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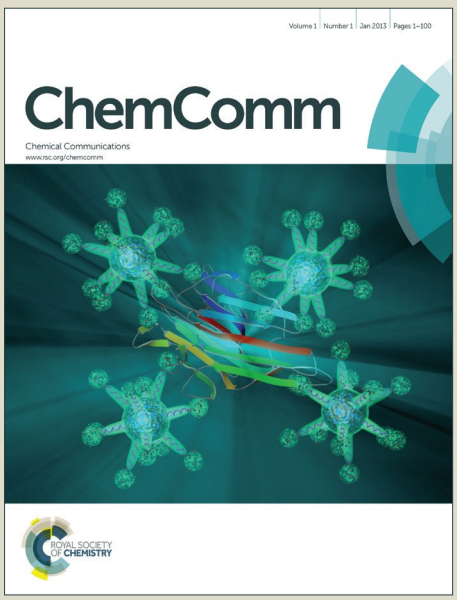

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N-Heterocyclic carbene-catalyzed diastereoselective synthesis of β-lactone-fused cyclopentanes using homoenolate annulation reaction

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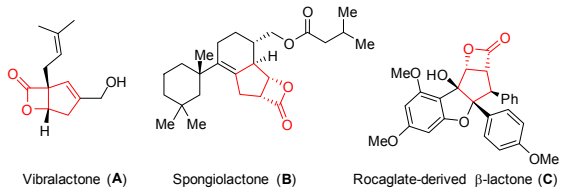
NHC-catalyzed annulation of enals with 2-enoylpyridines or 2-enoylpyridine *N*-oxides leading to the diastereoselective synthesis of β-lactone-fused cyclopentanes is reported. The reaction proceeds via the generation of homoenolate equivalent intermediates and tolerates a broad range of functional groups.

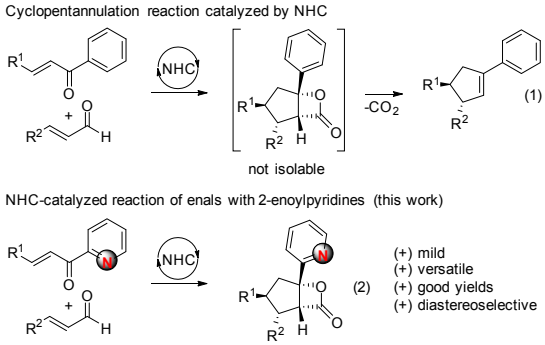
Functionalized β-lactones are ubiquitous in numerous biologically active natural products and various pharmaceutically relevant molecules.[1] Among the β-lactones, the β-lactone-fused cyclopentanes are important because these structural motifs are found in natural products such as vibralactone (**A**, a pancreatic lipase inhibitor),[2] and spongiolactone (**B**, antiproliferative activity towards the K562 cell line) (Figure 1).[3] Moreover, the rocaglate-derived β-lactone (**C**) has been recently reported to have serine hydrolase activity.[4] Due to the biological importance of β-lactone-fused cyclopentanes, development of atom-economic and flexible synthetic routes to these targets are highly desirable.



Vibralactone (**A**) Spongiolactone (**B**) Rocaglate-derived β-lactone (**C**)

Figure 1. Selected biologically important β-lactone-fused cyclopentanes

Romo and co-workers developed efficient methods for the synthesis of functionalized β-lactones.[1b,1d,1e] N-heterocyclic carbene (NHC)-catalyzed formal [2+2] cycloaddition of ketenes with aldehydes/activated ketones has been a convenient method for the construction of β-lactones.[5,6] In 2006, Nair and co-workers uncovered a conceptually new NHC-catalyzed reaction of enals with chalcones to afford functionalized cyclopentenes (eq 1).[7] The reaction proceeds via the generation of homoenolate equivalents,[8] and the product formation took place by the spontaneous decarboxylation of the β-lactone-fused cyclopentane intermediate. Subsequently, the enantioselective version of the Nair reaction was developed by Bode and co-workers (using chiral NHCs),[9] and Scheidt and co-workers (employing NHC/Lewis acid cooperative catalysis).[10] Moreover, the synthesis of β-lactone-fused cyclopentane derivatives was demonstrated by the groups of Bode,[11] Scheidt,[12] Lupton[13] and Studer.[14] However, the isolation of the β-lactone-fused cyclopentane intermediate in the NHC-catalyzed cyclopentannulation reaction of enals with chalcones has not been demonstrated.[15] In the context of our recent success on NHC-catalyzed reaction of enals with 2'-hydroxy chalocones leading to the diastereoselective synthesis of cyclopentane-fused coumarins,[16] we have carried out the reaction of enals with 2-enoylpyridines/2-enoylpyridine *N*-oxides under NHC-catalysis. Herein, we report the results of our studies leading to the diastereoselective synthesis of β-lactone-fused cyclopentane derivatives (eq 2).



