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COMMUNICATION

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N-Heterocyclic Carbene Catalyzed [3+2] Cycloaddition of Enals with *β,γ*-Unsaturated *α*-Ketimino Esters for the Synthesis of Multisubstituted Cyclopentane

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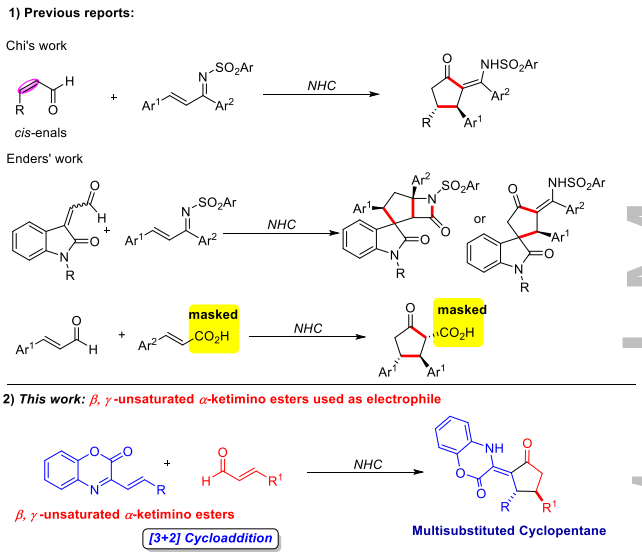
Abstract. A convenient strategy of *N*-heterocyclic carbene catalyzed [3+2] cycloaddition of enals with *β,γ*-unsaturated *α*-ketimino esters is developed. This effective protocol features mild reaction conditions and broad substrate scope, which enables the rapid assembly of various benzoxazinone derived cyclopentanone scaffolds in good to high yields with excellent diastereoselectivities.

Keywords: *N*-heterocyclic carbene; *β,γ*-unsaturated *α*-ketimino esters; cyclopentanone.

The benzoxazinone skeleton is one of the most important classes of organic scaffold that can be found in numerous biologically active natural products and pharmaceuticals.[1] Meanwhile, the functionalized cyclopentanone as an important chemical building block has attracted a lot of attention in the past few decades.[2] Owing to their unique biological activities and valuable applications in the field of natural products and drug molecules synthesis, many synthetic approaches have been extensively developed for the rapid construction of these core motifs.[3] In aim to develop new methods for the efficient synthesis of functional molecules, we have demonstrated a novel strategy for the quick access of benzoxazinone bearing a cyclopentanone moiety via *N*-heterocyclic carbene (NHC) catalyzed [3+2] cycloaddition of enals with *β,γ*-unsaturated *α*-ketimino esters.

In the last two decades , NHC has been developed as a powerful tool for the rapid construction of various organic molecules based on their unique polarity reversal strategy.[4] In 2007, Nair's group synthesized spirocyclopentanes from a NHC-catalyzed [3+2] annulation reaction between enals and cyclic Michael acceptors.[5] In 2013, Chi and co-workers reported an



Scheme 1. NHC-Catalyzed Cycloaddition of Enals with *α,β*-Unsaturated Imines and Our Synthetic Design.

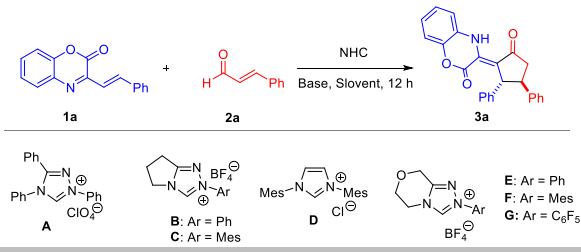
excellent work on NHC-catalyzed reactions of *cis*-enals and *α,β*-unsaturated imines to afford chiral cyclopentanones products.[6] The asymmetric formal [3+2] cycloadditions of enals with heterocyclic Michael acceptors were achieved by Glorius et al. and Ender's group respectively in recent years.[7] Meanwhile, Enders' group discovered a switchable annulation strategy for the selective synthesis of spirocyclopentane oxindoles and enaminones.[8] Impressively, the enantioselective synthesis of adipic acid derivatives was reported by the same group in 2017. In this efficient NHC-catalyzed formal [3+2] cycloaddition strategy, the masked cinnamates were used as linear Michael acceptors. Based on previous

10.1002/adsc.201901144

reports, we focused our attentions on explore NHC-catalyzed [3+2] cycloadditions with unconventional substrates. Recently, *β, γ*-unsaturated *α*-ketimino ester has been used as an excellent electrophile to construct functionalized indoles.[9] However, the application of *β, γ*-unsaturated *α*-ketimino esters in NHCs catalyzed annulation strategy has not been developed, probably due to their relatively weak electrophilicity towards nucleophiles. Herein we report our results on the NHC-catalyzed [3+2] cycloaddition of enals with *β,γ*-unsaturated *α*-ketimino esters for the rapid construction of multisubstituted cyclopentanones (Scheme 1).

