Chinese Chemical Letters 29 (2018) 1209–1211

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

N-Heterocyclic carbene-catalyzed [4 + 2] cyclization of α-chloroaldehydes and aurones: Highly enantioselective synthesis of benzofuran-fused dihydropyran-2-ones

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ARTICLE INFO

Article history:
Received 3 January 2018
Received in revised form 3 February 2018
Accepted 1 March 2018
Available online 3 March 2018

Keywords:
Carbene catalysis
Annulation
Enantioselectivity
Benzofuran
Dihydropranone

ABSTRACT

The chiral *N*-heterocyclic carbene-catalyzed [4 + 2] annulation of α-chloroaldehydes and aurones was developed, giving the corresponding benzofuran–fused dihydropyranones in good to high yields with good diastereoselectivities and excellent enantioselectivities. The catalytic cycle features with the generation of enolate from chloroaldehdye and its following [4 + 2] cycloaddtion with aurones.

Asymmetric catalysis plays a key role for the synthesis of chiral compounds. Following the classic *N*-heterocyclic carbenes (NHCs) catalyzed benzoin reaction [1,2] and Stetter reaction [3–5], a wide variety of NHC-catalyzed enantioselective reactions have been developed in recent years [6–9]. Being a key motif in many bioactive compounds [10] and versatile reagent for chemical transformation, dihydropyranone is an important target in organic synthesis [11–13]. Recently, the NHC-catalyzed synthesis of dihydropyran-2-ones has been well established *via* three routes (Scheme 1). In 2006, Bode *et al.* reported the NHC-catalyzed generation of azolium enoate from α-chloroaldehdye and the following [4 + 2] annulation with oxodiene to give dihydropyran-2-ones in high yields and excellent enantioselectivities [14–17]. The NHC-attached enolate could also be generated from α-aroylaldehydes [18], ketene, [19–21] simple aldehyde with oxidant [22,23] and formylcyclopropane (Scheme 1, route A).[24] The NHC-catalyzed generation of dienolate from α,β-unsaturated acyl chloride [25] or enals [26], and the following [4 + 2] reaction with ketones to give dihydropyran-2-ones was also reported (Scheme 1, route B). The NHC-catayzed generation of α,β-unsaturated acyl azolium from enals with oxidant [27–29], α-bromoenals [30–36], ynals [37–39], and α,β-unsaturated esters [40–43], followed by [3 + 3] of with enolates is the third route reported (Scheme 1, route C). In addition, several interesting alternative routes to dihydropyran-2-ones by rearrangement reaction of cyclopropyl enol esters [44] or γ,δ-epoxyenals [45] have also been pioneered.

Recently, we reported an NHC-catalyzed [3 + 4] annulation of enals and aurones to give benzofuran-fused ε-lactones [46]. Considering the wide presence of benzofuran [47–50] and dihydropyranone motifs in bioactive compound, we are interested to synthesize benzofuran-fused dihydropyranones *via* the [4 + 2] annulation of NHC-attached enolate with aurones.

Initially, the reaction of aurone **1a'** and α-chloroaldehyde **2a** was investigated under NHC catalysis (Scheme 2). However, no desired cycloadduct **3a'** was obtained in the presence of NHC precursor **A** derived from L-pyglutamic acid. We envisioned that a more electron-deficient oxodiene may be required for the reaction. Then, we were happy to find that the reaction of aurone **1a** with an electron-withdrawing ester group led to the expected benzofuran-fused dihydropyranone **3a** in 15% yield with 1:1 *dr* and 30% *ee*.

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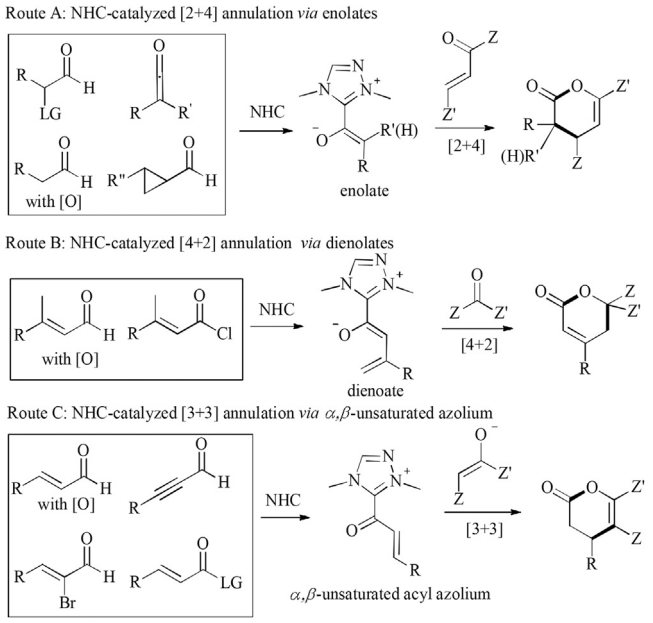
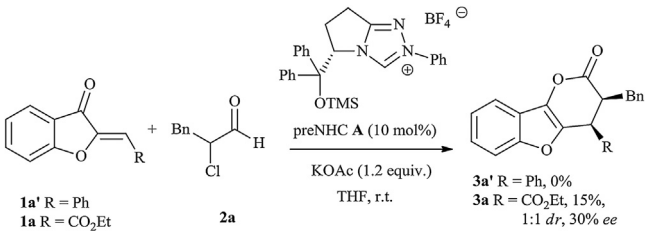
https://doi.org/10.1016/j.cclet.2018.03.003

