Asymmetric Catalysis

DOI: 10.1002/ange.201305148

Copper-Catalyzed Enantioselective Henry Reaction of Enals and Subsequent Iodocyclization: Stereoselective Construction of Chiral Azatricyclic Frameworks**

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Optically pure allylic alcohols represent an important type of highly versatile chiral building blocks for organic synthesis, especially for access to bioactive natural products and pharmaceutical agents.[1] Stereoselective nucleophilic 1,2-addition to the carbonyl group of an α,β-unsaturated aldehyde or ketone is one of the most direct and powerful methods to obtain chiral allylic alcohols.[1] Great interest has been shown in catalytic asymmetric variants and various nucleophiles have been successfully introduced.[2] Considering that nitroalkanes are a valuable source of stabilized carbanions, we envisioned that nitromethane may serve as a potential nucleophile for the addition of enals. However, up to now, there are few examples concerning this kind of asymmetric transformation, perhaps because of competitive nucleophilic 1,4-conjugated additions.[3] Azatricyclic hexahydrochromeno[4,3-*b*]pyrrole as a core structure is found in a large family of biologically active and naturally occurring molecules, which can play a significant role in medical chemistry. For example, the compound **1**, martinellic acid (**2**), and martinelline (**3**), etc. (Figure 1).[4]

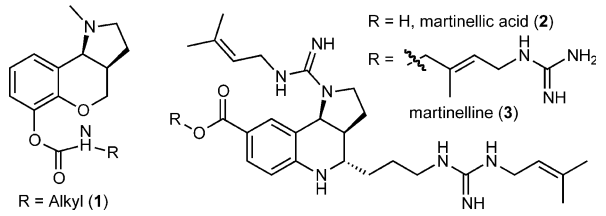
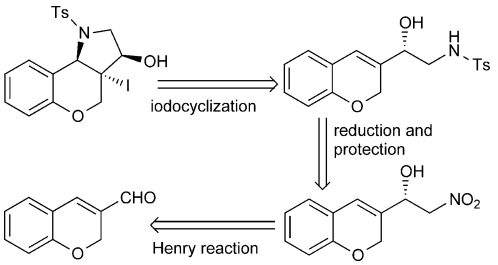


Figure 1. Examples of azatricyclic core structure.

Though some examples for the construction of this useful skeleton have been reported, the synthetic routes are relatively tedious and mainly limited to intramolecular [3+2] cycloadditions,[5] and very few strategies utilize a catalytic asymmetric approach.[6] We anticipated that the coupling reaction between nitromethane and 2*H*-chromene-3-carbaldehyde would deliver nitro-functionalized allylic alcohols which can be conveniently reduced to allylic amino alcohols as a result of the rich chemistry of nitro group.[7] At the same time, we found the intramolecular iodocyclization strategy to be effective for the construction of heterocyclic compounds.[8] Thus, combined with the subsequent intramolecular iodocyclization, this methodology will provide a straightforward process to furnish the desired chiral azatricyclic hexahydrochromeno[4,3-*b*]pyrrole scaffold (Scheme 1).



Scheme 1. Synthesis of the chiral azatricyclic framework by a Henry reaction/iodocyclization cascade sequence. Ts = 4-toluenesulfonyl.

Since the first example of a catalytic asymmetric Henry (nitroaldol) reaction reported by Shibasaki and co-workers,[9] much effort has been devoted to this area using both metal catalysis and organocatalysis.[10] While different kinds of new chiral catalysts have been established to achieve excellent yield, enantioselectivity, and distereoselectivity,[11] some examples employing alternative substrates including chiral aldehydes,[12] ynals,[13] and functionalized nitroalkanes[12a–d,14] have been disclosed. Very recently, our group designed and prepared a group of chiral diamines from natural amino acids and camphor, and they were successfully applied to asymmetric catalytic Henry reactions[15] and Michael additions.[16] This C_1-symmetrical chiral diamine copper(II) catalytic system was also suitable for the asymmetric nitroaldol reaction of *o*-alkynylbenzaldehydes and haloenals.[17] As part of our ongoing work, we investigated the asymmetric Henry reaction of α,β-unsaturated aldehydes under our catalytic reaction conditions and its application to the construction of chiral heterocycles. Herein, we present the unprecedented catalytic asymmetric Henry reaction of various cinnamaldehydes and 2*H*-chromene-3-carbaldehydes, and subsequent iodocyclization.