We began our investigation by using *β, γ*-unsaturated *α*-ketimino ester **1a** and cinnamaldehyde **2a** as the model substrates and DBU was chosen as the base, while THF was initially employed as the solvent. Screening of catalysts revealed that the triazolium-based catalyst **C** with an *N*-mesityl substituent played best catalytic activity compared to the other catalysts (Table 1, entries 1-7). Other commonly used bases, such as TBD, DIPEA, K_2CO_3 and Cs_2CO_3 were far less effective, furnished the desired product in reduced yields (Table 1, entries 8−11). A variety of organic solvents were also screened for this reaction, and the results showed that the yields were generally lower than in THF (Table 1, entries 12−15). Finally, the optimal conditions were identified, using NHC **C** as the catalyst, DBU as the base and THF as the solvent, with the desired multisubstituted cyclopentanones **3a** formed in 80 % yield (Table 1, entry 3). It was worthy to note that the *trans*-isomers were generated as a single diastereomer during the optimization process.

Table 1. Optimization of Reaction Condition[a)]

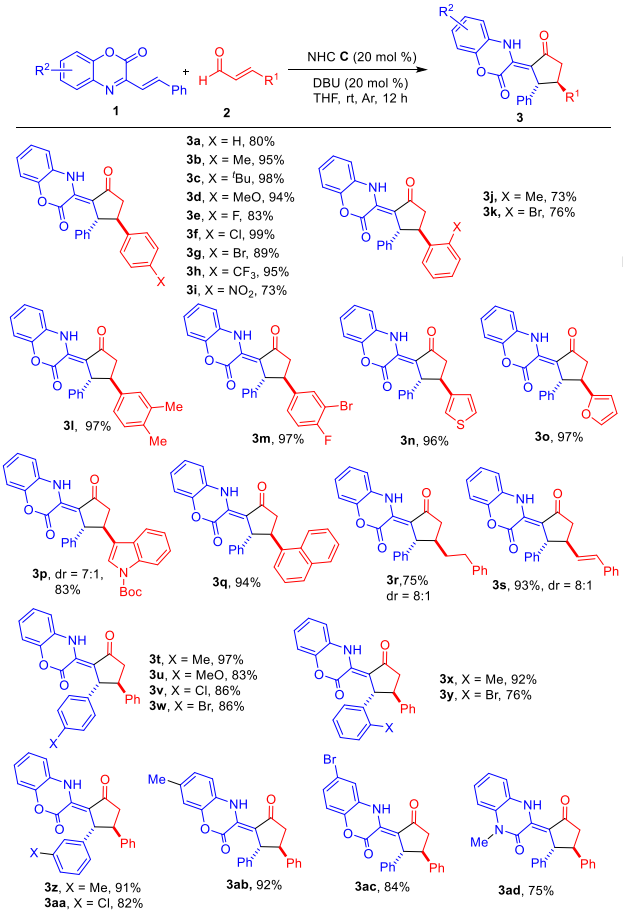


entry	NHC	base	slovent	yield (%)[b]
1	**A**	DBU	THF	37
2	**B**	DBU	THF	trace
3	**C**	DBU	THF	80
4	**D**	DBU	THF	trace
5	**E**	DBU	THF	76
6	**F**	DBU	THF	13
7	**G**	DBU	THF	60
8	**C**	TBD	THF	58
9	**C**	DIPEA	THF	32
10	**C**	K_2CO_3	THF	47
11	**C**	Cs_2CO_3	THF	68
12	**C**	DBU	DCM	66
13	**C**	DBU	CH_3CN	55
14	**C**	DBU	1,4-dioxane	71
15	**C**	DBU	DME	66

[a)]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.2 mmol, 2.0 equiv), NHC (20 mol %), base (20 mol %), solvent (1.0 mL), room temperature, 12 h. [b)] Isolated yield after flash chromatography. DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DIPEA = N,N-diisopropylethylamine, Mes = mesityl, DME = 1,2-Dimethoxyethane.

