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Substrate-Controlled, One-Pot Synthesis: Access to Chiral Chroman-2-one and Polycyclic Derivatives

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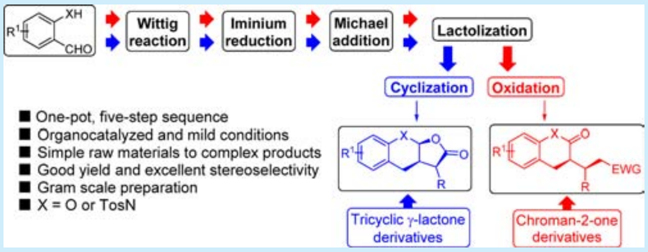
Supporting Information

ABSTRACT: Based on the appropriate choice of electrophiles, one-pot, multicomponent, enantioselective domino reactions have been realized which contain a five-step sequence and provide highly efficient access to potentially bioactive chroman-2-one derivatives as a single diastereoisomer with excellent enantioselectivities and in high yields. This new strategy could significantly improve the previous protocol by directly starting from commercial 2-hydroxybenzaldehydes rather than preformed lactols, which have to be synthesized in several additional steps.



The use of lactols or cyclic hemiaminals as nucleophiles in enamine catalysis represents an important expansion of normal aldehydes in asymmetric synthesis since they could provide facile access to a large variety of lactones, lactams, and even more complex heterocyclic frameworks with potential bioactivity.

Recently, we and others independently reported research on the utility of lactols or cyclic hemiaminals in enamine catalysis.[1] Generally, lactols or cyclic hemiaminals were preformed from the reduction of corresponding lactones or lactams with diisobutylaluminum hydride (DIBAL-H). However, even though we could directly use the in situ generated lactols or cyclic hemiaminals in the enamine catalytic process and realize a truly, complete one-pot procedure for this transformation, there are still several drawbacks: (1) not all the lactones or lactams are commercially available, and some are even needed to be synthesized in several additional steps; (2) low-temperature (generally, −78 °C) and anhydrous solvents are required for the DIBAL-H induced reduction step; and (3) moreover, a slightly complex workup is applied to quench the reduction reaction. Undoubtedly, all of the above-mentioned disadvantages would decrease the efficiency of the overall process. On the other hand, since the desired substituted chiral lactones[2] or lactams[3] are ubiquitous structural components presented in natural products and biologically active compounds, the quest for efficient methods to overcome the above-mentioned drawbacks is extremely appealing and in high demand.

In recent years, owing to the efficiently formation of multiple stereocenters and chemical bonds in a single operation, one-pot, multicomponent, enantioselective domino reactions are regarded as particularly attractive for accessing of chiral complex molecular architectures.[4] Although considerable efforts have been devoted to the development of such methodology, a more powerful domino process, which could maximize the elimination of time-consuming and costly purification procedures, is still highly desirable. Additionally, with the appropriate choice of substrates, the development of a substrate-controlled alternative to an existed cascade catalysis process is possible but challenging, since the newly selected substrate must control both the reactivity and selectivity to lead to diversity-oriented synthesis. With this in mind, we argued that the implementation of domino process into the chemistry of lactols or cyclic hemiaminals should be beneficial to provide increasingly rapid access to the synthesis of substituted chiral lactones or lactams.

Encouraged by the well-established iminium organocatalytic conjugate reduction,[5] we hypothesized the preformed chroman-2-ol **4a** in our previous work, the enamine-catalyzed Michael addition between chroman-2-ol **4a** and *trans*-*β*-nitrostyrene **2**,[1a] could be generated by the conjugate reduction of 2-hydroxycinnamaldehyde **1a**, and once the conjugate reductions occurred, we believe that the inherent hydroxy group of **1a** would then trigger the cyclization to form the required intermediate chroman-2-ol **4a** in situ, which then followed by the same catalyst directed asymmetric conjugate addition and subsequent oxidation to generate the designed chiral chroman-2-one derivatives **5** (Scheme 1, desired path C). However, several challenges have to be encountered in this straightforward process: (1) the Michael addition between 2-hydroxycinnamaldehyde **1a** and *trans*-*β*-nitrostyrene **2** must be rigorously avoided (Scheme 1, undesired path A);[6] and (2)

