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**Titel:** N-Heterocyclic Carbene Catalyzed Quadruple Domino Reactions through α,β-Unsaturated Acyl Azolium Intermediates: Asymmetric Synthesis of Cyclopenta[c]chromenones

**Autoren:** Dieter Enders, Qiang Liu, Xiang-Yu Chen, Rakesh Puttreddy, and Kari Rissanen



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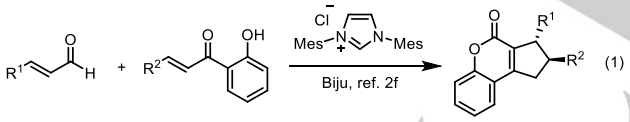
# N-Heterocyclic Carbene Catalyzed Quadruple Domino Reactions: Asymmetric Synthesis of Cyclopenta[c]chromenones

Qiang Liu, Xiang-Yu Chen,* Rakesh Puttreddy, Kari Rissanen, and Dieter Enders*

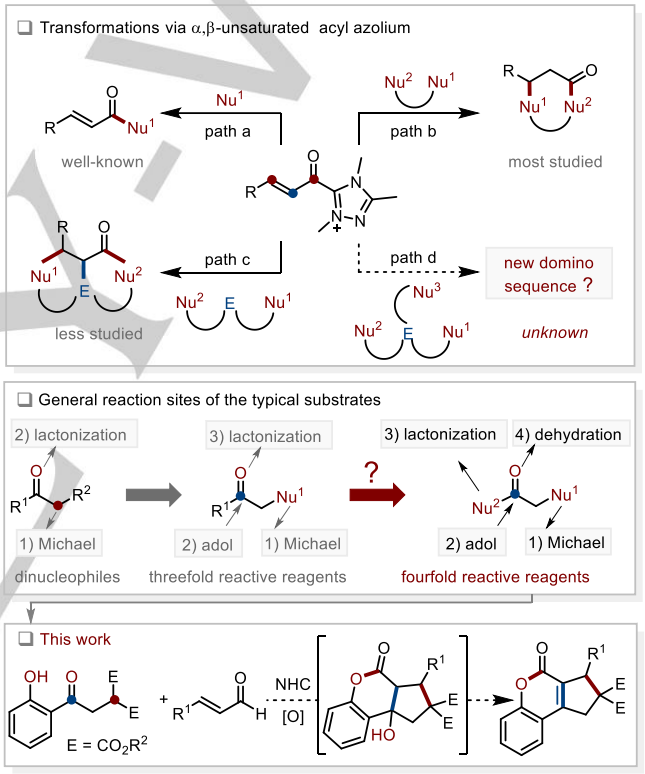
Dedication ((optional))

**Abstract:** A new type of an NHC-catalyzed domino sequence through α,β–unsaturated acyl azolium intermediates has been developed. The strategy provides a convenient asymmetric route to functionalized tricyclic coumarin derivatives and cyclopentanes. DFT studies and control experiments were performed to gain a better insight into the reaction mechanism.

Coumarins and related structures have a wide range of applications in the chemical and pharmaceutical field,[1] a great motivation for chemists to design practical and valuable methods for the synthesis of structurally diverse coumarin derivatives. In this regard, tricyclic cyclopenta[c]-fused chromenones and the *aza*-analogous dihydroquinolinones and their derivatives are characteristic structural motifs of various bioactive compounds and have thus received a great deal of attention. Although several elegant strategies already exist for their synthesis,[2] catalytic enantioselective methods to chiral cyclopenta[c]-fused chromenones with high asymmetric induction have not been realized so far. In 2013 Biju and co-workers reported a domino reaction of enals with *ortho*-hydroxy chalcones in their synthesis of racemic chromenones through homoenolate intermediates [eq. (1)].[2f] To address the challenge of efficient asymmetric syntheses of these compounds, we sought to design a new type of a practical strategy allowing high enantioselectivities and various substitution patterns.




