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Letter

NHC-Catalyzed Cascade Reaction between β-Methyl Enals and Dienones for Quick Construction of Complex Multicyclic Lactones

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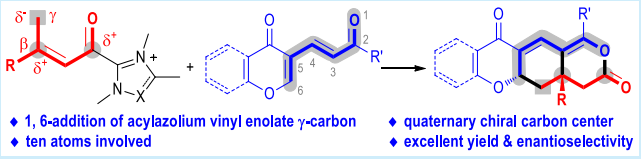
ABSTRACT: A NHC-promoted cascade reaction between β-methyl enal and dienone is developed for quick access to multicyclic lactone molecules bearing quaternary chiral carbon centers. Our study constitutes the first 1,6-addition of the acylazolium vinyl enolate γ-carbon via NHC catalysis and provides rapid access to complex lactone molecules that are otherwise difficult to prepare. The structurally sophisticated lactone products bearing up to four fused ring structures are afforded in up to quantitative yields with good to excellent enantioselectivities.



The construction of structurally sophisticated molecules through assembly of simple starting materials via short routes is of both fundamental and practical value in organic synthesis. One such class of complex molecules consists of lactones fused with multiple rings and challenging chiral centers.[1] Shown in Figure 1a are examples of several natural products and bioactive molecules containing multicyclic lactones bearing chiral quaternary carbon centers.[2] For instance, Limonin, a triterpenoid isolated from plants of the Rutaceae and Meliaceae families,[2a,b] contains a lactone moiety fused with five other rings and bears multiple challenging chiral centers. Limonin can be used as an anti-inflammatory,[2h] anticancer,[2i] antibacterial,[2g] and antioxidant[2e] reagent. Aglatomin B is a naturally existing pregnane steroid that has been isolated from *Aristolochia tomentosa*.[2c] Oxandrolone,[2d,f] can be used as a steroid drug to help promote the growth of muscle tissues. Therefore, the construction of multicyclic lactone molecules bearing quaternary chiral carbon centers is of great interest and significance.

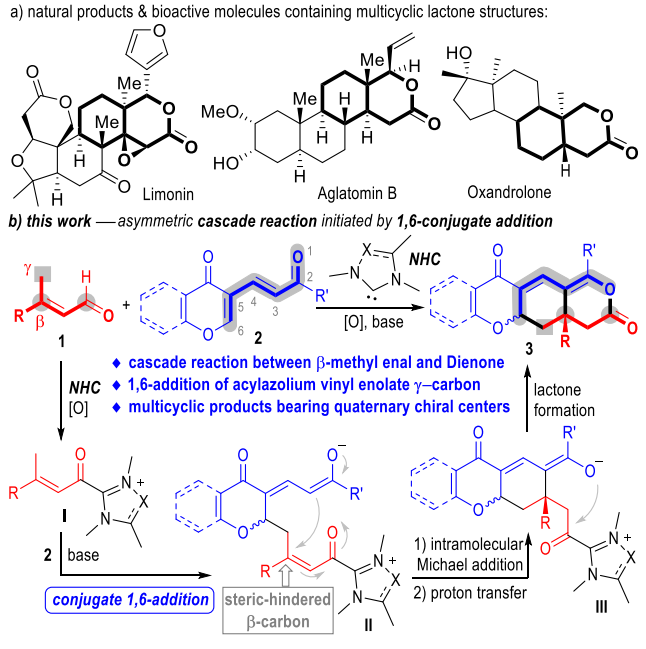


Figure 1. Bioactive multicyclic lactone molecules and the NHC catalytic protocol for facile synthesis of multicyclic lactones.

Due to the structural complexity and the frequent presence of challenging chiral centers, it remains difficult to prepare this class of multicycles and typically long synthetic steps are required.[3] Precisely designed cascade reactions can in principle provide shortcut routes toward these complex molecules.[4] In the area of organocatalysis, the use of chiral amine catalysts (via enamine and/or iminium catalytic pathways)[5] has led to a relatively large set of impressive cascade reactions, as pioneered by List,[5a] MacMillan,[5b] and others. N-Heterocyclic carbene (NHC) organocatalysis offers several activation modes and multiple reactive intermediates that can be nicely designed into cascade reactions.[6] However, the reported reactions mostly involve a relatively small number of atoms in the cascade reactions.