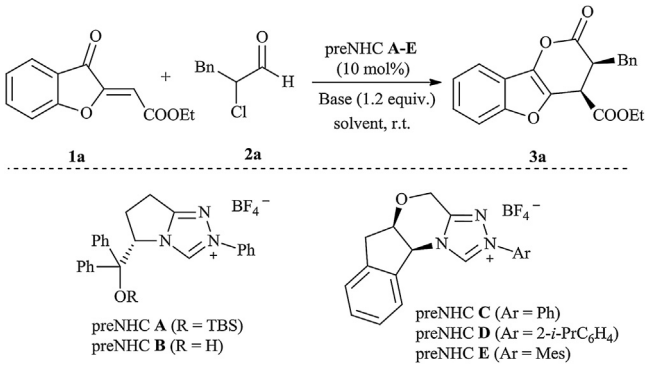


Scheme 1. NHC-catalyzed synthesis of dihydropyran-2-ones.



Scheme 2. Initial results of the reaction with aurones.

Table 1
Optimization of conditions.



Entry	Cat.	Base	Solvent	Yield (%)[a]	*cis*:*trans*[b]	*ee* (%)[c]
1	**A**	KOAc	THF	15	1:1	30
2	**B**	KOAc	THF	15	1:1	-62
3	**C**	KOAc	THF	21	>20:1	95
4	**D**	KOAc	THF	50	11:1	96
5	**E**	KOAc	THF	74	20:1	99
6	**E**	Cs_2CO_3	THF	34	1:1	85
7	**E**	K_2CO_3	THF	23	3:1	99
8	**E**	NaOAc	THF	65	4:1	98
9	**E**	DABCO	THF	45	1:1	82
10	**E**	DIPEA	THF	79	20:1	99
11	**E**	DIPEA[d]	Et_2O	48	14:1	99
12	**E**	DIPEA[d]	Toluene	45	15:1	90
13	**E**	DIPEA[d]	DCM	67	19:1	99
14	**E**	DIPEA[d]	CH_3CN	trace	/	/
15	**E**	DIPEA[d]	1,4-Dioxane	84	15:1	99

[a] Isolated yield.
[b] Determined by ^1H NMR spectroscopy of the raw product.
[c] Enantiomeric excess of the *cis*-**3a**, determined by HPLC using a chiral stationary phase.
[d] DIPEA (2 equiv.) was used.
DABCO = 1,4-diazabicyclo[2.2.2]octane, DIPEA = diisopropylethylamine, TBS = *tert*-butylbismethylsilyl, Mes = Mesityl, DCM = dichloromethane.

The model reaction of α-chloroaldehyde and aurone **1a** was then optimized under various conditions (Table 1). It was found that the reaction catalyzed by NHC precursor **B** with a free hydroxyl group afforded **3a** with better enantioselectivity but the yield and diastereoselectivity were still quite low (entry 2). High diastereo- and enantioselectivity were reached when the tetracyclic NHC precursors **C**-**E** were employed (entries 3-5). More importantly, the yield was improved to 74% when the NHC **E** with strong electron-donating group on the triazolium *N*-aryl group (Ar = mesityl) was used (entry 5). Several other inorganic or organic bases were also tested for the reaction, and diisopropylethylamine was the best of choice (entry 10). Screening of the solvents revealed that reaction performed best in 1,4-dioxane, giving the cycloadduct **3a** in 84% yield with 15:1 *dr* and 99% *ee* (entries 11-14 *vs.* 15).

With the optimized conditions in hand, the scope of the reaction was then investigated (Fig. 1). Both electron-donating group (Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$,) and electron-withdrawing group (Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4) were tolerable on the 3-arylpropanal, giving the cycloadducts **3b-3f** in good to high yields with good diastereoselectivities and excellent enantioselectivites. Substitutent at the *meta*- and *ortho*-position (Ar = 3-ClC_6H_4, 2-ClC_6H_4) were also tolerated (**3g**, **3h**). It was noteworthy that the aliphatic α-chloroaldehydes worked as well as the aromatic ones with either short or long alkyl chains (**3i-3n**). Substituent on the phenyl ring of aurone had no apparent negative effect for the reaction (**3o**). The aurone derivative with isopropyl ester resulted some decrease of enantioselectivity (**3p**) compared to ethyl ester. Unfortunately, the reaction of 2-chloro-2-phenylacetaldehyde (R = Ph) did not give the desired cycloadduct under current condition.