One approach to rapidly assemble such complex chiral compounds is by using organocatalytic domino reactions as defined by Tietze and Beifuss,[3] which have proven to be one of the most efficient strategies. In recent years, *N*-heterocyclic carbene (NHC) catalyzed processes[4], for instance via α,β-unsaturated acyl azolium intermediates, have provided new opportunities for organocatalytic domino reactions.[5] The research groups of Zeitler,[6] Scheidt[7] and Studer[8] carried out early studies on α,β-unsaturated acyl azolium intermediates for simple esterifications (Scheme 1, path a). In 2009 Lupton[9] and Bode,[10] independently, developed an interesting α,β-unsaturated acyl azolium mediated domino reaction with enals, while at the same time Studer and co-workers successfully developed the oxidative NHC-catalyzed domino reaction of enols and diketones with diphenoquinone,[11] which has become a most widely used oxidant in NHC catalysis. Later, the




Scheme 1. Motivation and synthetic strategy.

enantioselective version of this domino process has been successfully realized by You and co-workers.[12] Since then a series of NHC-catalyzed domino processes via α,β-unsaturated acyl azoliums intermediates with dinucleophiles have been developed by several groups (Scheme 1, path b).[13] Recently, this strategy has been successfully extended to domino reactions with threefold reactive reagents by Lupton,[14] Studer,[15] Biju,[16] Wang,[17] Chi,[18] Ye[19] and our group[20] (Scheme 1, path c). It is noteworthy that this process becomes much more complex, if another nucleophilic group is introduced to the substrate, and several chemoselectivity issues can arise in the reaction with α,β-unsaturated acyl azolium intermediates. Thus, it will be difficult to selectively control the reactivities of $Nu^1$, $Nu^2$, $Nu^3$ and E of the substrate (Scheme 1, path d). To the best of our knowledge, domino reactions of α,β-unsaturated acyl azoliums with fourfold reactive reagents is still unknown. To investigate these new possibilities of NHC catalysis and given our strong interest in organocatalytic domino reactions, we were

[*] Q. Liu, Dr. X.-Y. Chen, Prof. Dr. D. Enders
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: xiangyu.chen@rwth-aachen.de, enders@rwth-aachen.de

Dr. R. Puttreddy, Prof. K. Rissanen
Department of Chemistry, University of Jyväskylä,
P.O. Box 35, 40014 Jyväskylä (Finland)

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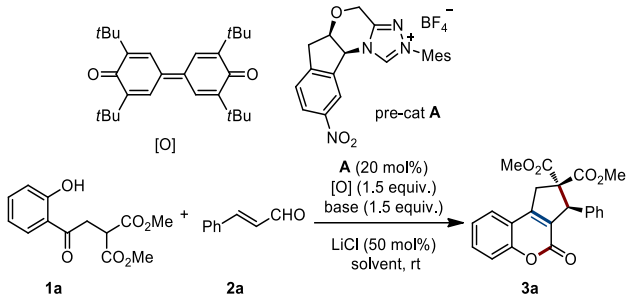
attracted by the idea of designing reaction partners with four disparate reactive sites to develop new domino processes (Scheme 1, middle). We envisioned that malonates bearing an ortho-hydroxy phenyl group may be employed as fourfold reactive substrates to react with α,β-unsaturated acyl azolium intermediates. However, several challenges need to be overcome, the more difficult ones being suppressing the paths a–c and finding conditions to achieve high enantioselectivities. Herein we report a new Michael-aldol-lactonization-dehydration domino sequence for the catalytic asymmetric synthesis of cyclopenta[c]-fused chromenones (Scheme 1, bottom).

