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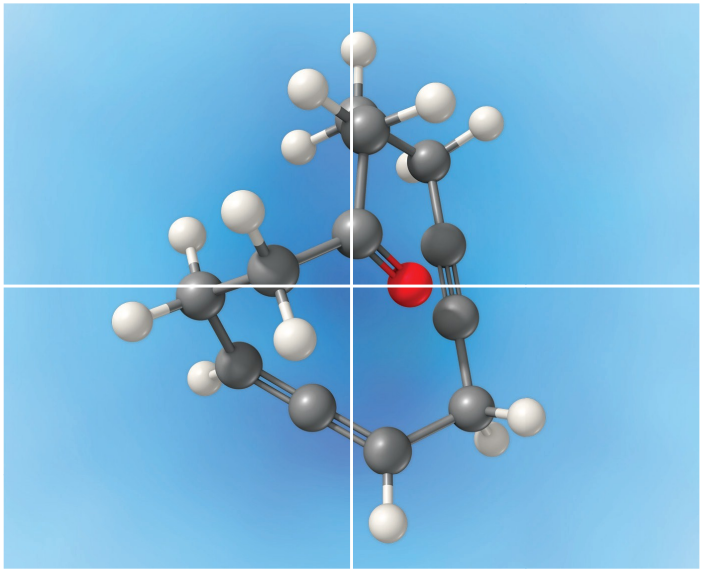

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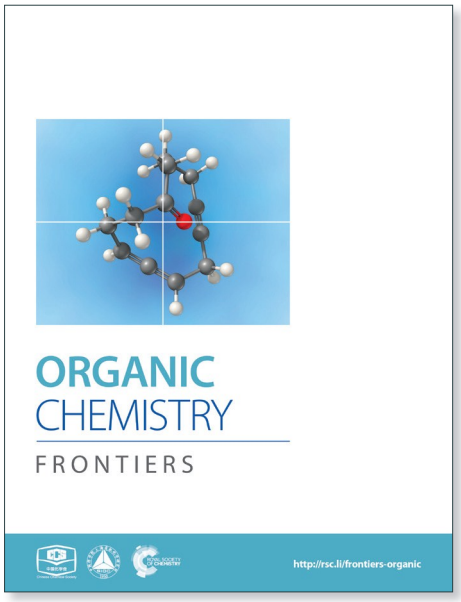

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ARTICLE

Rapid Access to Bicyclic δ-Lactones via Carbene-Catalyzed Activation and Cascade Reaction of Unsaturated Carboxylic Esters †

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Zhenqian Fu,[‡a] Xingxing Wu,[‡a] and Yonggui Robin Chi *[a, b]

Carboxylic esters are excellent choice of substrates in organic synthesis. Here we demonstrate that carbene-catalyzed activation of α,β-unsaturated ester can be developed to synthesis sophisticated multi-cyclic molecules in a single step cascade process. The iridoid-type lactone products are obtained with highly stereo-selectivities, and can readily undergo further transformations.

Introduction

Iridoids are a class of secondary metabolites found in a wide variety of plants and in some animals.[1] This class of molecules and their natural or synthetic analogs usually consist of a cyclopentane ring fused to a six-membered oxygen heterocycle (Figure **1a**). Significantly, these molecules have been found to exhibit useful bioactivity, such as neuroprotective effect,[2a] anti-cancer,[2b] anti-tumour,[2c] anti-inflammatory,[2d] anti-oxidant,[2e] and anti-bacterial[2f] activity. Considerable effort has been spent in the synthesis of this class of molecules via both biosynthetic approach[3] and organic synthesis.[4, 5] However, the majority of methods involve relatively long synthetic steps, sometimes harsh conditions and often result in racemic products.[5] Our laboratory is interested in catalytically activating readily available substrates for rapid (ideally single-step) asymmetric synthesis of functional molecules.[6] We have demonstrated that stable esters[7] and α,β-unsaturated esters[8] can be activated by carbene organic catalysts for efficient and selective reactions.[9] Here we report a single step access to optically enriched iridoids by using our catalytic ester activation approach (Figure **1b**). Mechanistically, the reaction starts via the addition of a carbene catalyst to an α,β-unsaturated ester followed by a cascade process[10, 11] involving two Michael additions and a lactonization step. The bicyclic products were obtained in excellent yields, diastereoselectivities and enantioselectivities. It is of special note that during the preparation of the manuscript Ye[11a] and Studer[11b] groups independently reported similar cascade reactions using enals as the substrates via oxidative NHC catalysis.

