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Enantioselective Synthesis of Bicyclic δ-Lactones via N-Heterocyclic Carbene-Catalyzed Cascade Reaction

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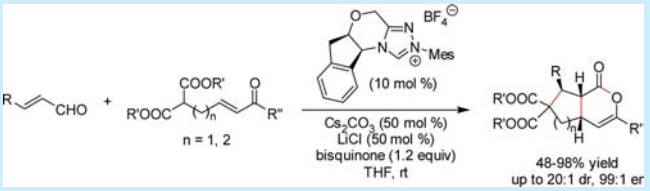
Supporting Information

ABSTRACT: The N-heterocyclic carbene-catalyzed cascade reaction of enals with malonates to give bicyclic δ-lactones was developed. The cyclopentane- and cyclohexane-fused δ-lactones with three continued stereocenters were obtained in high yields with excellent diastereo- and high enantioselectivities.

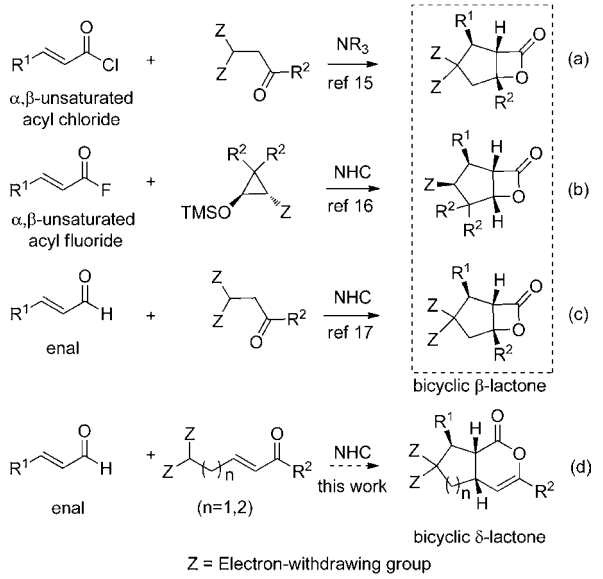


In the past, N-heterocyclic carbenes (NHCs) have been demonstrated as powerful catalysts for various organic reactions. Beyond the classical NHC-catalyzed benzoin reactions[1] and Stetter reactions[2] of aldehydes, the NHC-catalyzed extended umpolung of functionalized aldehydes, such as enals[3] and α-chloroaldehydes,[4] have been extremely successful. In 2007 Scheidt et al. reported the NHC-catalyzed generation of α,β-unsaturated acyl azolium from allylic alcohols under the oxidation of MnO_2.[5] The generation of this α,β-unsaturated acyl azolium from α,β-unsaturated esters,[6] enals with oxidant,[7] ynals,[8] and α-bromoenals[9] has also been successfully established. As a versatile 1,3-biselectrophile, the α,β-unsaturated acyl azolium has been applied for the synthesis of various heterocycles via its [3 + 2][10] and [3 + 3] annulation reaction.[11]

Cascade reactions, which form multiple bonds in a single operation, are very useful in organic synthesis,[12] especially for the synthesis of cyclic compounds.[13] In 2011, Studer et al. reported the NHC-catalyzed cascade reaction for the synthesis of indanodihydropyranones.[14] In 2013, Romo et al. reported the chiral amine-catalyzed generation of α,β-unsaturated acyl ammonium from acyl chloride and its following cascade Michael addition/aldol/lactonization for the synthesis of cyclopentane-fused β-lactones (Scheme 1, reaction a).[15] At the same time, Lupton et al. reported the related NHC-catalyzed cascade of acyl fluoride with donor−acceptor cyclopropanes (Scheme 1, reaction b).[16] Recently, the cascade reaction of enals for bicyclic β-lactones was explored by Studer et al. (Scheme 1, reaction c).[17] In this letter, we report the NHC-catalyzed cascade reaction for the synthesis of cyclopentane- and cyclohexane-fused δ-lactones (Scheme 1, reaction d), which is a key motif in many pharmaceutical compounds and natural products.[18]

Initially, the reaction of ε-oxo-γ,δ-malonate **1a** and cinnamaldehyde **2a** was investigated as the model reaction (Table 1). We were encouraged to find that the desired bicyclic δ-lactone **4aa** was obtained in 10% yield for the reaction catalyzed by 10 mol % of achiral NHC **A**′ in the presence of 1.2 equiv of bisquinone **3** as the oxidant and 1,8-diazabicylo-[5.4.0]undec-7-ene (DBU) as a base (Table 1, entry 1). More encouraging, using the aminoindanol-derived tetracyclic NHC **B**′[19] as the catalyst led to better results, giving the product **4aa** in 39% yield with exclusive diastereoselectivity but very low enantioselectivity (entry 2).