Here we disclose a new cascade reaction between β-methyl enals and dienones promoted by NHC catalysts for quick construction of structurally complex multicyclic lactone molecules (Figure 1b). The reaction starts with β-methyl enals **1** and dienones[7] **2** as the substrates. Ten atoms from the

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two substrates were involved in the reaction cascade via a formal [4+2] followed by a lactone formation process to be installed in the multicyclic lactone products bearing challenging quaternary carbon centers. Briefly, β-methyl enal **1** can react with NHC catalysts under oxidative conditions and gives the acylazolium intermediate **I** bearing a nucleophilic γ-carbon.[8] Intermediate **I** then reacts with the dienone substrate **2** through a conjugate 1,6-addition process and gives intermediate **II**. An intramolecular aldol reaction readily occurs within intermediate **II**, and intermediate **III** bearing a sterically congested quaternary carbon center is then generated after an additional proton transfer process. Finally, the target multicyclic lactone product **3** is afforded through lactone formation reaction of intermediate **III**, with the NHC catalyst released to complete the catalytic cycle.

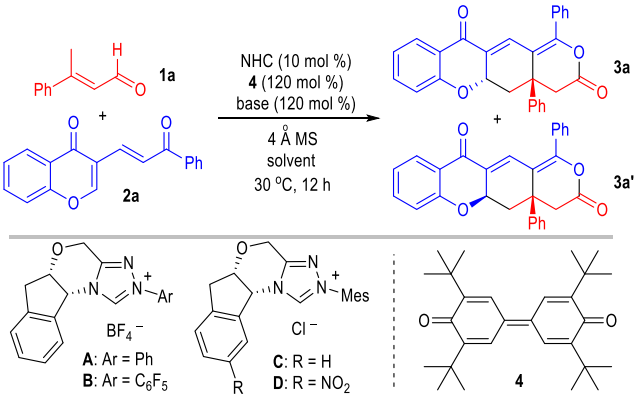
In the past decade, NHC-catalyzed 1,6-conjugate addition reactions[9] have been reported by Enders,[9b,d,h] Lupton,[9e] Ye,[9g] and others. Our study constitutes the first 1,6-addition of the acylazolium vinyl enolate γ-carbon via NHC catalysis and provides rapid access to complex lactone molecules that are otherwise difficult to prepare.

β-Methyl cinnamaldehyde **1a** and dienone substrate **2a** were chosen as the model substrates to evaluate the reaction conditions of the NHC-catalyzed cascade reaction in the presence of oxidant **4**[10] (Table 1). Various NHC precatalysts were first evaluated with Cs_2CO_3 used as the base in THF (Table 1, entries 1−4). Aminoindanol-derived NHC precatalysts bearing N-Ph[11] and N-C_6F_5[12] groups were not effective for this process (entries 1 and 2, respectively), while those bearing N-Mes groups[13] could give the desired products in promising yields and enantioselectivities (entries 3 and 4). The use of basic additives with weak basicities could give the products in higher yields with retention of the enantio- and diastereoselectivities (entries 6 and 7). The er and dr values of the product could be further increased with diethyl ether used as the reaction solvent (entry 8). Additional screening of the reaction solvents did not show further improvements in the reaction outcomes (entries 9 and 10).

Having identified a suitable reaction condition for the formal cascade reaction (Table 1, entry 8), we then examined the scope of the enal substrates (**1**) (Scheme 1). Both electron-donating and electron-withdrawing substituents could be installed at positions 3 and 4 of the phenyl ring of enal **1a**, with both diastereomers of the corresponding products afforded in excellent yields and enantioselectivities (Scheme 1, **3b** + **3b′** to **3e** + **3e′**). The dr values of the final products could be dramatically increased when using enal substrates (**1**) bearing 2-substituents on the β-phenyl rings (**3f** and **3g**). The β-phenyl ring of **1a** could also be switched to a 2-naphthyl group (**3h**) and various heteroaromatic groups (**3i** + **3i′** to **3k** + **3k′**), with the target products afforded in good to excellent yields and enantioselectivities. Note that aliphatic enal substrates also worked well in this cycloaddition process, and the desired multicyclic latone products could be obtained in good yields and er values with inverse diastereoselectivities (**3l** + **3l′** and **3m** + **3m′**).