Results and discussion

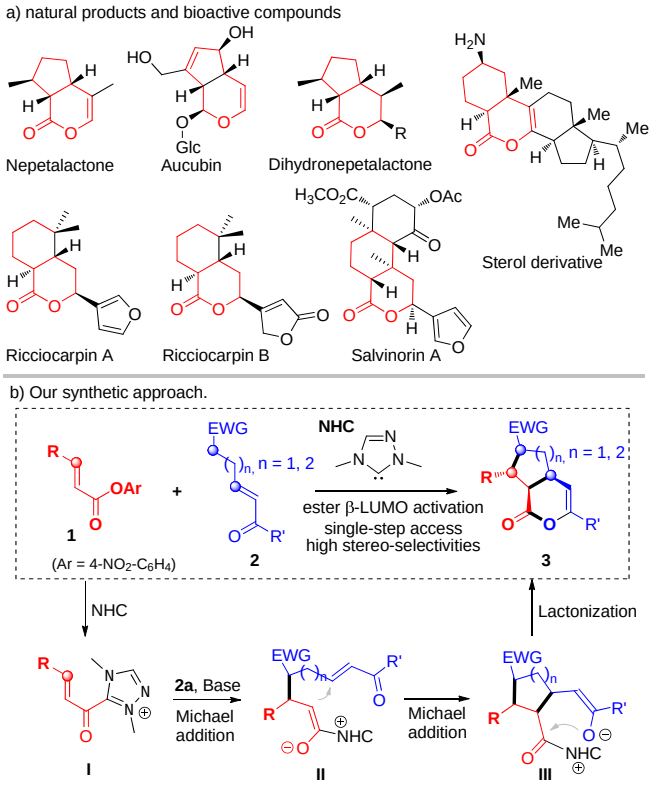
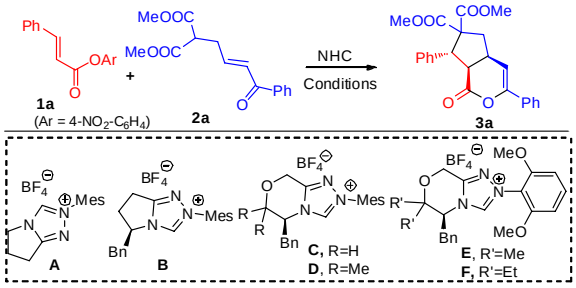


Figure 1. a) Iridoids derivatives in natural products, b) our synthetic approach. Detailed proposed mechanism and stereochemical modes are provided in SI (page S7). (Glc = β-glucopyranosyl; EWG = electron-withdrawing group)

We started by using unsaturated ester **1a** and enone malonate **2a** as model substrates to search for suitable conditions, as shown in Table 1. Achiral triazolium pre-catalyst **A**[12] in the presence of DBU as a base and LiCl[13, 14] as an additive could mediate this reaction to afford proposed cascade product **3a** in 90% (entry 1). The use of chiral triazolium pre-catalyst (e.g. **B**[15]) based on the scaffold of **A** led to **3a** with poor er (entry 2). We also found that

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Nanyang Link 21, Singapore 637371 (Singapore). E-mail rkinjo@ntu.edu.sg
[b] Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025 (China)
‡These authors contributed equally.
†Electronic supplementary information (ESI) available: Experimental and spctra details, and other electronic format see DOI: 10.1039/x0xx00000x.

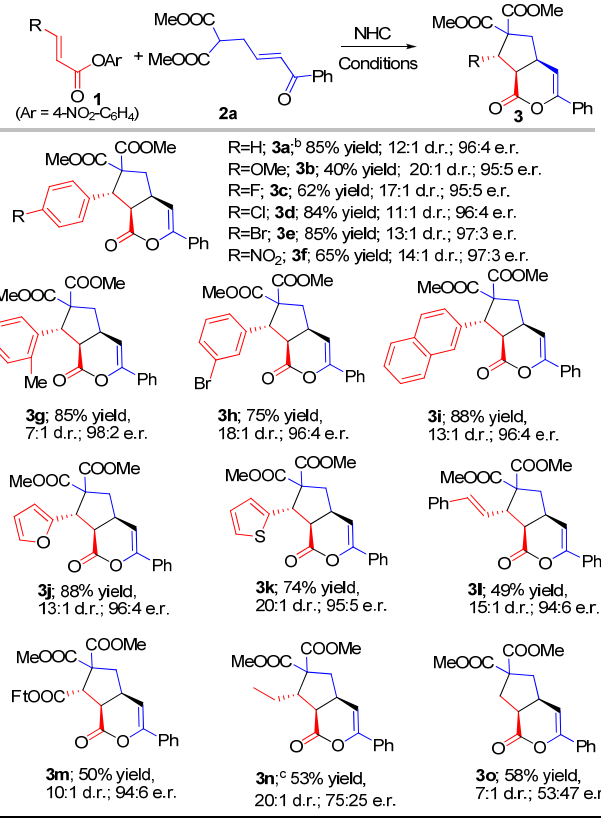
Table 1. Screening of reaction conditions for the reaction of **1a** with **2a.**[a]



