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Enantioselective Synthesis of Substituted δ-Lactones by Cooperative Oxidative N-Heterocyclic Carbene and Lewis Acid Catalysis

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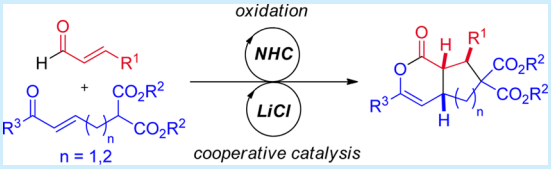
Supporting Information

ABSTRACT: Efficient construction of complex cylcopentane- or cyclohexane-fused δ-lactones employing redox activation of enals using a chiral N-heterocyclic carbene and LiCl as cooperative catalysts is described. The organocascade proceeds with excellent diastereo- (>99:1) and enantioselectivity (up to >99% ee) and comprises the formation of three bonds with three contiguous stereocenters.



Several powerful strategies have been developed for the stereoselective construction of complex molecules starting from readily accessible materials using organocatalysis.[1] Along these lines, N-heterocyclic carbene (NHC) catalyzed cascade reactions have been found to be highly valuable.[2] Stereoselective construction of highly substituted five- and six-membered carbocycles by NHC catalysis is a highly active research area. Notably, such carbocycles can be found as important substructures in many bioactive natural products[3] and pharmaceuticals.

For example, iridoids are a class of compounds consisting of a cyclopentane ring fused to a six-membered oxygen heterocycle (Figure 1). Iridoids are monoterpenoid natural products with

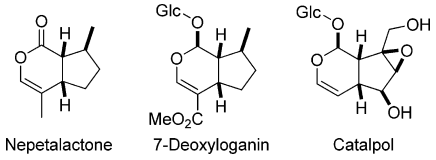
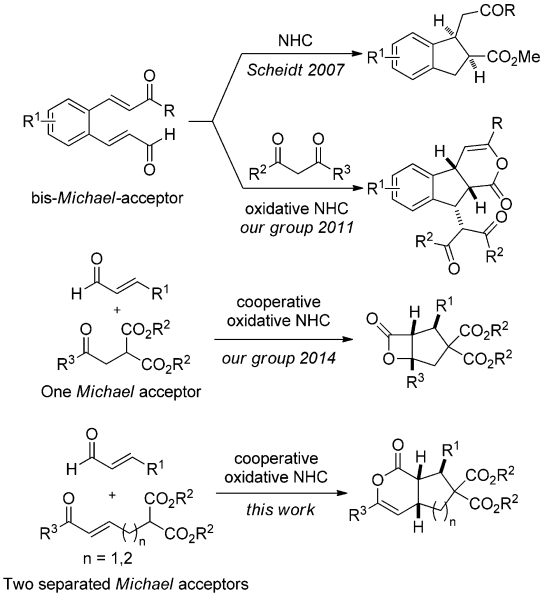


Figure 1. Biologically active iridoids.

over 250 known members occurring in marine and terrestrial ecosystems.[4a] They have gained widespread attention due to their diverse pharmacological effects, showing anticancer, antibacterial, and antiflammatory activities.[4b,c,5] Surprisingly, only a few methods are known for the synthesis of iridoid type lactones which mostly require multiple synthetic steps.[6]

We report herein a strategy for the construction of the iridoid core structure using oxidative NHC catalysis.[7,8] NHC-catalysis has been successfully used to build up 5-membered carbocycles via conjugate addition reactions. For example, in 2007 Scheidt and co-workers published an elegant NHC-catalyzed sequence for the preparation of disubstituted indanes using intramolecular homoenolate chemistry (Scheme 1).[9] Four years later, we disclosed an efficient organocascade for the synthesis of 1,2,3-substituted indanes by oxidative NHC catalysis.[10] In this work, the two Michael acceptors used in the cascade to build up the 5-membered carbocycle are integrated into the same molecule separated from each other by an arene moiety. This particular

Scheme 1. NHC-Catalyzed Reactions



substrate design restricts the method to the preparation of indane derivatives, and fully saturated cyclopentane compounds cannot be accessed by this approach. We also showed that α-substituted malonates react by oxidative NHC catalysis with enals to give highly substituted cyclopentanes bearing a β-lactone moiety.[11] LiCl was used as a cooperative catalyst, and only a single Michael acceptor is involved in the cascade.