The present studies were initiated by treating 2-enoylpyridine (**1a**)[17] with cinnamaldehyde (**2a**) in the presence of carbene generated from the imidazolium salt **4** using DBU as base. Interestingly, under these conditions, the β-lactone-fused

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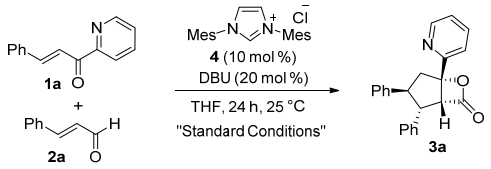
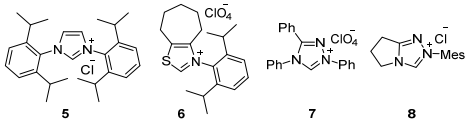
cyclopentane **3a** was isolated in 63% yield as a single diastereomer (Table 1, entry 1).[18] It is noteworthy that the reaction of enals with 3-enoylpyridine and 4-enoylpyridine afforded the corresponding cyclopentene derivatives via the spontaneous decarboxylation.[19] Compared to the NHC derived from **4**, other common NHCs derived from precursors **5-8** are not found to be beneficial in this reaction (entries 2-5). Additionally, other organic and inorganic bases afforded the desired β-lactone in reduced yield, but as a single diastereomer (entries 6-9). A rapid solvent screen revealed that solvents other than THF furnished the β-lactone in only moderate yield (entries 10-13). Interestingly, when the NHC precursor **4** loading was increased in 20 mol %, the yield of **3a** was improved to 76% (entry 14). Finally, by employing 20 mol % of **4** and 1.2 equiv of **2a**, the β-lactone **3a** was isolated in 86% yield as a single diastereomer (entry 15).[20]

Table 1. Optimization of the reaction conditions[a]

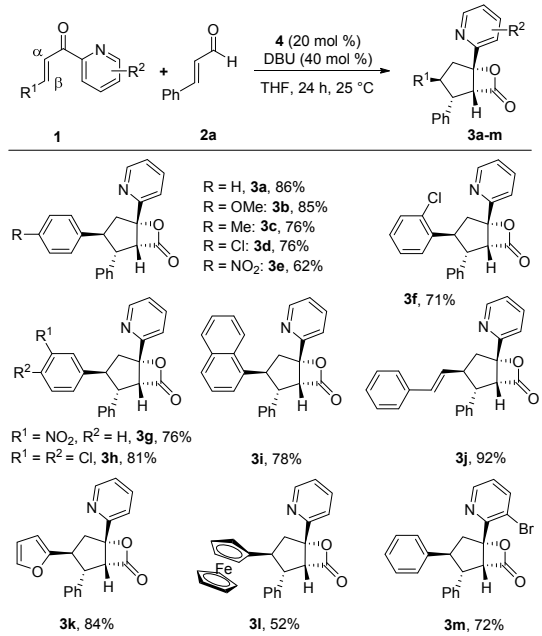


entry	variation of the standard conditions[a]	yield of **3a** (%)[b,c]
1	none	63
2	**5** instead of **4**	<5
3	**6** instead of **4**	<5
4	**7** instead of **4**	<5
5	**8** instead of **4**	32
6	Et_3N instead of DBU	15
7	DABCO instead of DBU	25
8	KO*t*-Bu instead of DBU	27
9	Cs_2CO_3 instead of DBU	35
10	DME instead of THF	57
11	1,4-dioxane instead of THF	41
12	toluene instead of THF	44
13	CH_2Cl_2 instead of THF	57
14[d]	20 mol % of **4** instead of 10 mol %	76
15[d]	*20 mol % of **4**, 1.2 equiv of **2a***	*86*

[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), **4** (10 mol %), DBU (20 mol %), THF (1.0 mL), 25 °C and 24 h. [b] Isolated yield after column chromatography. [c] A single diastereomer was observed in all cases. [d] 40 mol % of DBU was used.



