Organic LETTERS

Letter

pubs.acs.org/OrgLett

Open−Close: An Alternative Strategy to α-Functionalization of Lactone via Enamine Catalysis in One Pot under Mild Conditions

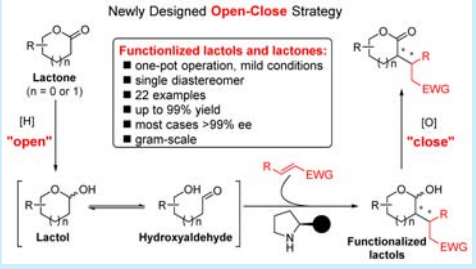
Yan-Kai Liu,*[,†] Zhi-Long Li,[‡] Ji-Yao Li,[†] Huan-Xi Feng,[†] and Zhi-Ping Tong[‡]

[†]Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, P. R. China

[‡]School of Life Science and Engineering, Southwest Jiaotong University, Chengdu, Sichuan 610031, P. R. China

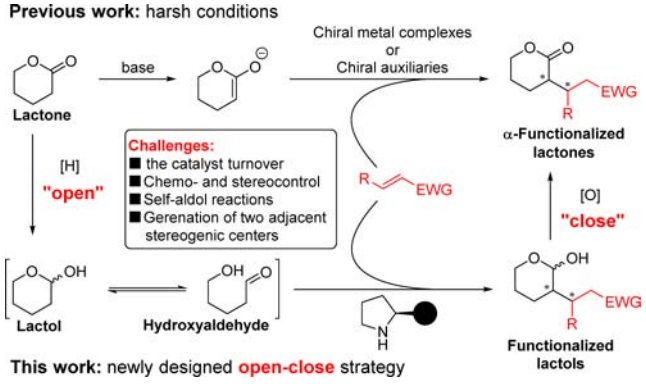
Supporting Information

ABSTRACT: An open−close strategy in asymmetric catalysis is newly developed. With this powerful strategy, lactols are directly applied as potential precursors of lactones in enamine-based asymmetric Michael reactions providing a facile access to α-functionalized lactones containing two adjacent stereogenic centers as a single diastereomer in good to excellent yields (up to 99%) and with excellent enantioselectivities (most cases >99%). Moreover, the reaction products are shown to give highly functionalized derivatives by stepwise systematic transformations.



The cyclic ester group, named lactone, is widely distributed in bioactive natural products, generally acting as an important pharmacophore,[1] which has triggered considerable attention for asymmetric catalytic modification, especially the α-functionalization of this cyclic ester group.[2] Previous asymmetric examples focused mainly on the deprotonation of the α-carbon atom to make the enolates, which were then catalyzed by chiral metal complexes to have the α-functionalized lactones.[3] Besides this, chiral auxiliaries represent another powerful tool to install substituents at the α-position of lactones (Scheme 1).[4] However, based on the above-mentioned approaches, the α-functionalization of lactones was hindered by the drawbacks of the relative difficulties in either accessing geometrically pure enolate intermediates or providing excellent diastereoselectivity when two adjacent stereogenic centers were generated in the catalytic process. Thus, the development of a flexible method for the α-functionalization of a lactone with a range of nucleophilic coupling partners remains highly demanding and challenging.

Scheme 1. Open−Close Strategy: the Reactions of Lactols in Enamine Catalysis



Enamine catalysis[5] which allows the direct use of aldehydes and ketones as nucleophiles has effectively emerged as a reliable strategy for the enantioselective α-functionalizations of carbonyl compounds.[6]

Notably, whereas all types of ketones and aldehydes, including branched, unbranched, cyclic, and acyclic, as well as aliphatic and aromatic ones, even the "simplest" acetaldehyde,[7] have found utility as nucleophiles, the direct use of lactols in enamine catalysis is rare,[8,9] albeit the lactols have been demonstrated to be promising intermediates in asymmetric organocatalysis.[10]

Considering the convenient transformations between lactones and lactols, we then questioned whether it would be possible to use lactols as the potential precursors of lactones in the enamine-based reactions. In this proposed reaction process, first, the lactone is opened by a simple reduction reaction to produce the lactol, which is often found as an equilibrium mixture with the corresponding hydroxyaldehyde, and then, an appropriate electrophilic partner would be employed to react with the lactol via enamine activation, leading to a highly enantioenriched substituted lactol, which is then closed by a subsequential oxidation reaction to finish the facile access to an asymmetric α-functionalized lactone in one pot (Scheme 1). To the best of our knowledge, there is no reported work on directly utilizing lactols as the precursors of lactones in an enamine catalyzed Michael reaction providing facile access to α-functionalized lactones in a one-pot process. Herein we report the realization of this concept for the stereodivergent

Received: March 18, 2015
Published: April 9, 2015

DOI: 10.1021/acs.orglett.5b00794
Org. Lett. 2015, 17, 2022−2025

organocatalytic α-functionalization of lactones involving the direct application of lactols in the enamine activation process.

