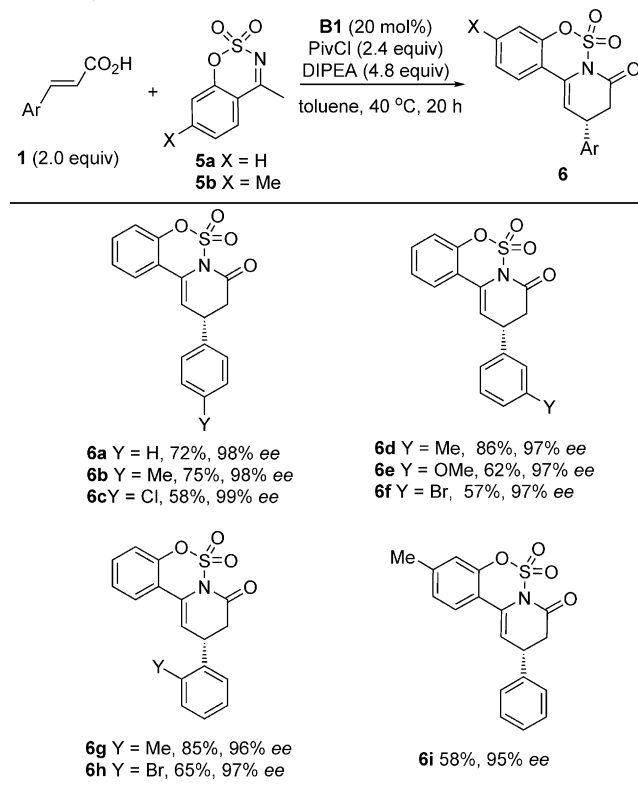
With the optimized reaction conditions in hand, a variety of α,β -unsaturated carboxylic acids were briefly investigated

Table 2: Enantioselective [3+2] cyclocondensation.

1 (3.0 equiv)	2	4
4a ^[a] X = H, d.r. = 5:1, 64%, 96% ee	4e X = OMe, d.r. = 4:1, 69%, 94% ee	
4b X = Me, d.r. = 3:1, 60%, 92% ee	4f ^[a] X = Br, d.r. = 4:1, 69%, 90% ee	
4c ^[a] X = Cl, d.r. = 6:1, 63%, 92% ee	4g ^[a] X = Cl, d.r. = 4:1, 63%, 90% ee	
4d ^[a] X = Br, d.r. = 5:1, 68%, 92% ee		
4h d.r. = 5:1, 67%, 95% ee		
4m X = Me, d.r. = 5:1, 73%, 96% ee		
4n X = Cl, d.r. = 7:1, 65%, 97% ee		
4o X = Br, d.r. = 6:1, 55%, 95% ee		
	4p d.r. = 12:1, 52%, 95% ee	

[a] Used **1** (2.0 equiv) and PivCl (2.4 equiv).