**Table 1.** Optimization of the reaction conditions.

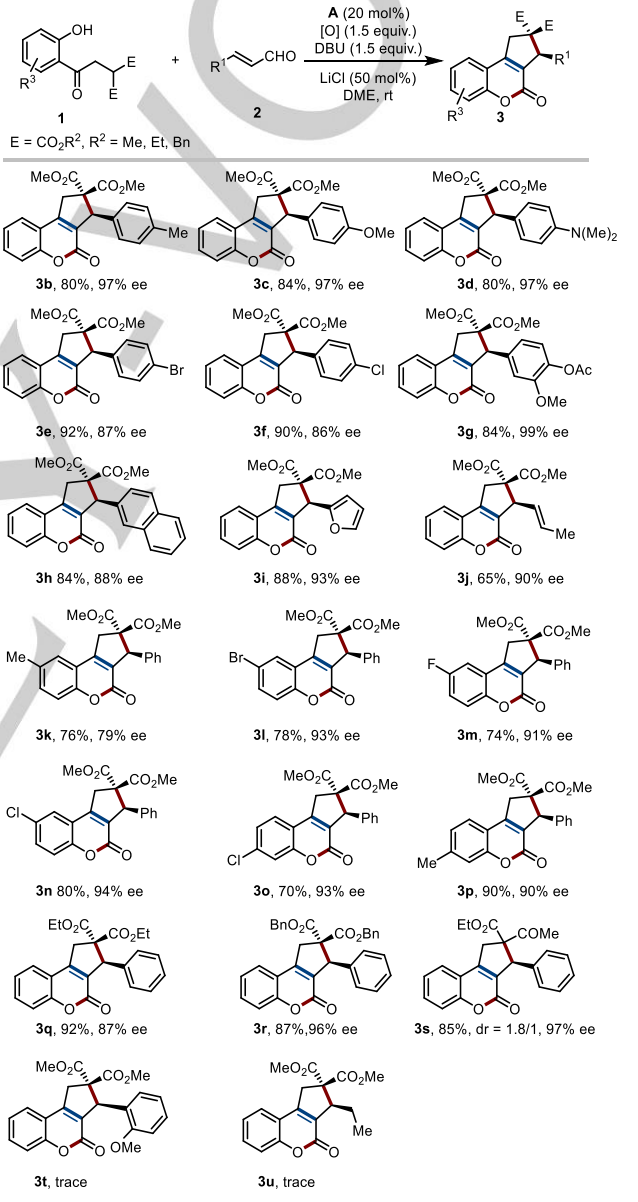



| Entry | Base | Solvent | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | TMEDA | DCM | 48 | 95 |
| 2 | DBU | DCM | 60 | 96 |
| 3 | DIPEA | DCM | trace | -- |
| 4 | $NEt_3$ | DCM | trace | -- |
| 5 | $Cs_2CO_3$ | DCM | trace | -- |
| 6 | $K_2CO_3$ | DCM | trace | -- |
| 7 | DBU | THF | 30 | 99 |
| 8 | DBU | Toluene | 75 | 95 |
| 9 | DBU | $CH_3CN$ | 34 | 99 |
| 10 | DBU | $CHCl_3$ | 47 | 99 |
| 11 | DBU | DCE | 70 | 98 |
| 12 | DBU | Dioxane | 33 | 96 |
| 13 | DBU | DME | 86 | 99 |
| 14[c] | DBU | DME | 73 | 60 |

[a] Yield of isolated product **3a** after chromatography. [b] The ee was determined by HPLC analysis of the purified product on a chiral stationary phase. [c] No LiCl was added. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TMEDA = tetramethylethylenediamine; DIPEA = N,N-diisopropylethylamine; DME = 1,2-dimethoxyethane; DCM = dichloromethane; THF = tetrahydrofuran; DCE = 1,2-dichloroethane.

To validate the feasibility of the proposed process, the model reaction of the malonate **1a** bearing an *ortho*-hydroxy phenyl group with the enal **2a** was investigated under NHC catalysis (Table 1). In the presence of the tetracyclic NHC **A** derived from aminoindanol, TMEDA as the base, diphenoquinone as the oxidant and LiCl as a cooperative Lewis acid, the desired domino product **3a** could be obtained in 48% yield, with 95% ee (entry 1). Encouraged by this promising result, a variety of bases were then screened. The yield and the enantioselectivity improved when DBU was employed as the base (entries 2-6). Next we explored the influence of solvents and demonstrated that DME was the best choice as the reaction outcome was improved to 86% yield and 99% ee (entries 7-13). It should be noted that poorer results were obtained without the addition of LiCl (entry 14).

**Table 2.** Reaction scope.




Yields of isolated products **3** after chromatography. The ee was determined by HPLC analysis of the purified product on a chiral stationary phase.