Scheme 1. Catalytic Cascade Reactions for the Synthesis of Bicyclic β- and δ-Lactones



Pioneered by Scheidt et al.,[20] Lewis acids were found to be efficient cooperative catalysts in the NHC-catalyzed reactions to improve the reactivity and selectivities.[21] Thus, several Lewis acids were then investigated for the reaction, and we were satisfied to find that the reaction with 50 mol % LiCl as the additive gave the product in 73% yield with dramatically

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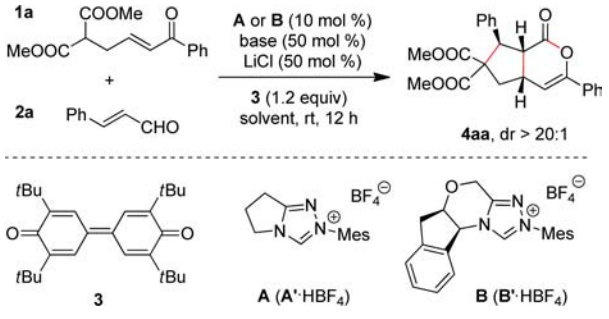
Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	base	solvent	yield (%)[b]	er[c]
1[d]	A	DBU	THF	10	–
2[d]	B	DBU	THF	39	59:41
3	B	DBU	THF	73	93:7
4	B	DBU	CH_2Cl_2	61	84:16
5	B	DBU	toluene	49	74:26
6	B	DBU	CH_3CN	59	80:20
7	B	DIPEA	THF	66	90:10
8	B	DMAP	THF	78	93:7
9	B	K_2CO_3	THF	86	92:8
10	B	Cs_2CO_3	THF	91	93:7
11[d]	B	Cs_2CO_3	THF	35	69:31

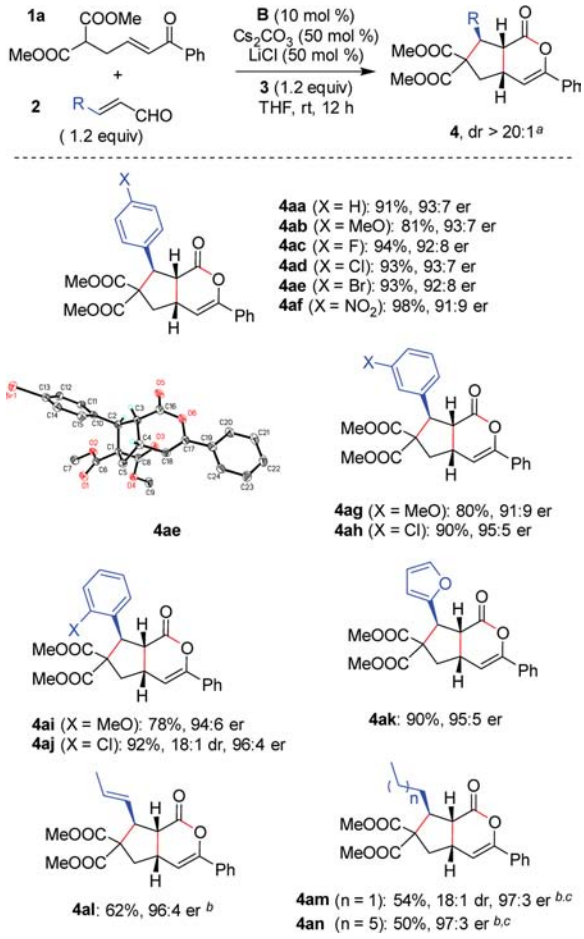
[a]General reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), cat **A**/**B** (10 mol %), base (50 mol %), LiCl (50 mol %), and bisquinone **3** (1.2 equiv). [b]Isolated yield. [c]Determined by HPLC analysis. [d]No LiCl was added.

improved enantioselectivity (93:7 er, entry 3). Screening of solvents revealed that the reaction succeeded in dichloromethane, toluene, and acetonitrile, while THF was the best choice (entries 3−6). Several bases were then examined for the reaction. It was found that all the bases DIPEA, DMAP, K_2CO_3 and Cs_2CO_3 worked well (entries 7−10), while the base Cs_2CO_3 afforded the best yield with a high enantiomeric ratio (entry 10). It should be noted that only a low yield and er resulted when LiCl was not added for the reaction with Cs_2CO_3 as the base (entry 11).