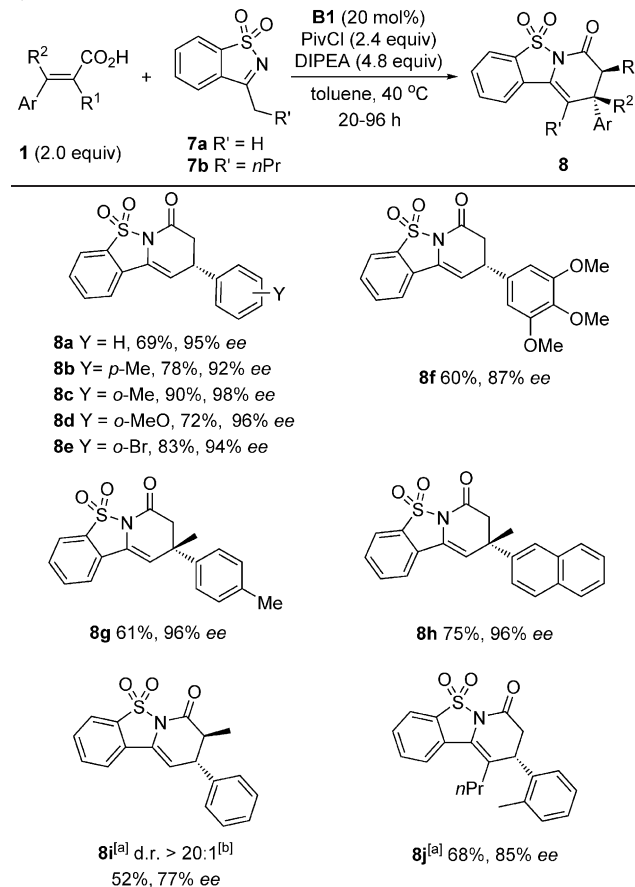
for the reaction (Table 2). Both electron-donating (4-MeC₆H₄) and electron-withdrawing groups (4-ClC₆H₄ and 4-BrC₆H₄) were tolerated and gave the desired pyrrolidinones **4b–d** in good yields with high enantioselectivities. Cinnamic acids having a *meta*-substituent (3-MeOC₆H₄, 3-BrC₆H₄, and 3-ClC₆H₄) also worked well (**4e–g**). Reaction of a disubstituted cinnamic acid derivative (3,4-Cl₂C₆H₃) gave the desired pyrrolidinone **4h** in 67% yield with d.r. = 5:1 and 95% ee. Notably, the reaction of challenging *ortho*-substituted substrates (2-MeOC₆H₄, 2-MeC₆H₄, 2-BrC₆H₄, and 2-ClC₆H₄) were also successful (**4i–l**). The scope of the reaction with respect to the amino ketones was also examined. Amino ketones with electron-withdrawing or electron-donating substituents (4-MeC₆H₄, 4-ClC₆H₄, and 4-BrC₆H₄) were tolerated and gave the desired pyrrolidinones **4m–o** in good yields with excellent enantioselectivities. The reaction of an amino ketone with a 2-naphthyl group gave the corresponding pyrrolidinone **4p** in moderate yield with excellent diastereoselectivity and enantioselectivity. However, it should be noted that the alkyl α,β -unsaturated carboxylic acids did not work under the current reaction conditions. The 4*R*,5*S* configura-

Table 3: Enantioselective [3+3] cyclocondensation with sulfamate-derived cyclic imines.


tion of the cycloadduct **4k** was determined by the X-ray analysis of a single crystal.^[20]

The NHC-catalyzed direct functionalization of α,β -unsaturated carboxylic acids was then extended to the [3+3] cyclocondensation with sulfamate-derived cyclic imines to give dihydropyridinones (Table 3). It was found that the optimized reaction conditions for the [3+2] cyclocondensation with α -amino ketones also worked well for the [3+3] reaction with cyclic imines. A range of α,β -unsaturated carboxylic acids with electron-donating (4-MeC₆H₄) and electron-withdrawing groups (4-ClC₆H₄) reacted smoothly with the cyclic imine **5a** to give the corresponding dihydropyridinones (**6b** and **6c**) in good yields with excellent enantioselectivities. *ortho*-Substituted (2-MeC₆H₄ and 2-BrC₆H₄) or *meta*-substituted substrates (3-MeC₆H₄, 3-OMeC₆H₄ and 3-BrC₆H₄) showed no negative effect for the reaction (**6d–h**). The cyclic imine **5b** having a methyl substituent also worked well to give the desired cycloadduct **6i** in 58% yield and 95% ee. The *S* configuration of **6c** was determined by the X-ray analysis of a single crystal.^[20]

The [3+3] cyclocondensation with sultam-derived cyclic imines **7** were also investigated under the optimized reaction conditions (Table 4).^[6d] As expected, a range of α,β -unsaturated carboxylic acids reacted well with the cyclic imine **7a** to give the desired cycloadduct in good yields with high enantioselectivities (**8a–e**). Cinnamic acid with a 3,4,5-trimethoxyphenyl group also worked well albeit with decreased yield and enantioselectivity (**8f**). Notably, the reaction of β,β -disubstituted α,β -unsaturated carboxylic acids were successful

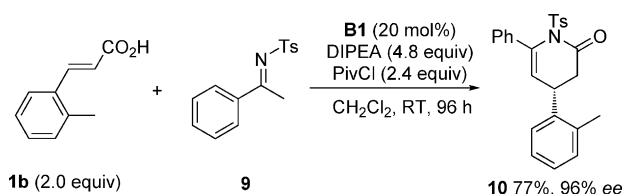
Table 4: Enantioselective [3+3] cyclocondensation with sultam-derived cyclic imines.