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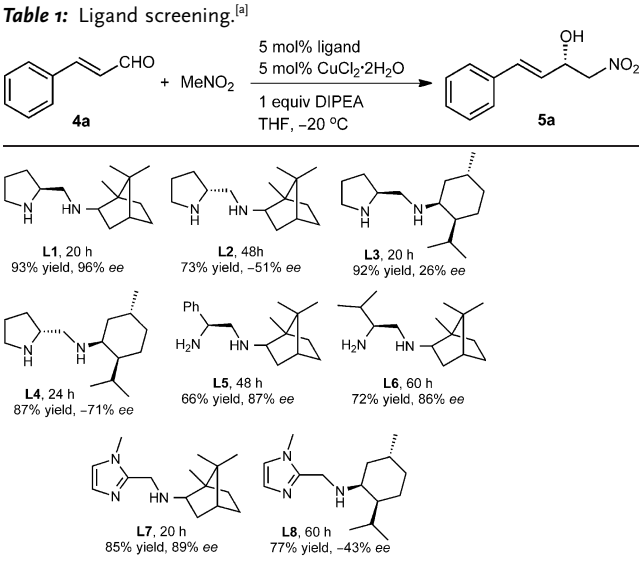
[**] This work was supported by grants from the National Natural Science Foundation of China (no. 21172082, 20872041). The Analysis and Testing Center of Huazhong University of Science and Technology is acknowledged for characterization of the new compounds.

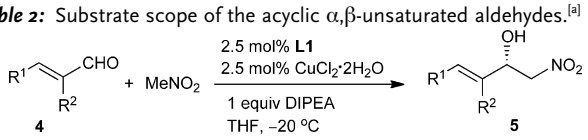
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201305148.

Table 1: Ligand screening.[a]



[a] Reactions were carried out on a 0.5 mmol scale of **4a** with 10 equiv of nitromethane in a mixture of 2.0 mL THF, 5 mol% ligand and $CuCl_2{\cdot}2H_2O$ in the presence of 1.0 equiv of DIPEA at −20°C. Yield is that of isolated product. The *ee* value was determined by HPLC analysis using a chiral stationary phase. DIPEA = diisopropylethlyamine, THF = tetrahydrofuran.

Table 2: Substrate scope of the acyclic α,β-unsaturated aldehydes.[a]



Entry	Enal **4**		Product	Yield [%][b]	*ee* [%][c]
	R^1	R^2			
1	Ph	H	**5a**	95	96
2	2-ClC_6H_4	H	**5b**	93	97
3	2-FC_6H_4	H	**5c**	90	95
4	2-MeC_6H_4	H	**5d**	87	92
5	4-MeC_6H_4	H	**5e**	84	93
6	4-ClC_6H_4	H	**5f**	95	97
7	4-FC_6H_4	H	**5g**	94	96
8[d]	3,4(OCH_2O)C_6H_3	H	**5h**	76	95
9[d]	2-furyl	H	**5i**	70	95
10[d]	PhCHCH	H	**5j**	94	96
11[e]	Me	H	**5k**	72	94
12[e]	*n*Pr	H	**5l**	85	96
13[e]	H	Bn	**5m**	93	98
14[e]	H	*n*Pr	**5n**	81	97
15[e]	H	*n*Val	**5o**	83	96

[a] Identical reaction conditions (see footnote [a] in Table 1) for 30 h. [b] Yield of isolated product. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] The reaction time was 48 h. [e] The reaction time was 60 h.