During the development of this new open−close strategy to functionalize the α-carbon of lactone, we chose the Michael reaction as the model reaction which is one of the most powerful and efficient methods for carbon−carbon bond formations. Our optimization studies began with the reaction of (*E*)-β-nitrostyrene **5a** and the racemic chroman-2-ol **4a**, which is to easy handle and readily available from the reduction of hydrocoumarin by diisobutylaluminum hydride (DIBAL-H). Indeed, in the presence of diphenylprolinol trimethylsilyl ether **1** as the catalyst[11] and *p*-NO_2-PhCOOH as the cocatalyst, the desired product **6a** could be detected for the first time after 72 h. For a clear understanding of the selectivity and also for clean HPLC separation, we then subjected the crude **6a** to oxidation with pyridine chlorochromate (PCC) in CH_2Cl_2 at 25 °C for 20 h, yielding lactone **7a** as a single diastereomer in 78% yield with >99% enantiomeric excess (ee) in one pot (Table 1, entry 1). Surprisingly, this Michael reaction works extremely well under neat conditions (Table 1, entry 2), and a full conversion was obtained after only 8 h to give **7a** in both high yield and enantioselectivity (73% and >99%, respectively). However, considering not all the substituted β-nitrostyrene could dissolve well under the neat conditions, 50 μL of solvent were finally added to have a homogeneous solution during the reaction process. To our delight, even a higher yield was obtained, without any variation in the enantioselectivity, albeit a longer time is needed to have a complete reaction (Table 1, entry 3). Not surprisingly, L-proline **2** and prolinol **3** did not provide the desired product even in combination with *p*-NO_2PhCOOH (Table 1, entries 4 and 5). Importantly, more experiments revealed that both solvents and an acid additive had no effect on the enantioselectivity (>99% ee); only a slight drop in the yield was observed (Table 1, entries 6−10). Consistent with the recent work by Wang and co-workers,[12] the highest yield could be achieved when a slight excess of **4a** (e.g., 1.2 equiv) was used in this highly enantioselective process (Table 1, entry 11). Delightfully, the cocatalyst could be decreased to 10 mmol %, affording **7a** in a higher yield without erosion of enantioselectivity (Table 1, entry 12).

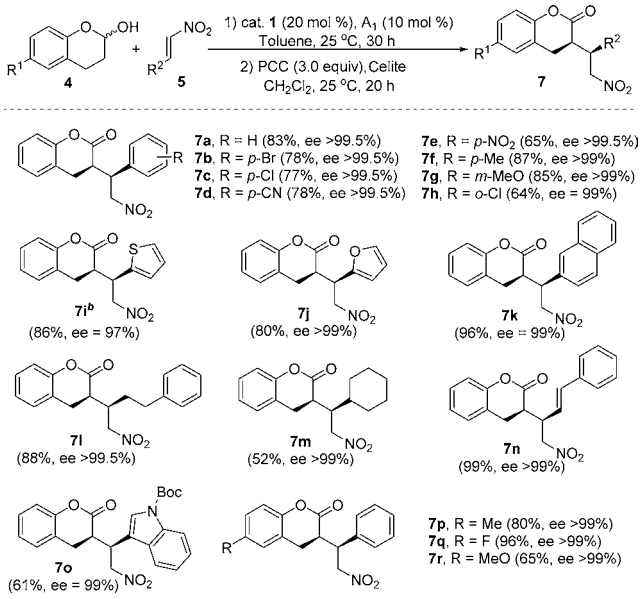
Table 1. Selected Screening Results of the One-Pot Asymmetric Michael Addition Involving Chroman-2-ol 4a and β-Nitrostyrene 5a[a]