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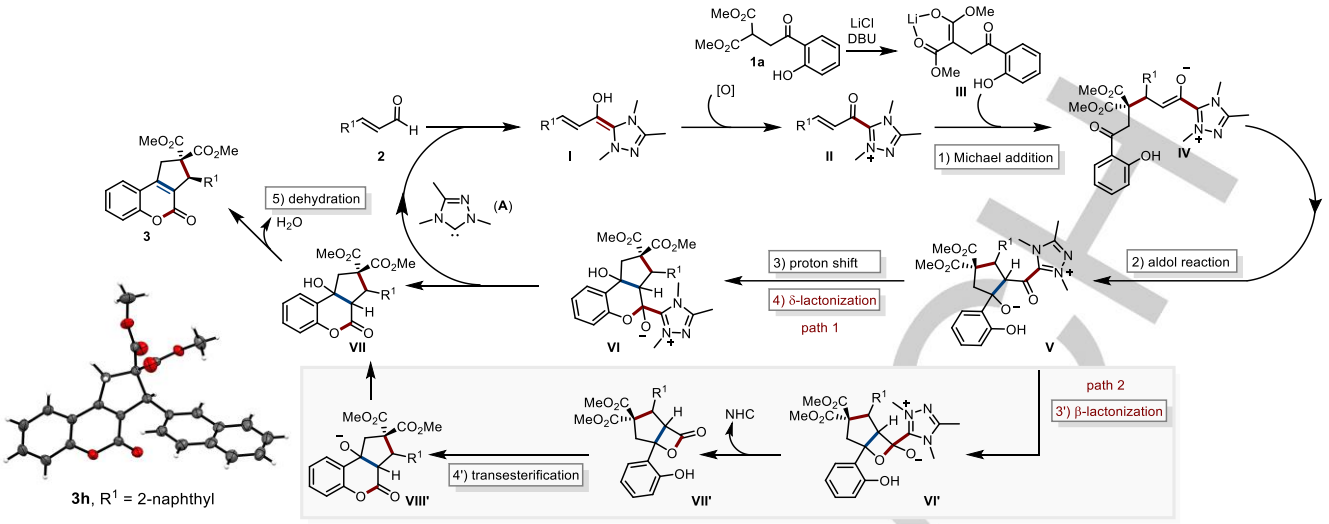
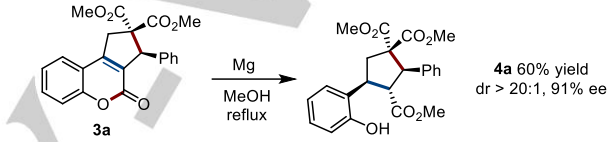



**Figure 1.** Plausible catalytic cycle

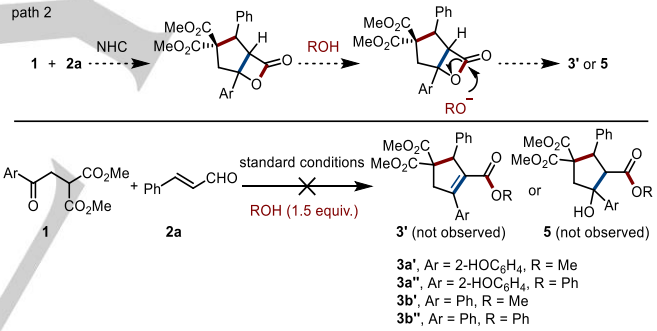
With the optimized conditions in hand, the scope of the new type of domino reaction was studied (Table 2). A series of enals **2** bearing electron-donating or electron-withdrawing substituents ($R^1$ = 4-Me$C_6H_4$, 4-MeO$C_6H_4$, 4-$Me_2NC_6H_4$, 4-Br$C_6H_4$ and 4-Cl$C_6H_4$) reacted smoothly and gave the desired domino products **3b–f** in good yields and high enantioselectivities. The reaction of an enal bearing a disubstituted aromatic ring also proceeded well without apparent change in the yield and enantioselectivity (**3g**). The enal bearing a 2-naphthyl group worked as well to give the corresponding domino product **3h** in 89% yield with 88%ee. This was also true for a heterocyclic substituent ($R^1$ = furyl) giving rise to product **3i**. Notably, the alkenyl enal **2j** also worked well in the reaction albeit in somewhat decreased yield. The scope of the reaction with respect to the ortho-hydroxy aryl malonates was also examined. The electronic properties of the substituents ($R^3$ = 5-Me, 5-Br, 5-F and 5-Cl) at the aromatic ring of **1** had a limited effect on the yields and enantioselectivities (**3k–n)**. Substituents at the 4-position ($R^3$ = 4-Cl and 4-Me) were also tolerated as well and gave the desired products **3o–p** with very high enantioselectivities. Furthermore, the effect of the ester substituents $R^2$ at the malonate moiety was studied too, and the desired domino products **3q** ($R^2$ = Et) and **3r** ($R^2$ = Bn) were obtained in high yields with excellent enantioselectivities. The reaction of ethyl acetoacetate derived substrate **1s** also worked, thus providing the product **3s** in 85% yield with 1.8:1 dr and very good ee. Unfortunately, the *ortho*-substituent and β-alkyl substituted enal gave only a trace amount of the products under our reaction conditions (**3t** and **u**).

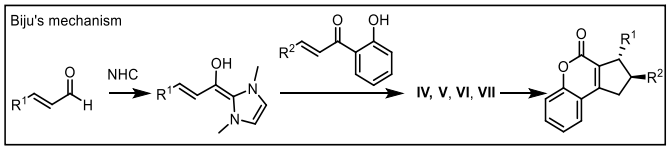
The absolute configuration of the cyclohexene **3h** was determined by the X-ray structure analysis[21] and the configurations of all other products were assigned accordingly.