This NHC-catalyzed formal cascade reaction also proceeded well with dienone substrates (**2**) bearing different substitution patterns (Scheme 2). For example, substituents could be installed on the chromanone moiety of dienone substrate **2a**, with the target products afforded in good to excellent yields and enantioselectivities regardless of their electronic properties (Scheme 2, **3n** + **3n′** to **3s** + **3s′**). The phenyl group of enone

Table 1. Optimization of Reaction Conditions[a]



entry	NHC	base	yield (%)[b]	dr (**3a**:**3a′**)[c]	er[d]
1	**A**	Cs_2CO_3	<5	–	–
2	**B**	Cs_2CO_3	<5	–	–
3	**C**	Cs_2CO_3	74	2:1	83:17/53:47
4	**D**	Cs_2CO_3	57	2:1	94:6/96:4
5	**D**	DBU	<5	–	–
6	**D**	DIEA	89	3:1	94:6/97:3
7	**D**	NaOAc	99	3:1	94:6/97:3
8[e]	**D**	NaOAc	96	4:1	99:1/98:2
9[f]	**D**	NaOAc	90	2:1	95:5/91:9
10[g]	**D**	NaOAc	93	1:1	88:12/75:25

[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), NHC (0.01 mmol), base (0.12 mmol), **4** (0.12 mmol), 4 Å molecular sieves (100 mg), THF (2.0 mL), 30 °C, 12 h. Absolute configurations of products **3a** and **3a′** were assigned by X-ray analysis of their single crystals. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, and DIEA = *N*,*N*-diisopropylethylaminediisopropylethylamine. [b]Combined isolated yield of **3a** and **3a′**. [c]dr values of the products (**3a**:**3a′**) were determined by ^{1}H NMR on the crude reaction mixture. [d]er values of **3a** and **3a′** were determined via HPLC on a chiral stationary phase. [e]Ether as the solvent, 24 h. [f]CH_2Cl_2 as the solvent. [g]CH_3CN as the solvent.

substrate **2a** could be replaced with various substituted benzene rings (**3t** + **3t′** to **3w** + **3w′**) or a styryl group (**3x** + **3x′**) without obvious erosion of the product yields or stereoselectivities. Replacing the phenyl group on **2a** with a methyl group resulted in a decrease in the product dr value, with both diastereomers of the product (**3y** + **3y′**) afforded in a 1:1 ratio with excellent enantioselectivities.

As a technical note, both diastereomers of the final products (**3** and **3′** in Schemes 1 and 2) could be easily separated through column chromatography and were obtained as single diastereomers. Moreover, the diastereoisomers of products **3** and **3′** could not be transformed into each other under strong basic conditions. The formal cascade reaction between enal **1** and dienone **2** could also be carried out on a large scale (Scheme 3). For example, the single diastereomer of **3a** could be easily isolated in 70% yield from the 1 mmol scale reaction between enal **1a** and dienone **2a**, with the product er value slightly increased.

The lactone moiety of product **3a** could be selectively reduced to give chiral aldehyde **5** in 80% yield without obvious erosion of the optical purity (Scheme 3). Chiral aldehyde **5** can be used in various transformations to give chiral functional molecules. For example, a chiral α,β-unsaturated ester **6** could be afforded in excellent yield and enantioselectivity through a Horner−Wadsworth−Emmons reaction.