The plausible catalytic cycle was depicted in Fig. 2. Removal of the proton of the NHC precursor **E** by base gives the free *N*-heterocyclic carbene **E'** as the active catalyst, which reacts with the aldehyde to afford classic Breslow intermediate **I**. The leaving of the chloride under base gives enolate intermediate **II**, which reacts with aurones in a Diels-Alder mode to give cycloadduct **III**. The elimination of NHC catalyst from adduct **III** affords the desired benzofuran-fused dihydropranone **3** and furnish the catalytic cycle.

The *cis*-configuration of dihydropyranone was established by the analysis of its NOE spectra (Supporting information for details) and supported by our previous work [17]. The *cis*-selectivity could be rationalized by the traditional transitional state in Diels-Alder reaction (Fig. 2, TS A).

In summary, the NHC-catalyzed [4 + 2] annulation of α-chloroaldehydes and aurones was developed, giving the corresponding benzofuran-fused dihydropyranones in good to high yields with good diastereoselectivities and excellent enantioselectivities. The related NHC-catalyzed annulation reactions are underway in our laboratory.

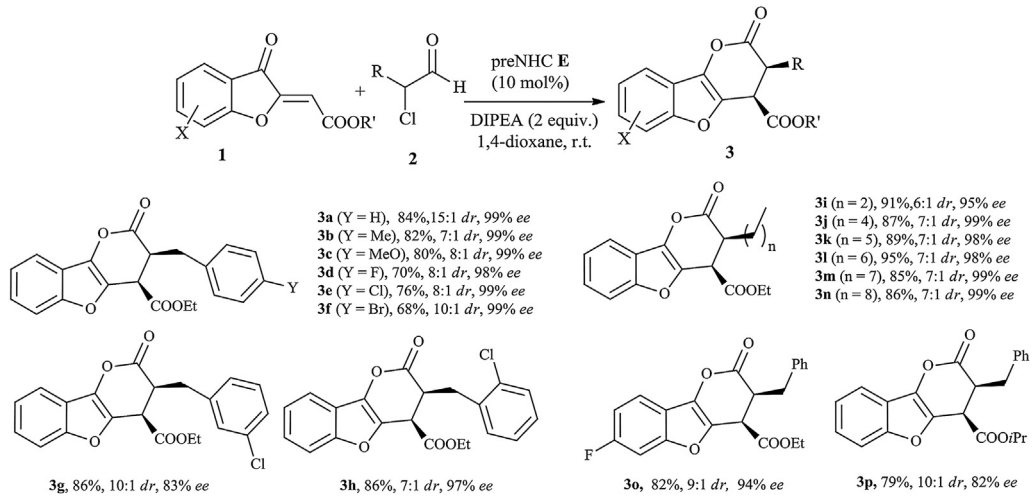


Fig. 1. NHC-catalzyed synthesis of benzofuran-fused dihydropyranones. (**3a-n**) Variation of α-chloraldehydes, (**3o** and **3p**) variation of aurones.

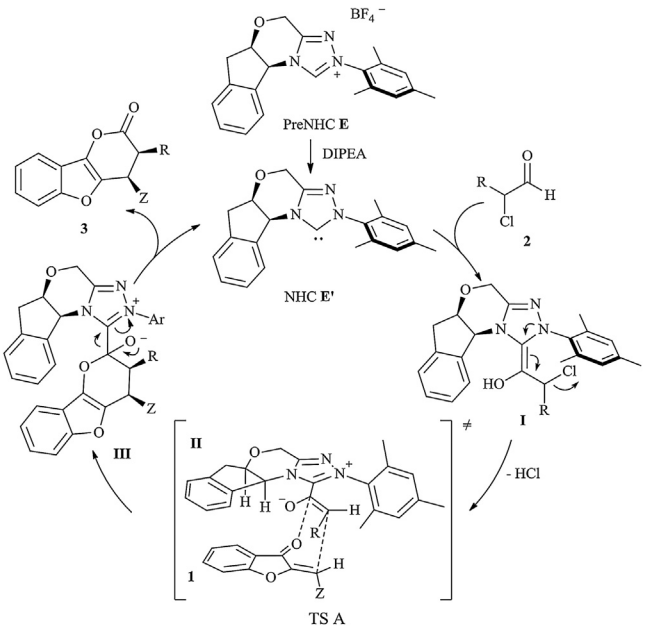


Fig. 2. Plausible catalytic cycle.

Acknowledgments

The Financial support from the National Natural Science Foundation of China (Nos. 21425207, 21521002), and the Chinese Academy of Sciences is greatly acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cclet.2018.03.003.

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