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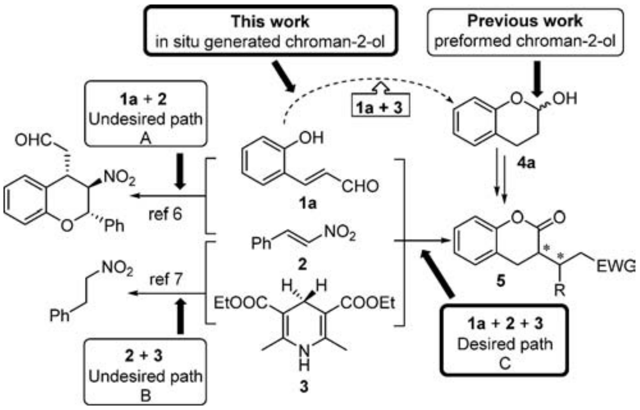
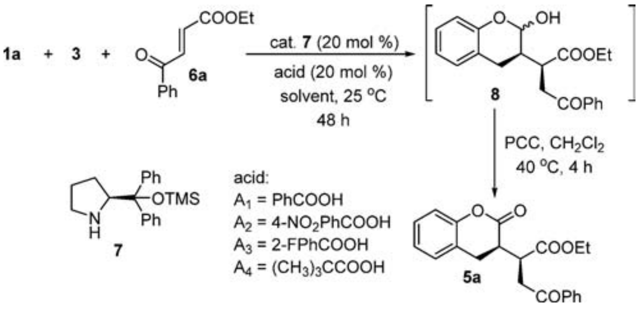
Scheme 1. Designed Competing Pathways To Synthesize Substituted Chiral Lactones



in order to have a full reduction of 2-hydroxycinnamaldehyde **1a** with Hantzsch ester **3** based on iminium activation, the potential H-bonding interaction between the acidic additives and *trans-β*-nitrostyrene **2** must be blocked, which may cause the reduction of *trans-β*-nitrostyrene **2** and then consume the only hydride donor, Hantzsch ester **3** (Scheme 1, undesired path B).[7] Taking these considerations into account, it is clear that central to the success of our hypothetical domino process is to find a suitable Michael acceptor, which could greatly balance the chemically selectivity and reactivity to take out the elucidated challenges. We communicate herein our preliminary results on this one-pot, multicomponent, organocatalytic enantioselective domino reaction, which involved a multistep sequence, iminium/enamine/lactolization/oxidation, leading to substituted chiral chroman-2-one **5** with excellent diastereo- and enantioselectivities in good yields and with control of two adjacent stereogenic centers. It should be noted that the single commercial catalyst could enable both iminium and enamine activation in the designed domino process.

Initially, we investigated this domino process with 2-hydroxycinnamaldehyde **1a** and *trans*-benzoylacrylic ester **6a** in the presence of commercial catalyst **7** and Hantzsch ester **3** as the hydride donor in toluene solvent at room temperature. It should be pointed out that, in contrast to *trans-β*-nitrostyrene **2**, the *trans*-benzoylacrylic ester **6a** is a good electrophile but weak H-bond acceptor,[8] which could avoid the H-bonding interaction induced reduction, and thus, it was selected as the suitable Michael acceptor. After the completion of the iminium-reduction/enamine–Michael addition sequence, the original solvent was replaced with DCM, and the pyridine chlorochromate (PCC)-directed oxidation proved successful leading to the final chroman-2-one **5a**. Pleasingly, the one-pot, multicomponent, enantioselective domino process proceeded extremely well, and the desired product **5a** was isolated as a single diastereoisomer in 85% yield with excellent enantioselectivity (ee >99%) when PhCOOH was employed as the acidic additive (Table 1, entry 1). Stimulated by these results, we further investigated the effects of different reaction media and acidic additives on the reactivity. Surprisingly, this reaction is not limited by these screened conditions, and almost no erosion of the yield or stereoselectivity was observed except for THF as the solvent, which gave consistently excellent diastereo- and enantioselectivity but slightly lower yields (Table 1, entries 2–9). Undoubtedly, these results indicated the powerful synthetic applicability of our domino strategy under a variety of reaction conditions. However, it is clear that only DCM, which could be used in the whole domino process without any unnecessary workup, stands out as the best solvent (Table 1, entry 7).

Table 1. Selected Optimization Studies[a]