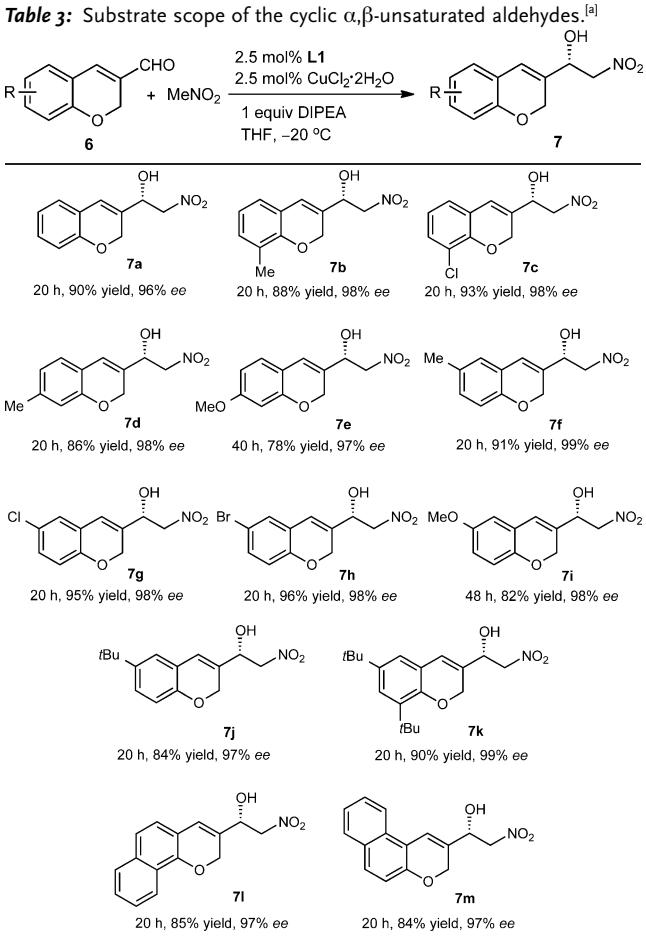
The initial model reaction of cinnamaldehyde (**4a**) with nitromethane was chosen to screen the library of C_1-symmetrical chiral diamine ligands. As summarized in Table 1, the transformation proceeded smoothly to afford the expected Henry product without any detectable 1,4-conjugated addition adduct. A small amount of its dehydration product, the nitroolefin, was detected clearly by TLC analysis with a prolonged reaction time. Evidently, the stereochemistry outcomes for the process were mainly controlled by the configuration of the proline moiety (entries 1–4), and the camphor scaffold showed better chiral induction ability than menthone in these cases. In addition, some synergistic effects between the two chiral components of the ligands were also observed, and the combination of L-proline with D-camphor proved to be the best match. Among all the ligands, **L1** turned out to be the best, and was consistent with our previous observations in cases of other aldehydes.[15,17] Moreover, some primary amino acids derivatives (**L5**, **L6**) can also promote this reaction to achieve good enantiomeric excess, albeit with lower efficiency (entries 5 and 6). The imidazole-type ligand **L7** showed good performance in this reaction as well (entry 7).

After systematic optimization of the reaction parameters,[18] the scope of acyclic α,β-unsaturated aldehydes was further probed under the established reaction conditions. The results are depicted in Table 2. In general, neither the electronic nature nor the positions of the substituent on the aromatic ring exert an influence on the course of the asymmetric catalytic progress. The desired products were obtained in greater than 95% *ee* with good yields in most cases. Electron-rich enals required a longer reaction time to complete the transformation and afforded a little more of the nitroolefin byproduct (entries 8 and 9). (2*E*, 4*E*)-5-phenylpenta-2,4-dienal (**4j**), bearing two conjugated carbon–carbon double bonds, was also suitable for this catalytic system and afforded **5j** in 94% yield and 96% *ee* (entry 10). Having explored the aromatic substrates, we moved on to the aliphatic unsaturated aldehydes to test the generality of this catalytic protocol (entries 11–15). Without activation of the aryl ring, all the aliphatic unsaturated aldehydes tested showed lower reactivity and their reactions proceeded more slowly, but yielded the desired Henry adducts with a little higher enantiopurity. Moreover, much bulkier α-substituted unsaturated aldehydes were also compatible in this catalytic system, and the 2-benzylacrylaldehyde (**4m**) gave the highest *ee* value of 98% (entry 13). It is noteworthy that neither the carbon chain length nor the steric bulk has an effect on the enantioselectivity and yield.

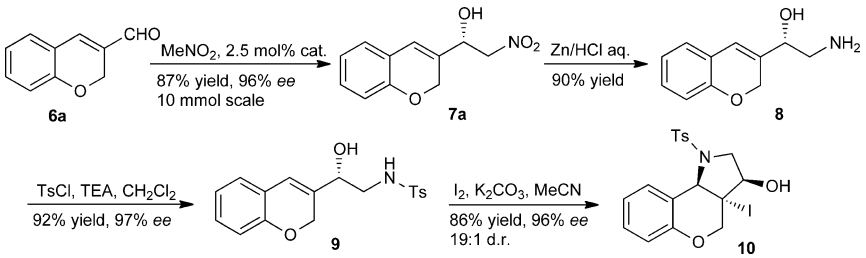
The substrate scope was also extended to cyclic chromeno enals (**6**) prepared from various substituted salicylaldehydes and acrolein though a one-pot oxa-Michael addition/intramolecular aldol/dehydration cascade reaction.[18] The results are given in Table 3. Generally, cyclic enals provided slightly higher *ee* values relative to the open-chain α,β-unsaturated aldehydes. It was noteworthy that substrates bearing an electron-donor group (**6e** and **6i**) can be employed to generate the Henry products in excellent enantioselectivity and moderate yield. The positions of the substituent on the aromatic ring did not have an influence on the transformation. In the cases of **6f** and **6k**, enantiopurities of up to 99% were delivered (entries 6 and 11). Furthermore, the large planar enals **6l** and **6m** also worked well with nitromethane to afford reasonable results (entries 12 and 13).