With suitable conditions in hand, the substrate scope of enals **2** was then investigated for the cascade reaction (Scheme 2). The aryl enals with electron-donating (R = 4-$MeOC_6H_4$) or electron-withdrawing substituents (R = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$) all worked well, giving the desired bicyclic δ-enollactones **4ab**−**4af** in high yields with excellent diastereo- and high enantioselectivities. The absolute configuration of bicyclic δ-lactone **4ae** was established by the X-ray analysis of its crystal. In addition, the *meta*-substituent and *ortho*-substituents of enals were well tolerated (**4ag**−**4aj**). The enal with 2-furyl afforded the bicyclic δ-lactone **4ak** in 90% yield with high enantioselectivity. Notably, enal with β-alkenyl worked well for the reaction albeit some excess of the enal (1.5 equiv) was required to give a good yield of product **4al**. Furthermore, the reaction of enals with β-alkyl gave the products (**4am**−**4an**) in moderate yields with high diastereo- and enantioselectivities when the reaction was carried out at 40 °C instead of room temperature.

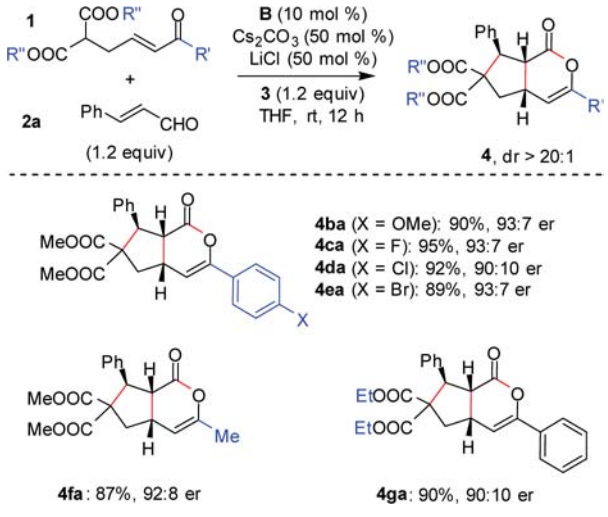
Subsequently, variation of the malonates was examined (Scheme 3). As expected, both electron-donating and -withdrawing substituents of cinnamylmethyl malonates worked well to give the bicyclic δ-enollactones (**4ba**−**4ea**) in high yields with exclusive diastereo- and excellent enantioselectivities. ε-

Scheme 2. Variation of Enals



[a]dr >20:1 unless otherwise specified. [b]1.5 equiv of enal **2** and bisquinone **3** were used. [c]Conducted at 40 °C.

Scheme 3. Variation of Malonates



Oxo-γ,δ-malonate with alkyl (R′ = Me) also worked, affording the bicyclic δ-lactone **4fa** in 87% yield with 92:8 er. Ethyl malonate worked as well as methyl malonate (**4ga**).

The reaction for the synthesis of cyclohexane-fused δ-lactone **6** from malonate **5** was then explored (Scheme 4). We were happy to find that the desired δ-lactone **6a** was obtained in 68%

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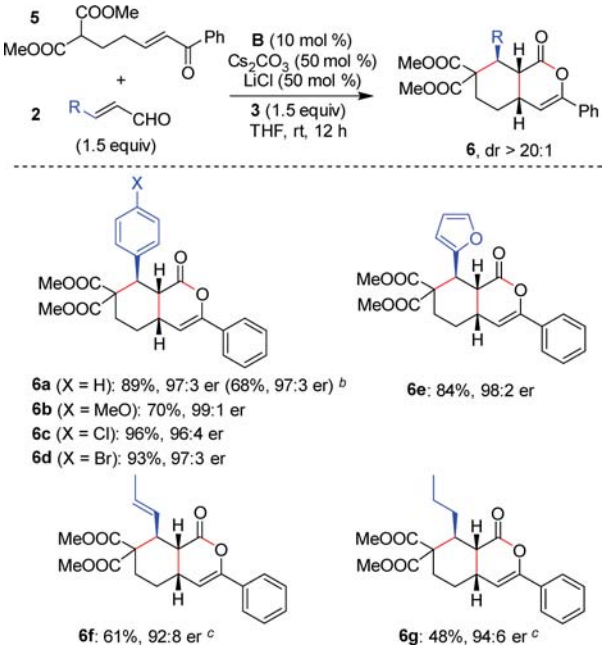
Scheme 4. Synthesis of Cyclohexane-Fused δ-Lactones[a]



[a]General reactions: **5** (0.2 mmol), **2** (1.5 equiv), **B** (10 mol %), Cs_2CO_3 (50 mol %), LiCl (50 mol %), **3** (1.5 equiv). [b]Reaction using 1.2 equiv of enal **2** and bisquinone **3**. [c]Conducted at 40 °C.