To demonstrate the synthetic utility of this new domino strategy, a convenient protocol for the synthesis of the highly functionalized cyclopentane **4a** was developed starting from the resulting domino product **3a**.[22] Thus, this reductive lactone ester conversion under ring opening opens an efficient stereoselective entry to highly *all-trans* substituted cyclopentanes (Scheme 2).




**Scheme 2.** Asymmetric synthesis of all-*trans* substituted cyclopentanes.




**Scheme 3.** Control experiments

A plausible catalytic cycle is depicted in Figure 1. The addition of the NHC catalyst to the enal **2** leads to the formation of the Breslow intermediate **I**, which is oxidized by the bisquinone to afford the α,β–unsaturated acyl azolium intermediate **II**. The reactive enolate **III** is readily generated from the malonate **1a** in the presence of DBU and LiCl. The Michael addition of the enolate **III** to the α,β-unsaturated acyl azolium **II** forms the C−C bond and generates the azolium enolate **IV**. Subsequent intramolecular aldol reaction followed by proton shift and δ-lactonization via **V** and **VI** leads to **VII** regenerating the NHC catalyst and final dehydration of **VII** affords the desired product **3** (path 1). Alternatively, as shown in path 2, the intermediate **VII** could be formed by the transesterification of the β-lactone **VII'**, which is generated by β-lactonization of **V**. However, this possibility was ruled out by control experiments in which the

corresponding cinnamyl esters were observed as the major products, and no products **3'** or **5** were formed under the reaction conditions in the presence of an external alcohol to open the β-lactone (Scheme 3). A similar mechanism was also proposed by Biju for the reaction of enals with *ortho*-hydroxy chalcones through homoenolate intermediates (Scheme 3, bottom).[2f]

To further evaluate which mechanism is possible, we carried out DFT calculations for the key intermediates involved in the pathways as well. As shown in Figure 2, the free energies of **VI** and **VII,** being -6.7 and -14.2 kcal mol$^{-1}$, respectively, indicate that the δ-lactonization mechanism is thermodynamically downhill and reasonable, while the high free energy (34.7 kcal mol$^{-1}$) of **VII'** unambiguously rules out the β-lactonization pathway.

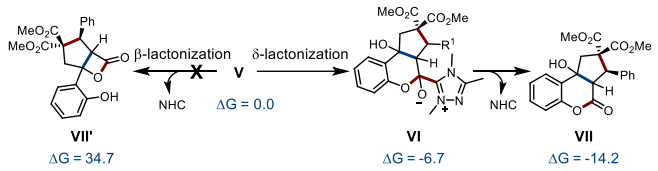



**Figure 2.** Relative free energies (in kcal mol$^{-1}$) of the key intermediates. The optimized structures of the intermediates and computational details are given in supporting information.

In conclusion, we have developed a new NHC-catalyzed domino Michael-aldol-lactonization-dehydration reaction of enals with fourfold reactive malonates. This protocol enables the direct organocatalytic assembly of cyclopenta[c]-fused chromenones in good yields with high enantioselectivities. By a subsequent reductive lactone ester conversions under ring opening highly functionalized cyclopentanes can be easily prepared. Finally, DFT calculations and control experiments provided a deeper insight into the reaction mechanism.

## Acknowledgements ((optional))

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**Keywords:** N-heterocyclic carbene • domino reaction • chromenone • organocatalysis • DFT calculation

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[21] CCDC 1864513 (**3h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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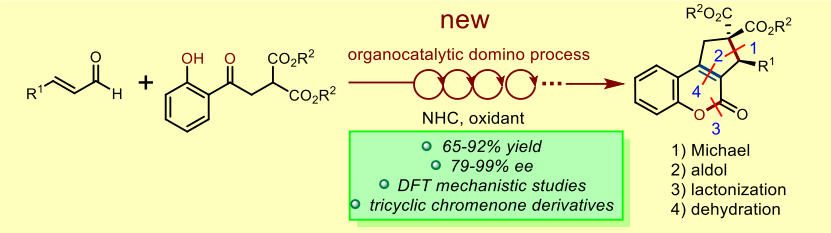


**Domino via Acyl Azoliums:** An NHC-catalyzed quadruple domino sequence through α,β–unsaturated acyl azolium intermediates has been developed. The strategy provides a convenient direct route to functionalized tricyclic chromenone derivatives and cyclopentanes. DFT studies and control experiments provided a deeper insight into the reaction mechanism.

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**N-Heterocyclic Carbene Catalyzed Quadruple Domino Reactions: Asymmetric Synthesis of Cyclopenta[c]chromenones**