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N-Heterocyclic carbene-catalyzed cascade epoxide-opening and lactonization reaction for the synthesis of dihydropyrone derivatives†

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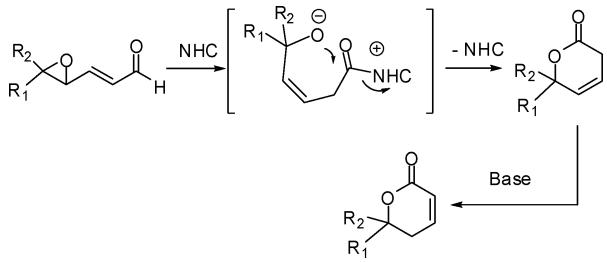
_N_-Heterocyclic carbene was employed as an efficient organic catalyst to catalyze a cascade epoxide-opening and lactonization reaction. This organocatalytic process could transform various readily accessible γ-epoxy-α,β-enals into dihydropyrone derivatives in good to excellent yields.

N-Heterocyclic carbenes (NHCs) as organocatalysts have attracted a great deal of attention in the past decades, as they provide a broad range of useful synthetic transformations.[1] Among the reactions found to be promoted by this family of catalysts, the benzoin-type condensation,[2] the Stetter-type reaction,[3] the intra/intermolecular redox reaction,[4] and the generation of homoenolate species followed by a C–C bond formation were involved.[5] Remarkably, the Bode group and the Rovis group respectively reported that α-reducible aldehydes led to a novel reaction pathway under NHC catalysis in the presence of alcohols as nucleophiles.[6] Upon formation of the acyl anion equivalent, redox reaction occurs, with addition of an alcohol resulting in the desired esters. However, the NHC-catalyzed redox reaction of γ-reducible-α,β-enals have received extremely rare consideration. To the best of our knowledge, there has been only one report on the application of NHCs to this type of organocatalytic transformations.[4i] Herein, we report the first example of an NHC-catalyzed intramolecular redox reaction of γ-epoxy-α,β-enals to afford dihydropyrones *via* a cascade epoxide-opening and lactonization pathway.

Although dihydropyrone subunits are widely recognized in a large class of bioactive natural products, the typical strategies applied for constructing this type of molecules usually require the utilization of either expensive or toxic metals and lacked step economy.[7] To overcome such limitations, we decided to develop a facile synthesis of dihyropyrones during our work. Inspired by the elegant work from Bode and Rovis, we reasoned that γ-epoxy-α,β-enals in the presence of an NHC catalyst would, in principle, undergo an epoxide-opening reaction followed by intramolecular esterification resulting in the formation of dihydropyrone derivatives (Scheme 1). Successful implementation of this idea would constitute a novel route to synthetic dihydropyrone derivatives and also broaden the scope of application of NHCs.



Scheme 1 NHC-catalyzed epoxide-opening and lactonization reaction.

Our initial efforts were focused on the systematic evaluation of various catalysts and optimization of reaction conditions. The simple readily prepared aldehyde **1a** was selected as the model substrate while DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) was used as the base, then a number of different catalysts were screened, and the results are summarized in Table 1. Among the tested catalysts, the commonly used catalysts **A–D** did not provide any reactivity (entry 1). The thiazolium salt **E** reported by Glorius group was found to be efficient for this reaction.[8] As we observed, the results were extremely dependant on the base and solvent. When the reaction was performed in DCM with 0.3 equiv of thiazolium salt **E** and 0.3 equiv of DBU as the base under reflux, **3a** was generated in low yield as the desired product (entry 2). It was worth noting that when 0.3 equiv of K_2CO_3 was used as the base, a mixture of **2a** and **3a** was observed in a ratio of 1 : 2 (entry 3). We envisaged that the use of a stronger base would facilitate the subsequent C=C bond migration to give the more thermodynamically stable **2a** as the major product. To our great delight, utilization of 0.3 equiv of ^{t}BuOK afforded **2a** as the major product along with a small amount of **3a** in 89% overall yield (entry 5). No improvement was observed for the reaction in acetonitrile, toluene or 1,2-dichloroethane (entry 6–8). However, when the reaction was carried out with 0.6 equiv of ^{t}BuOK, the yield dropped sharply (entry 9). Thiazolium salt **F** also worked well for this reaction (entry 10). Interestingly, when the reaction was performed in the presence of 5 equiv MeOH as the nucleophile, we did not detect the formation of the non-cyclized product and the yield was decreased (entry 11). Thus, the optimized conditions