yield with 97:3 er under the same conditions as in Schemes 2 and 3. The yield could be improved to 89% when excess enal **2a** and bisquinone **3** (1.5 equiv) were applied. Various enals were then tested for the reaction. Enals with *para*-electron-donating (R = 4-$MeOC_6H_4$) or electron-withdrawing substituents (R = 4-ClC_6H_4, 4-BrC_6H_4) worked well, giving the bicyclic δ-lactones (**6b**−**6d**) in high yields with high enantioselectivities. The enal with 2-furyl afforded the product **6e** in 84% yield with 98:2 er. As expected, the reaction of enals with the β-alkenyl and alkyl chain gave the desired bicyclic δ-lactones **6f**−**6g** in moderate yield with high enantioselectivities when carried out at 40 °C.

The plausible catalytic cycle is depicted in Figure 1. The addition of NHC to enal **2** gives the vinyl Breslow intermediate **I**, which is oxidized by bisquinone **3** to afford the key intermediate of α,β-unsaturated acyl azolium **II**. The reactive enolate **III** could be readily generated from malonate **1** or **5** in the presence of a base.[15] The Michael addition of enolate **III** to α,β-unsaturated acyl azolium **II** forms the first C−C bond and generates a new enolate **IV**. The intramolecular Michael addition of enolate **IV** makes the second C−C bond and furnishes the intermediate **V** with a cyclopentane or cyclohexane ring. The δ-lactonization of intermediate **V** finalizes the bicyclic δ-lactone **4** or **6** and regenerates the NHC catalyst. Currently, an alternative pathway with acylation followed by Clasien rearrangement, Michael addition, and lactonization could not be ruled out.[22]

The possible transition states to rationalize the stereochemical outcome are depicted in Figure 2. The coordination of the lithium with the enolate of malonate and α,β-unsaturated acyl azolium helps to assemble the complex and directs the enolate to attack α,β-unsaturated acyl azolium in a Michael addition manner from the less sterically demanded Re face (TS A). A chair-type conformation of intermediate **IV** may facilitate the second Michael addition and result in high stereoselectivity

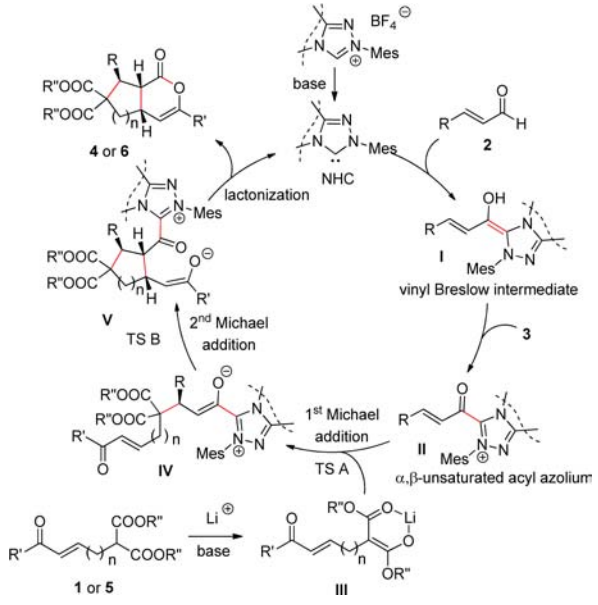


Figure 1. Plausible catalytic cycle.

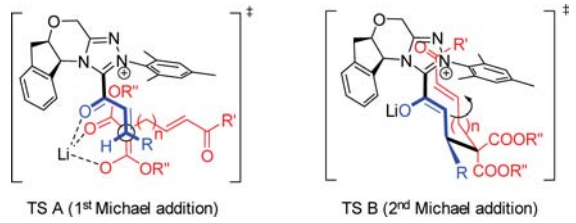


Figure 2. Proposed stereochemical modes.

for the formation of the second C−C bond (TS B) to give the cyclopentane or cyclohexane ring.

In conclusion, the NHC-catalyzed cascade reaction via Michael/Michael addition/lactonization of enals with malonates to generate bicyclic δ-lactones was developed. The cyclopentane- and cyclohexane-fused δ-lactones with three continued stereocenters were obtained in high yields with excellent diastereo- and high enantioselectivities. In this reaction, two C−C bonds and one C−O bond were formed stereoselectively in one catalytic operation. Further development of the NHC-catalyzed cascade reactions is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02695.

Experimental details and NMR and HPLC spectra for obtained compounds (PDF)
X-ray data for **4ae** (CIF)

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Notes

The authors declare no competing financial interest.

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