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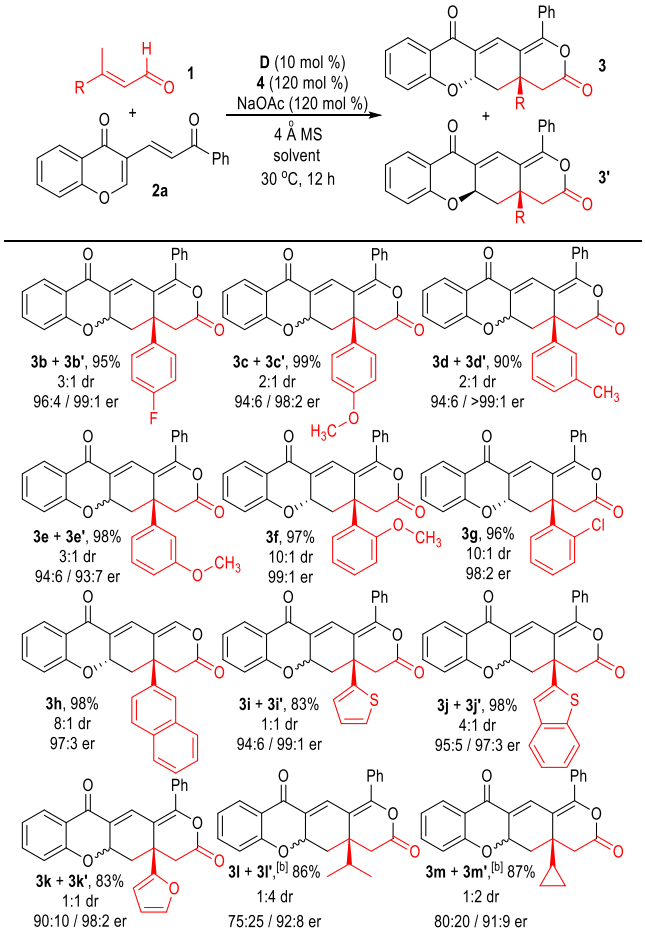
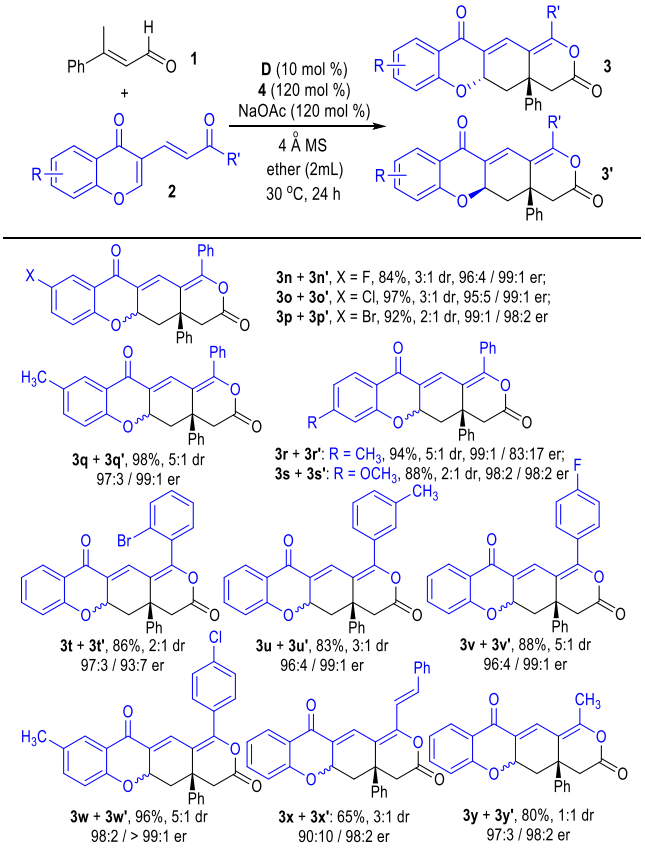
Scheme 1. Scope of β-Methyl-α,β-Unsaturated Aldehydes 1[a]



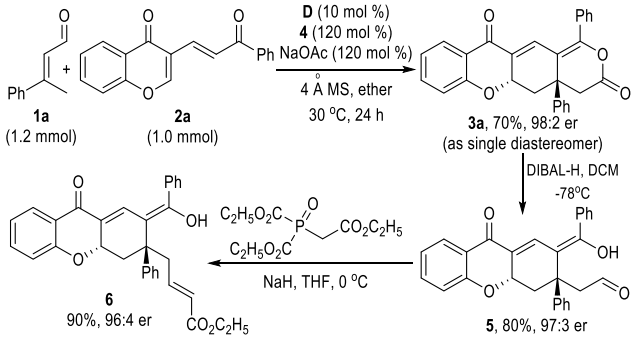
[a]Reaction conditions as stated in entry 8 of Table 1. Yields are combined isolated yields of **3** and **3′** after purification by column chromatography. dr values (**3**:**3′**) were determined by ^{1}H NMR on the crude reaction mixture. er values were determined via HPLC on the chiral stationary phase. Absolute configurations of the products were estimated on the basis of X-ray analysis of the single crystals of **3a**, **3a′**, and **3m′**. [b]Reaction conditions: **1** (0.12 mmol), **2a** (0.1 mmol), **D** (0.01 mmol), DIEA (0.12 mmol), **4** (0.12 mmol), 4 Å molecular sieves (100 mg), THF (2.0 mL), 30 °C, 24 h.