After establishing the optimal reaction conditions, we next examined the substrate scope. With *β, γ*-unsaturated *α*-ketimino ester **1a** as the model substrate (Scheme 2), enals derived from aryl aldehydes bearing various electron-withdrawing or electron-donating substituents all worked well, afforded the corresponding [3+2] cycloaddition adducts **3a**−**m** with good to excellent yields (up to 99% yield). When the *β*-phenyl substituent of enals replaced by heterocyclic units, such as thienyl and furyl were also worked well in this strategy (**3n**-**o**). Moreover, the indole derived enal was compatible in this reaction with lower diastereoselectivity (**3p**). Enals containing a sterically demanding group such as 1-naphthyl was well tolerated, thus affording the corresponding product in

Table 2. Substrate Scope[a), b), c)]

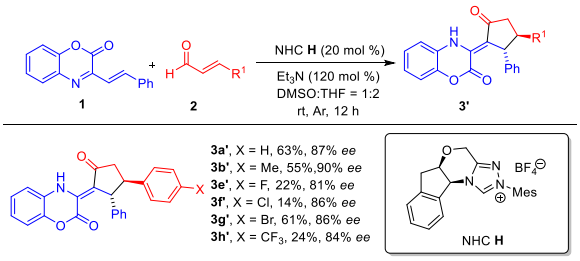


[a)] **1** (0.1 mmol), **2** (0.2 mmol), catalyst (20 mol %), base (20 mol %). Yields given are for the isolated products following column chromatography. [b)] Unless otherwise noted dr > 20:1. [c)] Diastereomers ratios were determined by HNMR

10.1002/adsc.201901144

excellent yield (**3r**, 94% yield). When *β*-alkyl and *β*-vinyl substituted enals were used as the starting materials under the standard conditions, the reactions processed smoothly to afford the corresponding products in moderate yields (**3r-s**), while the diastereoselectivities were reduced. Placing a vinyl substituent on the enal *β*-carbon was also tolerated (**3s**). With enal **2a** as the model substrate, the scope of *β, γ*-unsaturated *α*-ketimino esters was also examined. Not surprisingly, different aryl substituents on the *β, γ*-unsaturated *α*-ketimino esters were all well tolerated (**3t-3aa**). When the benzoxazinone unit bore an electron-withdrawing or electron-donating substituent (**3ab**, **3ac**), the reaction afforded their corresponding products in high yields. Notably, the benzoxazinone part could be replace by a quinoxalinone unit (**3ad**).

Table 3. Enantioselective studies of this methodology



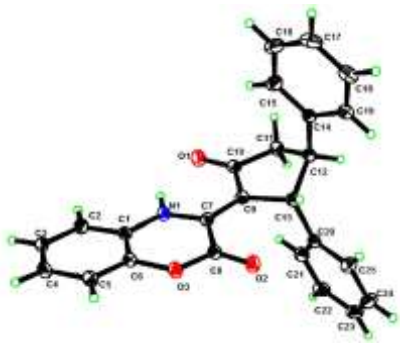


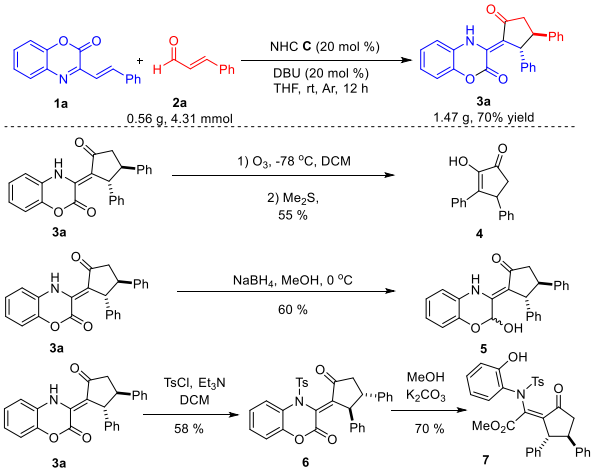
Figure 1. ORTEP diagram of **3a'**.