Entry	NHC	Yield [%][b]	dr[b]	*er*[c]
1	**A**	90	20:1	-
2	**B**	55	20:1	57:43
3	**C**	43	10:1	77:23
4	**D**	25	12:1	90:10
5[d]	**E**	88	11:1	91:9
6[d]	**F**	74	12:1	96:4
7[d,e]	**F**	92(85)[f]	12:1	96:4

[a] Standard condition: NHC precursor (20 mol%), **1a** (0.1 mmol), **2a** (0.1 mmol), DBU (1.0 equiv), LiCl (1.0 equiv), THF (1.0mL), 4Å MS, rt, 3h. [b] Yields and diastereomeric ratio of **3a**, determined *via* ^{1}H NMR analysis of unpurified reaction mixtures. 1,3,5-trimethoxybenzene was used as an internal standard. Absolute configuration of product was determined *via* X-ray of **4o** (Table 3). [c] Determined *via* chiral phase HPLC analysis. [d] 0.3 eq DABCO was added, then 1.0 eq DBU was added after 20min. [e] 0.2 eq HOBt was added and 1.2 eq **2a** and 1.4 eq DBU was used instead. [f] Isolated yield in parenthesis. DBU=1, 8-diazabicyclo [5.4.0] undec-7-ene; Mes=mesityl (2, 4, 6-trimethylphenyl); DABCO = 1,4-Diazabicyclo[2.2.2]octane; HOBt = Hydroxybenzotriazole.

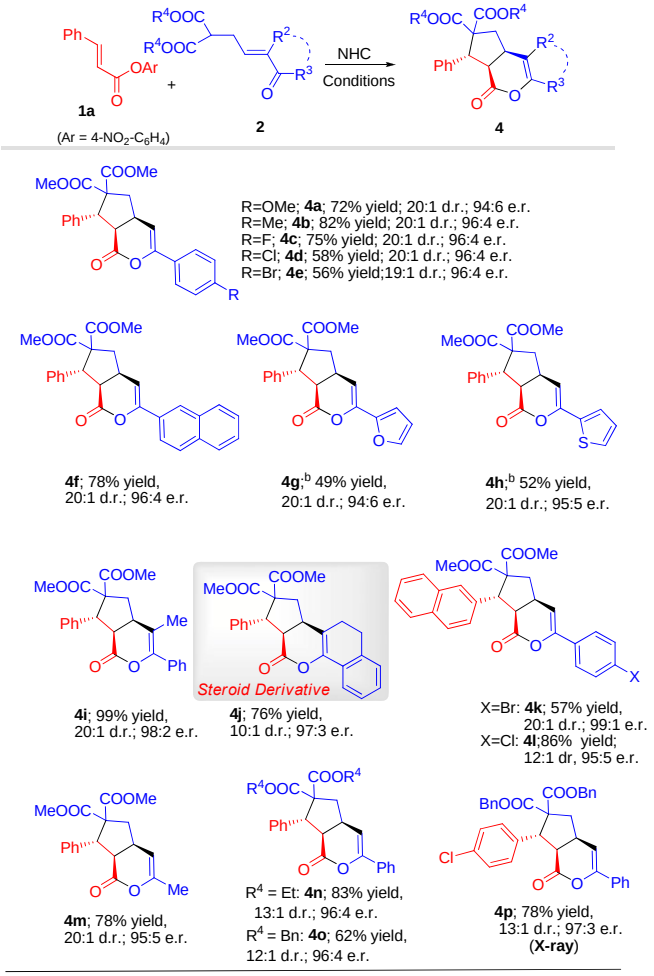
Table 2. Scope of ester **1.**[a]



[a] Conditions as in Table 1, entry 7; isolated yields were based on ester **1**. [b] The reaction at 2.0 mmol scale gave 86% yield, 12:1 dr, 96:4 er. [c] 20% yield, 71:29 er was obtained using the indanol derived NHC in Ye's[11a] work.