As a further extension, we planned to design an intermolecular organocascade with two separated Michael acceptors as reaction partners. As compared to the previous reports, substrates are more readily prepared and the iridoid skeleton should be easily accessible via this double Michael pathway using oxidative NHC catalysis. The organocascade involves the formation of two C−C

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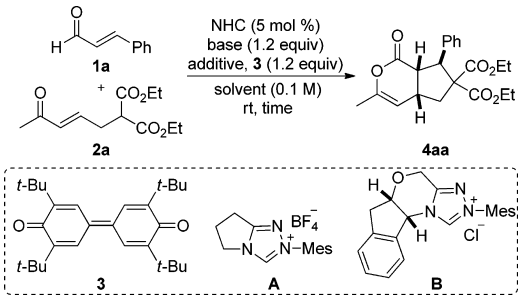
bonds along with one C−O bond with three contiguous stereogenic centers. Notably, there are only a few examples of double Michael addition reactions using α,β-unsaturated acyl azoliums as intermediates.[12]

Investigations of this organocascade commenced with cinnamaldehyde **1a** and malonate **2a** as the model substrates. Bisquinone **3**[13] (1.2 equiv) was chosen as the oxidant, and triazolium salts **A**[14] and **B**[15] were selected as achiral and chiral NHC precatalysts in the optimization studies. It was found that, with achiral triazolium salt **A** (10 mol %) and DBU as a base in THF, **4aa** comprising the core structure of the iridoid natural products was obtained in 65% yield (Table 1, entry 1). Lactone

Table 1. Reaction Optimization



entry	LiCl (mol %)	base	cat.	solvent	time (h)	yield (%)[a]	ee (%)[b]
1	–	DBU	**A**[c]	THF	3	65	–
2	–	DBU	**B**[c]	THF	24	trace	n.d.
3	–	DBU	**B**[c]	CH_2Cl_2	24	trace	n.d.
4	–	DBU	**B**[c]	toluene	4	15	n.d.
5	20	DBU	**B**[c]	THF	2.5	65	74
6	20	DBU	**B**[c]	CH_2Cl_2	1	13	n.d.
7	20	iPr$_2$EtN	**B**	THF	2	97	88
8	20	iPr$_2$EtN	**B**	CH_2Cl_2	5.5	62	87
9	20	iPr$_2$EtN	**B**	toluene	7	49	84
10	20	iPr$_2$EtN	**B**	MeCN	7	<15	n.d.
11	20	Cs_2CO_3	**B**	THF	5	86	88
12	20	DABCO	**B**	THF	0.5	97	90
13	10	DABCO	**B**	THF	2	78	82[d]

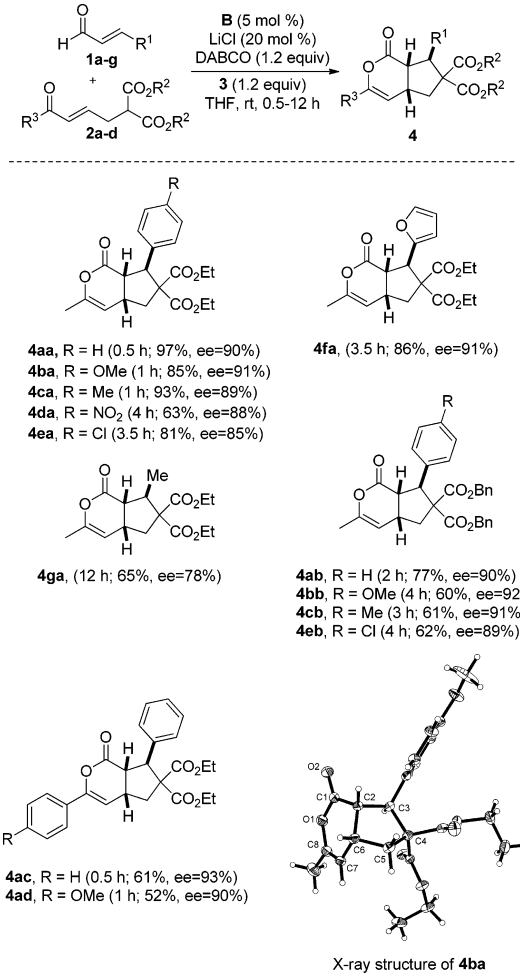
[a]Yield of the isolated product, and all reactions were run with 0.1 mmol of **2a**. [b]Determined by HPLC (see Supporting Information). [c]10 mol % catalyst was used. n.d. = not determined. [d]Run with 0.2 mmol of **2a**.

4aa was formed with complete diastereocontrol. Disappointingly, the enantioselective version upon switching from catalyst **A** to **B** (10 mol %) provided only a trace amount of the desired bicycle **4aa**. Varying solvents from THF to toluene and prolonging the reaction time afforded a slightly improved result. However, a poor yield (15%) was still obtained in the best case and decomposition of the starting material was noticed under the applied conditions (Table 1, entries 2−4).