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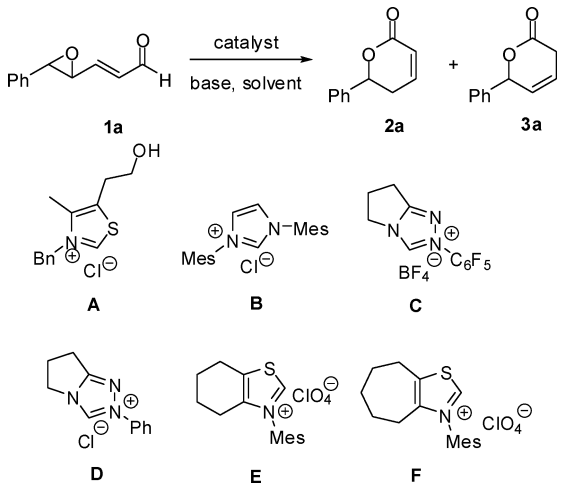
Table 1 Optimization of reaction conditions[a]



entry	NHC[b]	solvent	base[c]	products[d]	yield[e]
1	**A–D**	DCM	DBU	—	0
2	**E**	DCM	DBU	**3a**	33
3	**E**	DCM	K_2CO_3	**2a** : **3a** = 1 : 2	22
4	**E**	DCM	Cs_2CO_3	—	0
5	**E**	**DCM**	**^{t}BuOK**	**2a:3a = 3 : 1**	**89**
6	**E**	CH_3CN	^{t}BuOK	**2a**	58
7	**E**	Toluene	^{t}BuOK	**2a** : **3a** = 8 : 1	40
8	**E**	DCE	^{t}BuOK	**2a** : **3a** = 1 : 1	48
9[f]	**E**	DCM	^{t}BuOK	N.D.[h]	< 10
10	**F**	DCM	^{t}BuOK	**2a** : **3a** = 3 : 1	63
11[g]	**E**	DCM/MeOH	^{t}BuOK	**2a**	35

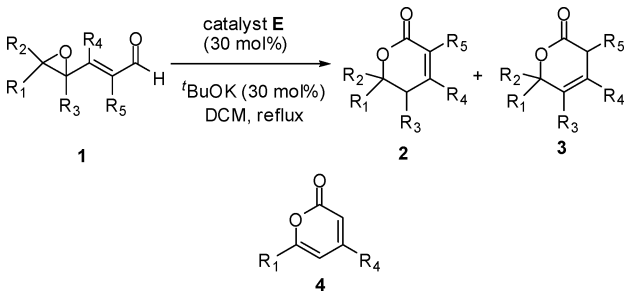
[a] All reactions were performed on a 0.5 mmol scale at 0.02 M under reflux for 24 h. [b] 30 mmol% catalyst was used. [c] 30 mmol% base was used unless otherwise noted. [d] The ratios were determined by ^{1}H NMR. [e] Isolated overall yields. [f] 60 mol% ^{t}BuOK was used. [g] 5 equiv MeOH was used. [h] Not determined.

were established to be as follows: thiazolium salt **E** as the pre-catalyst, ^{t}BuOK as the base, DCM as the solvent and stirring under reflux for 24 h.

Under the optimized reaction conditions, various aldehydes were tested to investigate the scope of the reaction (Table 2). For the R_1 group, various phenyl groups bearing different electron-donating and -withdrawing groups at *o*, *m*, *p*-positions all underwent the proposed tandem epoxide-opening and lactonization sequence smoothly to afford the corresponding dihydropyrones in moderate to excellent yields (entry 1–10).

When the substrate **1e** was used, **2e** was generated in 54% yield along with **4e** as minor product and the reason is still unclear (entry 5). A significant exception was noted, when methyl or phenyl substituents were included at the R_2 position under the standard reaction conditions, the dihydropyrones **2k**, **2l** and **2m** were generated as the only products in moderate to good yields (entry 11–13). The probable reason is that the substrates **1k–1m** suffer from an increased 1,3-strain over **1a–1j**, therefore they are more likely to transform to the thermodynamically stable products under the same reaction conditions. Unfortunately, reaction of the alkyl-substituted substrate **1n** failed to produce any products under the standard conditions (entry 14). It should be noted that phenylethynyl substituted aldehyde **1o** could also be used in this reaction although the yield was slightly decreased (entry15).

Table 2 Reaction scope[a]