catalyst **C**[16] could promote this reaction with much improved er (entry 3). Replacing of the two hydrogen substituents in **C** with methyl units (catalyst **D**[17]) could enhance the product er from 77:23 to 90:10, albeit with a lower yield (entry 4). The low yield in the reactions (entries 2-4) was due to the competing ester hydrolysis. We reasoned that increasing the nucleophilicity of the carbene catalyst could likely promote the desired reaction between the ester and the carbene. Thus we next replaced the methyl substituents on the N-mesityl group of catalyst **D** with methoxyl units to give catalyst **E**.[18] By using catalyst **E** with DABCO (0.3 equivalent) and DBU (1.0 equivalent) as the base, the reaction proceeded smoothly to give **3a** in 88% yield, 11:1 dr and 91:9 er (entry 5). Replacing the methyl units in **E** with ethyl substituents (to give catalyst **F**) could further improve the reaction stereoselectivities (entry 6). The reaction yield (with catalyst **F**) could be further improved by using a catalytic amount of HOBt as an additive without affecting the product er (85% yield, 12:1 dr, 96:4 er; entry 7).

Table 3. *Scope of β-enone malonate* **2.**[a]

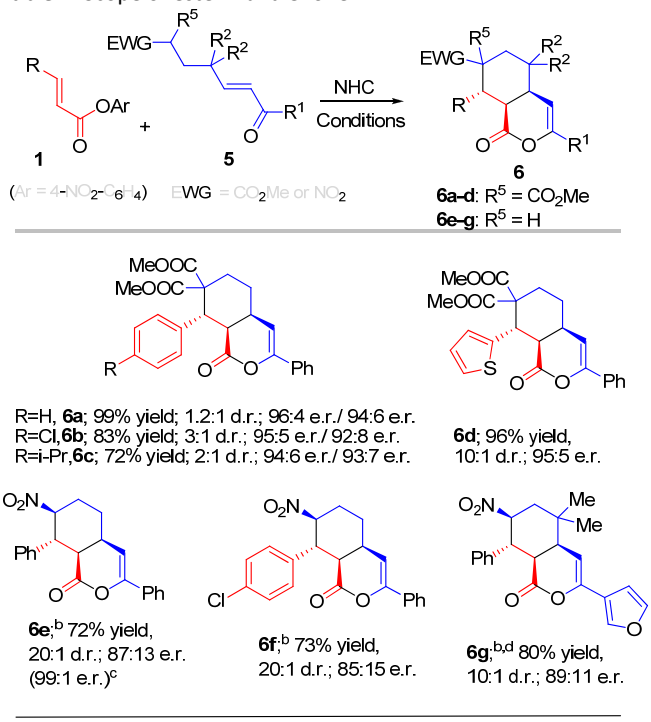


[a] Conditions as in Table 1, entry 7; yields (after SiO_2 chromatography purification) were based on ester **1**. [b] Reactions run with 30 mol% NHC and 1.6 equivalents of enone.

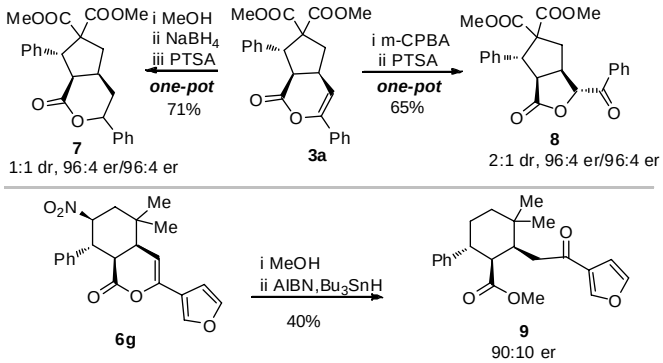
With an acceptable condition in hand (Table 1, entry 7), we next studied the generality of the ester substrate in our reaction by

using β-enone malonate **2a** as a model substrate (Table 2). Installation of various substituents (**1b**-**h**) at the *para*-carbon of the beta-phenyl group of unsaturated ester **1** was all tolerated, except strong electron-releasing group (CH_3O, **1b**) where a lower yield was observed under standard conditions. Placing the substituent at different positions of the β-phenyl group of **1** has no apparent effect on the reaction outcome (**3e** and **3h**). The β-phenyl unit of **1** could be replaced by napthathyl (**1i**) or heteroaryl (**1j**-**k**) units. The β-aryl unit of unsaturated ester could also be replaced by an alkenyl (**1l**) or ester (**1m**) substituent. Esters with β-alkyl substituent (**1n**) and acetic ester (**1o**) could also undergo desired reactions, albeit with a dropped yield and er.

Table 4. Scope of ester **1** and enone **4.**[a]



[a] Conditions as in Table 1, entry 7; yields (after SiO_2 chromatography purification) were based on ester **1**. [b] Reactions run at -78 °C. [c] After one recrystalization. [d] Reactions run with 30 mol% NHC and 1.5 equivalents of ester. Yield (after SiO_2 chromatography purification) was based on enone **5**.