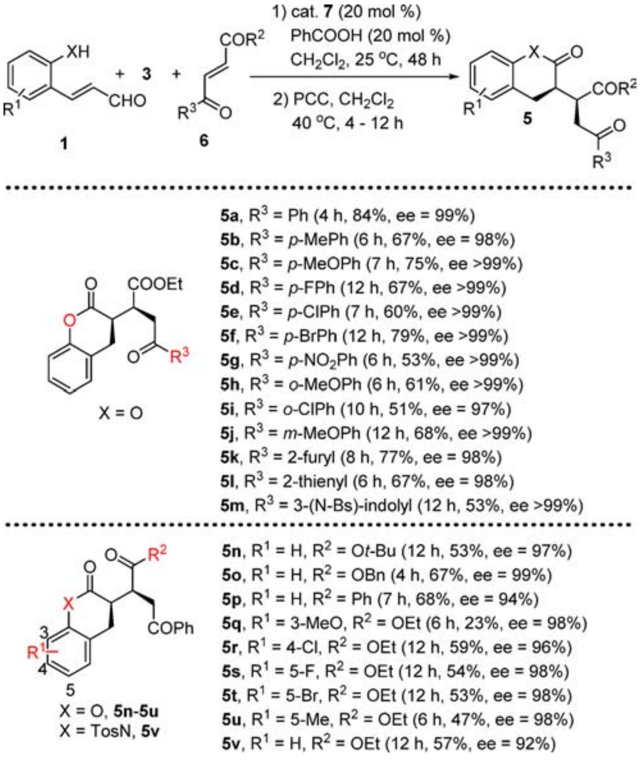
entry	solvent	acid	yield[b] (%)	ee[c] (%)
1	toluene	A_1	85	>99
2	toluene	A_2	84	99
3	toluene	A_3	72	99
4	toluene	A_4	87	99
5	CH_3CN	A_1	57	99
6[d]	CH_3CN	A_1	65	>99
7	CH_2Cl_2	A_1	84	99
8	Et_2O	A_1	88	>99
9	THF	A_1	33	>99

[a] See the Supporting Information for experimental details. Diastereomeric ratios were determined by chiral HPLC analysis. [b] Isolated yields for two steps of product **5a**. [c] Determined by HPLC analysis over chiral stationary phases of **5a**. [d] 10% (v/v) H_2O was added. PCC = pyridine chlorochromate, TMS = trimethylsilyl, THF = tetrahydrofuran, MTBE = methyl *tert*-butyl ether.

As summarized in Scheme 2, with the optimized conditions (Table 1, entry 7), the substrate generality of this domino reaction was investigated with respect to both electrophiles and nucleophiles. Concerning the scope of electrophile **6**, both substituent positions and electronic properties changed in the aryl moiety were shown to be well tolerated, and excellent stereoselectivities were obtained in all examined cases (**5a–j**). Heteroaromatic groups, such as furan, thiophene, and indole, could also be employed as the substituent of the electrophile leading to the desired product with excellent enantioselectivity (**5k–m**). Additionally, the ester moiety has no effect on the reaction outcomes (**5n** and **5o**). Moreover, *trans*-1,2-dibenzoylethylene could also be applied in this elegant domino process (**5p**). Furthermore, various nucleophiles, regardless of the substituents on the aromatic groups, proved to have high reactivity in this reaction (**5q–u**). It should be noted that when the nucleophile having a TosNH group instead of an OH group was used, the efficiency of this domino process was maintained and thus led to the formation of chiral 3,4-dihydroquinolin-2-one derivative (**5v**).

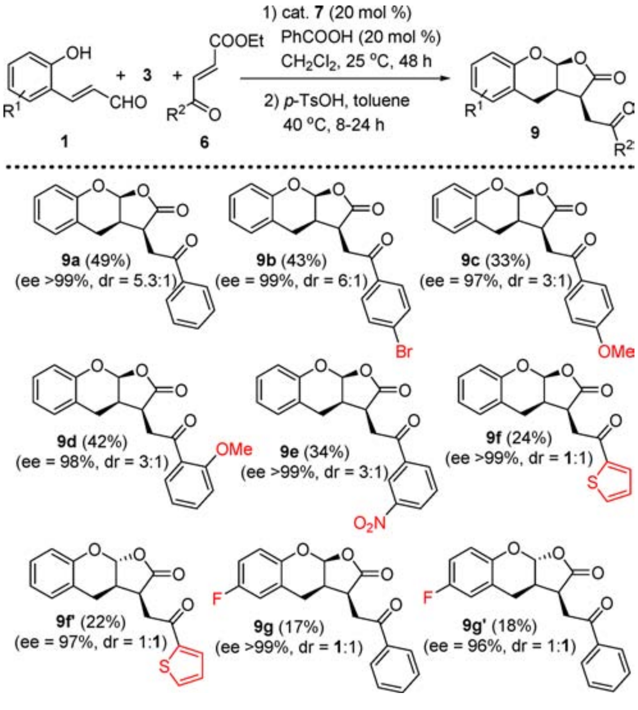
With the successful application of the above reaction protocol for the construction of highly functionalized chiral chroman-2-one and 3,4-dihydroquinolin-2-one structures, we then turned our attention to the preparation of more complex heterocyclic frameworks. A iminium/enamine/lactolization/transesterification sequence was designed to further illustrate the potential of this novel strategy. Surprisingly, catalyzed by *p*-TsOH of the last step, this one-pot, multistep sequence proceeded smoothly to give the fused heterocycle derivatives with high molecular complexity (Scheme 3). Different

Scheme 2. Substrate Scope[a]



[a]See the Supporting Information for experimental details. The isolated yield is reported. The ee values are determined by HPLC analysis of **5** on chiral stationary phases. Tos = *p*-methylbenzenesulfonyl. Bs = benzenesulfonyl.