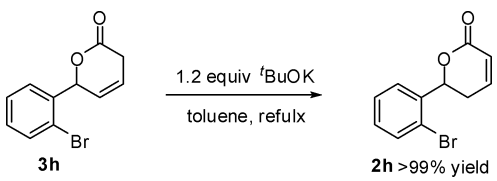


entry	R_1, R_2,	R_3, R_4, R_5	product	yield (%)	ratio (2 : 3)
1	**1a** C_6H_5, H	H, H, H	**2a, 3a**	89	3 : 1
2	**1b** *p*-Cl-C_6H_5, H	H, H, H	**2b, 3b**	91	3 : 1
3	**1c** *p*-Br-C_6H_5, H	H, H, H	**2c, 3c**	95	2 : 1
4	**1d** *p*-Me-C_6H_5, H	H, H, H	**2d, 3d**	58	3 : 1
5	**1e** *p*-NO_2-C_6H_5, H	H, H, H	**2e, 4e**	68	4 : 1
6	**1f** *o*-Me-C_6H_5, H	H, H, H	**2f, 3f**	68	2 : 1
7	**1g** *m*-Cl-C_6H_5, H	H, H, H	**2g, 3g**	80	1.5 : 1
8	**1h** *o*-Br-C_6H_5, H	H, H, H	**2h, 3h**	98	3 : 1
9	**1i** 3,4-Me-C_6H_5, H	H, H, H	**2i, 3i**	50	2 : 1
10	**1j** 1-Naphth, H	H, H, H	**2j, 3j**	70	3 : 1
11	**1k** C_6H_5, Me	H, H, H	**2k**	45	—
12	**1l** *p*-NO_2-C_6H_5, Me	H, H, H	**2l**	82	—
13	**1m** C_6H_5, C_6H_5	H, H, H	**2m**	98	—
14	**1n** $BnCH_2$, H	H, H, H	N.R.[b]	—	
15	**1o** phenylethynyl, H	H, H, H	**2o**	56	—
16	**1p** C_6H_5, H	Me, H, H	N.R.[b]	—	—
17	**1q** C_6H_5, H	H, C_6H_5, H	**4q**	42	—
18	**1r** *m*-Cl-C_6H_5, H	H, H, Me	N.R.[b]	—	—

[a] All reactions were performed on a 0.5 mmol scale at 0.02 M. [b] No reaction.

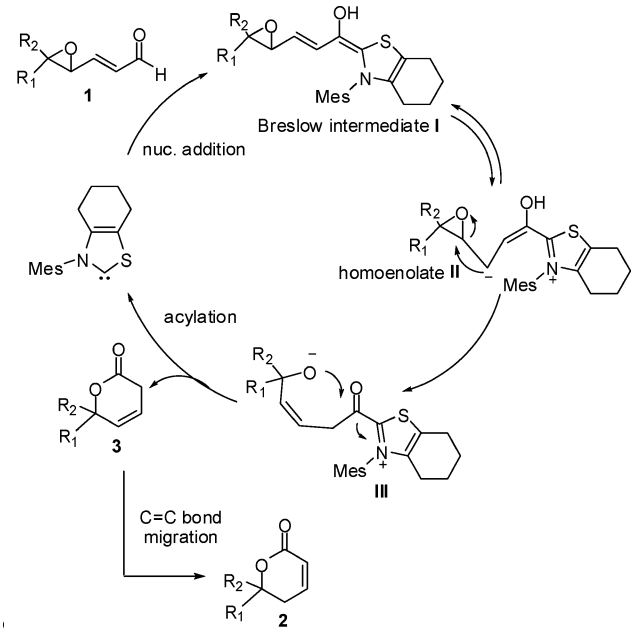
In view of these interesting results, we further investigated the scope of the reaction by using phenyl or methyl substituents at the α, β or γ positions of the aldehyde. To our disappointment, the α-substituted **1r** and γ-substituted **1p** did not work in this transformation. Importantly, the reaction of the β-disubstituted aldehyde **1q** provided the elimination product **4q** as the only product in moderate yield. (entry 17).

A preliminary study on the transformation of 3,6-dihydro-2*H*-pyran-2-one to 5,6-dihydro-2*H*-pyran-2-one was also performed.[9] For instance, upon treatment with 1.2 equiv of ^{t}BuOK under reflux for 1 h, **3h** was easily covered to **2h** in quantitative yield (Scheme 2).



Scheme 2 Conversion 3,6-dihydro-2*H*-pyran-2-one to 5,6-dihydro-2*H*-pyran-2-one.

The postulated catalytic cycle for this NHC-catalyzed reaction is shown in Scheme 3. In the first step, the *N*-heterocyclic carbene, generated by base induced deprotonation of the corresponding thiazolium salt, adds to the aldehyde **1** to afford the "Breslow intermediate" **I**.[10] Then, the extended homoenolate **II** equivalent undergoes the epoxide-opening pathway and subsequently generates the intermediate **III**.[11] In the



Scheme 3 Proposed mechanism of the reaction.

epoxide-opening step, a *Z*-carboxylate is formed probably due to the electronic interaction. Finally an intramolecular attack of the alkoxide moiety provides the product **3** while the NHC catalyst releases back to the catalytic cycle. Then the product **3** subsequently isomerizes to the thermodynamically more stable product **2** under the alkaline conditions.

In summary, we have developed a highly efficient *N*-heterocyclic carbene catalyzed cascade epoxide-opening and lactonization reaction, which is a more direct and efficient way to construct the skeleton of dihydropyrones. A variety of readily accessible substrates underwent the reaction in good to excellent yield. We postulated a mechanism for this reaction forming dihydropyrones, which proceeds *via* the NHC-catalyzed tandem epoxide-opening and lactonization reaction. Further investigations into the precise mechanism of this reaction as well as the use of chiral carbenes as organocatalysts in other asymmetric reaction are currently underway in our laboratory.

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