[a] The reaction was carried in CH₂Cl₂ at RT. [b] Determined by ¹H NMR spectroscopy (300 MHz) of the unpurified reaction mixture.

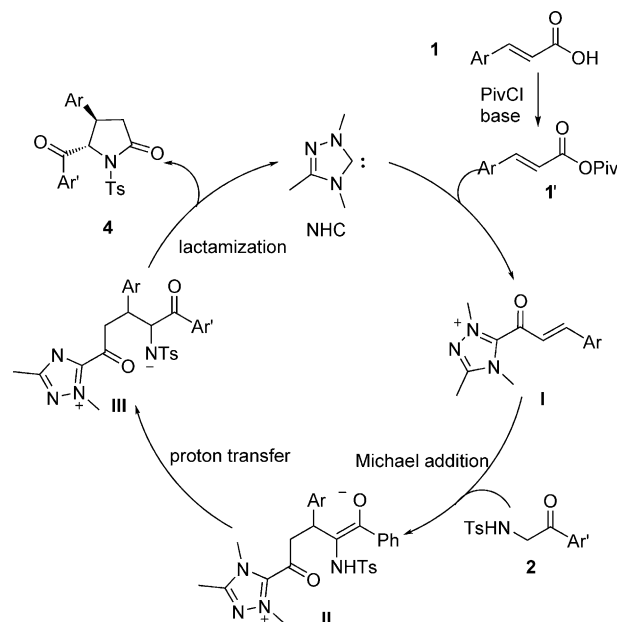
and gave the desired cycloadducts **8g** and **8h**, bearing chiral quaternary carbon centers, in good yields with high enantioselectivities. In addition, the α,β -disubstituted α,β -unsaturated carboxylic acid also worked well to give **8i** in 52% yield with excellent diastereo- and good enantioselectivity. The sultam-derived cyclic imine **7b** with an *n*-butyl group was also examined. Under the standard reaction conditions in toluene, the reaction went very slow with only trace amounts of product observed, while the reaction in dichloromethane gave the cycloadduct **8j** in 68% yield with 85% ee.

Besides the cyclic imines **6** and **7**, the reaction with the acyclic imine **9** also proceeded to give the cycloadduct **10** in 77% yield with 96% ee (Scheme 3).^[10b]

A plausible catalytic cycle for the NHC-catalyzed [3+2] cyclocondensation of α,β -unsaturated acid is depicted in Figure 1. The addition of NHC to the mixed anhydride **1'**, which is formed in situ from the α,β -unsaturated acid, gives the corresponding α,β -unsaturated acyl azolium intermediate **I**. In presence of a base, the Michael addition of the α -amino ketone **2** to **I** gives the adduct **II**, with a subsequent proton transfer to afford the intermediate **III**. The intramolecular lactamization affords the final cycloadduct **4** and regenerates the NHC catalyst.



Scheme 3. Reaction with the acyclic imine 9.



In summary, the NHC-catalyzed enantioselective [3+2] cyclocondensation of in situ activated α,β -unsaturated carboxylic acids with α -amino ketones, and [3+3] cyclocondensation with imines were developed.^[21] A variety of pyrrolidones and dihydropyridinones were obtained in good yields with high to excellent enantioselectivities. The ready availability and convenience in handling of α,β -unsaturated carboxylic acids makes it a favorable starting material for the NHC-catalyzed generation of α,β -unsaturated acyl azonium key intermediate. Other related NHC-catalyzed direct reactions of carboxylic acids are underway in our laboratory.

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- [21] During the resubmission of the manuscript, Scheidt et al. reported an NHC-catalyzed enantioselective annulation for dihydroquinolones by in situ generation of azolium enolates from carboxylic acids; see: A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, 136, 10589.