Scheme 3. Synthesis of Tricyclic γ-Lactones[a]

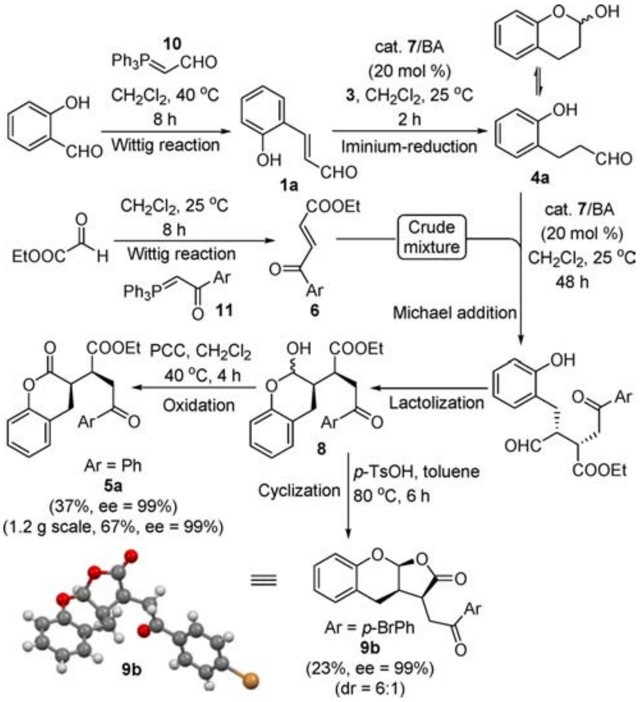


[a]See the Supporting Information for experimental details. **9f**/**9f′** and **9g**/**9g′** are the isolable corresponding epimers, respectively. *p*-TsOH = *p*-toluenesulfonic acid.

substituents in the structures of both **1** and **6** were well-tolerated, regardless of their positions and electronic properties. Notably, the corresponding tricyclic γ-lactones, which are frequently found as privileged intermediates in the synthesis of numerous natural products and medicines,[9] were obtained in good yield and very high levels of stereocontrol (dr up to 6:1, ee = 96 to >99%).

As indicated by the retrosynthetic analysis, both 2-hydroxycinnamaldehyde **1** and *trans*-benzoylacrylic ester **6** could be easily derivatized from the Wittig reaction. We then tried to set up this domino reaction via a five-step sequence in one pot (Scheme 4).[10] The overall process started from the in situ generated **1a** from the Wittig reaction of 2-hydroxybenzaldehyde and ylide **10**,[11] followed by iminium reduction to give the chroman-2-ol **4a**. It should be highlighted that the crude reaction mixture of **6** from the Wittig reaction of ethyl 2-oxoacetate and ylide **11**[12] could be directly used in the Michael reaction with **4a** under the optimized conditions, and the subsequent lactolization yielded substituted chroman-2-ol **8**, which delivered the chroman-2-one **5a** after PCC-directed oxidation reaction in good yield (37% for five steps) and excellent enantioselectivities (ee = 99%) as a single isomer. To further demonstrate the synthetic utility of this method, the reaction could be performed on gram scale, and **5a** was obtained in 67% yield (1.2 g) with excellent diastereo- and enantioselectivity. Moreover, the one-pot, five-step preparation of **9b** could also be realized, affording the enantiomerically enriched tricyclic γ-lactone with good results (23% for five steps, ee = 99%, dr = 6:1). The absolute configuration of **9b** was unambiguously determined by X-ray crystallography, and the absolute configurations of other products were assigned by analogy.[13]

Scheme 4. Five-Step, One-Pot Synthesis of Substituted Chiral Chroman-2-one and Tricyclic γ-Lactone



In conclusion, we have developed one-pot, multicomponent, enantioselective domino reactions that contain a five-step sequence and lead to substituted chiral chroman-2-one derivatives in good isolated yields and excellent diastereo- and enantioselectivities with control of two adjacent stereogenic centers. The choice of appropriate electrophiles is the key to successfully realizing this competitive domino process. It should be noted that this simplified and atom-economic strategy significantly improved our previous protocol by directly starting from commercial 2-hydroxybenzaldehydes rather than preformed lactols, which have to be synthesized individually in several separate steps. The potentially bioactive chroman-2-ol derivatives could be easily transformed into polycyclic building blocks that are difficult to access from traditional methods. Further applications of this highly efficient method are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00160.

Detailed optimization, experimental procedures, and spectroscopic data for all new compounds (PDF)

X-ray data for **9b** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1438377 (**9b**) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.