To increase reactivity, LiCl was added as a Lewis acid because we and others have shown that cooperative Lewis acids improve the efficiency of such organocascades.[11,16] LiCl as a cocatalyst should have the ability to interact with both the substrate **2a** as well as the *in situ* generated acyl azolium ion (LUMO activation). Pleasingly, in the presence of 20 mol % LiCl and DBU as a stoichiometric base, lactone **4aa** was formed with chiral catalyst **B** in 65% yield with complete diastereocontrol and 74% enantioselectivity (Table 1, entry 5). Varying the solvent from THF to CH_2Cl_2 provided a diminished result (only 13% of **4aa** was isolated) (Table 1, entry 6). A far better outcome (nearly quantitative yield and an increase in ee from 74% to 88%) was observed upon switching to iPr$_2$EtN as a base in THF (Table 1, entry 7). Other solvents such as CH_2Cl_2, toluene, and MeCN in combination with iPr$_2$EtN did not provide better results (Table 1, entries 8−10). With Cs_2CO_3 in THF, selectivity remained high but the yield slightly decreased (Table 1, entry 11). The best result was achieved with 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base in THF, and **4aa** was isolated in an excellent yield (97%) and high enantioselectivity (90% ee) (Table 1, entry 12). Reducing the loading of LiCl provided a lower yield and a lower selectivity (Table 1, entry 13).

With optimized reaction conditions in hand, we explored the scope and limitations of the organocascade (Scheme 2). Keeping

Scheme 2. Scope of the Reaction and X-ray Structure of 4ba (Structure Is Shown with 50% Probability)



substrate **2a** as a ketone component, various enals were tested first. We found that cinnamaldehyde derivatives bearing electron-donating substituents at the *para*-position of the arene ring are working well while a slight decrease in ee was observed for the corresponding derivatives bearing para-electron-withdrawing substituents. In particular the para-chloro-substituted compound provided a lower ee (see **4ea**). The absolute configuration of **4ba** was unambiguously assigned by X-ray crystallography (see Scheme 2). The configuration of all other iridoid type lactones **4** prepared in this study was assigned in analogy. Notably, all compounds prepared in this series were formed with complete

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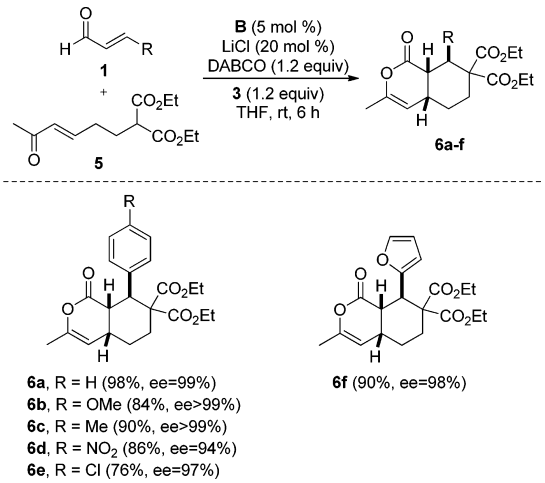
diastereocontrol. The 2-furylenal **1f** also delivered the targeted lactone **4fa** which was isolated in 86% yield with 91% ee. A lower selectivity was achieved with crotonal (see **4ga**) showing the aryl substituent in the cinnamaldehyde derivatives positively influences selectivity.

We next investigated the effect of the ester groups in the malonate component **2** on the selectivity and found that benzyl malonate **2b** (R^2 = Bn, R^3 = Me) provides the lactones **4ab**−**4cb** and **4eb** in the reaction with enals **1a**−**c** and **1e**, as compared to the ethyl malonates with slightly improved enantioselectivities. A malonate of type **2** bearing two different ester groups (CO_2Et, CO_2Bn) reacted with **1a** in low diastereoselectivity with respect to the quaternary malonate C-center (dr = 1.6:1, 63%, ee = 87% for each isomer; not shown in Scheme 2, see Supporting Information). We next replaced the methyl group in vinyl ketone **2a** by an aryl substituent. Reactivity in the reaction with **1a** was lower, but selectivity remained high for the phenyl or *p*-methoxyphenyl-substituted vinyl ketones **2c** and **2d** (see **4ac** and **4ad**).

To demonstrate flexibility, we tested homologue **5** in the reaction with various enals under the optimized conditions which should deliver bicyclic lactones comprising two 6-membered rings (Scheme 3). Gratifyingly, with cinnamaldehyde **1a** the