Scheme 1. Synthetic transformations of the cascade product**.**

The scope of the β-enone malonate was then evaluated (Table 3). Different (hetero)aryl substituents on the enone part were all tolerated (**4a**-**h**). Remarkably, substituting on the α-carbon of the enone part did not affect the reaction outcome (**4i**-**j**). The tolerance of substituent on the enone α-carbon allows us to prepare the multi-cyclic Steroid derivative[19] **4j** in 76% yield, 10:1 dr and 97:3 er. Moreover, enone derived with the alkyl group (Me) can also give good result (**4m**). Not surprisingly, the two methyl alcohol ester groups of the malonate substrates could be changed to ethyl (**4n**) or benzyl (**4o**) alcohol ester units.

Our strategy of forming bicyclic product (**3** and **4**) with fused five and six-membered rings could be directly extended to prepare fused six and six-ring products. When γ-enone malonate **5** was used to react with the unsaturated ester substrate, fused bicyclic product **6** could be obtained with excellent yield, and er under the above conditions without further optimizations (Table 4). Interestingly, γ-nitro enone was also an effective substrate, leading to product **6e**-**g** bearing synthetically useful nitro group. Notably, the use of related β-nitro enone substrate could not give the corresponding five-membered ring product due to the elimination of HNO_2 (to form the corresponding γ,δ-unsaturated enone) under basic conditions. The reaction of γ-nitro enone was performed at -78 °C to give **6e** in 87:13 er (99:1 er after a single recrystallization).

The optically enriched products from our catalytic reactions could undergo further transformations under simple conditions. For example, the enol ester carbon-carbon double bond of **3a** could be reduced to give **7** or oxidized to give **8**, bearing a significant core structure in many biologically active natural products[20]. The nitro group of **6g** could be removed to give **9** (with a ring opening ester exchange of the lactone).

Conclusions

In summary, we have developed a highly efficient single-step approach for the preparation of multi-cyclic lactones products with excellent optical purity. Our reactions proceed through carbene-catalyzed activation of unsaturated esters as the key step, followed by a highly selective cascade process. The multi-cyclic products from our catalytic reaction can readily undergo further transformations. Our study demonstrates the synthetic power in turning readily available and stable ester substrates to sophisticated products via an extremely short route, and shall encourage further development and application of carbene catalysis and ester activation.

Experimental

A dry Schlenk tube with stir bar was charged with ester **1** (0.10 mmol, 1.0 equiv.), NHC **F** (9.9 mg, 20 mol%), LiCl (5.0 mg, 1.0 equiv.), HOBt (2.7 mg, 20 mol%), DABCO (3.4 mg, 30 mol%) and molecular sieves (50 mg). The tube was evacuated, and refilled with nitrogen. Then the enone **2** (0.12 mmol, 1.2 equiv.) was added and the mixture was dissolved with newly distilled solvent THF (1.0 mL). After stirring at rt for 20 mins, DBU (21 μL, 1.4

equiv.) was added. Then the mixture was continued to stir at room temperature for another 3h when the substrate was consumed completely (monitored by TLC). The mixture was concentrated under vacuum and purified by column chromatography on silica gel (hexane/EtOAc) to afford desired product **3** as yellow oil .

$[\alpha]_D^{23}$ (c 1.70, $CHCl_3$) = -16.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.59 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 2 H); 7.24–7.39 (m, 8 H); 5.56 (d, *J* = 3.2 Hz, 1 H); 4.70 (d, *J* = 8.8 Hz, 1 H); 3.71 (s, 3 H); 3.52–3.61 (m, 2 H); 3.13 (m, 4 H); 2.27 (dd, J_1 = 12.0 Hz, J_2 = 4.0 Hz, 1 H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 171.6, 170.2, 168.4, 149.2, 137.3, 132.2, 129.2, 128.7, 128.5, 128.3, 127.8, 124.8, 102.2, 65.1, 53.7, 53.1, 52.3, 47.6, 41.3, 36.7 ppm. **IR (film)**: ν_{max} 2952, 1731, 1515, 1425, 1272, 1211, 1008 cm^{-1}. **HRMS (ESI)**: $C_{24}H_{23}O_6$ $[M+H]^+$ calcd: 407.1495, found: 407.1492; 96:4 *er* as determined by HPLC (Chiralcel IB, 90:10 hexanes/*i*-PrOH, 0.7 mL/min), t_r (major) = 13.4 min, t_r (minor) = 16.6 min.

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