The synthetic utility of this asymmetric catalytic procedure was demonstrated by its application to the synthesis of a chiral azatricyclic hexahydrochromeno[4,3-*b*]pyrrole scaf-

Table 3: Substrate scope of the cyclic α,β-unsaturated aldehydes.[a]



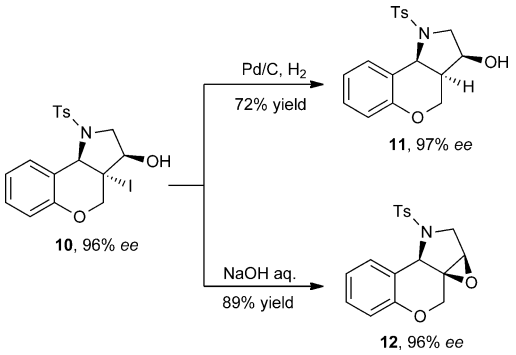
[a] Identical reaction conditions (see footnote [a] in Table 1). Yield is that of the isolated product. The *ee* value was determined by HPLC analysis using a chiral stationary phase.



Scheme 2. Synthesis of chiral azatricyclic framework. TEA = triethylamine.

fold (Scheme 2). The enal **6a** was used as the starting material to react with nitromethane on a 10 mmol scale (20 times enlarged) to afford the adduct **7a** in 87% yield and 96% *ee*. The nitro alcohol can be readily reduced to the amino alcohol **8** in 90% yield by zinc powder in a mixture of methanol and dilute aqueous hydrochloric acid. Subsequent protection of the amino group using *p*-toluenesulfonyl chloride in dry dichloromethane generated **9** as a white crystal in 92% yield. Then, in the presence of 3 equivalents of molecular iodine and potassium carbonate in acetonitrile, **9** was converted into the fused azatricyclic hexahydrochromeno[4,3-*b*]pyrrole framework **10** bearing three adjacent chiral carbon atoms, one of which is a quaternary stereogenic center, in high efficiency and stereoselective manner by intramolecular iodocyclization. The absolute configuration of **9** was determined by X-ray crystallographic analysis, while **10** and **11** were characterized through NOE experiments.[18]

The iodine atom offered a special opportunity for further transformations, and the synthetic versatility of the functional-group-rich intermediate **10** was also explored. As illustrated in Scheme 3, the iodine atom can be conveniently



Scheme 3. Various synthetic transformations of **10**.

reduced though catalytic hydrogenation to afford **11**. Treatment of **10** with aqueous sodium hydroxide provided the fused tetracyclic epoxide **12** bearing a quaternary stereocenter. The results showed that there was no loss of stereochemical information during these practical manipulations.

In summary, the highly enantioselective Henry reaction of enals with nitromethane was elaborated by a C_1-symmetrical chiral copper(II) complex for the first time. With a low to 2.5 mol% catalyst loading, the catalytic asymmetric transformation provided the expected functionalized β-nitro allylic alcohols in high yields (up to 96%) and enantioselectivities (up to 99%) for a broad substrate scope including acyclic and cyclic α or β-substituted unsaturated aldehydes. The reaction conditions were mild and robust and did not require special precautions to exclude moisture or air. More importantly, the synthetic utility of this asymmetric catalytic procedure was demonstrated by its application to the synthesis of the core structure of biologically and pharmaceutically useful fused azatricyclic hexahydrochromeno[4,3-*b*]pyrroles, which underwent subsequent intramolecular stereoselective iodocyclization to provide three continuous chiral carbon atoms, one of which is a quaternary stereogenic center. The reaction proceeds with good yield with excellent distereoselectivity and enantioselectivity. This methodology represents an alternative synthetic way to access such complex molecules. Additionally, the iodine atom on the quaternary carbon atom can be transformed into a number of interesting derivatives by several kinds of practical operations. Further investigations on the applications of this new

chiral catalyst, as well as exploration of the substrate scope, are currently underway in our laboratory.

Received: June 15, 2013
Published online: August 9, 2013

Keywords: asymmetric catalysis · asymmetric synthesis · copper · heterocycles · synthetic methods

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[18] For more detailed information, see the Supporting Information. CCDC 943499 (**9**) 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.