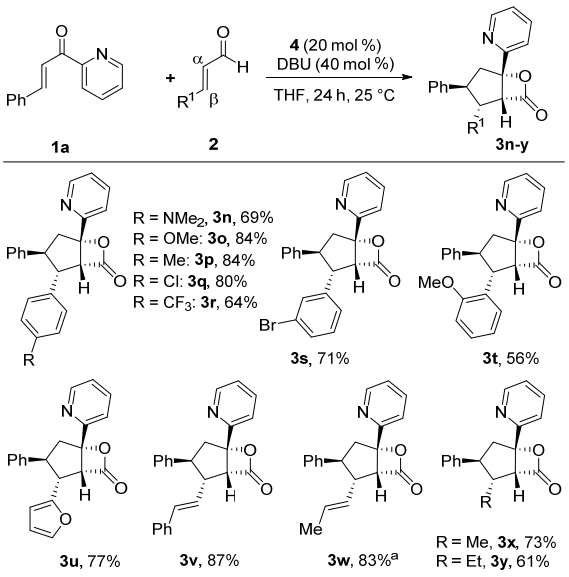
With these conditions in hand, we then evaluated the substrate scope of this reaction. First we examined the variation of 2-enoylpyridine moiety (Scheme 1). The unsubstituted β-phenyl 2-enoylpyridine worked well and a variety of electron-releasing and -withdrawing groups at the 4-position of the β-aryl ring was well-tolerated leading to the synthesis of β-lactone-fused cyclopentanes as a single diastereomer in good yields (**3a-3e**). In the case of **3e**, the structure and the *trans* geometry of the two aryl groups are confirmed by single-crystal X-ray analysis.[21] Moreover, β-aryl ring having substituents at the 3-position and 2-position as well as disubstitution did not affect the reactivity, and the corresponding products were isolated in good yields (**3f-3i**). The substrate having the extended conjugation at the β-position afforded the desired product **3j** in 92% yield. Additionally, enones having heteroaryl group and ferrocenyl moiety at the β-position underwent smooth annulation reaction to afford the target products in moderate to good yields (**3k-3l**). Furthermore, bromo substitution at the pyridine ring of **1** was also tolerated to afford the β-lactone **3m** in 72% yield thus showing the versatile nature of the present reaction.



Scheme 1. Substrate scope for the synthesis of β-lactone-fused cyclopentanes. Variation of 2-enoylpyridines. General reaction conditions: **1** (0.50 mmol), **2a** (0.60 mmol), **4** (20 mol %), DBU (40 mol %), THF (2.5 mL) at 25 °C for 24 h. Given are isolated yields after flash column chromatography.

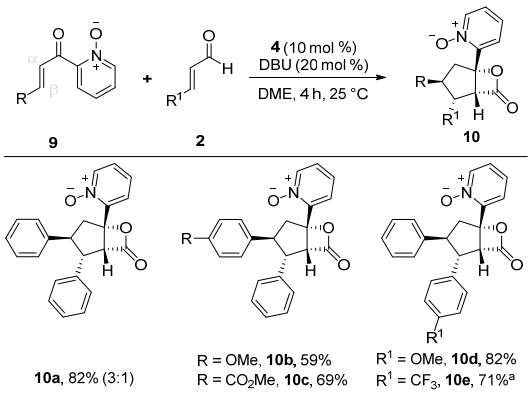
Next, we studied the scope of this reaction with substituted enals (Scheme 2). A series of substrates having electron-releasing and -withdrawing groups at the 4-position of the β-aryl ring of **2** underwent smooth annulation reaction affording the β-lactone derivatives as a single diastereomer in good yields (**3n-3r**). Besides, substitution at the 3-position and 2-position was well-tolerated (**3s-3t**). Additionally, enals having β-heteroaryl group, dienals having δ-aryl and alkyl substitution, and enals bearing β-alkyl groups furnished the desired products in good yields thereby further expanding the scope of this annulation reaction.

With the interesting results obtained using 2-enoylpyridines, we then focused our attention on 2-enoylpyridine *N*-oxides as the enal coupling partner in this reaction. Gratifyingly, treatment of unsubstituted β-aryl 2-enoylpyridine *N*-oxide **9a**[17a,22] with enal **2a** under the NHC-catalyzed reaction conditions resulted in the formation of