Scheme 3. Synthesis of Cyclohexane-Fused *δ*-Lactones

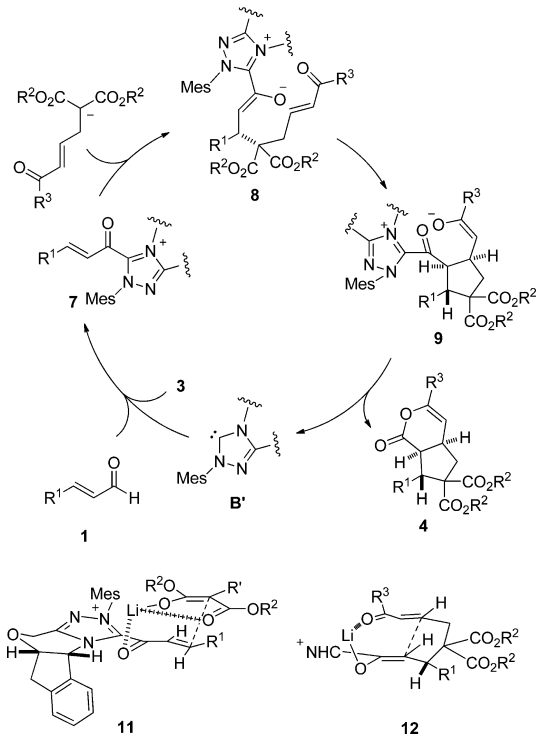


targeted cyclohexane-fused *δ*-lactone **6a** was formed in 98% yield with excellent diastereoselectivity (99:1) and excellent enantioselectivity (99% ee).

The higher reactivity and selectivity obtained with **5** as compared to the lower homologues **4** are general as could be shown by the reactions of enals **1b** and **1c** bearing electron-rich substituents at the *para*-position of the aryl group. The lactones **6b** and **6c** were isolated in excellent yields and enantioselectivities (>99% ee). The relative and absolute configurations of **6b** were assigned on the basis of X-ray analysis (see Supporting Information), and the other derivatives were assigned in analogy. Also the more electron-poor enal **1d** with the *p*-nitro substituent (a problematic substrate with **2a**) gave, in the reaction with **5**, the corresponding lactone **6d** with high yield and selectivity, and even the para-chloro substituted cinnamaldehyde **1e** showed, in the formation of **6e**, good yield and selectivity. Moreover, a very good result was also achieved with the furyl substituted enal **1f** to provide **6f** with complete diastereocontrol with 98% ee and high isolated yield (90%).

Our suggested reaction mechanism for the formation of lactone products of type **4** is depicted in Scheme 4. Formation of

Scheme 4. Suggested Mechanism



homologues **6** works in analogy. At first, enal **1** reacts with carbene **B**′ generated by deprotonation of **B** to generate the Breslow intermediate which is oxidized by **3** to provide the corresponding acyl azolium ion **7**. Deprotonated **2** then engages in a 1,4 addition[8f] to the acylazolium species to give enolate **8**. Michael-type cyclization of the enolate onto the enone moiety affords **9** which eventually undergoes intramolecular lactonization to release the product and catalyst **B**′. Alternatively, enolate **8** can undergo an *endo*-hetero-Diels−Alder reaction which after fragmentation of **B**′ also delivers the product **4**.

The absolute stereochemistry can be explained by considering model **11**, where the Li-ion interacts with both the acylazolium and malonate. The *cis*-selective second C−C bond formation is controlled by complexation of the Li-enolate with the enone oxygen atom (see **12**). The significantly higher enantioselectivities obtained for the 6,6-bicyclic systems **6** as compared to those of compounds **5** deserve some comments. It is not obvious why the initial conjugate addition of the malonate derived from **5** occurs with far higher stereoselectivity than the initial addition of the **2**-derived malonates. We currently assume that in both cases the addition is not perfectly stereoselective. In the case of intermediate **8**, *cis*-5-*exo* cyclization is fast for both diastereoisomers and the initial selectivity is reflected by the ee obtained for the final product. However, for the corresponding enolate derived from **5**, only the major diastereoisomer cyclizes after lactonization eventually leading to **6**. The minor diastereoisomer likely undergoes a retro-Michael-addition to **7** and **5**-Li. Hence, the nonperfect selectivity is corrected by the reversibility of the initial Michael addition accompanied by an inefficient (very slow) *cis*-cyclization of the minor diasteroisomer enolate. This error correction[10] ensures high selectivity and also allows very high overall yields to be obtained.

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In summary, the introduced organocascade utilizing NHC and LiCl as cooperative catalysts offers an efficient approach to cyclopentane- and cyclohexane-anellated δ-lactones by successive formation of three new σ-bonds along with three stereocenters and two rings in a single sequence from readily prepared starting materials. LiCl turned out to be essential for obtaining high yields in the enantioselective version of the cascade. Our approach opens novel routes to the synthesis of valuable natural product analogues containing substituted cyclcopentanes and cyclohexanes fused with a lactone moiety. The described organocascade reactions are experimentally easy to perform by simply mixing the catalyst, substrates, and reagents at ambient temperature. All reactions occur with complete diastereocontrol with good to excellent enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01932.

Experimental details, characterization data for the products (PDF)

Supplementary crystallographic data (CCDC-1414262 and CCDC-1414263) (CIF)

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Notes

The authors declare no competing financial interest.

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