entry	cat.	acid	solvent	time[b] (h)	yield[c] (%)	ee[d] (%)
1	1	A_1	toluene	72	70	>99
2	1	A_1	neat	8	73	>99
3[e]	1	A_1	toluene	30	76	>99
4[e]	2	−	toluene	30	−	−
5[e]	3	A_1	toluene	30	−	−
6[e]	1	A_1	CH_2Cl_2	30	73	>99
7[e]	1	A_1	Et_2O	30	70	>99
8[e]	1	A_2	toluene	30	71	>99
9[e]	1	A_3	toluene	30	68	>99
10[e]	1	A_4	toluene	30	73	>99
11[e,f]	1	A_1	toluene	30	80	>99
12[e,f,g]	1	A_1	toluene	30	83	>99

[a]See the Supporting Information for details. [b]For the first step. [c]Isolated yields of product **7a**. [d]Determined by HPLC analysis over chiral stationary phases of **7a**. [e]50 μL of solvent were used. [f]1.2 equiv of **4a** was used. [g]10 mmol % acid was used.

On the basis of these studies, the scope of the reaction was evaluated by using the optimized reaction conditions (Scheme 2). Indeed, this one-pot process serves as a general approach to the preparation of highly functionalized chiral dihydrocoumarins, nitroalkenes bearing diversely substituted aryl or heteroaryl groups could be well tolerated, and the corresponding α-functionalized lactones generally were obtained in good yield and excellent enantioselectivities (**7a**−**k**). In addition, all possible monosubstituted aryl groups (*ortho*, *meta*, or *para*) and even a sterically bulkier naphthyl substituent are well tolerated. Notably, alkyl-substituted nitroalkenes showed good reactivity, and both the branched and unbranched alkyl substituents on the nitroolefin were well tolerated, giving the corresponding products in excellent enantioselectivities and good yields (**7l** and **7m**).

Scheme 2. Scope of the One-Pot Sequential Asymmetric Michael Addition Delivering α-Functionalized Chroman-2-one[a,b]



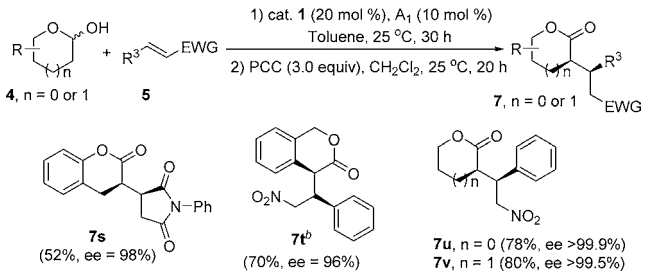
[a]See the Supporting Information for experimental details. [b]The absolute configuration of compound **7i** was determined by X-ray crystallography,[13] and the remaining compounds **7** were assigned by analogy; see the Supporting Information for details.

Furthermore, 4-phenyl-1-nitro-1,3-butadiene can also act as an effective Michael acceptor in this open−close strategy yielding **7n** with both excellent yield and enantioselectivity. In addition, similar good results were attained for a nitroalkene substituted with an N-Boc protected indol group (**7o**). Gratifyingly, different substituents on the chroman core of lactol **4** are well tolerated, since electronic modification of the aromatic ring can be accomplished without affecting the efficiency of the system (**7p**−**r**).

The general applicability of a chemical strategy is a crucial parameter for evaluating its usefulness for future endeavors to synthesize complex chiral molecules. To further expand the scope of this open−close strategy, we explored the possibility of using different lactones and Michael acceptors, and the results are summarized in Scheme 3. Notably, *N*-phenyl-maleimide worked extremely well with this strategy providing an enantiopure product albeit in a moderate yield (52%, **7s**). This Michael addition can also be performed with isochroman-

DOI: 10.1021/acs.orglett.5b00794
Org. Lett. 2015, 17, 2022−2025

Scheme 3. Scope of Different Lactones and Michael Acceptors[a,b]