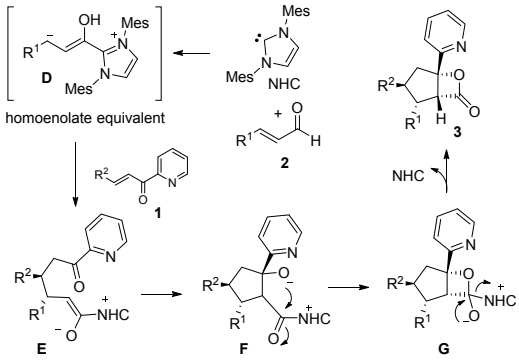
Scheme 2. Variation of the enal moiety. General reaction conditions: **1a** (0.50 mmol), **2** (0.60 mmol), **4** (20 mol %), DBU (40 mol %), THF (2.5 mL) at 25 °C for 24 h. Given are isolated yields after flash column chromatography. [a] The product was formed in 5:1 *dr* determined by ^{1}H-NMR of the crude reaction mixture.

separable mixture of diastereomers in 3:1 ratio and 82% yield (Scheme 3). The structure of the major diastereomer **10a** was confirmed by single-crystal X-ray analysis.[21] Notably, the 2-enoylpyridine *N*-oxides react faster compared to the corresponding 2-enoylpyridines in the present annulation reaction. Interestingly, electronically dissimilar β-aryl 2-enoylpyridine *N*-oxides readily afforded the β-lactone-fused cyclopentanes as a single diastereomer in good yields (**10b-10c**). Moreover, electronically different cinnamaldehyde derivatives also furnished the desired β-lactones as a single diastereomer in good yields (**10d-10e**).



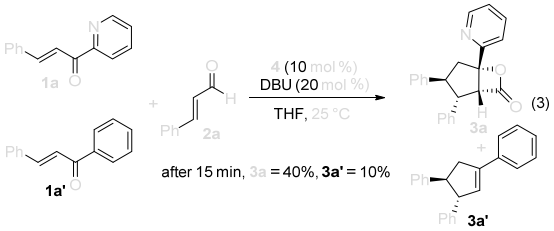
Scheme 3. NHC-catalyzed annulation of enals with 2-enoylpyridine *N*-oxides. General reaction conditions: **9** (0.50 mmol), **2** (0.50 mmol), **4** (10 mol %), DBU (20 mol %), DME (2.5 mL) at 25 °C for 4 h. Given are isolated yields after flash column chromatography. [a] The reaction performed in 0.25 mmol scale.

The proposed mechanism of this NHC-catalyzed β-lactonization reaction can be delineated as follows (Scheme 4). The initially generated homoenolate equivalent intermediate **D** from enal and NHC undergoes a conjugate addition to the 2-enoylpyridine **1** followed by an intramolecular proton transfer results in the formation of the enolate intermediate **E**. This intermediate **E** undergoes an intramolecular aldol reaction to generate acylazolium intermediate **F**, which on highly selective β-lactonization affords the β-lactone **3** via the intermediate **G**.[23]

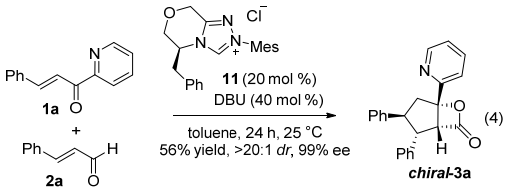


Scheme 4. Tentative mechanism of the reaction.

To shed light on the kinetics of the reaction, intermolecular competition experiments were carried out. Competition experiment performed between the 2-enoylpyridine **1a** and chalcone **1a'** indicated that **1a** reacted ~4 times faster than 1**a'** showing the preferential formation of **3a** over **3a'** (eq 3).[20] The fast rate of formation of **3a** over **3a'** indicates the relatively high reactivity of 2-enoylpyridine **1a** due to the pyridine moiety, which makes the double bond electron deficient for the facile addition of homoenolate equivalent intermediate **D**.



We have also carried out the preliminary studies on the enantioselective version of this reaction. Interestingly, treatment of enone **1a** with enal **2a** in the presence of chiral NHC derived from **11** using DBU resulted in the enantioselective synthesis of the β-lactone-fused cyclopentane ***chiral*-3a** in 56% yield, and in excellent diastereoselectivity of >20:1, and enantiomeric excess of 99% (eq 4).



In conclusion, we have developed the NHC-organocatalyzed homoenolate annulation with 2-

enoylpyridines or 2-enoylpyridine *N*-oxides leading to the diastereoselective synthesis of β-lactone-fused cyclopentanes in moderate to good yields. The pyridine moiety in the enone plays a vital role in stabilizing the β-lactone intermediate. Mild reaction conditions, broad substrate scope and good yield of products are the notable features of the present reaction. Further studies towards the asymmetric version of this reaction and the related NHC-catalyzed reactions are ongoing in our laboratory.

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