To further investigate this strategy, we next turned our attention to the asymmetric catalytic version of this reaction. Unfortunately, all the reaction conditions led to unsatisfactory ee values or yields.[10] Finally, the acceptable reaction conditions were identified, using chiral triazolium salt **H** as the catalyst, Et_3N as the base and a mixture of DMSO/THF (1:2, v/v) as the solvent, afforded the desired product in 63% yield with 87% ee (**3a'**, Table 3). Then, we roughly screened the substrate scope, and the results showed that all the examples afforded low to moderate yields with acceptable ee values (**3b'-3i'**).

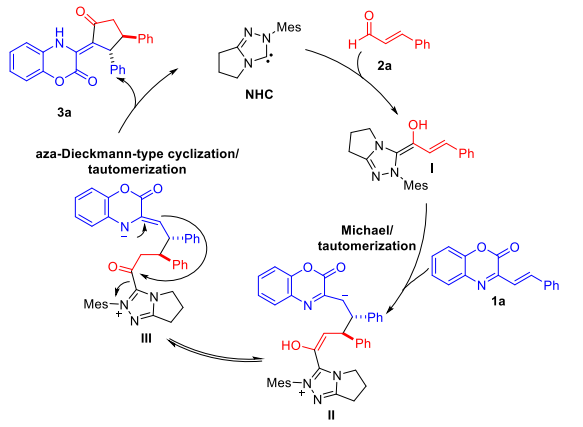
The absolute configuration (2R, 3R) of the stereogenic centers in compound **3a'** were unambiguously determined by X-ray crystallographic analysis (Figure 1). [11]

In order to further demonstrate the practicality of this strategy, a gram-scale synthesis of **3a** was carried out under the standard condition. To our great delight, no obvious loss of yield was observed. Then, further synthetic transformation of **3a** was performed as shown in Scheme 2. Under oxidative cleavage with ozone, **3a** could easily transformed to 2-hydroxy cyclopentenone **4**. Interestingly, reduction of **3a** by $NaBH_4$ gave the acetal **5** as the product. Moreover, protecting the N-atom of **3a** with tosyl group afforded the compound **6**. Ring opening reaction was subsequently carried out in methanol, and cyclopentenone **7** was generated as essentially a single diastereomer (Scheme 2).

The proposed reaction pathway for the [3+2] cycloaddition of *β, γ*-unsaturated *α*-ketimino esters **1a** and enal **2a** is illustrated in Scheme 3. Addition of NHC **C** to enal **2a** led to the formation of NHC-homoenolate **I**. Then the intermediate **I** undergo a Michael/tautomerization reaction to *β, γ*-unsaturated *α*-ketimino esters **2a** to create a new carbon−carbon bond and the intermediate **II** was generated. The intermediate **II** is in equilibrium with its tautomer **III**.



Scheme 2. Scale-up synthesis and further transformations .



Scheme 3. Proposed Reaction Pathways.

Then after an aza-Dieckmann-type cyclization and final tautomerization, the product **3a** was generated and NHC catalyst was released to enter next catalytic cycle (Scheme 3).

In conclusion, the NHC-catalyzed [3+2] cycloadditions of enals with *β,γ*-unsaturated *α*-ketimino esters were developed. This unique and effective strategy features mild reaction conditions and broad substrate scope, which enables the rapid assembly of various benzoxazinone derived cyclopentanone scaffolds in good to high yields with excellent diastereoselectivities. Other investigations concerning the construction of relevant targets, as well as the asymmetric study are currently underway in our laboratory.

Experimental Section

A dry 25 mL Schlenk tube with stir bar was charged with β,γ-unsaturated α-ketimino ester **1a** (25 mg, 0.1 mmol, 1.0 equiv), NHC **C** (6.3 mg, 0.01 mmol, 20 mol %), DBU (3 mg, 0.02 mmol, 20 mol %). The tube was evacuated, and refilled with nitrogen. Then enals **2a** (26.4 mg, 0.2 mmol, 2.0 equiv) was added and the mixture was dissolved with newly distilled THF (1 mL). The mixture was stirred at room temperature for 12 hours when the substrate was consumed completely (monitored by TLC). The reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel using Petroleum ether/EtOAc (15:1) as eluent to afford desired product **3a** as yellow solid (30.5 mg, 80% yield).

Acknowledgements

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[10] For the detail of optimization of enantioselective please see the supporting information.

[11] Single crystal X-ray analysis of **3a'** using CuK radiation with oxygen as the heavy atom for absolute stereochemistry (CCDC 1964949). These data are available free of charge from the Cambridge Crystallographic Data Centre.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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