Scheme 2. Scope of Dienone Substrates 2[a]



[a]Reaction conditions as stated in entry 8 of Table 1. Yields are isolated yields after purification by column chromatography. dr values were determined by ^{1}H NMR on the crude reaction mixture. er values were determined via HPLC on the chiral stationary phase.

Scheme 3. One Millimole Scale Reaction between 1a and 2a and Synthetic Applications of 3a



To further demonstrate the generality of this formal cascade reaction, we also examined the use of dienone substrates bearing pyranone moieties (**7**) in this transformation (Scheme 4). To our great delight, the cascade cycloaddition reaction between enals **1** and pyranone dienones **7** proceeded smoothly with THF used as the reaction solvent under otherwise identical conditions as stated in Schemes 1 and 2. The R groups on the enal substrates (**1**) could be substituted phenyl groups (**8a**–**8d**), naphthyl groups (e.g., **8e**), and heteroaromatic groups (e.g., **8f**). The corresponding products could be afforded in moderate to good yields with excellent enantioselectivities as single diastereomers. The R′ groups on the dienone substrates (**7**) can be changed from phenyl groups (**8a**–**8g**) to a simple methyl group (**8h**) without erosion of the reaction outcomes. Aliphatic enal substrates could also be used as the acylazolium precursors in this transformation, although the products could be afforded in only moderate yields and enantioselectivities under the current reaction conditions (e.g., **8i**).

In summary, we have developed an NHC-catalyzed cascade reaction between β-methyl enals and dienone substrates. The cascade reaction is initiated by an unprecedented 1,6-conjugate addition of the acylazolium vinyl enolate γ-carbon. A broad scope of enal and dienone substrates worked well in this transformation. Various chiral functional molecules bearing multiple ring systems can be effectively afforded in good to excellent yields and enantioselectivities through simple operations. Further investigations of the development of new activation modes with NHC organocatalysis for the synthesis of complex molecules are in progress in our laboratories.

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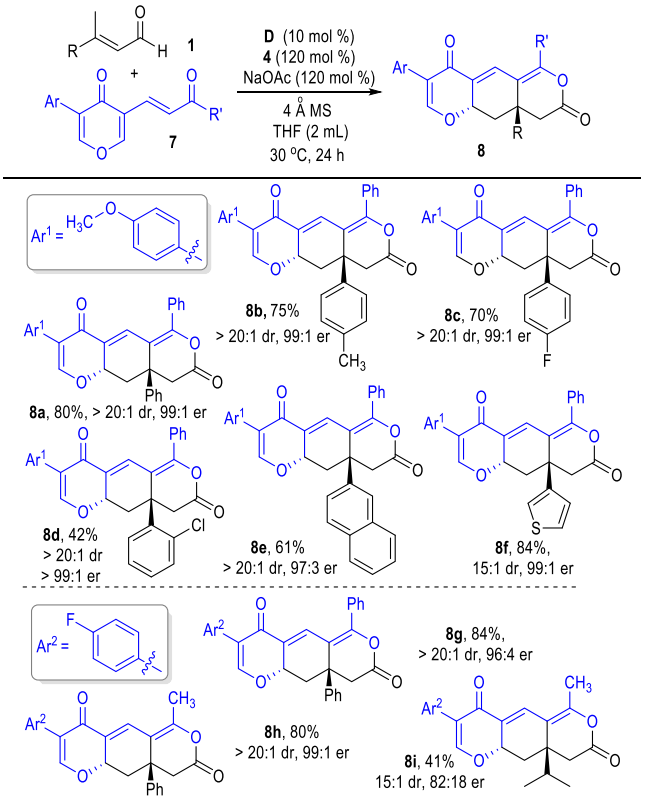
Scheme 4. Scope of Enals 1 and Pyranone Dienones 7[a]



[a]Yields are isolated yields after purification by column chromatography. dr values were determined by ^{1}H NMR on the crude reaction mixture. er values were determined via HPLC on the chiral stationary phase. The absolute configuration of **8b** was determined via X-ray analysis of its single crystals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00533.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1937771−1937773 and 1946481 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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