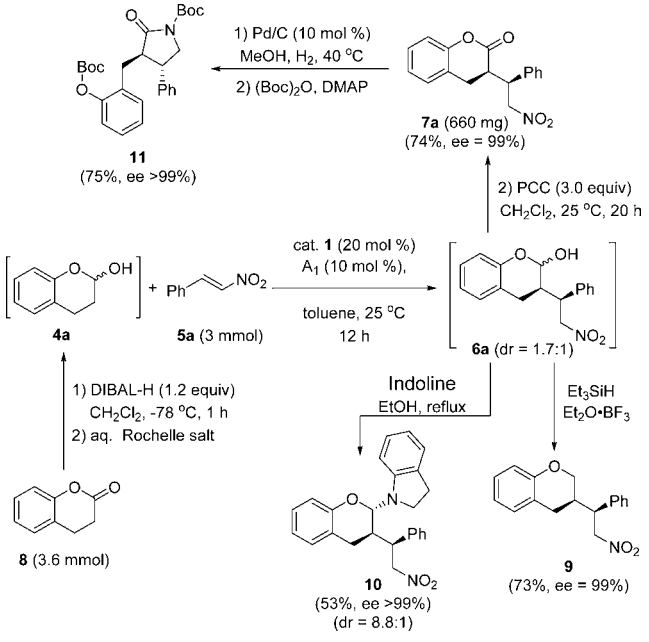


[a]See the Supporting Information for experimental details. Yields are of isolated product after column chromatography. Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [b]Pivalic acid was used as the cocatalyst.

3-ol providing **7t** without changing the enantioselectivity, although slightly altered reaction conditions were necessary in this case. Gratefully, both functionalized δ-valerolactone and γ-butyrolactone, which have found widespread application as biologically important substructures in medicinal chemistry, were generated with high yields and excellent stereoselectivities (**7u** and **7v**).

Lactol, which is from the "open" step of the open−close strategy, is used in our present study. To realize a complete procedure containing both "open" and "close" steps in one pot, a larger scale reaction was carried out directly starting from a lactone to highlight the practicality of this new method. As shown in Scheme 4, when 3.6 mmol of chroman-2-one **8** was subjected to the "open" step with DIBAL-H, the reaction proceeded smoothly providing **4a** for the next step without purification. It should be noted that the Michael addition was finished only in 12 h while generating **6a** with 1.7:1 diastereoselectivity. The "close" step with PCC gave **7a** in one pot with almost no reduction in yield (74%, for three steps), and the enantioselectivity remained excellent (Scheme 4). After reduction of **6a** using Et_3SiH/TFA at 0 °C for 0.5 h, the chiral functionalized chromans **9**, which are found in many natural products and synthetic molecules, could be readily generated with a good yield and excellent enantioselectivity (73% and >99%, respectively). To convert the lactol moiety into a hemiaminal ether, **6a** worked with indoline in refluxing ethanol to give **10** in good yield and diastereoselectivity with no loss of the enantioselectivities.[14] Finally, a reductive cyclization of the Michael adduct **7a** was easily achieved by hydrogenation using Pd/C (10% w/w) and H_2; after removal of the solvent, the crude product was directly transferred into its N,O-Boc-protected derivative **11** in 75% yield.

Scheme 4. Synthetic Transformations[a,b]



[a]See the Supporting Information for experimental details. Yields are of isolated product after column chromatography. Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [b]Isolated yield for two steps.

In summary, we have reported a newly developed open−close strategy which provided an alternative access to α-functionalized lactones in a one-pot, three-step procedure from simple starting materials.[15] In this successful process, the starting lactones were reduced in situ to give the lactols, and the lactols could be directly catalyzed by an aminocatalyst affording synthetically important substituted lactols or α-functionalized lactones after a sequential oxidation reaction. This promising approach proceeded well to furnish the corresponding adducts containing two adjacent stereogenic centers as a single diastereomer in good to excellent yields and with excellent enantioselectivities. Notably, the use of lactols as the nucleophiles in enamine catalysis is rare. The results and the information presented seem to open the possibility for a new series of enantioselective transformations. Further exploration of this open−close strategy and application to other transformations are underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed optimization, experimental procedures, spectroscopic data for all new compounds, and X-ray data (cif) for **7i**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuyankai@ouc.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Nature Science Foundation of China (No. 21302156), NSFC-Shandong Joint Fund for Marine Science Research Centers (No. U1406402), and Ocean University of China (OUC).

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(13) CCDC 1042020 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.
(14) The absolute configuration of the new chiral center in **10** was determined by ^{1}H NMR analysis; see the Supporting Information.
(15) For a proposed mechanism, see the Supporting Information.

DOI: 10.1021/acs.orglett.5b00794
Org. Lett. 2015, 17, 2022−2025